```
<?xml version="1.0" encoding="UTF-8" standalone="true"?>
<?mso-application progid="Word.Document"?>
<pkg:package xmlns:pkg="http://schemas.microsoft.com/office/2006/xmlPackage">
  - <pkg:part pkg:padding="512" pkg:contentType="application/vnd.openxmlformats-package.relationships+xml" pkg:name="/_rels/.rels">
      - <pkg:xmlData>
          - <Relationships xmlns="http://schemas.openxmlformats.org/package/2006/relationships">
              <Relationship Target="docProps/app.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/extended-properties"
                  Id="rId3"/>
              <Relationship Target="docProps/core.xml" Type="http://schemas.openxmlformats.org/package/2006/relationships/metadata/core-properties"
                  Id="rId2"/>
              <Relationship Target="word/document.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/officeDocument"
                  Id="rId1"/>
            </Relationships>
        </pkg:xmlData>
    </pkg:part>
  - <pkg:part pkg:padding="256" pkg:contentType="application/vnd.openxmlformats-package.relationships+xml" pkg:name="/word/_rels/document.xml.rels">
      - <pkg:xmlData>
          - <Relationships xmlns="http://schemas.openxmlformats.org/package/2006/relationships">
              <Relationship Target="https://doi.org/10.1016/j.jand.2017.07.005"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId117" TargetMode="External"/>
              <Relationship Target="footer1.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/footer" Id="rId21"/>
              <Relationship Target="https://doi.org/10.1007/978-1-4614-6015-2_9"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId42" TargetMode="External"/>
              <Relationship Target="http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId63" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/s00535-016-1198-9"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId84" TargetMode="External"/>
              <Relationship Target="media/image5.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId16"/>
              <Relationship Target="http://www.who.int/mediacentre/factsheets/fs311/en/"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId107" TargetMode="External"/>
              <Relationship Target="https://www.najfnr.org" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink"
                  Id="rId11" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/978-3-7091-0715-7_30"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId32" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/978-3-7091-1331-8_3"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId37" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1111/jhn.12395"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId53" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1038/srep46527"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId58" TargetMode="External"/>
              <Relationship Target="https://www.jstatsoft.org/v036/i03"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId74" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1097/CEJ.0b013e32834dbc81"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId79" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1111/j.1440-1746.2009.06117.x"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId102" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1016/j.jomh.2009.01.005"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId123" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1097/MAJ.0b013e3181df9055"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId128" TargetMode="External"/>
              <Relationship Target="webSettings.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/webSettings" Id="rId5"/>
              <Relationship Target="https://doi.org/10.1038/ajg.2009.541"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId90" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/s10552-009-9428-6"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId95" TargetMode="External"/>
              <Relationship Target="header2.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/header" Id="rId22"/>
              <Relationship Target="media/image9.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId27"/>
              <Relationship Target="https://doi.org/10.1007/978-94-017-9078-9_29"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId43" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/s10552-013-0201-5"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId48" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1002/jrsm.12" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink"
                  Id="rId64" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1111/j.0006-341X.2000.00455.x"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId69" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1016/j.metabol.2014.10.008"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId113" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1016/j.ecl.2013.09.008"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId118" TargetMode="External"/>
              <Relationship Target="fontTable.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/fontTable" Id="rId134"/>
              <Relationship Target="https://doi.org/10.1158/1055-9965.EPI-16-0761"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId80" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1186/1471-2407-14-881"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId85" TargetMode="External"/>
              <Relationship Target="media/image3.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId12"/>
              <Relationship Target="media/image6.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId17"/>
              <Relationship Target="https://idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId33" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1038/nrdp.2015.65"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId38" TargetMode="External"/>
              <Relationship Target="https://doi.org/10.1007/s12020-013-9939-5"
                  Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId59" TargetMode="External"/>
```

<Relationship Target="https://doi.org/10.1111/j.1440-1746.2007.05125.x" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId103" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.canep.2016.01.003" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId108" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s10552-010-9590-x" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId124" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/978-1-4419-9911-5_5" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId129" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1038/srep08797" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId54" TargetMode="External"/>
<Relationship Target="https://community.cochrane.org" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId70" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s11033-014-3157-y" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId75" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1002/oby.22001" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId91" TargetMode="External"/>
<Relationship Target="https://doi.org/10.3346/jkms.2015.30.9.1288" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId96" TargetMode="External"/>
<Relationship Target="../customXml/item1.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/customXml" Id="rId1"/>
<Relationship Target="footnotes.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/footnotes" Id="rId6"/>
<Relationship Target="footer2.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/footer" Id="rId23"/>
<Relationship Target="header3.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/header" Id="rId28"/>
<Relationship Target="https://doi.org/10.1016/j.clcc.2016.02.008" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId49" TargetMode="External"/>
<Relationship Target="https://doi.org/10.3748/wjg.15.5141" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId114" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.jand.2017.08.112" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId119" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1002/ijc.29210" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId44" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1002/cncr.25772" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId60" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1136/bmj.327.7414.557" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId65" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1097/DCR.0000000000000876" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId81" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1177/0003319711421164" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId86" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.bbrc.2016.02.034" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId130" TargetMode="External"/>
<Relationship Target="theme/theme1.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/theme" Id="rId135"/>
<Relationship Target="media/image30.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId13"/>
<Relationship Target="media/hdphoto1.wdp" Type="http://schemas.microsoft.com/office/2007/relationships/hdphoto" Id="rId18"/>
<Relationship Target="https://doi.org/10.1007/s11888-016-0312-y" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId39" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.medcle.2014.05.011" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId109" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1155/2014/943162" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId34" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/978-88-470-2670-4_4" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId50" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1093/annonc/mdx171" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId55" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1111/codi.12172" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId76" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1158/1055-9965.EPI-14-0132" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId97" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1158/1055-9965.EPI-07-0199" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId104" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.bbrc.2015.05.066" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId120" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1017/S1368980015000646" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId125" TargetMode="External"/>
<Relationship Target="endnotes.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/endnotes" Id="rId7"/>
<Relationship Target="https://doi.org/10.1002/jrsm.11" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId71" TargetMode="External"/>
<Relationship Target="https://doi.org/10.5754/hge12895" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId92" TargetMode="External"/>
<Relationship Target="numbering.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/numbering" Id="rId2"/>
<Relationship Target="footer3.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/footer" Id="rId29"/>
<Relationship Target="media/image7.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId24"/>
<Relationship Target="https://doi.org/10.1016/j.critrevonc.2010.01.010" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId40" TargetMode="External"/>
<Relationship Target="https://doi.org/10.3390/ijms140816365" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId45" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1002/sim.1186" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId66" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1158/1940-6207.CAPR-11-0218" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId87" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1371/journal.pone.0053916" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId110" TargetMode="External"/>

<Relationship Target="https://doi.org/10.1016/j.canlet.2012.10.012" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId115" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.lungcan.2008.01.015" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId131" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1097/MCG.0b013e3182688c15" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId61" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1155/2017/8750967" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId82" TargetMode="External"/>
<Relationship Target="mailto:khaled@khaledmb.co.uk" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId19" TargetMode="External"/>
<Relationship Target="http://www.najfnr.or" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId14" TargetMode="External"/>
<Relationship Target="header4.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/header" Id="rId30"/>
<Relationship Target="https://doi.org/10.1007/978-1-60327-502-6_2" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId35" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.ctarc.2016.07.002" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId56" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s10552-012-9942-9" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId77" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/S0929-6646(11)60016-8" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId100" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1097/MD.0000000000005453" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId105" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s10552-014-0507-y" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId126" TargetMode="External"/>
<Relationship Target="media/image1.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId8"/>
<Relationship Target="https://doi.org/10.1016/B978-1-4377-2232-1.00017-6" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId51" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1002/sim.1221" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId72" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s12029-013-9476-8" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId93" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/s10620-013-2974-5" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId98" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1038/srep17591" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId121" TargetMode="External"/>
<Relationship Target="styles.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/styles" Id="rId3"/>
<Relationship Target="file:///G:\1st%20Partition\My%20Activities\Editing\The%20NAJFNR\Submitted%20Manuscripts\Volume%2002\Issue%2004\El%20Harag%20et%20al\Included%20Studies\Shin,%202017.pdf" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId25" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.suc.2017.01.001" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId46" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1136/bmj.315.7109.629" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId67" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.jdiacomp.2011.11.003" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId116" TargetMode="External"/>
<Relationship Target="header1.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/header" Id="rId20"/>
<Relationship Target="https://doi.org/10.1007/978-3-7091-0715-7_24" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId41" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1371/journal.pmed.1000097" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId62" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1038/sj.ijo.0803713" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId83" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1111/j.1445-2197.2009.05084.x" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId88" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/978-3-319-19821-7_16" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId111" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.annepidem.2008.06.006" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId132" TargetMode="External"/>
<Relationship Target="media/image4.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId15"/>
<Relationship Target="https://doi.org/10.1007/978-1-59745-572-5" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId36" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.cgh.2009.02.016" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId57" TargetMode="External"/>
<Relationship Target="https://doi.org/10.5281/zenodo.1245604" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId106" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.canep.2014.02.002" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId127" TargetMode="External"/>
<Relationship Target="https://www.najfnr.org" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId10" TargetMode="External"/>
<Relationship Target="header5.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/header" Id="rId31"/>
<Relationship Target="https://doi.org/10.1016/j.cgh.2012.01.010" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId52" TargetMode="External"/>
<Relationship Target="https://www.R-project.org/" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId73" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1093/aje/kwj253" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId78" TargetMode="External"/>
<Relationship Target="http://journal.waocp.org/?sid=Entrez:PubMed&id=pmid:16435997&key=2005.6.4.485" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId94" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1620/tjem.223.297" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId99" TargetMode="External"/>

```
<Relationship Target="https://doi.org/10.1016/j.gie.2010.06.022"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId101" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1007/978-3-319-05068-3"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId122" TargetMode="External"/>
<Relationship Target="settings.xml" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/settings" Id="rId4"/>
<Relationship Target="media/image2.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId9"/>
<Relationship Target="media/image8.png" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/image" Id="rId26"/>
<Relationship Target="https://doi.org/10.1016/B978-1-4160-4686-8.50006-3"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId47" TargetMode="External"/>
<Relationship Target="https://doi.org/10.2307/2533446" Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink"
    Id="rId68" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.ejca.2010.03.010"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId89" TargetMode="External"/>
<Relationship Target="https://doi.org/10.3748/wjg.v22.i36.8103"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId112" TargetMode="External"/>
<Relationship Target="https://doi.org/10.1016/j.canep.2011.03.007"
    Type="http://schemas.openxmlformats.org/officeDocument/2006/relationships/hyperlink" Id="rId133" TargetMode="External"/>
</Relationships>
</pkg:xmlData>
</pkg:part>
- <pkg:part pkg:contentType="application/vnd.openxmlformats-officedocument.wordprocessingml.document.main+xml" pkg:name="/word/document.xml">
  - <pkg:xmlData>
    - <w:document mc:Ignorable="w14 w15 w16se w16cid wp14" xmlns:wps="http://schemas.microsoft.com/office/word/2010/wordprocessingShape"
      xmlns:wne="http://schemas.microsoft.com/office/word/2006/wordml" xmlns:wpi="http://schemas.microsoft.com/office/word/2010/wordprocessingInk"
      xmlns:wpg="http://schemas.microsoft.com/office/word/2010/wordprocessingGroup"
      xmlns:w16se="http://schemas.microsoft.com/office/word/2015/wordml/symex"
      xmlns:w16cid="http://schemas.microsoft.com/office/word/2016/wordml/cid" xmlns:w15="http://schemas.microsoft.com/office/word/2012/wordml"
      xmlns:w14="http://schemas.microsoft.com/office/word/2010/wordml" xmlns:w="http://schemas.openxmlformats.org/wordprocessingml/2006/main"
      xmlns:w10="urn:schemas-microsoft-com:office:word" xmlns:wp="http://schemas.openxmlformats.org/drawingml/2006/wordprocessingDrawing"
      xmlns:wp14="http://schemas.microsoft.com/office/word/2010/wordprocessingDrawing" xmlns:v="urn:schemas-microsoft-com:vml"
      xmlns:m="http://schemas.openxmlformats.org/officeDocument/2006/math"
      xmlns:r="http://schemas.openxmlformats.org/officeDocument/2006/relationships" xmlns:o="urn:schemas-microsoft-com:office:office"
      xmlns:am3d="http://schemas.microsoft.com/office/drawing/2017/model3d" xmlns:aink="http://schemas.microsoft.com/office/drawing/2016/ink"
      xmlns:mc="http://schemas.openxmlformats.org/markup-compatibility/2006"
      xmlns:cx8="http://schemas.microsoft.com/office/drawing/2016/5/14/chartex"
      xmlns:cx7="http://schemas.microsoft.com/office/drawing/2016/5/13/chartex"
      xmlns:cx6="http://schemas.microsoft.com/office/drawing/2016/5/12/chartex"
      xmlns:cx5="http://schemas.microsoft.com/office/drawing/2016/5/11/chartex"
      xmlns:cx4="http://schemas.microsoft.com/office/drawing/2016/5/10/chartex"
      xmlns:cx3="http://schemas.microsoft.com/office/drawing/2016/5/9/chartex"
      xmlns:cx2="http://schemas.microsoft.com/office/drawing/2015/10/21/chartex"
      xmlns:cx1="http://schemas.microsoft.com/office/drawing/2015/9/8/chartex" xmlns:cx="http://schemas.microsoft.com/office/drawing/2014/chartex"
      xmlns:wpc="http://schemas.microsoft.com/office/word/2010/wordprocessingCanvas">
      - <w:body>
        - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="2F6FC753">
          - <w:pPr>
              <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
              <w:ind w:right="0" w:left="235"/>
              <w:jc w:val="left"/>
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                <w:sz w:val="16"/>
                <w:szCs w:val="16"/>
              </w:rPr>
            </w:pPr>
          - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                <w:sz w:val="16"/>
                <w:szCs w:val="16"/>
              </w:rPr>
              <w:t>The North African Journal of Fo</w:t>
            </w:r>
          - <w:r>
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                <w:sz w:val="16"/>
                <w:szCs w:val="16"/>
              </w:rPr>
              <w:t>od and Nu</
          - <w:r w:rsidR="00ED4AB9">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                <w:sz w:val="16"/>
                <w:szCs w:val="16"/>
              </w:rPr>
              <w:t xml:space="preserve">trition Research: (2018) 02; (04): </
```

```
</w:r>
- <w:r w:rsidRPr="005C028C">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
      <w:sz w:val="16"/>
      <w:szCs w:val="16"/>
    </w:rPr>
    <w:t>9</w:t>
  </w:r>
- <w:r w:rsidR="00ED4AB9">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
      <w:sz w:val="16"/>
      <w:szCs w:val="16"/>
    </w:rPr>
    <w:t>3-110</w:t>
  </w:r>
</w:p>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00008B0DCA" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="6E3E76DE"
w:rsidRPr="005C028C">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
      <w:ind w:right="0" w:left="235"/>
      <w:jc w:val="left"/>
    - <w:rPr>
      <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
      <w:b/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
      <w:spacing w:val="20"/>
      <w:sz w:val="16"/>
      <w:szCs w:val="16"/>
    </w:rPr>
  </w:pPr>
  - <w:r>
    - <w:rPr>
        <w:noProof/>
      </w:rPr>
    - <w:drawing>
      - <wp:anchor wp14:editId="38A68A7D" wp14:anchorId="6CB6B765" allowOverlap="1" layoutInCell="1" locked="0"
      behindDoc="0" relativeHeight="251707392" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
          <wp:simplePos y="0" x="0" />
        - <wp:positionH relativeFrom="column">
            <wp:posOffset>5179237</wp:posOffset>
          </wp:positionH>
        - <wp:positionV relativeFrom="paragraph">
            <wp:posOffset>16637</wp:posOffset>
          </wp:positionV>
          <wp:extent cx="948985" cy="385156" />
          <wp:effectExtent t="0" b="0" r="3810" l="0" />
          <wp:wrapNone />
          <wp:docPr name="Picture 33" descr="Image result for open access logo" id="33" />
        - <wp:cNvGraphicFramePr>
            <a:graphicFrameLocks noChangeAspect="1" xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main" />
          </wp:cNvGraphicFramePr>
        - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
          - <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
            - <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
              - <pic:nvPicPr>
                  <pic:cNvPr name="Picture 1" descr="Image result for open access logo" id="0" />
                - <pic:cNvPicPr>
                    <a:picLocks noChangeAspect="1" noChangeArrowheads="1" />
                  </pic:cNvPicPr>
                </pic:nvPicPr>
              - <pic:blipFill>
                - <a:blip cstate="print" r:embed="rId8">
                  - <a:extLst>
                    - <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
                        <a14:useLocalDpi val="0"
                          xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main" />
                      </a:ext>
                    </a:extLst>
                  </a:blip>
                  <a:srcRect />
                - <a:stretch>
                    <a:fillRect />
                  </a:stretch>
                </pic:blipFill>
              - <pic:spPr bwMode="auto">
                - <a:xfrm>
                    <a:off y="0" x="0" />
```

```
                                        <a:ext cx="948985" cy="385156"/>
                                    </a:xfrm>
                                - <a:prstGeom prst="rect">
                                        <a:avLst/>
                                    </a:prstGeom>
                                    <a:noFill/>
                                - <a:ln>
                                        <a:noFill/>
                                    </a:ln>
                                </pic:spPr>
                            </pic:pic>
                        </a:graphicData>
                    </a:graphic>
                - <wp14:sizeRelH relativeFrom="margin">
                        <wp14:pctWidth>0</wp14:pctWidth>
                    </wp14:sizeRelH>
                - <wp14:sizeRelV relativeFrom="margin">
                        <wp14:pctHeight>0</wp14:pctHeight>
                    </wp14:sizeRelV>
                </wp:anchor>
            </w:drawing>
        </w:r>
    - <w:r w:rsidR="00C62C26">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"
                w:eastAsia="Leelawadee UI Semilight"/>
            <w:color w:val="0563C1"/>
            <w:sz w:val="16"/>
            <w:u w:val="single" w:color="0563C1"/>
        </w:rPr>
        <w:t>https://doi.org/10.5281/zenodo.</w:t>
    </w:r>
    - <w:r w:rsidR="0035656E" w:rsidRPr="0035656E">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="14"/>
            <w:szCs w:val="14"/>
        </w:rPr>
        <w:t>1478870</w:t>
    </w:r>
</w:p>
- <w:p w:rsidP="008B0DCA" w:rsidRDefault="005B7D45" w:rsidR="00C62C26" w:rsidRPr="00722F22" w14:textId="77777777" w14:paraId="6D6319EF">
    - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
        <w:ind w:right="-406" w:left="255"/>
        <w:jc w:val="left"/>
        - <w:rPr>
            <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
            <w:b/>
            <w:color w:val="auto"/>
            <w:spacing w:val="20"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
    </w:pPr>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
            <w:b/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:spacing w:val="20"/>
            <w:sz w:val="24"/>
        </w:rPr>
        <w:t>Review Article</w:t>
    </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
            <b/>
            <color w="385623" w:themeShade="80" w:themeColor="accent6"/>
            <spacing w:val="20"/>
            <sz w:val="24"/>
        </w:rPr>
        <w:tab/>
    </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
            <b/>
            <color w="385623" w:themeShade="80" w:themeColor="accent6"/>
```

```
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
<w:b/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:spacing w:val="20"/>
<w:sz w:val="24"/>
</w:rPr>
<w:tab/>
</w:r>
</w:p>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="003932A6" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="0DE6C643"
w:rsidRPr="005C028C">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="161" w:before="0"/>
<w:ind w:right="-28" w:left="212" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r w:rsidRPr="005C028C">
- <w:rPr>
<w:noProof/>
</w:rPr>
- <mc:AlternateContent>
- <mc:Choice Requires="wps">
- <w:drawing>
- <wp:anchor wp14:editId="08D674FF" wp14:anchorId="681BAD5B" allowOverlap="1" layoutInCell="1" locked="0"
behindDoc="0" relativeHeight="251661312" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
```

```
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="page">
    <wp:posOffset>1056005</wp:posOffset>
  </wp:positionH>
- <wp:positionV relativeFrom="paragraph">
    <wp:posOffset>995045</wp:posOffset>
  </wp:positionV>
  <wp:extent cx="5981065" cy="12065"/>
  <wp:effectExtent r="635" b="6985" t="0" l="0"/>
  <wp:wrapNone/>
  <wp:docPr name="Shape 13825" id="36"/>
  <wp:cNvGraphicFramePr/>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
  - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
    - <wps:wsp>
        <wps:cNvSpPr/>
      - <wps:spPr>
        - <a:xfrm>
            <a:off y="0" x="0"/>
            <a:ext cx="5981065" cy="12065"/>
          </a:xfrm>
        - <a:custGeom>
            <a:avLst/>
            <a:gdLst/>
            <a:ahLst/>
            <a:cxnLst/>
            <a:rect r="0" b="0" t="0" l="0"/>
          - <a:pathLst>
            - <a:path w="5981426" h="12192">
              - <a:moveTo>
                  <a:pt y="0" x="0"/>
                </a:moveTo>
              - <a:lnTo>
                  <a:pt y="0" x="5981426"/>
                </a:lnTo>
              - <a:lnTo>
                  <a:pt y="12192" x="5981426"/>
                </a:lnTo>
              - <a:lnTo>
                  <a:pt y="12192" x="0"/>
                </a:lnTo>
              - <a:lnTo>
                  <a:pt y="0" x="0"/>
                </a:lnTo>
              </a:path>
            </a:pathLst>
          </a:custGeom>
        - <a:ln w="0" cap="flat">
            <a:miter lim="127000"/>
          </a:ln>
        </wps:spPr>
      - <wps:style>
        - <a:lnRef idx="0">
          - <a:srgbClr val="000000">
              <a:alpha val="0"/>
            </a:srgbClr>
          </a:lnRef>
        - <a:fillRef idx="1">
            <a:srgbClr val="000000"/>
          </a:fillRef>
        - <a:effectRef idx="0">
            <a:scrgbClr r="0" b="0" g="0"/>
          </a:effectRef>
          <a:fontRef idx="none"/>
        </wps:style>
        <wps:bodyPr/>
      </wps:wsp>
    </a:graphicData>
  </a:graphic>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
  - <w:pict>
    - <v:shape w14:anchorId="2ECFF043" id="Shape 13825" strokeweight="0" stroked="f" fillcolor="black"
      path="m,l5981426,r,12192l,12192,,e"
      o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
      90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
      0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
      OITrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
      SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
      JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
```

bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQA0jQkRNwIAACgFAAAOAAAAZHJzL2Uyb0RvYy54bWysVNtuGyEQfa/Uf0C813tJ7TqW13lo1L5U
bdSkH4BZ8CJxExCv/fcdZi+20qqRou4DO8DMYc4Zhu3dyWhyFCEqZxtaLUpKhOWuVfbQ0F9PXz6s
KYmJ2ZZpZ0VDzyLSu937d9veb0TtOqdbEQiA2LjpfUO7lPymKCLvhGFx4bywsCldMCzBNByKNrAe
0I0u6rJcFb0LrQ+Oixhh9X7YpDvEl1Lw9EPKKBLRDYXcEo4Bx30ei92WbQ6B+U7xMQ32hiwMUxYO
naHuWWLkOag/oIziwUUn04I7UzgpFRfIAdhU5Qs2jx3zArmAONHPMsX/B8u/Hx8CUW1Db1aUWGag
RngsqW7W9TLr0/u4AbdH/xDGWQQzkz3JYPIfaJATanqeNRWnRDgsLm/XVblaUsJhr6qzCSjFJZg/
x/RVOARix28xDSVpJ4t1k8VPdjIDFPafJfUs5bicXTZJP2TysQaWXU6kuq2xYMYdxZNDv/SCBCR5
2dX22iuzQqyJMPhOHtPfI96153DqQH/ymv6DN1xRlCln97ofXt/5ZDAyVRR3pg+L1wJrm5WAUziD
ZpOapUEElaALtTJZmU9leQEGtFz/oeJopbMWWS5tfwoJNwcLnxdiOOw/60COLPcafgjOtO/YuDqS
Gl0xVcTJ8VJpPUNWGPo3yEGW0TnHCWzzObIcIvmYzdDr8BgB6anjQZQ5CE92Ns3xFt4pTPOKbTb3
rj1jB6Ag0I6Y/fh05H6/nqNslwdu9xsAAP//AwBQSwMEFAAGAAgAAAAhAMrIrkDfAAAADAEAAA8A
AABkcnMvZG93bnJldi54bWxMj8FOwzAQRO9I/IO1SFwQtdMKN0rjVAVEOVO49ObGJo4a28F20vD3
bE70trM7mn1TbifbkVGH2HonIFswINrVXrWuEfD1+faYA4lJOiU777SAXx1hW93elLJQ/uI+9HhI
DcEQFwspwKTUF5TG2mgr48L32uHt2wcrE8rQUBXkBcNtR5eMcWpl6/CDkb1+Mbo+HwYrIO39w+rn
uGfvPuzW51dvhjF7FuL+btptgCQ9pX8zzPiPiIDhUynfzgVCQdas5XaMXhia+BzI6M5Usgp3mVc6BV
Sa9LVH8AAAD//wMAUEsBAi0AFAAGAAgAAAAhALaDOJL+AAAA4QEAABMAAAAAAAAAAAAAAAAAAAAA
AFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAOP0h/9YAAACUAQAACwAAAAAAAAAA
AAAAAAAvAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEANI0JETcCAAAoBQAADgAAAAAAAAAA
AAAAAAAuAgAAZHJzL2Uyb0RvYy54bWxQSwECLQAUAAYACAAAACEAysiuQN8AAAAMAQAADwAAAAA
AAAAAAAAAACRBAAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAAEAAQA8wAAAJ0FAAAAAAA== "
coordsize="5981426,12192" style="position:absolute;margin-left:83.15pt;margin-top:78.35pt;width:470.95pt;height:.95pt;z-index:251661312;visibility:visible;mso-wrap-style:square;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:page;mso-position-vertical:absolute;mso-position-vertical-relative:text;v-text-anchor:top" o:spid="_x0000_s1026">
<v:stroke joinstyle="miter" miterlimit="83231f"/>
<v:path textboxrect="0,0,5981426,12192" arrowok="t"/>
<w10:wrap anchorx="page"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:r w:rsidRPr="005C028C">
- <w:rPr>
<w:noProof/>
</w:rPr>
- <mc:AlternateContent>
- <mc:Choice Requires="wps">
- <w:drawing>
- <wp:anchor wp14:editId="5C487515" wp14:anchorId="2653148F" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251660288" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="column">
<wp:posOffset>143815</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>38735</wp:posOffset>
</wp:positionV>
<wp:extent cx="5981065" cy="12065"/>
<wp:effectExtent r="635" b="6985" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Shape 13825" id="35"/>
<wp:cNvGraphicFramePr/>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
- <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
- <wps:wsp>
<wps:cNvSpPr/>
- <wps:spPr>
- <a:xfrm>
<a:off y="0" x="0"/>
<a:ext cx="5981065" cy="12065"/>
</a:xfrm>
- <a:custGeom>
<a:avLst/>
<a:gdLst/>
<a:ahLst/>
<a:cxnLst/>
<a:rect r="0" b="0" t="0" l="0"/>
- <a:pathLst>
- <a:path w="5981426" h="12192">
- <a:moveTo>
<a:pt y="0" x="0"/>
</a:moveTo>
- <a:lnTo>
<a:pt y="0" x="5981426"/>
</a:lnTo>
- <a:lnTo>

<a:pt y="12192" x="5981426"/>
</a:lnTo>
- <a:lnTo>
<a:pt y="12192" x="0"/>
</a:lnTo>
- <a:lnTo>
<a:pt y="0" x="0"/>
</a:lnTo>
</a:path>
</a:pathLst>
</a:custGeom>
- <a:ln w="0" cap="flat">
<a:miter lim="127000"/>
</a:ln>
</wps:spPr>
- <wps:style>
- <a:lnRef idx="0">
- <a:srgbClr val="000000">
<a:alpha val="0"/>
</a:srgbClr>
</a:lnRef>
- <a:fillRef idx="1">
<a:srgbClr val="000000"/>
</a:fillRef>
- <a:effectRef idx="0">
<a:scrgbClr r="0" b="0" g="0"/>
</a:effectRef>
<a:fontRef idx="none"/>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</a:graphicData>
</a:graphic>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:shape w14:anchorId="33DE327D" id="Shape 13825" strokeweight="0" stroked="f" fillcolor="black"
path="m,l5981426,r,12192l,12192,,e"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQAjCv4gNwIAACgFAAAOAAAAZHJzL2Uyb0RvYy54bWysVNtuGyEQfa/Uf0C813tJ7TqW13lo1L5U
bdSkH4BZ8CJxExCv/fcdZi+20qqRou4DO8DMYc4Zhu3dyWhyFCEqZxtaLUpKhOWuVfbQ0F9PXz6s
KYmJ2ZZpZ0VDzyLSu937d9veb0TtOqdbEQiA2LjpfUO7lPymKCLvhGFx4bywsCldMCzBNByKNrAe
0I0u6rJcFb0LrQ+Oixhh9X7YpDvEl1Lw9EPKKBLRDYXcEo4Bx30ei92WbQ6B+U7xMQ32hiwMUxYO
naHuWWLkOag/oIziwUUn04I7UzgpFRfIAdhU5Qs2jx3zArmAONHPMsX/B8u/Hx8CUW1Db5aUWGag
RngsqW7W9TLr0/u4AbdH/xDGWQQzkz3JYPIfaJATanqeNRWnRDgsLm/XVbkCbA57VZ1NQCkuwfw5
pq/CIRA7fotpKEk7WaybLH6ykxmgsP8sqWcpx+Xsskn6IZOP9YqSLidS3dZYMOOO4smhX3pBApK8
7Gp77ZVZIdZEGHwnj+nvEe/aczh1oD95Tf/BG64oypSze90Pr+98MhiZKoo704fFa4G1zUrAKZxB
s0nN0iCCStCFWpmszKeyvAADWq7/UHG00lmLLJe2P4WEm4OFzwsxHPafdSBHlnsNPwRn2ndsXB1J
ja6YKuLkeKm0niErDP0b5CDL6JzjBLb5HFkOkXzMZuh1eIyA9NTxIMochCc7m+FNpt7
156xA1AQaEfMfnw6cr9fz1G2ywO3+w0AAP//AwBQSwMEFAAGAAgAAAAhAG2lBFPbAAAABgEAAA8A
AABkcnMvZG93bnJldi54bWxMjsFOwzAQRO9I/IO1SFwQtRMgLSGbqoAoZ0ov3NzYxFHjdbCdNPw9
5gTH0YzevGo9255N2ofOEUK2EMA0NU511CLs31+uV8BClKRk70gjfOsA6/r8rJKlcid609MutixB
KJQSwcQ4lJyHxmgrw8INmlL36byVMUXfcuXlKcFtz3MhCm5lR+nByEE/Gd0cd6NFiFt3dfP1sRWv
zm+Wx2dnxil7RLy8mDcPwKePwKKe498YfvWTOtJ6eBGUoH1CHlepCVCkQFL9X1xewfsgLASwOuK/9ev
fwAAAP//AwBQSwECLQAUAAYACAAAACEAtoM4kv4AAADhAQAAEwAAAAAAAAAAAAAAAAAAAAAAW
bnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAAAAAAAAAAAAA
AC8BAABfcmVscy8ucmVsc1BLAQItABQABgAIAAAAIQAjCv4gNwIAACgFAAAOAAAAAAAAAAAAAAAA
AC4CAABkcnMvZTJvRG9jLnhtbFBLAQItABQABgAIAAAAIQBtpQRT2wAAAAYBAAAPAAAAAAAAAAAA
AAAAAJEEAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAQABADzAAAAmQUAAAAA "
coordsize="5981426,12192" style="position:absolute;margin-left:11.3pt;margin-
top:3.05pt;width:470.95pt;height:.95pt;z-index:251660288;visibility:visible;mso-wrap-style:square;mso-wrap-
distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-
horizontal:absolute;mso-position-horizontal-relative:text;mso-position-vertical:absolute;mso-position-vertical-
relative:text;v-text-anchor:top" o:spid="_x0000_s1026">
<v:stroke joinstyle="miter" miterlimit="83231f"/>
<v:path textboxrect="0,0,5981426,12192" arrowok="t"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>

```
- <w:r w:rsidR="00C62C26" w:rsidRPr="005C028C">
  - <w:rPr>
      <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
      <w:b/>
      <w:noProof/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
      <w:sz w:val="30"/>
      <w:szCs w:val="30"/>
    </w:rPr>
  - <mc:AlternateContent>
    - <mc:Choice Requires="wps">
      - <w:drawing>
        - <wp:anchor wp14:editId="125D1B9C" wp14:anchorId="62C09D3D" allowOverlap="1" layoutInCell="1" locked="0"
          behindDoc="0" relativeHeight="251663360" simplePos="0" distR="114300" distL="114300" distB="45720"
          distT="45720">
            <wp:simplePos y="0" x="0"/>
          - <wp:positionH relativeFrom="margin">
              <wp:posOffset>5050155</wp:posOffset>
            </wp:positionH>
          - <wp:positionV relativeFrom="paragraph">
              <wp:posOffset>70485</wp:posOffset>
            </wp:positionV>
            <wp:extent cx="1155622" cy="252442"/>
            <wp:effectExtent r="6985" b="0" t="0" l="0"/>
            <wp:wrapNone/>
            <wp:docPr name="Text Box 2" id="217"/>
          - <wp:cNvGraphicFramePr>
              <a:graphicFrameLocks xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
            </wp:cNvGraphicFramePr>
          - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
            - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
              - <wps:wsp>
                - <wps:cNvSpPr txBox="1">
                    <a:spLocks noChangeArrowheads="1"/>
                  </wps:cNvSpPr>
                - <wps:spPr bwMode="auto">
                  - <a:xfrm>
                      <a:off y="0" x="0"/>
                      <a:ext cx="1155622" cy="252442"/>
                    </a:xfrm>
                  - <a:prstGeom prst="rect">
                      <a:avLst/>
                    </a:prstGeom>
                  - <a:solidFill>
                      <a:srgbClr val="FFFFFF"/>
                    </a:solidFill>
                  - <a:ln w="9525">
                      <a:noFill/>
                      <a:miter lim="800000"/>
                      <a:headEnd/>
                      <a:tailEnd/>
                    </a:ln>
                  </wps:spPr>
                - <wps:txbx>
                  - <w:txbxContent>
                    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
                      w14:textId="77777777" w14:paraId="3A08E2A2" w:rsidRPr="00073AAE">
                      - <w:pPr>
                          <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
                          <w:ind w:left="11" w:hanging="11"/>
                          <w:jc w:val="right"/>
                        - <w:rPr>
                            <w:b/>
                            <w:bCs/>
                            <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                            <w:lang w:val="fr-FR"/>
                          </w:rPr>
                        </w:pPr>
                      - <w:r w:rsidRPr="00073AAE">
                        - <w:rPr>
                            <w:b/>
                            <w:bCs/>
                            <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                          </w:rPr>
                          <w:t>eISSN</w:t>
                        </w:r>
                      - <w:r w:rsidRPr="00073AAE">
                        - <w:rPr>
                            <w:b/>
                            <w:bCs/>
                            <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                            <w:lang w:val="fr-FR"/>
                          </w:rPr>
```

</w:rPr>
<w:t>: 2588-1582</w:t>
</w:r>
</w:p>
</w:txbxContent>
</wps:txbx>
- <wps:bodyPr anchorCtr="0" anchor="t" bIns="45720" rIns="91440" tIns="45720" lIns="91440" wrap="square" vert="horz" rot="0">
<a:noAutofit/>
</wps:bodyPr>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:shapetype w14:anchorId="62C09D3D" id="_x0000_t202" path="m,l,21600r21600,l21600,xe" coordsize="21600,21600" o:spt="202">
<v:stroke joinstyle="miter"/>
<v:path o:connecttype="rect" gradientshapeok="t"/>
</v:shapetype>
- <v:shape id="Text Box 2" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQAD/VnRIAIAAB0EAAAOAAAAZHJzL2Uyb0RvYy54bWysU11v2yAUfZ+0/4B4XxxbcT+sOFWXLtOk
rpvU9gdgjGM04DIgsbNfvwtO06h7m+oHxPW9HM4997C8GbUie+G8BFPTfDanRBgOrTTbmj4/bT5d
UeIDMy1TYERND8LTm9XHD8vBVqKAHlQrHEEQ46vB1rQPwVZZ5nkvNPMzsMJgsgOnWcDQbbPWsQHR
tcqK+fwiG8C11gEX3uPfuylJVwm/6wQPP7rOi0BUTZFbSKtLaxPXbLVk1dYx20t+pMH+g4Vm0uCl
J6g7FhjZOfkPlJbcgYcuzDjoDLpOcpF6wG7y+ZtuHntmReoFxfH2JJN/P1j+sP/piGxrWuSXlBim
cUhPYgzkM4ykiPoM1ldY9mixMIz4G+ecevX2HvgvTwyse2a24tY5GHrBWuSXx5PZ2dEJx0eQZvgO
LV7DdgES0Ng5HcVDOQii45wDP9lEKjxemZfl3RVFQwjFXlMVikchlrHo5bZ0PXwVoEjc1dTj7
9z5ENqx6KYmXeVCy6zJh6mDaVU3N7NSBZDc0dPbq8HdbEo37O+EN2SMh5wNkDTg54Tt7dtXvXNQF9j/4n6yn3zQh0s5ILkUqY5azOqQwaBHqmn6l2Rm6k4T+wnDVmXsPcg8fVC
9z5ENqx6KYmXeVCy3UilUuC2zVo5smfok036UgNvypQhQ02vy6JMyAbi+WQhLQP6WEld06t5/CZn
RTW+mDaVBCbVtEcmyhzliYpM2oSxGbEwatZAe0ChHEx+xfeFmx7cH0oG9GpN/e8dc4IS9c2g2Nf5
YhHNnYJFeVlg4M4zzXmGGY5QNQ2UTNt1SA8i6mDgFofSyaTXK5MjV/RgkvH4XqLJz+NU9fqqV38B
AAD//wMAUEsDBBQABgAIAAAAIQAMhMmf3QAAAAkBAAAPAAAAZHJzL2Rvd25yZXYueG1sTI/BTsMw
DIbvSLxDZCQuiKUFutDSdAIkENeNPYDbZG1F41RNtnZvjzmxo/1/+v253CxuECc7hd6ThnSVgLDU
eNNTq2H//XH/DCJEJIODJ6vhbANsquurEgvjZ9ra0y62gksoFKihi3EspAxNZx2GlR8tcXbwk8PI
49RKM+HM5W6QD0mylg574gsdjva9s83P7ug0HL7muyyf68+4V9un9RvqtcXENEu8R+G
P31Wh4qdan8kE8SgQeXZI6McpCkIBnKleFFryJIcZFXKyw+qXwAAAP//AwBQSwECLQAUAAYACAAA
ACEAtoM4kv4AAADhAQAAEwAAAAAAAAAAAAAAAAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQIt
ABQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAAAAAAAAAAAAAAC8BAABfcmVscy8ucmVsc1BLAQIt
ABQABgAIAAAAIQAD/VnRIAIAAB0EAAAOAAAAAAAAAAAAAAAAAAAC4CAABkcnMvZTJvRG9jLnhtbFBL
AQItABQABgAIAAAAIQAMhMmf3QAAAAkBAAAPAAAAAAAAAAAAAAAAAAAHoEAABkcnMvZG93bnJldi54
bWxQSwUGAAAAAAQABADzAAAAhAUAAAAA " style="position:absolute;left:0;text-align:left;margin-left:397.65pt;margin-top:5.55pt;width:91pt;height:19.9pt;z-index:251663360;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:3.6pt;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:3.6pt;mso-position-horizontal:absolute;mso-position-horizontal-relative:margin;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-relative:margin;mso-height-relative:margin;v-text-anchor:top"
o:spid="_x0000_s1026" type="#_x0000_t202">
- <v:textbox>
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="3A08E2A2" w:rsidRPr="00073AAE">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
<w:ind w:left="11" w:hanging="11"/>
<w:jc w:val="right"/>
- <w:rPr>
<w:b/>
<w:bCs/>
<w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
<w:lang w:val="fr-FR"/>
</w:rPr>
</w:pPr>
<w:proofErr w:type="spellStart"/>

```
- <w:r w:rsidRPr="00073AAE">
  - <w:rPr>
      <w:b/>
      <w:bCs/>
      <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
    </w:rPr>
    <w:t>eISSN</w:t>
  </w:r>
  <w:proofErr w:type="spellEnd"/>
- <w:r w:rsidRPr="00073AAE">
  - <w:rPr>
      <w:b/>
      <w:bCs/>
      <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
      <w:lang w:val="fr-FR"/>
    </w:rPr>
    <w:t>: 2588-1582</w:t>
  </w:r>
</w:p>
</w:txbxContent>
</v:textbox>
<w10:wrap anchorx="margin"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:r w:rsidR="00C62C26" w:rsidRPr="005C028C">
  - <w:rPr>
      <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
      <w:b/>
      <w:noProof/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
      <w:sz w:val="30"/>
      <w:szCs w:val="30"/>
    </w:rPr>
  - <w:drawing>
    - <wp:anchor wp14:editId="1DADCBCF" wp14:anchorId="18F8D91C" allowOverlap="1" layoutInCell="1" locked="0"
      behindDoc="0" relativeHeight="251659264" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
        <wp:simplePos y="0" x="0"/>
      - <wp:positionH relativeFrom="margin">
          <wp:posOffset>141399</wp:posOffset>
        </wp:positionH>
      - <wp:positionV relativeFrom="paragraph">
          <wp:posOffset>44450</wp:posOffset>
        </wp:positionV>
        <wp:extent cx="1442720" cy="951230"/>
        <wp:effectExtent r="5080" b="1270" t="0" l="0"/>
        <wp:wrapNone/>
        <wp:docPr name="Picture 34" descr="H:\1st Partition\My Activities\The NAJFNR\Website\Images\NAJFNR Logo.png"
          id="34"/>
      - <wp:cNvGraphicFramePr>
          <a:graphicFrameLocks noChangeAspect="1" xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
        </wp:cNvGraphicFramePr>
      - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
        - <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
          - <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
            - <pic:nvPicPr>
                <pic:cNvPr name="Picture 4" descr="H:\1st Partition\My Activities\The
                  NAJFNR\Website\Images\NAJFNR Logo.png" id="0"/>
              - <pic:cNvPicPr>
                  <a:picLocks noChangeAspect="1" noChangeArrowheads="1"/>
                </pic:cNvPicPr>
              </pic:nvPicPr>
            - <pic:blipFill>
              - <a:blip cstate="print" r:embed="rId9">
                - <a:extLst>
                  - <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
                      <a14:useLocalDpi val="0"
                        xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main"/>
                    </a:ext>
                  </a:extLst>
                </a:blip>
                <a:srcRect/>
              - <a:stretch>
                  <a:fillRect/>
                </a:stretch>
              </pic:blipFill>
            - <pic:spPr bwMode="auto">
              - <a:xfrm>
                  <a:off y="0" x="0"/>
                  <a:ext cx="1442720" cy="951230"/>
```

```
                                    </a:xfrm>
                                - <a:prstGeom prst="rect">
                                      <a:avLst/>
                                    </a:prstGeom>
                                    <a:noFill/>
                                - <a:ln>
                                      <a:noFill/>
                                    </a:ln>
                                </pic:spPr>
                            </pic:pic>
                        </a:graphicData>
                    </a:graphic>
                - <wp14:sizeRelH relativeFrom="margin">
                      <wp14:pctWidth>0</wp14:pctWidth>
                    </wp14:sizeRelH>
                - <wp14:sizeRelV relativeFrom="margin">
                      <wp14:pctHeight>0</wp14:pctHeight>
                    </wp14:sizeRelV>
                </wp:anchor>
            </w:drawing>
        </w:r>
    - <w:r w:rsidR="00C62C26" w:rsidRPr="005C028C">
        - <w:rPr>
              <w:noProof/>
              <w:sz w:val="22"/>
            </w:rPr>
        - <mc:AlternateContent>
            - <mc:Choice Requires="wpg">
                - <w:drawing>
                    - <wp:inline wp14:editId="0ADF602D" wp14:anchorId="2F70865D" distR="0" distL="0" distB="0" distT="0">
                          <wp:extent cx="5988055" cy="1014412"/>
                          <wp:effectExtent r="0" b="0" t="0" l="0"/>
                          <wp:docPr name="Group 10991" id="10991"/>
                          <wp:cNvGraphicFramePr/>
                        - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
                            - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingGroup">
                                - <wpg:wgp>
                                      <wpg:cNvGrpSpPr/>
                                  - <wpg:grpSpPr>
                                    - <a:xfrm>
                                          <a:off y="0" x="0"/>
                                          <a:ext cx="5988055" cy="1014412"/>
                                          <a:chOff y="39628" x="-43766"/>
                                          <a:chExt cx="5988055" cy="1122214"/>
                                      </a:xfrm>
                                  </wpg:grpSpPr>
                                  - <wps:wsp>
                                        <wps:cNvPr name="Rectangle 147" id="147"/>
                                        <wps:cNvSpPr/>
                                    - <wps:spPr>
                                        - <a:xfrm>
                                              <a:off y="39628" x="2990669"/>
                                              <a:ext cx="42144" cy="186477"/>
                                          </a:xfrm>
                                        - <a:prstGeom prst="rect">
                                              <a:avLst/>
                                          </a:prstGeom>
                                        - <a:ln>
                                              <a:noFill/>
                                          </a:ln>
                                      </wps:spPr>
                                    - <wps:txbx>
                                        - <w:txbxContent>
                                          - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="378DD19B">
                                              - <w:pPr>
                                                    <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                                                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                                                    <w:jc w:val="left"/>
                                                </w:pPr>
                                              - <w:r>
                                                - <w:rPr>
                                                      <w:sz w:val="22"/>
                                                  </w:rPr>
                                                    <w:t xml:space="preserve"> </w:t>
                                                </w:r>
                                            </w:p>
                                        </w:txbxContent>
                                    </wps:txbx>
                                    <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0" horzOverflow="overflow">
                                          <a:noAutofit/>
```

```
        </wps:bodyPr>
    </wps:wsp>
- <wps:wsp>
        <wps:cNvPr name="Rectangle 148" id="148"/>
        <wps:cNvSpPr/>
    - <wps:spPr>
        - <a:xfrm>
            <a:off y="507496" x="2990669"/>
            <a:ext cx="42144" cy="186477"/>
          </a:xfrm>
        - <a:prstGeom prst="rect">
            <a:avLst/>
          </a:prstGeom>
        - <a:ln>
            <a:noFill/>
          </a:ln>
        </wps:spPr>
    - <wps:txbx>
        - <w:txbxContent>
            - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
              w14:textId="77777777" w14:paraId="0EEC441A">
                - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:jc w:val="left"/>
                  </w:pPr>
                - <w:r>
                    - <w:rPr>
                        <w:sz w:val="22"/>
                      </w:rPr>
                    <w:t xml:space="preserve"> </w:t>
                  </w:r>
                </w:p>
            </w:txbxContent>
        </wps:txbx>
    - <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
        horzOverflow="overflow">
            <a:noAutofit/>
        </wps:bodyPr>
    </wps:wsp>
- <wps:wsp>
        <wps:cNvPr name="Rectangle 149" id="149"/>
        <wps:cNvSpPr/>
    - <wps:spPr>
        - <a:xfrm>
            <a:off y="975365" x="2990669"/>
            <a:ext cx="42144" cy="186477"/>
          </a:xfrm>
        - <a:prstGeom prst="rect">
            <a:avLst/>
          </a:prstGeom>
        - <a:ln>
            <a:noFill/>
          </a:ln>
        </wps:spPr>
    - <wps:txbx>
        - <w:txbxContent>
            - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
              w14:textId="77777777" w14:paraId="4768D7D2">
                - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:jc w:val="left"/>
                  </w:pPr>
                - <w:r>
                    - <w:rPr>
                        <w:sz w:val="22"/>
                      </w:rPr>
                    <w:t xml:space="preserve"> </w:t>
                  </w:r>
                </w:p>
            </w:txbxContent>
        </wps:txbx>
    - <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
        horzOverflow="overflow">
            <a:noAutofit/>
        </wps:bodyPr>
    </wps:wsp>
- <wps:wsp>
        <wps:cNvPr name="Rectangle 239" id="239"/>
        <wps:cNvSpPr/>
    - <wps:spPr>
```

```
- <a:xfrm>
    <a:off y="517241" x="1971991"/>
    <a:ext cx="1781790" cy="168235"/>
  </a:xfrm>
- <a:prstGeom prst="rect">
    <a:avLst/>
  </a:prstGeom>
- <a:ln>
    <a:noFill/>
  </a:ln>
</wps:spPr>
- <wps:txbx>
  - <w:txbxContent>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
      w14:textId="77777777" w14:paraId="711E08BE" w:rsidRPr="00B409E3">
      - <w:pPr>
          <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
          <w:ind w:right="0" w:left="0" w:firstLine="0"/>
          <w:jc w:val="center"/>
        - <w:rPr>
            <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
          </w:rPr>
        </w:pPr>
      - <w:r w:rsidRPr="00B409E3">
        - <w:rPr>
            <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
          </w:rPr>
          <w:t>Contents lists available at</w:t>
        </w:r>
      </w:p>
    </w:txbxContent>
</wps:txbx>
- <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
  horzOverflow="overflow">
    <a:noAutofit/>
  </wps:bodyPr>
</wps:wsp>
- <wps:wsp>
    <wps:cNvPr name="Rectangle 242" id="242"/>
    <wps:cNvSpPr/>
  - <wps:spPr>
    - <a:xfrm>
        <a:off y="555884" x="3543881"/>
        <a:ext cx="38021" cy="168235"/>
      </a:xfrm>
    - <a:prstGeom prst="rect">
        <a:avLst/>
      </a:prstGeom>
    - <a:ln>
        <a:noFill/>
      </a:ln>
    </wps:spPr>
  - <wps:txbx>
    - <w:txbxContent>
      - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
        w14:textId="77777777" w14:paraId="1268648C">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
          </w:pPr>
        - <w:r>
            <w:t xml:space="preserve"> </w:t>
          </w:r>
        </w:p>
    </w:txbxContent>
  </wps:txbx>
  - <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
    horzOverflow="overflow">
      <a:noAutofit/>
    </wps:bodyPr>
</wps:wsp>
- <wps:wsp>
    <wps:cNvPr name="Shape 13829" id="13829"/>
    <wps:cNvSpPr/>
  - <wps:spPr>
    - <a:xfrm>
        <a:off y="673229" x="-43766"/>
        <a:ext cx="5981064" cy="365760"/>
      </a:xfrm>
    - <a:custGeom>
        <a:avLst/>
```

```
                    <a:gdLst/>
                    <a:ahLst/>
                    <a:cxnLst/>
                    <a:rect r="0" b="0" t="0" l="0"/>
                  - <a:pathLst>
                      - <a:path w="5467472" h="365760">
                          - <a:moveTo>
                                <a:pt y="0" x="0"/>
                            </a:moveTo>
                          - <a:lnTo>
                                <a:pt y="0" x="5467472"/>
                            </a:lnTo>
                          - <a:lnTo>
                                <a:pt y="365760" x="5467472"/>
                            </a:lnTo>
                          - <a:lnTo>
                                <a:pt y="365760" x="0"/>
                            </a:lnTo>
                          - <a:lnTo>
                                <a:pt y="0" x="0"/>
                            </a:lnTo>
                        </a:path>
                    </a:pathLst>
                </a:custGeom>
              - <a:solidFill>
                  - <a:schemeClr val="accent6">
                        <a:lumMod val="40000"/>
                        <a:lumOff val="60000"/>
                    </a:schemeClr>
                </a:solidFill>
              - <a:ln w="0" cap="rnd">
                    <a:miter lim="127000"/>
                </a:ln>
            </wps:spPr>
          - <wps:style>
              - <a:lnRef idx="0">
                  - <a:srgbClr val="000000">
                        <a:alpha val="0"/>
                    </a:srgbClr>
                </a:lnRef>
              - <a:fillRef idx="1">
                    <a:srgbClr val="F2F2F2"/>
                </a:fillRef>
              - <a:effectRef idx="0">
                    <a:scrgbClr r="0" b="0" g="0"/>
                </a:effectRef>
                <a:fontRef idx="none"/>
            </wps:style>
            <wps:bodyPr/>
        </wps:wsp>
      - <wps:wsp>
            <wps:cNvPr name="Rectangle 244" id="244"/>
            <wps:cNvSpPr/>
          - <wps:spPr>
              - <a:xfrm>
                    <a:off y="697360" x="1835110"/>
                    <a:ext cx="2933739" cy="168235"/>
                </a:xfrm>
              - <a:prstGeom prst="rect">
                    <a:avLst/>
                </a:prstGeom>
              - <a:ln>
                    <a:noFill/>
                </a:ln>
            </wps:spPr>
          - <wps:txbx>
              - <w:txbxContent>
                  - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
                    w14:textId="77777777" w14:paraId="1BD9E20A" w:rsidRPr="00B409E3">
                      - <w:pPr>
                            <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                            <w:jc w:val="left"/>
                          - <w:rPr>
                                <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                            </w:rPr>
                        </w:pPr>
                      - <w:r w:rsidRPr="00B409E3">
                          - <w:rPr>
                                <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                            </w:rPr>
                            <w:t xml:space="preserve">Journal homepage: </w:t>
```

```
                    </w:r>
                - <w:hyperlink r:id="rId10" w:history="1">
                    - <w:r w:rsidRPr="00B409E3">
                        - <w:rPr>
                            <w:rStyle w:val="Hyperlink"/>
                            <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                        </w:rPr>
                        <w:t>https://www.najfnr.org</w:t>
                    </w:r>
                </w:hyperlink>
                - <w:r w:rsidRPr="00B409E3">
                    - <w:rPr>
                        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    </w:rPr>
                    <w:t xml:space="preserve"> </w:t>
                </w:r>
            </w:p>
        </w:txbxContent>
    </wps:txbx>
- <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
    horzOverflow="overflow">
        <a:noAutofit/>
    </wps:bodyPr>
</wps:wsp>
- <wps:wsp>
    <wps:cNvPr name="Rectangle 246" id="246"/>
    <wps:cNvSpPr/>
- <wps:spPr>
    - <a:xfrm>
        <a:off y="697616" x="3882209"/>
        <a:ext cx="38021" cy="168235"/>
    </a:xfrm>
    - <a:prstGeom prst="rect">
        <a:avLst/>
    </a:prstGeom>
    - <a:ln>
        <a:noFill/>
    </a:ln>
</wps:spPr>
- <wps:txbx>
    - <w:txbxContent>
        - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
        w14:textId="77777777" w14:paraId="66D12DA3">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                <w:jc w:val="left"/>
            </w:pPr>
            - <w:r>
                <w:t xml:space="preserve"> </w:t>
            </w:r>
        </w:p>
    </w:txbxContent>
</wps:txbx>
- <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
    horzOverflow="overflow">
        <a:noAutofit/>
    </wps:bodyPr>
</wps:wsp>
- <wps:wsp>
    <wps:cNvPr name="Rectangle 255" id="255"/>
    <wps:cNvSpPr/>
- <wps:spPr>
    - <a:xfrm>
        <a:off y="906785" x="5902145"/>
        <a:ext cx="42144" cy="186477"/>
    </a:xfrm>
    - <a:prstGeom prst="rect">
        <a:avLst/>
    </a:prstGeom>
    - <a:ln>
        <a:noFill/>
    </a:ln>
</wps:spPr>
- <wps:txbx>
    - <w:txbxContent>
        - <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130"
        w14:textId="77777777" w14:paraId="4013F728">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                <w:jc w:val="left"/>
```

```
                                    </w:pPr>
                                - <w:r>
                                    - <w:rPr>
                                        <w:sz w:val="22"/>
                                      </w:rPr>
                                      <w:t xml:space="preserve"> </w:t>
                                    </w:r>
                                </w:p>
                            </w:txbxContent>
                        </wps:txbx>
                    - <wps:bodyPr bIns="0" rIns="0" tIns="0" lIns="0" vert="horz" rtlCol="0"
                      horzOverflow="overflow">
                          <a:noAutofit/>
                      </wps:bodyPr>
                  </wps:wsp>
              </wpg:wgp>
          </a:graphicData>
      </a:graphic>
  </wp:inline>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
  - <w:pict>
    - <v:group w14:anchorId="2F70865D" id="Group 10991"
      o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
      90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
      0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
      OITrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
      SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
      JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
      bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
      JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
      22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
      OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
      IQBRUXBwkAQAAG4VAAAOAAAAZHJzL2Uyb0RvYy54bWzkWG1v2zYQ/j5g/0HQ4ZYZ2CQZs
      bdF2P4DRiy2AIgVSiZ39+t0dRdmxg6HugKRoEsCijsfj3fOQ1B0v3+56Gdw3xnZarUJ2EYVBoypd
      d2q9Cv/+ev2mCAM7ClULqVWzCh8aG769+vWXy+2wbLjeaFk3JgAjyi63wyrcjOOwXCxstWl6YS/0
      0CjobLXpxQivZr2ojdiC9V4ueBRli6029WB01VgL0veuM7wi+23bVOPHtrXNGMhVCL6N9Gvo9xZ/
      F1eXYrk2Yth01eSG+A4vetEpmHQ29V6MIrgz3YmpvquMtrodLyrdL3TbdlVDMUA0LDqK5sbou4Fi
      WS+362GGCaA9wum7zVYf7j+ZoKuBu6gsWRgo0QNNNHPgRADRdlgvQfPGDF+GT2YSrN0bRr1rTY9P
      iCfYEbgPM7jNbgwqEKZlUURpGgYV9LGIJQnjDv5qAxzhuDdJnGdZGIBCXGa88N2/P2mCcc5ZgjoL
      78ECHZ392g6wpuweNvv/YPuyEUNDbFgEw8OW5B60z7DahFrLJmAgJJRIc8bMLi3A9wRgvCyjLCuP
      I/fQJRBnMgFXZElOxuegxXIwdrxpdB9gYxUa8IMWo7j/044OH6+Ck0uFv0pfd1K6XpQAdt4/bI27
      251bFz6SW10/QNAbbf75CDu+lXq7CvXUCvEQgLmxNwzkHwrAxv3mG8Y3bn3DjPKdpl3pvPntbtRt
      R+7i/G62yS1gERfhs9AJB5bbA4d00lJEB4D48+hMozwpM7eSfwg+adPtEf7p+YRddcpn6Rf12XyW
      eRpn6Q/EZ+xDeRX7k8dP8InCc45bVuaMPnbwoUlZzhP2mE+WFywv4fiiT1VW8JgIf64Tl75pr2aH
      8oSf7lAUnsNonCZxUUD6goymaVEQhmLpT9y4iDj0vgyftHheDZ8sLvi8RylnCpzoHD4PMsEsjzkY
      hNF7OiGXZFE2pURwHOcZZfIHG7S6cykRjvJpEGTntUuIQLbxrWqnfBMTp/8sFAYx4jg0is0AEqA0
      yfIkhyW8gaTVeYLdPSRGXzUpjkcpMXi575XqUGs2BsvYR+Q1/HMge4eajwDwav7p1OEsw6T6ECmv
      4J+Hio/nBocxWsqzZwRAeIix1bKrMaHEkKl6a95JE9wLyPBEVTVqzCgllXf9X7p28iSCP0csiLEG
      IPXMi2GK2RJN/mgSqRB+PKQF1I1G1WS/70aoJ2XXQ43B88k+GHoiw7Xjg2zQXak+Ny3kulS5kP9m
      fTt7j96AmygXctgI56RHyDpVco/soF4LOMwmGQ2d9Nzga47/GDl4NinjuIYK1nmkm9RWkzeuaoXa
      D2L2tSuMnwfRzFqN83gFFTdNgmfPFO3+GMLZ8e35cmuORcxxLoZCcAU9+aZcjBVxyphbz1mZx27n
      748GXsZxjknCy5z1lOnvQf7Js2ueQLV+yugMwjcxCh9uziNgDE4oYDRjR9XSi3675zr+dWTXeD9z
      wicIz9mhaQm5VgKGgE+41sgLGr7foS96mzEX8i/NJ11VwaUefQOmC0i8NTx8pxN6f0169S8AAAD/ /wMAUEsDBB(
      gv9hGcGb3cRabWM2pRT1VARbQXqbJtMkNDsbstsk/feOXvQy8HiPN99Ll6NtVE+drx0biCcRKOLc
      FTWXBj53r3dzUD4gF9g4JgMX8rDMrq9STAo38Af121AqKWGfoIEqhDbR2ucVWfQT1xKLd3SdxSCy
      K3XR4SDlttH3UfSoLdYsHypsaV1RftqerYG3AYfVNH7pN6fj+rLfzd6/NjEZc3szrp5BBRrDXxh+
      8AUdMmE6uDMXXjUGZEj4veItHqYiDxKaLZ5AZ6n+T599AwAA//8DAFBLAQItABQABgAIAAAAIQC2
      gziS/gAAAOEBAAATAAAAAAAAAAAAAAAAAAAAAABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAG
      AAgAAAAhADj9If/WAAAAlAEAAAsAAAAAAAAAAAAAAAAALwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAG
      AAgAAAAhAFFRcHCQBAAAbhUAAA4AAAAAAAAAAAAAAAAALgIAAGRycy9lMm9Eb2MueG1sUEsBAi0A
      FAAGAAgAAAAhAIfuwTDcAAAABQEAAA8AAAAAAAAAAAAAAAAA6gYAAGRycy9kb3ducmV2LnhtbFBL
      BQYAAAAABAAEAPMAAADzBwAAAAA= " coordsize="59880,11222" style="width:471.5pt;height:79.85pt;mso-
      position-horizontal-relative:char;mso-position-vertical-relative:line" o:spid="_x0000_s1027" coordorigin="-437,396">
      - <v:rect id="Rectangle 147" stroked="f"
        o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
        70i8Q+QralM4IITa7kDhCAiNB7AStt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
        jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
        VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
        r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
        AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
        X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
        Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
        gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
        AAD//wMAUEsDBBQABgAIAAAAIQDWuM3+wgAAANwAAAPAAAAZHJzL2Rvd25yZXYueG1sRE9Li8Iv
        EL4L/ocwgjdNXcRHNYrsAz36AvU2NGNbbCalydq6v34jCN7m43vOfNmYQtypcrllBYN+BII4sTrn
        VMHx8NObgHAeWWNhmRQ8yMFy0W7NMda25h3d9z4VIYRdjAoy78tYSpdkZND1bUkcuKutDPoAq1Tq
        CusQbgr5EUUjaTDn0JBhSZ8ZJbf9r1GwnpSr88b+1WnxfVmftqfp12Hqlep2mtUMhKfGv8Uv90aH
        +cMxPJ8JF8jFPwAAAP//AwBQSwECLQAUAAYACAAAACEA2+H2y+4AAACFAQAAEwAAAAAAAAAA
        AAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQBa9CxbvwAAABUBAAALAAA
        AAAAAAAAAAAAAB8BAABfcmVscy8ucmVsc1BLAQItABQABgAIAAAAIQDWuM3+wgAAANwAAAPAA
```

AAAAAAAAAAAAAAAcCAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAMAAwC3AAAA9gIAAAAA "
style="position:absolute;left:29906;top:396;width:422;height:1865;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1028" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="378DD19B">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
- <w:rPr>
<w:sz w:val="22"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 148" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AD//wMAUEsDBBQABgAIAAAAIQCnJ1mMxgAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Ba8JA
EIXvBf/DMkJvdaOUojEbEW3RY9WC9TZkp0lodjZktybtr+8cBG8zvDfvfZOtBteoK3Wh9mxgOklA
ERfe1lwa+Di9Pc1BhYhssfFMBn4pwCofPWSYWt/zga7HWCoJ4ZCigSrGNtU6FBU5DBPfEov25TuH
Udau1LbDXsJdo2dJ8qId1iwNFba0qaj4Pv44A7t5u/7c+7++bF4vu/P7ebE9LaIxj+NhvQQVaYh3
8+16bwX/WWjlGZlA5/8AAAD//wMAUEsBAi0AFAAGAAgAAAAhANvh9svuAAAAhQEAABMAAAAAAAAA
AAAAAAAAAAAAAFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAWvQsW78AAAAV
CwAAAAAAAAAAAAAAAAAAAfAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEApydZjMYAAAD
DwAAAAAAAAAAAAAAAAAAAHAgAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAADAAMAtwAAAPoCAAAA
" style="position:absolute;left:29906;top:5074;width:422;height:1865;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1029" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="0EEC441A">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
- <w:rPr>
<w:sz w:val="22"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 149" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AD//wMAUEsDBBQABgAIAAAAIQDIa/wXwgAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRE9Ni8Iw
EL0L/ocwgjdNXURs1yjiKnp0VdC9Dc1S1W7az83K3BPmS1aU4ob1a6wrGA0jEAQp1YX
nCk4HTeDKQjnkTWWlknBnRws5t3ODBNtG/7n2VSOnSnAy6oa2IA/dra4M+wDqT
usYmhJtSfkTRRBosODTkWNEqp/TvcDUKttNqednZR5OV65/teX+Ov46xV6rfa5efIDy1/i1+uXc6
zB/H8P9MuEDOnwAAAP//AwBQSwECLQAUAAYACAAAACEA2+H2y+4AAACFAQAAEwAAAAAAAAAAAA
AAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQBa9CxbvwAAABUBAAALAAA
AAAAAAAAAAAAAB8BAABfcmVscy8ucmVsc1BLAQItABQABgAIAAAAIQDIa/wXwgAAANwAAAAPAAA
AAAAAAAAAAAAAAcCAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAMAAwC3AAAA9gIAAAAA "
style="position:absolute;left:29906;top:9753;width:422;height:1865;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1030" filled="f">
- <v:textbox inset="0,0,0,0">

- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="4768D7D2">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
- <w:rPr>
<w:sz w:val="22"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 239" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AD//wMAUEsDBBQABgAIAAAAIQBLSO4WxgAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Ba8JA
FITvBf/D8oTe6qYRiomuIlpJjm0UbG+P7DMJzb2a4N2a1J++u7BcHjMDPfMKvNaFpxpd41lhU8zyIQ
xKXVDVcKTsfD0wKE88gaW8uk4IccbNaThxWm2g78TtfCVyJA2KWooPa+S6V0ZU0G3cx2xMG72N6g
D7KvpO5xCHDTyjiKXqTBhsNCjR3taiq/im+jIFt024/c/g5V+/qZnd/Oyf6YeKUep+N2CcLT6O/h
WzvXCuJ5Av9nwhGQ6z8AAAD//wMAUEsBAi0AFAAGAAgAAAAhANvh9svuAAAAhQEAABMAAAAAAAA
AAAAAAAAAAAAAAFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAWvQsW78AAAAV
CwAAAAAAAAAAAAAAAAAAAfAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEAS0juFsYAAADc
DwAAAAAAAAAAAAAAAAAAAAHAgAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAADAAMAtwAAAPoCAAAA
" style="position:absolute;left:19719;top:5172;width:17818;height:1682;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1031" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="711E08BE" w:rsidRPr="00B409E3">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="center"/>
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00B409E3">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
</w:rPr>
<w:t>Contents lists available at</w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 242" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AD//wMAUEsDBBQABgAIAAAAIQAd6g8axQAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Pi8Iw
FMTvwn6H8Ba8aWpZRKtRZNdFj/5ZUG+Wm5f5ZUm5V2pbnf2CARx
anXBmYK//W9vBMJ5ZI2lZVJwJwfz2Udniom2DW/ptvOZCBB2CSrIva8SKV2ak0H0tvOZCBB2CSrIva8SKV2ak0HXtxVx8M62NuiD
rDOpa2wC3JQyjqKhNFhwWMixou+c0svuahSsRtXiuLaPJiuXp9Vhcxj/7Mdeqe5Nu5iA8NT6/C7
vdYK4q8YXmfCEZCzJwAAAP//AwBQSwECLQAUAAYACAAAACEA2+H2y+4AAACFAQAAEwAAAAAAAA
AAAAAAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQBa9CxbvwAAABUBAAA
AAAAAAAAAAAAAAAAAB8BAABfcmVscy8ucmVscy1BLAQItABQABgAIAAAAIQAd6g8axQAAANwAAAA
AAAAAAAAAAAAAAAAAAcCAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAMAAwC3AAAA+QIAAAAA
" style="position:absolute;left:35438;top:5558;width:381;height:1683;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1032" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>

- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="1268648C">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:shape id="Shape 13829" strokeweight="0" stroked="f" fillcolor="#c5e0b3 [1305]" path="m,l5467472,r,365760l,365760,,e"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2Cy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQDRhM0+xQAAAN4AAAAPAAAAZHJzL2Rvd25yZXYueG1sRE9La8JA
EL4X/A/LFLzVjUqLpq4iheLjUHwEeh2y0ySYnV2yaxL7612h0Nt8fM9ZrHpTi5YaX1lWMB4lIIhz
qysuFGTnz5cZCB+QNdaWScGNPKyWg6cFptp2fKT2FAoRQ9inqKAMwaVS+rwkg35kHXHkfmxjMETY
FFI32MVwU8tJkrxJgxXHhhIdfZSUX05Xo4DP2WvnLuPN9/73Smuet9+OVRq+Nyv30EE6sO/+M+9
1XH+dDaZw+OdeINc3gEAAP//AwBQSwECLQAUAAYACAAAACEA2+H2y+4AAACFAQAAEwAAAAAAAA
AAAAAAAAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQBa9CxbvwAAABUBAAA
AAAAAAAAAAAAAAAAAAAB8BAABfcmVscy8ucmVsc1BLAQItABQABgAIAAAAIQDRhM0+xQAAAN4AAA
AAAAAAAAAAAAAAAAAAAAcCAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAMAAwC3AAAA+QIAAAAA
" coordsize="5467472,365760"
style="position:absolute;left:-437;top:6732;width:59809;height:3657;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1033">
<v:stroke joinstyle="miter" miterlimit="83231f" endcap="round"/>
<v:path textboxrect="0,0,5467472,365760" arrowok="t"/>
</v:shape>
- <v:rect id="Rectangle 244" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQD9TzL1xgAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Ba8JA
FITvgv9heYXezKYioqmriK2YY5sU0t4e2dckNPs2ZFeT+uu7BcHjMDPPfFpxod41o+ud41U1hhU8R
4tLqhisFH/lxtgLhPLLG1jIp+CUHu10ssFE24Hf6ZL5SgQmgi2xHHLxv2xv0
QfaV1D0OAW5aOY/jpTTYcFiosaNDTeVPdjYKTqtu/5na61C1r1r1+n4q1Yv+Rrr9Tjw7h/BuFp9Pfw
rZ1qBfPFAv7PhCMgt38AAAD//wMAUEsBAi0AFAAGAAgAAAAhANvh9svuAAAAhQEAABMAAAAAAAA
AAAAAAAAAAAAAAFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAWvQsW78AAAAV
CwAAAAAAAAAAAAAAAAAAAAAAAfAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEA/U8y9cYAAADc
DwAAAAAAAAAAAAAAAAAAAAAAAHAgAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAADAAMAtwAAAPoCAAAA
" style="position:absolute;left:18351;top:6973;width:29337;height:1682;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1034" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="1BD9E20A" w:rsidRPr="00B409E3">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00B409E3">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
</w:rPr>
<w:t xml:space="preserve">Journal homepage: </w:t>
</w:r>
- <w:hyperlink r:id="rId11" w:history="1">
- <w:r w:rsidRPr="00B409E3">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>

</w:rPr>
<w:t>https://www.najfnr.org</w:t>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00B409E3">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 246" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQBi0QkZxAAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Pi8Iw
FMTvgt8hPMGbpoqIVqOIuuhx/QPq7dE822LzUpqsrX76jbCwx2FmfsPMl40pxJMql1tWMOhHIIgT
q3NOFZxPX70JCOeRNRaWScGLHCwX7dYcY21rPtDz6FMRIOxiVJB5X8ZSuiQjg65vS+Lg3W1l0AdZ
pVJXWAe4KeQwisbSYM5hIcOS1hklj+OPUbCblKvr3r7rtNjedpfvy3Rzmnqlup1mNQPhqfH/4b/2
XisYjsbwOROOgFz8AgAA//8DAFBLAQItABQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAAAAAAAAA
AAAAAAAAAABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsA
AAAAAAAAAAAAAAAAAHwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAGAAgAAAAhAGLRCRnEAAAA3AAA
AAAAAAAAAAAAAAAABwIAAGRycy9kb3ducmV2LnhtbFBLBQYAAAAAAwADALcAAAD4AgAAAAA=
" style="position:absolute;left:38822;top:6976;width:380;height:1682;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1035" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777"
w14:paraId="66D12DA3">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
</v:rect>
- <v:rect id="Rectangle 255" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQAX2gGzxgAAANwAAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Ba8JA
FITvgv9heYXezKaCoqmriK2YY5sU0t4e2dckNPs2ZFeT+uu7BcHjMDPfMJvdaFpxod41lhU8RTEI
4tLqhisFH/lxtgLhPLLLG1jIp+CUHu+10ssFE24Hf6ZL5SgQIuwQV1N53iZSurMmgi2xHHLxv2xv0
QfaV1D0OAW5aOY/jpTTYcFiosaNDTeVPdjYKTqtu/5na61C1r1+n4q+Rrr9Tjw7h/BuFp9Pfw
rZ1qBfPFAv7PhCMgt38AAAD//wMAUEsBAi0AFAAGAAgAAAAhANvh9svuAAAAhQEAABMAAAAAAAAA(
AAAAAAAAAAAAFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAWvQsW78AAAAV
CwAAAAAAAAAAAAAAAAAfAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEAF9oBs8YAAADc
DwAAAAAAAAAAAAAAAAAHAgAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAADAAMAtwAAAPoCAAAA(
" style="position:absolute;left:59021;top:9067;width:421;height:1865;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1036" filled="f">
- <v:textbox inset="0,0,0,0">
- <w:txbxContent>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777"
w14:paraId="4013F728">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="160" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
</w:pPr>
- <w:r>
- <w:rPr>
<w:sz w:val="22"/>

```
                                                    </w:rPr>
                                                    <w:t xml:space="preserve"> </w:t>
                                                </w:r>
                                            </w:p>
                                        </w:txbxContent>
                                    </v:textbox>
                                </v:rect>
                                <w10:anchorlock/>
                            </v:group>
                        </w:pict>
                    </mc:Fallback>
                </mc:AlternateContent>
            </w:r>
        </w:p>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="6950A31F"
        w:rsidRPr="005C028C">
            - <w:pPr>
                <w:pStyle w:val="Heading1"/>
                <w:spacing w:lineRule="auto" w:line="277" w:after="147"/>
                <w:ind w:left="240"/>
                <w:jc w:val="center"/>
              - <w:rPr>
                    <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="30"/>
                    <w:szCs w:val="30"/>
                </w:rPr>
            </w:pPr>
            - <w:r>
              - <w:rPr>
                    <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
                    <w:b/>
                    <w:bCs/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="30"/>
                    <w:szCs w:val="30"/>
                </w:rPr>
                <w:t>Metabolic Syndrome Components Correlation with Colorectal Neoplasms: A Systematic Review and a M</w:t>
            </w:r>
            - <w:r w:rsidRPr="00DD0224">
              - <w:rPr>
                    <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
                    <w:b/>
                    <w:bCs/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="30"/>
                    <w:szCs w:val="30"/>
                </w:rPr>
                <w:t>eta-analysis</w:t>
            </w:r>
        </w:p>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="558ED199">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
                <w:ind w:right="0" w:left="235"/>
                <w:jc w:val="center"/>
              - <w:rPr>
                    <w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
                    <w:color w:val="000000" w:themeColor="text1"/>
                    <w:vertAlign w:val="superscript"/>
                </w:rPr>
            </w:pPr>
            - <w:r w:rsidRPr="00C35468">
              - <w:rPr>
                    <w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
                    <w:color w:val="000000" w:themeColor="text1"/>
                </w:rPr>
                <w:t xml:space="preserve">Salah Eddine ELHERRAG </w:t>
            - <w:r w:rsidR="002D35A0">
              - <w:rPr>
                    <w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
                    <w:color w:val="000000" w:themeColor="text1"/>
                    <w:vertAlign w:val="superscript"/>
                </w:rPr>
                <w:t>1</
            - <w:r w:rsidRPr="00C35468">
              - <w:rPr>
                    <w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
                    <w:color w:val="000000" w:themeColor="text1"/>
                </w:rPr>
```

```
<w:t xml:space="preserve">, Youssouf TRAORÉ </w:t>
</w:r>
- <w:r w:rsidR="002D35A0">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:color w:val="000000" w:themeColor="text1"/>
<w:vertAlign w:val="superscript"/>
</w:rPr>
<w:t>1</w:t>
</w:r>
- <w:r w:rsidRPr="00C35468">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:color w:val="000000" w:themeColor="text1"/>
</w:rPr>
<w:t xml:space="preserve">, </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000" w:themeColor="text1"/>
<w:u w:val="single"/>
</w:rPr>
<w:t>Méghit Boumediène KHALED</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000" w:themeColor="text1"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidR="002D35A0" w:rsidRPr="002D35A0">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000" w:themeColor="text1"/>
<w:vertAlign w:val="superscript"/>
</w:rPr>
<w:t>1, 2</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorBidi" w:asciiTheme="minorBidi"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000" w:themeColor="text1"/>
</w:rPr>
<w:t xml:space="preserve"> *</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="630BC5A7" w:rsidRPr="00DD0224">
  - <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
<w:ind w:right="0" w:left="235"/>
<w:jc w:val="center"/>
  - <w:rPr>
<w:rFonts w:hAnsiTheme="minorHAnsi" w:asciiTheme="minorHAnsi" w:cstheme="minorHAnsi"/>
<w:color w:val="000000" w:themeColor="text1"/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
</w:pPr>
</w:p>
- <w:p w:rsidP="006C5E23" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="55AA8729" w:rsidRPr="00C35468">
  - <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
<w:ind w:right="0" w:left="235"/>
<w:jc w:val="center"/>
  - <w:rPr>
<w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
<w:bCs/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
```

```
      </w:pPr>
    - <w:r>
      - <w:rPr>
          <w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
          <w:bCs/>
          <w:sz w:val="16"/>
          <w:szCs w:val="16"/>
          <w:vertAlign w:val="superscript"/>
        </w:rPr>
        <w:t>1</w:t>
      </w:r>
    - <w:r w:rsidR="00C62C26" w:rsidRPr="00C35468">
      - <w:rPr>
          <w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
          <w:bCs/>
          <w:sz w:val="16"/>
          <w:szCs w:val="16"/>
        </w:rPr>
        <w:t xml:space="preserve"> Department of Biology, Faculty of Natural and Life Sciences, Djillali Liabes University, PO Box 89, Sidi-
          Bel-Abbes (22000), Algeria</w:t>
      </w:r>
    </w:p>
  - <w:p w:rsidP="00C62C26" w:rsidRDefault="006C5E23" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="0A101487">
    - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
        <w:ind w:right="0" w:left="235"/>
        <w:jc w:val="center"/>
      - <w:rPr>
          <w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
          <w:bCs/>
          <w:sz w:val="16"/>
          <w:szCs w:val="16"/>
        </w:rPr>
      </w:pPr>
    - <w:r>
      - <w:rPr>
          <w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
          <w:bCs/>
          <w:sz w:val="16"/>
          <w:szCs w:val="16"/>
          <w:vertAlign w:val="superscript"/>
        </w:rPr>
        <w:t>2</w:t>
      </w:r>
    - <w:r w:rsidR="00C62C26" w:rsidRPr="00C35468">
      - <w:rPr>
          <w:rFonts w:hAnsiTheme="majorHAnsi" w:asciiTheme="majorHAnsi" w:cstheme="majorHAnsi"/>
          <w:bCs/>
          <w:sz w:val="16"/>
          <w:szCs w:val="16"/>
        </w:rPr>
        <w:t xml:space="preserve"> Laboratory of Health & Environment, Djillali Liabes University, PO Box 89, Sidi-Bel-Abbes (22000),
          Algeria</w:t>
      </w:r>
    </w:p>
  - <w:tbl>
    - <w:tblPr>
        <w:tblStyle w:val="TableGrid"/>
        <w:tblpPr w:tblpY="564" w:tblpX="240" w:vertAnchor="text"/>
        <w:tblOverlap w:val="never"/>
        <w:tblW w:w="5130" w:type="dxa"/>
        <w:tblInd w:w="0" w:type="dxa"/>
        <w:tblLook w:val="04A0" w:noVBand="1" w:noHBand="0" w:lastColumn="0" w:firstColumn="1" w:lastRow="0" w:firstRow="1"/>
      </w:tblPr>
    - <w:tblGrid>
        <w:gridCol w:w="3442"/>
        <w:gridCol w:w="264"/>
        <w:gridCol w:w="1424"/>
      </w:tblGrid>
    - <w:tr w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="49A4D1D9" w:rsidRPr="005C028C" w:rsidTr="009B08AB">
      - <w:trPr>
          <w:trHeight w:val="562"/>
        </w:trPr>
      - <w:tc>
        - <w:tcPr>
            <w:tcW w:w="3442" w:type="dxa"/>
          - <w:tcBorders>
              <w:top w:val="nil"/>
              <w:left w:val="nil"/>
              <w:bottom w:val="nil"/>
              <w:right w:val="nil"/>
            </w:tcBorders>
```

```
</w:tcPr>
- <w:p w:rsidP="009B08AB" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="25F03059"
w:rsidRPr="005C028C">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
      <w:ind w:right="0" w:left="0" w:firstLine="0"/>
      <w:contextualSpacing/>
      <w:jc w:val="left"/>
    - <w:rPr>
        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
        <w:b/>
        <w:bCs/>
      </w:rPr>
    </w:pPr>
</w:p>
- <w:p w:rsidP="008B0DCA" w:rsidRDefault="008B0DCA" w:rsidR="00C62C26" w14:textId="77777777"
w14:paraId="0A7B8DBE" w:rsidRPr="008B0DCA">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
      <w:ind w:right="0" w:left="0" w:firstLine="0"/>
      <w:contextualSpacing/>
      <w:jc w:val="left"/>
    - <w:rPr>
        <w:rFonts w:cs="Times New Roman" w:hAnsi="Times New Roman" w:ascii="Times New Roman"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="00695689">
    - <w:rPr>
        <w:rFonts w:cs="Times New Roman" w:hAnsi="Times New Roman" w:ascii="Times New Roman"/>
        <w:noProof/>
      </w:rPr>
      <w:t>A R</w:t>
    </w:r>
  - <w:r w:rsidRPr="00C11383">
    - <w:rPr>
        <w:rFonts w:cs="Times New Roman" w:hAnsi="Times New Roman" w:ascii="Times New Roman"/>
      </w:rPr>
      <w:t xml:space="preserve"> T I C L E </w:t>
  - <w:r>
    - <w:rPr>
        <w:rFonts w:cs="Times New Roman" w:hAnsi="Times New Roman" w:ascii="Times New Roman"/>
      </w:rPr>
      <w:t xml:space="preserve"> I N F O</w:t>
  - <w:r w:rsidR="00C62C26" w:rsidRPr="005C028C">
      <w:t xml:space="preserve"> </w:t>
    </w:r>
  </w:p>
- <w:tc>
  - <w:tcPr>
      <w:tcW w:w="264" w:type="dxa"/>
    - <w:tcBorders>
        <w:top w:val="nil"/>
        <w:left w:val="nil"/>
        <w:bottom w:val="nil"/>
        <w:right w:val="nil"/>
      </w:tcBorders>
      <w:vAlign w:val="bottom"/>
    </w:tcPr>
- <w:p w:rsidP="009B08AB" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="40F96978"
w:rsidRPr="005C028C">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
      <w:ind w:right="0" w:left="0" w:firstLine="0"/>
      <w:contextualSpacing/>
      <w:jc w:val="left"/>
    - <w:r w:rsidRPr="005C028C">
      <w:t xml:space="preserve"> </w:t>
    </w:r>
  </w:p>
- <w:tc>
  - <w:tcPr>
      <w:tcW w:w="1424" w:type="dxa"/>
    - <w:tcBorders>
        <w:top w:val="nil"/>
        <w:left w:val="nil"/>
        <w:bottom w:val="nil"/>
        <w:right w:val="nil"/>
```

```
                    </w:tcBorders>
                </w:tcPr>
            - <w:p w:rsidP="009B08AB" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="3B500A51"
                w:rsidRPr="00611197">
                - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:contextualSpacing/>
                - <w:rPr>
                    <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    <w:b/>
                    <w:bCs/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                </w:pPr>
            </w:p>
            - <w:p w:rsidP="008F595A" w:rsidRDefault="008F595A" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="08A8AA95"
                w:rsidRPr="008F595A">
                - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:contextualSpacing/>
                - <w:rPr>
                    <w:rFonts w:hAnsi="Bell MT" w:ascii="Bell MT"/>
                </w:rPr>
                </w:pPr>
                - <w:r w:rsidRPr="00C11383">
                - <w:rPr>
                    <w:rFonts w:hAnsi="Bell MT" w:ascii="Bell MT"/>
                </w:rPr>
                    <w:t xml:space="preserve">A B S T R A C T </w:t>
                </w:r>
                - <w:r w:rsidR="00C62C26" w:rsidRPr="005C028C">
                    <w:t xml:space="preserve"> </w:t>
                </w:r>
                </w:r>
            </w:p>
        </w:tc>
    </w:tr>
</w:tbl>
- <w:tbl>
    - <w:tblPr>
        <w:tblStyle w:val="TableGrid0"/>
        <w:tblpPr w:tblpY="1306" w:tblpX="90" w:vertAnchor="text" w:horzAnchor="margin" w:rightFromText="180"
            w:leftFromText="180"/>
        <w:tblW w:w="9490" w:type="dxa"/>
    - <w:tblBorders>
        <w:top w:val="none" w:space="0" w:color="auto" w:sz="0"/>
        <w:left w:val="none" w:space="0" w:color="auto" w:sz="0"/>
        <w:bottom w:val="none" w:space="0" w:color="auto" w:sz="0"/>
        <w:right w:val="none" w:space="0" w:color="auto" w:sz="0"/>
        <w:insideH w:val="none" w:space="0" w:color="auto" w:sz="0"/>
        <w:insideV w:val="none" w:space="0" w:color="auto" w:sz="0"/>
    </w:tblBorders>
        <w:tblLook w:val="04A0" w:noVBand="1" w:noHBand="0" w:lastColumn="0" w:firstColumn="1" w:lastRow="0" w:firstRow="1"/>
    </w:tblPr>
    - <w:tblGrid>
        <w:gridCol w:w="3701"/>
        <w:gridCol w:w="5789"/>
    </w:tblGrid>
    - <w:tr w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="759E68F8" w:rsidTr="00033A39">
        - <w:tc>
            - <w:tcPr>
                <w:tcW w:w="3701" w:type="dxa"/>
            </w:tcPr>
            - <w:p w:rsidP="00033A39" w:rsidRDefault="00033A39" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="531342C1"
                w:rsidRPr="005C028C">
                - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:jc w:val="left"/>
                - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    <w:b/>
                    <w:bCs/>
                    <w:iCs/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                </w:pPr>
                - <w:r w:rsidRPr="005C028C">
                - <w:rPr>
                </w:rPr>
```

```
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    <w:b/>
                    <w:bCs/>
                    <w:iCs/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t xml:space="preserve">Article history: </w:t>
            </w:r>
        </w:p>
    - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="24F4C68C"
    w:rsidRPr="005C028C">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                <w:jc w:val="left"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
            </w:pPr>
        - <w:r>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>Received</w:t>
            </w:r>
        - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t xml:space="preserve"> </w:t>
            </w:r>
        - <w:r>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>02 September </w:t>
            </w:r>
        - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>201</w:t>
            </w:r>
        - <w:r>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>8</w:t>
            </w:r>
        - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t xml:space="preserve"> </w:t>
            </w:r>
    </w:p>
    - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="5D71B9EE"
    w:rsidRPr="005C028C">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
```

```
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
</w:pPr>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t>Accepted 26 October</w:t>
</w:r>
- <w:r w:rsidRPr="005C028C">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t xml:space="preserve"> 201</w:t>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t>8</w:t>
</w:r>
- <w:r w:rsidRPr="005C028C">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="00C62C26" w14:textId="62E4B07E" w14:paraId="6EF6CDD4" w:rsidRPr="005C028C">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="120" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
</w:pPr>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t xml:space="preserve">Available online </w:t>
</w:r>
- <w:r w:rsidR="0037697D">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t xml:space="preserve">06 </w:t>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
```

```
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>November</w:t>
            </w:r>
        - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t xml:space="preserve"> </w:t>
            </w:r>
        - <w:r>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
                <w:t>2018</w:t>
            </w:r>
    </w:p>
- <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="0D432D36"
    w:rsidRPr="005C028C">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                <w:b/>
                <w:bCs/>
                <w:iCs/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
        </w:pPr>
        - <w:r w:rsidRPr="005C028C">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                <w:b/>
                <w:bCs/>
                <w:iCs/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t xml:space="preserve">Keywords: </w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="652A395F"
    w:rsidRPr="005C028C">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
        </w:pPr>
        - <w:r w:rsidRPR="00577ADA">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>Colorectal </w:t>
        - <w:r>
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:noProof/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>N</w:t>
```

```
        </w:r>
      - <w:r w:rsidRPr="002233CE">
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:noProof/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>eoplasms</w:t>
        </w:r>
    </w:p>
  - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="1FE7D9AA"
  w:rsidRPr="005C028C">
      - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
        </w:pPr>
      - <w:r w:rsidRPr="00577ADA">
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>Hyperglycemia</w:t>
        </w:r>
    </w:p>
  - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="1C9614AB"
  w:rsidRPr="005C028C">
      - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
        </w:pPr>
      - <w:r w:rsidRPr="00577ADA">
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>Hypertension</w:t>
        </w:r>
    </w:p>
  - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="44A3A9A8">
      - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="0" w:firstLine="0"/>
            <w:jc w:val="left"/>
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
        </w:pPr>
      - <w:r w:rsidRPr="00577ADA">
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:sz w:val="14"/>
                <w:szCs w:val="14"/>
            </w:rPr>
            <w:t>Visceral obesity</w:t>
        </w:r>
    </w:p>
  - <w:p w:rsidP="00AF7978" w:rsidRDefault="00C62C26" w:rsidR="00AF7978" w14:textId="77652208" w14:paraId="2530A79B">
      - <w:pPr>
```

```
<w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00577ADA">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t>Dyslipidemia</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00AF7978" w:rsidRDefault="002D35A0" w:rsidR="00C62C26" w14:textId="1EA46E85" w14:paraId="55B05B16">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00577ADA">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t>Meta-analysis</w:t>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
<w:t>.</w:t>
</w:r>
</w:p>
- <w:tbl>
- <w:tblPr>
<w:tblStyle w:val="TableGrid0"/>
<w:tblpPr w:tblpY="228" w:vertAnchor="text" w:horzAnchor="margin" w:rightFromText="180" w:leftFromText="180"/>
<w:tblOverlap w:val="never"/>
<w:tblW w:w="0" w:type="auto"/>
<w:tblLook w:val="04A0" w:noVBand="1" w:noHBand="0" w:lastColumn="0" w:firstColumn="1" w:lastRow="0" w:firstRow="1"/>
</w:tblPr>
- <w:tblGrid>
<w:gridCol w:w="1615"/>
<w:gridCol w:w="1620"/>
</w:tblGrid>
- <w:tr w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="35C13A75" w:rsidRPr="005C028C" w:rsidTr="0099201C">
- <w:tc>
- <w:tcPr>
<w:tcW w:w="3235" w:type="dxa"/>
<w:gridSpan w:val="2"/>
<w:shd w:val="clear" w:color="auto" w:themeFillShade="BF" w:themeFill="accent6" w:fill="538135"/>
</w:tcPr>
- <w:p w:rsidP="00033A39" w:rsidR="002D35A0" w:rsidRDefault="002D35A0" w14:textId="77777777" w14:paraId="69A338A6" w:rsidRPr="005C028C">
- <w:pPr>
<w:autoSpaceDE w:val="0"/>
<w:autoSpaceDN w:val="0"/>
<w:adjustRightInd w:val="0"/>
<w:snapToGrid w:val="0"/>
<w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
<w:ind w:right="0" w:left="0" w:firstLine="0"/>
```

```
                    <w:jc w:val="center"/>
                  - <w:rPr>
                        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                        <w:b/>
                        <w:bCs/>
                        <w:color w:val="FFFFFF" w:themeColor="background1"/>
                    </w:rPr>
                </w:pPr>
              - <w:r w:rsidRPr="005C028C">
                  - <w:rPr>
                        <w:rFonts w:cs="Arial-BoldMT" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Times
                            New Roman"/>
                        <w:b/>
                        <w:bCs/>
                        <w:color w:val="FFFFFF" w:themeColor="background1"/>
                        <w:sz w:val="14"/>
                        <w:szCs w:val="24"/>
                    </w:rPr>
                    <w:t>Access this article online</w:t>
                </w:r>
            </w:p>
        </w:tc>
    </w:tr>
  - <w:tr w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="6E659E6C" w:rsidRPr="005C028C"
    w:rsidTr="0099201C">
      - <w:trPr>
            <w:trHeight w:val="202"/>
        </w:trPr>
      - <w:tc>
          - <w:tcPr>
                <w:tcW w:w="1615" w:type="dxa"/>
            </w:tcPr>
          - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777"
            w14:paraId="50EC6189" w:rsidRPr="005C028C">
              - <w:pPr>
                    <w:autoSpaceDE w:val="0"/>
                    <w:autoSpaceDN w:val="0"/>
                    <w:adjustRightInd w:val="0"/>
                    <w:snapToGrid w:val="0"/>
                    <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:jc w:val="center"/>
                  - <w:rPr>
                        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    </w:rPr>
                </w:pPr>
              - <w:r w:rsidRPr="005C028C">
                  - <w:rPr>
                        <w:rFonts w:cs="Arial-BoldMT" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Times
                            New Roman"/>
                        <w:sz w:val="14"/>
                        <w:szCs w:val="24"/>
                    </w:rPr>
                    <w:t>Quick Response Code</w:t>
                </w:r>
              - <w:r w:rsidRPr="005C028C">
                  - <w:rPr>
                        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    </w:rPr>
                    <w:t>:</w:t>
                </w:r>
            </w:p>
        </w:tc>
      - <w:tc>
          - <w:tcPr>
                <w:tcW w:w="1620" w:type="dxa"/>
                <w:vMerge w:val="restart"/>
            </w:tcPr>
          - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777"
            w14:paraId="1766A61B" w:rsidRPr="005C028C">
              - <w:pPr>
                    <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
                    <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                    <w:jc w:val="left"/>
                  - <w:rPr>
                        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                        <w:b/>
                        <w:bCs/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                </w:pPr>
```

```
- <w:r w:rsidRPr="005C028C">
  - <w:rPr>
      <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
      <w:b/>
      <w:bCs/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">Website: </w:t>
  </w:r>
</w:p>
- <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="57FF0B69" w:rsidRPr="005C028C">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
      <w:ind w:right="0" w:left="0" w:firstLine="0"/>
      <w:jc w:val="left"/>
    - <w:rPr>
        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="005C028C">
    - <w:rPr>
        <w:rFonts w:hAnsi="Century Gothic" w:ascii="Century Gothic"/>
        <w:b/>
        <w:noProof/>
        <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
        <w:sz w:val="30"/>
        <w:szCs w:val="30"/>
      </w:rPr>
    - <mc:AlternateContent>
      - <mc:Choice Requires="wps">
        - <w:drawing>
          - <wp:anchor wp14:editId="66E321B8" wp14:anchorId="36794F47" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251705344" simplePos="0" distR="114300" distL="114300" distB="45720" distT="45720">
              <wp:simplePos y="0" x="0"/>
            - <wp:positionH relativeFrom="margin">
                <wp:posOffset>-36194</wp:posOffset>
              </wp:positionH>
            - <wp:positionV relativeFrom="paragraph">
                <wp:posOffset>280035</wp:posOffset>
              </wp:positionV>
              <wp:extent cx="863600" cy="252442"/>
              <wp:effectExtent r="0" b="0" t="0" l="0"/>
              <wp:wrapNone/>
              <wp:docPr name="Text Box 2" id="4"/>
            - <wp:cNvGraphicFramePr>
                <a:graphicFrameLocks xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
              </wp:cNvGraphicFramePr>
            - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
              - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
                - <wps:wsp>
                  - <wps:cNvSpPr txBox="1">
                      <a:spLocks noChangeArrowheads="1"/>
                    </wps:cNvSpPr>
                  - <wps:spPr bwMode="auto">
                    - <a:xfrm>
                        <a:off y="0" x="0"/>
                        <a:ext cx="863600" cy="252442"/>
                      </a:xfrm>
                    - <a:prstGeom prst="rect">
                        <a:avLst/>
                      </a:prstGeom>
                    - <a:solidFill>
                        <a:srgbClr val="FFFFFF"/>
                      </a:solidFill>
                    - <a:ln w="9525">
                        <a:noFill/>
                        <a:miter lim="800000"/>
                        <a:headEnd/>
                        <a:tailEnd/>
                      </a:ln>
                    </wps:spPr>
                  - <wps:txbx>
                    - <w:txbxContent>
                      -
```

```
<w:p w:rsidP="002D35A0" w:rsidRDefault="00164130"
w:rsidR="00164130" w14:textId="77777777"
w14:paraId="13C663C9" w:rsidRPr="00847784">
  - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="240"
            w:after="0" w:before="0"/>
        <w:ind w:left="11" w:hanging="11"/>
        <w:jc w:val="right"/>
      - <w:rPr>
            <w:lang w:val="fr-FR"/>
        </w:rPr>
    </w:pPr>
  - <w:r>
      - <w:rPr>
            <w:noProof/>
        </w:rPr>
      - <w:drawing>
          - <wp:inline wp14:editId="3CD1CF4B"
            wp14:anchorId="7AD447C2" distR="0"
            distL="0" distB="0" distT="0">
                <wp:extent cx="673100" cy="241300"/>
                <wp:effectExtent r="0" b="6350" t="0"
                    l="0"/>
                <wp:docPr name="Picture 40" id="40"/>
              - <wp:cNvGraphicFramePr>
                    <a:graphicFrameLocks
                        noChangeAspect="1"
                        xmlns:a="http://schemas.openxm
                </wp:cNvGraphicFramePr>
              - <a:graphic
                xmlns:a="http://schemas.openxmlformats.
                  - <a:graphicData
                    uri="http://schemas.openxmlformats.
                    - <pic:pic
                      xmlns:pic="http://schemas.openx
                      - <pic:nvPicPr>
                            <pic:cNvPr
                                name="Picture 1"
                                id="0"/>
                          - <pic:cNvPicPr>
                                <a:picLocks
                                    noChangeAspe
                                    noChangeArro
                            </pic:cNvPicPr>
                        </pic:nvPicPr>
                      - <pic:blipFill>
                          - <a:blip
                            r:embed="rId12">
                              - <a:extLst>
                                  - <a:ext
                                    uri="{28A0092
                                    C50C-407E-
                                    A947-
                                    70E740481C1
                                        <a14:useL
                                            val="
                                            xmln
                                    </a:ext>
                                </a:extLst>
                            </a:blip>
                            <a:srcRect/>
                          - <a:stretch>
                                <a:fillRect/>
                            </a:stretch>
                        </pic:blipFill>
                      - <pic:spPr bwMode="auto">
                          - <a:xfrm>
                                <a:off y="0"
                                    x="0"/>
                                <a:ext
                                    cx="673100"
                                    cy="241300"/>
                            </a:xfrm>
                          - <a:prstGeom
                            prst="rect">
                                <a:avLst/>
                            </a:prstGeom>
                            <a:noFill/>
                          - <a:ln>
                                <a:noFill/>
                            </a:ln>
                        </pic:spPr>
```

</pic:pic>
</a:graphicData>
</a:graphic>
</wp:inline>
</w:drawing>
</w:r>
</w:p>
</w:txbxContent>
</wps:txbx>
- <wps:bodyPr anchorCtr="0" anchor="t" bIns="45720" rIns="91440" tIns="45720" lIns="91440" wrap="none" vert="horz" rot="0">
<a:spAutoFit/>
</wps:bodyPr>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:shape w14:anchorId="36794F47" id="_x0000_s1037" stroked="f"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfV
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFM
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJ
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlK
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYv
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALA
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZ
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9f
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBB
IQD8viexHgIAAB8EAAAOAAAAZHJzL2Uyb0RvYy54bWysU8GO2yAQvVfqPyDujR3
dttKu/0AjHGMCgwCNnb69R1wkkbbW1UOiGGGx5s3M+vbUStyEM5LMDWdz3JKh
SnxgpmUKjKjpUXh6u3n7Zj3YShTQg2qFIwhifDXYmvYh2CrLPO+FZn4GVhh0duA0
VlmR58tsANdaB1x4j7f3k5NuEn7XCR6+dZ0XgaiaIreQdpf2Ju7ZZs2qvWO2l/xEg/0DC
UPcsMPLi5F9QWnIHHrow46Az6DrJRcoBs5nnr7J56pkVKRcUx9uLTP7/wfKvh++OyL
sxgD+QgjKaI6g/UVBj1ZDAsjXmOVU6bePgD/6YmBbc/MXtw5B0MvWIvs5vFldvV0wv
2EuABDR2TkfpUAyC6Fil46UykQrHy5vl+2WOHo6uYlGUZeKWser82DofPgvQJB5q6r
ZFh1Dol/eVCy3UmlkuH2zVY5cmDYJLu0Ev9XYcqQoaarRbFIyAbi+9Q/WgZsYiU1Es3
tCkkMKmmMzJR5qROFGSSJozNmMqwOoveQHtEuRxMPYszhoce3C9KBuzXmhocK
GeXiQ4GGu/Y01x5mOALVNFAyHbchjUQSw95hYXYyiRYrOPE4EcYuTFqeJia2+bW
70i8g7VI3FqnpPQnzaZCICQQUqWWPoBjb5OIeB1itwlvj3uC42hGM9/k29G24kK9bxw
TMMVwvHzdbIC4YNio1rHhPBDHrbF7U2uMuMG3tPlECoRS9hnCqEOocuk9Lomq/z
X0nTqyGW21Y+JMlCWtVwXKhVR8816a/D2SK8NH35rV36tlh+rPVu70/D+04i3t+NTx
fkSHIjKV7szGixZh8riMSYT5fAbi6qdJCqJEWKVrkEUu/x8ofgEAAP//AwBQSwECLQ
ACEAtoM4kv4AAADhAQAAEwAAAAAAAAAAAAAAAAAAAAAAAAAAW0NvbnRlbnRfV
ABQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAAAAAAAAAAAAAAAAAC8BAABfcm
ABQABgAIAAAAIQD8viexHgIAAB8EAAAOAAAAAAAAAAAAAAAAAAAAC4CAABkcn
AQItABQABgAIAAAAIQBT2kPa3wAAAAgBAAAPAAAAAAAAAAAAAAAAAAAAAHgEA
bWxQSwUGAAAAAAQABADzAAAAhAUAAAAA " style="position:absolute;margin-left:-2.85pt;margin-top:22.05pt;width:68pt;height:19.9pt;z-index:251705344;visibility:visible;mso-wrap-style:none;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:3.6pt;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:3.6pt;mso-position-horizontal:absolute;mso-position-horizontal-relative:margin;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-relative:margin;mso-height-relative:margin;v-text-anchor:top" type="#_x0000_t202">
- <v:textbox style="mso-fit-shape-to-text:t">
- <w:txbxContent>
- <w:p w:rsidP="002D35A0" w:rsidRDefault="00164130" w:rsidR="00164130" w14:textId="77777777" w14:paraId="13C663C9" w:rsidRPr="00847784">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
<w:ind w:left="11" w:hanging="11"/>
<w:jc w:val="right"/>
- <w:rPr>
<w:lang w:val="fr-FR"/>
</w:rPr>
</w:pPr>
- <w:r>
- <w:rPr>
<w:noProof/>
</w:rPr>

```
- <w:drawing>
  - <wp:inline wp14:editId="3CD1CF4B"
    wp14:anchorId="7AD447C2" distR="0" distL="0" distB="0"
    distT="0">
      <wp:extent cx="673100" cy="241300"/>
      <wp:effectExtent r="0" b="6350" t="0" l="0"/>
      <wp:docPr name="Picture 40" id="40"/>
    - <wp:cNvGraphicFramePr>
        <a:graphicFrameLocks noChangeAspect="1"
          xmlns:a="http://schemas.openxmlformats.org/d
      </wp:cNvGraphicFramePr>
    - <a:graphic
      xmlns:a="http://schemas.openxmlformats.org/drawingm
      - <a:graphicData
        uri="http://schemas.openxmlformats.org/drawingml
        - <pic:pic
          xmlns:pic="http://schemas.openxmlformats.org
          - <pic:nvPicPr>
              <pic:cNvPr name="Picture 1"
                id="0"/>
            - <pic:cNvPicPr>
                <a:picLocks noChangeAspect="1"
                  noChangeArrowheads="1"/>
              </pic:cNvPicPr>
            </pic:nvPicPr>
          - <pic:blipFill>
            - <a:blip r:embed="rId13">
              - <a:extLst>
                - <a:ext uri="{28A0092B-
                  C50C-407E-A947-
                  70E740481C1C}">
                    <a14:useLocalDpi
                      val="0"
                      xmlns:a14="http://
                  </a:ext>
                </a:extLst>
              </a:blip>
              <a:srcRect/>
            - <a:stretch>
                <a:fillRect/>
              </a:stretch>
            </pic:blipFill>
          - <pic:spPr bwMode="auto">
            - <a:xfrm>
                <a:off y="0" x="0"/>
                <a:ext cx="673100"
                  cy="241300"/>
              </a:xfrm>
            - <a:prstGeom prst="rect">
                <a:avLst/>
              </a:prstGeom>
              <a:noFill/>
            - <a:ln>
                <a:noFill/>
              </a:ln>
            </pic:spPr>
          </pic:pic>
        </a:graphicData>
      </a:graphic>
    </wp:inline>
  </w:drawing>
</w:r>
</w:p>
</w:txbxContent>
</v:textbox>
<w10:wrap anchorx="margin"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:hyperlink r:id="rId14" w:history="1">
  - <w:r w:rsidRPr="005C028C">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>www.najfnr.or</w:t>
    </w:r>
  </w:hyperlink>
```

```
- <w:r w:rsidRPr="005C028C">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>g</w:t>
  </w:r>
</w:p>
</w:tc>
</w:tr>
- <w:tr w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="15D17E13" w:rsidRPr="005C028C" w:rsidTr="0099201C">
  - <w:trPr>
      <w:trHeight w:val="1013"/>
    </w:trPr>
  - <w:tc>
    - <w:tcPr>
        <w:tcW w:w="1615" w:type="dxa"/>
      </w:tcPr>
    - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777"
      w14:paraId="4B7B88EC" w:rsidRPr="005C028C">
      - <w:pPr>
          <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
          <w:ind w:right="0" w:left="0" w:firstLine="0"/>
          <w:jc w:val="center"/>
        - <w:rPr>
            <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
          </w:rPr>
        </w:pPr>
      - <w:r w:rsidRPr="005C028C">
        - <w:rPr>
            <w:noProof/>
          </w:rPr>
        - <w:drawing>
          - <wp:anchor wp14:editId="133F05D5" wp14:anchorId="32918243" allowOverlap="1" layoutInCell="1"
            locked="0" behindDoc="0" relativeHeight="251704320" simplePos="0" distR="114300"
            distL="114300" distB="0" distT="0">
              <wp:simplePos y="0" x="0"/>
            - <wp:positionH relativeFrom="column">
                <wp:posOffset>207678</wp:posOffset>
              </wp:positionH>
            - <wp:positionV relativeFrom="paragraph">
                <wp:posOffset>90203</wp:posOffset>
              </wp:positionV>
              <wp:extent cx="486888" cy="457200"/>
              <wp:effectExtent r="8890" b="0" t="0" l="0"/>
              <wp:wrapNone/>
              <wp:docPr name="Picture 1" id="1"/>
            - <wp:cNvGraphicFramePr>
                <a:graphicFrameLocks noChangeAspect="1"
                  xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
              </wp:cNvGraphicFramePr>
            - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
              - <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
                - <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
                  - <pic:nvPicPr>
                      <pic:cNvPr name="" id="1"/>
                      <pic:cNvPicPr/>
                    </pic:nvPicPr>
                  - <pic:blipFill>
                    - <a:blip cstate="print" r:embed="rId15">
                      - <a:extLst>
                        - <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
                            <a14:useLocalDpi val="0"
                              xmlns:a14="http://schemas.microsoft.com/office/drawing
                          </a:ext>
                        </a:extLst>
                      </a:blip>
                    - <a:stretch>
                        <a:fillRect/>
                      </a:stretch>
                    </pic:blipFill>
                  - <pic:spPr>
                    - <a:xfrm>
                        <a:off y="0" x="0"/>
                        <a:ext cx="486888" cy="457200"/>
                      </a:xfrm>
                    - <a:prstGeom prst="rect">
                        <a:avLst/>
                      </a:prstGeom>
                    </pic:spPr>
```

```
                                    </pic:pic>
                                </a:graphicData>
                            </a:graphic>
                        - <wp14:sizeRelH relativeFrom="margin">
                                <wp14:pctWidth>0</wp14:pctWidth>
                            </wp14:sizeRelH>
                        - <wp14:sizeRelV relativeFrom="margin">
                                <wp14:pctHeight>0</wp14:pctHeight>
                            </wp14:sizeRelV>
                        </wp:anchor>
                    </w:drawing>
                </w:r>
            </w:p>
        </w:tc>
    - <w:tc>
        - <w:tcPr>
                <w:tcW w:w="1620" w:type="dxa"/>
                <w:vMerge/>
            </w:tcPr>
        - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777"
            w14:paraId="5D40B0F5" w:rsidRPr="005C028C">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                <w:jc w:val="left"/>
            - <w:rPr>
                    <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                </w:rPr>
            </w:pPr>
        </w:p>
    </w:tc>
</w:tr>
- <w:tr w:rsidR="002D35A0" w14:textId="77777777" w14:paraId="0C6CE084" w:rsidRPr="005C028C"
w:rsidTr="0099201C">
    - <w:trPr>
            <w:trHeight w:val="202"/>
        </w:trPr>
    - <w:tc>
        - <w:tcPr>
                <w:tcW w:w="3235" w:type="dxa"/>
                <w:gridSpan w:val="2"/>
            </w:tcPr>
        - <w:p w:rsidP="00033A39" w:rsidRDefault="002D35A0" w:rsidR="002D35A0" w14:textId="77777777"
            w14:paraId="20DE54EE" w:rsidRPr="00CD7A6F">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>
                <w:ind w:right="0" w:left="235"/>
                <w:jc w:val="center"/>
            - <w:rPr>
                    <w:rFonts w:hAnsi="Arial Black" w:ascii="Arial Black"/>
                    <w:b/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:spacing w:val="20"/>
                    <w:sz w:val="12"/>
                    <w:szCs w:val="12"/>
                </w:rPr>
            </w:pPr>
        - <w:r w:rsidRPr="00CD7A6F">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight"
                        w:ascii="Leelawadee UI Semilight" w:eastAsia="Leelawadee UI Semilight"/>
                    <w:color w:val="0563C1"/>
                    <w:sz w:val="12"/>
                    <w:szCs w:val="12"/>
                    <w:u w:val="single" w:color="0563C1"/>
                </w:rPr>
            <w:t>https://doi.org/10.5281/zenodo</w:t>
        </w:r>
        - <w:r w:rsidR="0035656E">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight"
                        w:ascii="Leelawadee UI Semilight" w:eastAsia="Leelawadee UI Semilight"/>
                    <w:color w:val="0563C1"/>
                    <w:sz w:val="12"/>
                    <w:szCs w:val="12"/>
                    <w:u w:val="single" w:color="0563C1"/>
                </w:rPr>
            <w:t>.</w:t>
        </w:r>
        - <w:r w:rsidR="0035656E" w:rsidRPr="0035656E">
            - <w:rPr>
```

```
                                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight"
                                        w:ascii="Leelawadee UI Semilight" w:eastAsia="Leelawadee UI Semilight"/>
                                    <w:color w:val="0563C1"/>
                                    <w:sz w:val="12"/>
                                    <w:szCs w:val="12"/>
                                    <w:u w:val="single" w:color="0563C1"/>
                                </w:rPr>
                                <w:t>1478870</w:t>
                            </w:r>
                        </w:p>
                    </w:tc>
                </w:tr>
            </w:tbl>
        - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="47EDE851">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="120" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
                <w:jc w:val="left"/>
              - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                        Semilight"/>
                    <w:sz w:val="14"/>
                    <w:szCs w:val="14"/>
                </w:rPr>
            </w:pPr>
        </w:p>
        - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="0CF64664">
            - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
                <w:ind w:right="0" w:left="0" w:firstLine="0"/>
              - <w:rPr>
                    <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                    <w:color w:val="000000" w:themeColor="text1"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
            </w:pPr>
        </w:p>
    </w:tc>
- <w:tc>
    - <w:tcPr>
        <w:tcW w:w="5789" w:type="dxa"/>
    </w:tcPr>
    - <w:p w:rsidP="00033A39" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="5EF7316F" w:rsidRPr="002D35A0">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="240" w:after="0" w:before="0"/>
            <w:ind w:right="0" w:left="-14" w:firstLine="0"/>
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="15"/>
                <w:szCs w:val="15"/>
            </w:rPr>
        </w:pPr>
        - <w:r w:rsidRPr="002D35A0">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Arial Narrow" w:ascii="Arial Narrow"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="15"/>
                <w:szCs w:val="15"/>
            </w:rPr>
            <w:t>Background:</w:t>
        </w:r>
        - <w:r w:rsidRPr="002D35A0">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="15"/>
                <w:szCs w:val="15"/>
            </w:rPr>
            <w:t> </w:t>
        - <w:r w:rsidRPr="002D35A0">
            - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI
                    Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="15"/>
                <w:szCs w:val="15"/>
            </w:rPr>
            <w:t>
```

```
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Patients with metabolic syndrome (MetS) have a higher risk of developing colorectal neoplasms (CRN) including colorectal adenoma (CRA) and colorectal cancer (CRC). Nonetheless, the role and implication of each component of the syndrome, i.e. (hyperglycemia, hypertension, dyslip</w:t>
</w:r>
- <w:r w:rsidR="00CB6CD1">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>idemia, and visceral obesity) are</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> not well ascertained. </w:t>
</w:r>
- <w:r w:rsidRPr="003B2F4B">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Arial Narrow" w:ascii="Arial Narrow"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Aims:</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>We conducted a systematic review and a meta-analysis in order to assess the association between MetS components and CRN.</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="003B2F4B">
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Arial Narrow" w:ascii="Arial Narrow"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
```

<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Methods and Material:</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>A systematic literature search using the PubMed database was performed with the objective of identifying relevant English studies. Effect estimates were measured. Heterogeneity, subgroup, sensitivity analyses, and publication bias analyses were performed.</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="003B2F4B">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Arial Narrow" w:ascii="Arial Narrow"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Results:</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Thirty-one studies met our inclusion criteria. Generally, subjects with hyperglycemia (RR = 1.33; 95% CI 1.14-1.54), high waist circumference (RR = 1.30; 95% CI 1.19-1.42), high triglycerides (RR = 1.30; 95% CI 1.13-1.49), and hypertension (RR = 1.26; 95% CI 1.17-1.36) showed a stronger positive significant association with CRA formation risk. A similar pattern was found between high fasting blood glucose (RR = 1.35; 95% CI 1.23-1.47) and high blood pressure (RR = 1.28; 95% CI 1.20-1.37) with CRC incidence. A moderate association was found between hypertriglyceridemia and visceral obesity with CRC risk. Conversely, no significant association was found between low high-density lipoprotein-cholesterol (HDL-C) with both outcomes. </w:t>
</w:r>
- <w:r w:rsidRPr="003B2F4B">
- <w:rPr>

```
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Arial Narrow" w:ascii="Arial Narrow"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>Conclusions:</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:b/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve">Our results indicate that hyperglycemia, hypertension, visceral obesity, </w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:noProof/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t>and</w:t>
</w:r>
- <w:r w:rsidRPr="002D35A0">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="15"/>
<w:szCs w:val="15"/>
</w:rPr>
<w:t xml:space="preserve"> hypertriglyceridemia increases CRA and CRC risk. Low HDL-C has no significant effect on those outcomes.</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00033A39" w:rsidRDefault="00695689" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="4C3057A0" w:rsidRPr="00695689">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="120"/>
<w:ind w:right="0" w:left="-14" w:firstLine="14"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="14"/>
<w:szCs w:val="14"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="000B08C1">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:i/>
<w:iCs/>
<w:noProof/>
<w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
<w:t xml:space="preserve">Article edited </w:t>
</w:r>
- <w:r w:rsidR="002D35A0" w:rsidRPr="000B08C1">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
```

```
                                <w:i/>
                                <w:iCs/>
                                <w:noProof/>
                                <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                                <w:sz w:val="16"/>
                                <w:szCs w:val="16"/>
                            </w:rPr>
                            <w:t>by</w:t>
                        </w:r>
                    - <w:r w:rsidR="002D35A0" w:rsidRPr="00695689">
                        - <w:rPr>
                                <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                                <w:i/>
                                <w:iCs/>
                                <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                                <w:sz w:val="16"/>
                                <w:szCs w:val="16"/>
                            </w:rPr>
                            <w:t xml:space="preserve"> Dr. Muthalib Murshida Asha </w:t>
                        </w:r>
                    - <w:r>
                        - <w:rPr>
                                <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                                <w:i/>
                                <w:iCs/>
                                <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                                <w:sz w:val="16"/>
                                <w:szCs w:val="16"/>
                            </w:rPr>
                            <w:t>and Dr. </w:t>
                        </w:r>
                    - <w:r w:rsidR="002D35A0" w:rsidRPr="00695689">
                        - <w:rPr>
                                <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
                                <w:i/>
                                <w:iCs/>
                                <w:color w:val="538135" w:themeShade="BF" w:themeColor="accent6"/>
                                <w:sz w:val="16"/>
                                <w:szCs w:val="16"/>
                            </w:rPr>
                            <w:t>Hajar KIAI</w:t>
                        </w:r>
                    </w:p>
                </w:tc>
            </w:tr>
        </w:tbl>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w:rsidRDefault="00C62C26" w14:textId="77777777" w14:paraId="592DD5BF">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
                <w:ind w:right="0" w:left="235"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="16"/>
                    <w:szCs w:val="16"/>
                </w:rPr>
            </w:pPr>
        </w:p>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w:rsidRDefault="00C62C26" w14:textId="77777777" w14:paraId="4E6DF0B4">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
                <w:ind w:right="0" w:left="235"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="16"/>
                    <w:szCs w:val="16"/>
                </w:rPr>
            </w:pPr>
        </w:p>
    - <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w:rsidRDefault="00C62C26" w14:textId="77777777" w14:paraId="6AB80DF1">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
                <w:ind w:right="0" w:left="235"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                    <w:sz w:val="16"/>
                    <w:szCs w:val="16"/>
                </w:rPr>
            </w:pPr>
        </w:p>
```

```
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="31FBCD9D">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
      <w:ind w:right="0" w:left="235"/>
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
        <w:sz w:val="16"/>
        <w:szCs w:val="16"/>
      </w:rPr>
    </w:pPr>
  </w:p>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00DF416C" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="240BCB91">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
      <w:ind w:right="0" w:left="235"/>
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
        <w:sz w:val="16"/>
        <w:szCs w:val="16"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="005C028C">
    - <w:rPr>
        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
        <w:noProof/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
    - <mc:AlternateContent>
      - <mc:Choice Requires="wpg">
        - <w:drawing>
          - <wp:anchor wp14:editId="7698C686" wp14:anchorId="73CF6669" allowOverlap="1" layoutInCell="1" locked="0"
            behindDoc="0" relativeHeight="251664384" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
              <wp:simplePos y="0" x="0"/>
            - <wp:positionH relativeFrom="column">
                <wp:posOffset>48260</wp:posOffset>
              </wp:positionH>
            - <wp:positionV relativeFrom="paragraph">
                <wp:posOffset>145720</wp:posOffset>
              </wp:positionV>
              <wp:extent cx="5981065" cy="12065"/>
              <wp:effectExtent r="635" b="6985" t="0" l="0"/>
              <wp:wrapSquare wrapText="bothSides"/>
              <wp:docPr name="Group 10992" id="10992"/>
              <wp:cNvGraphicFramePr/>
            - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
              - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingGroup">
                - <wpg:wgp>
                    <wpg:cNvGrpSpPr/>
                  - <wpg:grpSpPr>
                    - <a:xfrm>
                        <a:off y="0" x="0"/>
                        <a:ext cx="5981065" cy="12065"/>
                        <a:chOff y="0" x="0"/>
                        <a:chExt cx="5981389" cy="12192"/>
                      </a:xfrm>
                    </wpg:grpSpPr>
                  - <wps:wsp>
                      <wps:cNvPr name="Shape 13837" id="13837"/>
                      <wps:cNvSpPr/>
                    - <wps:spPr>
                      - <a:xfrm>
                          <a:off y="0" x="0"/>
                          <a:ext cx="2085082" cy="12192"/>
                        </a:xfrm>
                      - <a:custGeom>
                          <a:avLst/>
                          <a:gdLst/>
                          <a:ahLst/>
                          <a:cxnLst/>
                          <a:rect r="0" b="0" t="0" l="0"/>
                        - <a:pathLst>
                          - <a:path w="2085082" h="12192">
                            - <a:moveTo>
                                <a:pt y="0" x="0"/>
                              </a:moveTo>
                            - <a:lnTo>
                                <a:pt y="0" x="2085082"/>
                              </a:lnTo>
                            - <a:lnTo>
```

```
                                    <a:pt y="12192" x="2085082"/>
                                </a:lnTo>
                            - <a:lnTo>
                                    <a:pt y="12192" x="0"/>
                                </a:lnTo>
                            - <a:lnTo>
                                    <a:pt y="0" x="0"/>
                                </a:lnTo>
                            </a:path>
                        </a:pathLst>
                    </a:custGeom>
                - <a:solidFill>
                        <a:schemeClr val="accent6"/>
                    </a:solidFill>
                - <a:ln w="0" cap="flat">
                        <a:miter lim="127000"/>
                    </a:ln>
                </wps:spPr>
            - <wps:style>
                - <a:lnRef idx="0">
                    - <a:srgbClr val="000000">
                            <a:alpha val="0"/>
                        </a:srgbClr>
                    </a:lnRef>
                - <a:fillRef idx="1">
                        <a:srgbClr val="000000"/>
                    </a:fillRef>
                - <a:effectRef idx="0">
                        <a:scrgbClr r="0" b="0" g="0"/>
                    </a:effectRef>
                    <a:fontRef idx="none"/>
                </wps:style>
                <wps:bodyPr/>
            </wps:wsp>
        - <wps:wsp>
                <wps:cNvPr name="Shape 13838" id="13838"/>
                <wps:cNvSpPr/>
            - <wps:spPr>
                - <a:xfrm>
                        <a:off y="0" x="2353385"/>
                        <a:ext cx="3628003" cy="12192"/>
                    </a:xfrm>
                - <a:custGeom>
                        <a:avLst/>
                        <a:gdLst/>
                        <a:ahLst/>
                        <a:cxnLst/>
                        <a:rect r="0" b="0" t="0" l="0"/>
                    - <a:pathLst>
                        - <a:path w="3628003" h="12192">
                            - <a:moveTo>
                                    <a:pt y="0" x="0"/>
                                </a:moveTo>
                            - <a:lnTo>
                                    <a:pt y="0" x="3628003"/>
                                </a:lnTo>
                            - <a:lnTo>
                                    <a:pt y="12192" x="3628003"/>
                                </a:lnTo>
                            - <a:lnTo>
                                    <a:pt y="12192" x="0"/>
                                </a:lnTo>
                            - <a:lnTo>
                                    <a:pt y="0" x="0"/>
                                </a:lnTo>
                            </a:path>
                        </a:pathLst>
                    </a:custGeom>
                - <a:solidFill>
                        <a:schemeClr val="accent6"/>
                    </a:solidFill>
                - <a:ln w="0" cap="flat">
                        <a:miter lim="127000"/>
                    </a:ln>
                </wps:spPr>
            - <wps:style>
                - <a:lnRef idx="0">
                    - <a:srgbClr val="000000">
                            <a:alpha val="0"/>
                        </a:srgbClr>
                    </a:lnRef>
                - <a:fillRef idx="1">
```

<a:srgbClr val="000000"/>
</a:fillRef>
- <a:effectRef idx="0">
<a:scrgbClr r="0" b="0" g="0"/>
</a:effectRef>
<a:fontRef idx="none"/>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</wpg:wgp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:group w14:anchorId="7D35A84C" id="Group 10992"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQBXsbzW+QIAAG4KAAAOAAAAZHJzL2Uyb0RvYy54bWzsVk1v2zAMvQ/YfzB8X+3ESOoYTXpY116G
bVi7H6DK8gcgS4Kkxsm/H0VZipcC29ANww69WLJEUo+PerSvrg8DT/ZMm16Kbbq4yNOECSrrXrTb
9NvD7bsyTYwloiZcCrZNj8yk17u3b65GVbGl7CSvmU4giDDVqLZpZ62qsszQjg3EXEjFBGw2Ug/E
wqtus1qTEaIPPFvm+Tobpa6VlpQZA6s3fjPdYfymYdR+bhrDbMK3KWCz+NT4fHTPbHdFqlYT1fV0
gkFegGIgvYBDY6gbYknypPtnoYaeamlkYy+oHDLZND1lmANks8jPsrnT8klhLm01tirSBNSe8fTi
sPTT/otO+hpql282yzQRZIAy4cmJXwKKRtVWYHmn1b36oqeF1r+5rA+NHtwI+SQHJPcYyWUHm1BY
XG3KRb5epQmFvcXSTZF82kGFnnnR7sPMryg3wW8BIMEvC4dmDluEMiq4RubElPkzpu47ohgWWwLj8
A1NFWVwGptAkWeASEoOWkSZTGWDsdzla5uUqL6EKnqPzXElFn4y9YxLJJvuPxiKFbR1mpAszehBh
qkEFP73/iljn51C6aTJu04ikc8VyQNzuIPfsQaKdWlZYKlwJsg0UYFcabW/pTfamD
VRi9NegZr9KJprAfxrkdaj2eDBOXKl6kmD4szgk2kvf1bc+5Sxg7EnvPdbIn0EsIpUzY9XQVf7Dk
whEI4CiBhtZwYj13vYVOx/vBEXqZ5yc8AMLdW39RcGaPnLlDufjKGlAnagpR6PYxYoAYLoxbJ1x1
xCMLcY03xQwxjrNrIJsYcoGuk93k7EN61idj58ewlUZPf6ihExrfT6ErQdKhqwKX0QlPlsJGfwHf
AqRulq2bPsr6iP0FCQEhu9bzjxQNHyrf+06KLh1GBwC0/2tFL4tVUZTQ4MI1BwamHlasl2WeF/+B
riOSv6DrGCskHNV10rdX4NzyVdevugZd43cbfmqwP00/YO6vaf6OVqffxN13AAAA//8DAFBLAwQU
AAYACAAAACEAnE/vit4AAAAHAQAADwAAAGRycy9kb3ducmV2LnhtbEyOzU6DQBSF9ya+w+SauLMD
2NaCDE3TqKvGxNbEuJsyt0DK3CHMFOjbe13p8vzknC9fT7YVVA/a+caQgnkUgkEpnGqoUfB5eH1Yg
fNBkdOsIFVzRw7q4vcl1ZtxIHzjsQyV4hHymFdQhdJmUvqzRaj9zHRJnJ9dbHVj2lTS9HnnctjKJ
oqW0uiF+qHWH2xrL8/5iFbyNetw8xi/D7nzaXr8Pi/evXYxK3d9Nm2cQAafwV4ZffEaHgpmO7kLG
i1bB05KLCpIkBcFxOk8XII5szFcgi1z+5y9+AAAA//8DAFBLAQItABQABgAIAAAAIQC2gziS/gAA
AOEBAAATAAAAAAAAAAAAAAAAAAAAAABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAGAAgAAAAh
ADj9If/WAAAAlAEAAAsAAAAAAAAAAAAAAAAALwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAGAAgAAAAh
AFexvNb5AgAAbgoAAA4AAAAAAAAAAAAAAAAALgIAAGRycy9lMm9Eb2MueG1sUEsBAi0AFAAGAAgA
AAAhAJxP74reAAAABwEAAA8AAAAAAAAAAAAAAAAAUwUAAGRycy9kb3ducmV2LnhtbFBLBQYAAAAA
BAAEAPMAAABeBgAAAAA= " coordsize="59813,121" style="position:absolute;margin-left:3.8pt;margin-top:11.45pt;width:470.95pt;height:.95pt;z-index:251664384;mso-width-relative:margin;mso-height-relative:margin"
o:spid="_x0000_s1026">
- <v:shape id="Shape 13837" strokeweight="0" stroked="f" fillcolor="#70ad47 [3209]"
path="m,l2085082,r,12192l,12192,,e"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQBaKk8uxQAAAN4AAAAPAAAAZHJzL2Rvd25yZXYueG1sRE/basJA
EH0X/IdlhL6IbtqIhugqtlBsQSpGP2DIjkk0OxuyW41/7wqFvs3hXGex6S13bgXGex6kwtrtS6yrKC13EEgji3
uuJCwfHwOUpAOI+ssbZMCu7kYLXs9xaYanvjPV0zX4gQwi5FBaX3TSqly0sy6Ma2IQ7cybYGfYBt
IXWLtxBuavkWRVNpsOLQUGJDHyXll+zXKDj/DKfIm+37bp0dJ/XlO6bhfaPUy6Bbz0F46vy/+M/9
pcP8OIln8Hwn3CCXDwAAAP//AwBQSwECLQAUAAYACAAAACEA2+H2y+4AAACFAQAAEwAAAAAAAA
AAAAAAAAAAAAW0NvbnRlbnRfVHlwZXNdLnhtbFBLAQItABQABgAIAAAAIQBa9CxbvwAAABUBAAA
AAAAAAAAAAAAAAAAAB8BAABfcmVscy8ucmVsc1BLAQItABQABgAIAAAAIQBaKk8uxQAAAN4AAAA
AAAAAAAAAAAAAAAAAAcCAABkcnMvZG93bnJldi54bWxQSwUGAAAAAAMAAwC3AAAA+QIAAAAA
" coordsize="2085082,12192" style="position:absolute;width:20850;height:121;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1027">
<v:stroke joinstyle="miter" miterlimit="83231f"/>

<v:path textboxrect="0,0,2085082,12192" arrowok="t"/>
</v:shape>
- <v:shape id="Shape 13838" strokeweight="0" stroked="f" fillcolor="#70ad47 [3209]"
path="m,l3628003,r,12192l,12192,,e"
o:gfxdata="UEsDBBQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbHyQz(
70i8Q+QralM4IITa7kDhCAiNB7ASt43WOlEcyvb2pNu4IODoPz9/n1xv9vOkForiPDdwXVagiI23
jocG3rdPxR0oScgWJ8/UwIEENu3lRb09BBKV0ywNjCmFe63FjDSjlD4Q50nv44wpl3HQAc0OB9I3
VXWrjedEnIq03oC27qjHjympx31un0wiTQLq4bS4shrAECZnMGVTvbD9QSnOhDInjzsyuiBXWQP0
r4R18jfgnHvJr4nOknrFmJ5xzhraRtHWf3Kkpfz/yGo5S+H73hkquyhdjr3R8m2lj09svwAAAP//
AwBQSwMEFAAGAAgAAAAhAFr0LFu/AAAAFQEAAAsAAABfcmVscy8ucmVsc2zPwWrDMAwG4Ptg72B0
X5TuUMaI01uh19I+gLGVxCy2jGSy9e1nemrHjpL4P0nD4SetZiPRyNnCruvBUPYcYp4tXC/Htw8w
Wl0ObuVMFm6kcBhfX4Yzra62kC6xqGlKVgtLreUTUf1CyWnHhXKbTCzJ1VbKjMX5LzcTvvf9HuXR
gPHJNKdgQU5hB+ZyK23zHztFL6w81c5zQp6m6P9TMfB3PtPWFCczVQtB9N4U2rp2HOA44NMz4y8A
AAD//wMAUEsDBBQABgAIAAAAIQDrKdP0xwAAAN4AAAAPAAAAZHJzL2Rvd25yZXYueG1sRI9Pa8JA
EMXvgt9hmYIXqZsaEEldpZQK9uDBP9DrkJ1mg9nZmN2a+O07B8HbDO/Ne79ZbQbfqBt1sQ5s4G2W
gSIug625MnA+bV+XoGJCttgEJgN3irBZj0crLGzo+UC3Y6qUhHAs0IBLqS20jqUjj3EWWmLRfkPn
McnaVdp22Eu4b/Q8yxbaY83S4LClT0fl5fjnDUz3nJVVk8/dKV4Pfbx8/Xy7szGTl+HjHVSiIT3N
j+udFfx8mQuvvCMz6PU/AAAA//8DAFBLAQItABQABgAIAAAAIQDb4fbL7gAAAIUBAAATAAAAAAAA
AAAAAAAAAAAAAABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAGAAgAAAAhAFr0LFu/AAAAFQEA
AAsAAAAAAAAAAAAAAAAAHwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAGAAgAAAAhAOsp0/THAAAA3g
AA8AAAAAAAAAAAAAAAAABwIAAGRycy9kb3ducmV2LnhtbFBLBQYAAAAAAwADALcAAAD7AgAAA
" coordsize="3628003,12192" style="position:absolute;left:23533;width:36280;height:121;visibility:visible;mso-wrap-style:square;v-text-anchor:top" o:spid="_x0000_s1028">
<v:stroke joinstyle="miter" miterlimit="83231f"/>
<v:path textboxrect="0,0,3628003,12192" arrowok="t"/>
</v:shape>
<w10:wrap type="square"/>
</v:group>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:r w:rsidR="00A36C58" w:rsidRPr="005C028C">
- <w:rPr>
<w:noProof/>
</w:rPr>
- <mc:AlternateContent>
- <mc:Choice Requires="wps">
- <w:drawing>
- <wp:anchor wp14:editId="7E8F0966" wp14:anchorId="5E04F099" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251668480" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="column">
<wp:posOffset>19050</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>2979725</wp:posOffset>
</wp:positionV>
<wp:extent cx="6014720" cy="45085"/>
<wp:effectExtent r="24130" b="0" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Shape 258" id="3"/>
<wp:cNvGraphicFramePr/>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
- <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
- <wps:wsp>
<wps:cNvSpPr/>
- <wps:spPr>
- <a:xfrm>
<a:off y="0" x="0"/>
<a:ext cx="6014720" cy="45085"/>
</a:xfrm>
- <a:custGeom>
<a:avLst/>
<a:gdLst/>
<a:ahLst/>
<a:cxnLst/>
<a:rect r="0" b="0" t="0" l="0"/>
- <a:pathLst>
- <a:path w="5930891">
- <a:moveTo>
<a:pt y="0" x="0"/>
</a:moveTo>
- <a:lnTo>
<a:pt y="0" x="5930891"/>
</a:lnTo>
</a:path>
</a:pathLst>
</a:custGeom>
- <a:ln w="9525" cap="rnd">
- <a:solidFill>
<a:schemeClr val="accent6"/>

</a:solidFill>
<a:round/>
</a:ln>
</wps:spPr>
- <wps:style>
- <a:lnRef idx="1">
<a:srgbClr val="000000"/>
</a:lnRef>
- <a:fillRef idx="0">
- <a:srgbClr val="000000">
<a:alpha val="0"/>
</a:srgbClr>
</a:fillRef>
- <a:effectRef idx="0">
<a:scrgbClr r="0" b="0" g="0"/>
</a:effectRef>
<a:fontRef idx="none"/>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:shape w14:anchorId="4DF0FB68" id="Shape 258" path="m,l5930891,e"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQBlxLz/KwIAAM0EAAAOAAAAZHJzL2Uyb0RvYy54bWysVE1v2zAMvQ/YfxB0X+y4dZYEcXpY0V2G
rVi7H6DoIzYgS4KkxMm/H0V/JMuGHYrmoFAW+fgeKWrzcGo1OUofGmsqOp/llEjDrWjMvqK/Xp8+
LSkJkRnBtDWyomcZ6MP244dN59aysLXVQnoCICasO1fROka3zrLAa9myMLNOGjhU1rcswtbvM+FZ
B+itzoo8X2Sd9cJ5y2UI8PWxP6RbxFdK8vhDqSAj0RUFbhFXj+surdl2w9Z7z1zd8IEGewOLljUG
kk5QjywycvDNX1Btw70NVsUZt21mlWq4RA2gZp7fqHmpmZOoBYoT3FSm8H6w/Pvx2ZNGVPSOEsNa
aBFmJUW5TMXpXFiDz4t79sMugJmUnpRv0z9oICcs6HkqqDxFwuHjIp/ffy6g7hzO7st8WSbM7BLM
DyF+lRaB2PFbiH0/xGixerT4yYYmh67+t5+OxRSX2CWTdBUtV3f5cjXHHrX2KF8tnsYb6kDtcqrN
tdeIQEaZ4Nt7gJHSoLApNXy8FqdNYrEqixKKweCieyOQTLC6EU+RXtyZHBhGefSxMVQ
sz88vT0Y0ddSG8ic+tR3Bq141jIBavNTKmgv9KLXHvx+N+Hn+Bvg0TXFKCAzReU9yX9EJVemXc16
rjhKIHpIgMUYkJKnxFm8heUDbj+Q8GLAVRnHErCmIKRlTZziDTwmyPtKbTJ3VpzxpmJBYGaQxzDf
aSiv91i2yyu0/Q0AAP//AwBQSwMEFAAGAAgAAAAhAPtS/HjfAAAACQEAAA8AAABkcnMvZG93bnJl
di54bWxMj0FPwzAMhe9I/IfISFwQS9mgW0vTCSFx4gIDbRyzxjTVGqdKsq7795gT3Gy/p+fvVevJ
9WLEEDtPCu5mGQikxpuOWgWfHy+3KxaTK694QKzhhhXV9eVLo0/kTvOG5SKziEYqkV2JSGUsrY
WHQ6zvyAxNq3D04nXkMrTdAnDne9nGdZLp3uiD9YPeCzxeawOToFo4tpV4zn7cG+fWEh29fVzS4o
dX01PT2CSDilPzP84jM61My090cyUfQKFtwkKbjPizkI1ouHjIc9X5b5AmRdyf8N6h8AAAD//wMA
UEsBAi0AFAAGAAgAAAAhALaDOJL+AAAA4QEAABMAAAAAAAAAAAAAAAAAAAAAAFtDb250ZW50X1R
cGVzXS54bWxQSwECLQAUAAYACAAAACEAOP0h/9YAAACUAQAACwAAAAAAAAAAAAAAAAAvAQAAX
bHMvLnJlbHNQSwECLQAUAAYACAAAACEAZcS8/ysCAADNBAAADgAAAAAAAAAAAAAAAAAuAgAAZHJ
L2Uyb0RvYy54bWxQSwECLQAUAAYACAAAACEA+1L8eN8AAAAJAQAADwAAAAAAAAAAAAAAAACFBA
ZHJzL2Rvd25yZXYueG1sUEsFBgAAAAAEAAQA8wAAAJEFAAAAAA== " coordsize="5930891,45085"
style="position:absolute;margin-left:1.5pt;margin-top:234.6pt;width:473.6pt;height:3.55pt;z-index:251668480;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:text;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-relative:margin;mso-height-relative:margin;v-text-anchor:top" o:spid="_x0000_s1026" filled="f"
strokecolor="#70ad47 [3209]">
<v:stroke endcap="round"/>
<v:path textboxrect="0,0,5930891,45085" arrowok="t"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
</w:p>
- <w:p w:rsidP="00E75889" w:rsidRDefault="00A36C58" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="738D30BF">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="0" w:before="0"/>

```
<w:ind w:right="0"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="005C028C">
- <w:rPr>
<w:noProof/>
</w:rPr>
- <w:drawing>
- <wp:anchor wp14:editId="5856D294" wp14:anchorId="50689CDE" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0"
relativeHeight="251669504" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="column">
<wp:posOffset>1178560</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>2894635</wp:posOffset>
</wp:positionV>
<wp:extent cx="131445" cy="131445"/>
<wp:effectExtent r="1905" b="1905" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Picture 12" descr="Image result for telephone icon" id="12"/>
- <wp:cNvGraphicFramePr>
<a:graphicFrameLocks noChangeAspect="1" xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
</wp:cNvGraphicFramePr>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
- <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
- <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
- <pic:nvPicPr>
<pic:cNvPr name="Picture 3" descr="Image result for telephone icon" id="0"/>
- <pic:cNvPicPr>
<a:picLocks noChangeAspect="1" noChangeArrowheads="1"/>
</pic:cNvPicPr>
</pic:nvPicPr>
- <pic:blipFill>
- <a:blip cstate="print" r:embed="rId16">
- <a:duotone>
- <a:schemeClr val="accent6">
<a:shade val="45000"/>
<a:satMod val="135000"/>
</a:schemeClr>
<a:prstClr val="white"/>
</a:duotone>
- <a:extLst>
- <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
<a14:useLocalDpi val="0"
xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main"/>
</a:ext>
</a:extLst>
</a:blip>
<a:srcRect/>
- <a:stretch>
<a:fillRect/>
</a:stretch>
</pic:blipFill>
- <pic:spPr bwMode="auto">
- <a:xfrm>
<a:off y="0" x="0"/>
<a:ext cx="131445" cy="131445"/>
</a:xfrm>
- <a:prstGeom prst="rect">
<a:avLst/>
</a:prstGeom>
<a:noFill/>
- <a:ln>
<a:noFill/>
</a:ln>
</pic:spPr>
</pic:pic>
</a:graphicData>
</a:graphic>
</wp:anchor>
</w:drawing>
</w:r>
- <w:r w:rsidR="00E21B5A" w:rsidRPr="005C028C">
- <w:rPr>
<w:noProof/>
</w:rPr>
```

```
- <w:drawing>
  - <wp:anchor wp14:editId="4F6F7E36" wp14:anchorId="15D9611E" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0"
    relativeHeight="251670528" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
      <wp:simplePos y="0" x="0"/>
    - <wp:positionH relativeFrom="column">
        <wp:posOffset>2518410</wp:posOffset>
      </wp:positionH>
    - <wp:positionV relativeFrom="paragraph">
        <wp:posOffset>2887015</wp:posOffset>
      </wp:positionV>
      <wp:extent cx="127635" cy="153670"/>
      <wp:effectExtent r="5715" b="0" t="0" l="0"/>
      <wp:wrapNone/>
      <wp:docPr name="Picture 16" descr="Image result for email" id="16"/>
    - <wp:cNvGraphicFramePr>
        <a:graphicFrameLocks noChangeAspect="1" xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
      </wp:cNvGraphicFramePr>
    - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
      - <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
        - <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
          - <pic:nvPicPr>
              <pic:cNvPr name="Picture 5" descr="Image result for email" id="0"/>
            - <pic:cNvPicPr>
                <a:picLocks noChangeAspect="1" noChangeArrowheads="1"/>
              </pic:cNvPicPr>
            </pic:nvPicPr>
          - <pic:blipFill>
            - <a:blip cstate="print" r:embed="rId17">
              - <a:duotone>
                - <a:schemeClr val="accent6">
                    <a:shade val="45000"/>
                    <a:satMod val="135000"/>
                  </a:schemeClr>
                  <a:prstClr val="white"/>
                </a:duotone>
              - <a:extLst>
                - <a:ext uri="{BEBA8EAE-BF5A-486C-A8C5-ECC9F3942E4B}">
                  - <a14:imgProps xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main">
                    - <a14:imgLayer r:embed="rId18">
                      - <a14:imgEffect>
                          <a14:brightnessContrast contrast="-40000"/>
                        </a14:imgEffect>
                      </a14:imgLayer>
                    </a14:imgProps>
                  </a:ext>
                - <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
                    <a14:useLocalDpi val="0"
                      xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main"/>
                  </a:ext>
                </a:extLst>
              </a:blip>
              <a:srcRect/>
            - <a:stretch>
                <a:fillRect/>
              </a:stretch>
            </pic:blipFill>
          - <pic:spPr bwMode="auto">
            - <a:xfrm>
                <a:off y="0" x="0"/>
                <a:ext cx="127635" cy="153670"/>
              </a:xfrm>
            - <a:prstGeom prst="rect">
                <a:avLst/>
              </a:prstGeom>
              <a:noFill/>
            - <a:ln>
                <a:noFill/>
              </a:ln>
            </pic:spPr>
          </pic:pic>
        </a:graphicData>
      </a:graphic>
    - <wp14:sizeRelH relativeFrom="margin">
        <wp14:pctWidth>0</wp14:pctWidth>
      </wp14:sizeRelH>
    - <wp14:sizeRelV relativeFrom="margin">
        <wp14:pctHeight>0</wp14:pctHeight>
      </wp14:sizeRelV>
    </wp:anchor>
  </w:drawing>
</w:r>
- <w:r w:rsidR="00C62C26" w:rsidRPr="007B5FB4">
```

```
- <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:t>* Corresponding author</w:t>
 </w:r>
- <w:r w:rsidR="00C62C26" w:rsidRPr="007B5FB4">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:t xml:space="preserve"> </w:t>
 </w:r>
- <w:r w:rsidR="00C62C26" w:rsidRPr="007B5FB4">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:tab/>
  <w:t xml:space="preserve">Tel: +213 </w:t>
 </w:r>
- <w:r w:rsidR="00C62C26">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:t>551152261</w:t>
 </w:r>
- <w:r w:rsidR="00C62C26" w:rsidRPr="007B5FB4">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:t xml:space="preserve"> </w:t>
 </w:r>
 <w:bookmarkStart w:name="_GoBack" w:id="0"/>
 <w:bookmarkEnd w:id="0"/>
- <w:r w:rsidR="00C62C26" w:rsidRPr="007B5FB4">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="16"/>
    <w:szCs w:val="16"/>
  </w:rPr>
  <w:tab/>
 </w:r>
- <w:hyperlink r:id="rId19" w:history="1">
  - <w:r w:rsidR="00C62C26" w:rsidRPr="00006E5BD7">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="16"/>
      <w:szCs w:val="16"/>
    </w:rPr>
    <w:t>khaled@khaledmb.co.uk</w:t>
   </w:r>
  </w:hyperlink>
</w:p>
- <w:p w:rsidP="00C62C26" w:rsidRDefault="00C62C26" w:rsidRPr="00006E5BD7" w:rsidRDefault="00006E5BD7" w:rsidR="00C62C26" w14:textId="77777777" w14:paraId="0A93FCA3">
  - <w:pPr>
    <w:spacing w:lineRule="auto" w:line="259" w:after="5" w:before="0"/>
    <w:ind w:right="0" w:left="235"/>
    - <w:rPr>
      <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
      <w:b/>
      <w:caps/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
    </w:rPr>
   </w:pPr>
  - <w:r w:rsidR="00005C028C">
    - <w:rPr>
      <w:noProof/>
    </w:rPr>
   - <mc:AlternateContent>
    - <mc:Choice Requires="wps">
      - <w:drawing>
```

- <wp:anchor wp14:editId="3CA2C59A" wp14:anchorId="0349ADF2" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251667456" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="column">
<wp:posOffset>18085</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>60960</wp:posOffset>
</wp:positionV>
<wp:extent cx="5986145" cy="45085"/>
<wp:effectExtent r="14605" b="0" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Shape 258" id="258"/>
<wp:cNvGraphicFramePr/>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
- <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
- <wps:wsp>
<wps:cNvSpPr/>
- <wps:spPr>
- <a:xfrm>
<a:off y="0" x="0"/>
<a:ext cx="5986145" cy="45085"/>
</a:xfrm>
- <a:custGeom>
<a:avLst/>
<a:gdLst/>
<a:ahLst/>
<a:cxnLst/>
<a:rect r="0" b="0" t="0" l="0"/>
- <a:pathLst>
- <a:path w="5930891">
- <a:moveTo>
<a:pt y="0" x="0"/>
</a:moveTo>
- <a:lnTo>
<a:pt y="0" x="5930891"/>
</a:lnTo>
</a:path>
</a:pathLst>
</a:custGeom>
- <a:ln w="9525" cap="rnd">
- <a:solidFill>
<a:schemeClr val="accent6"/>
</a:solidFill>
<a:round/>
</a:ln>
</wps:spPr>
- <wps:style>
- <a:lnRef idx="1">
<a:srgbClr val="000000"/>
</a:lnRef>
- <a:fillRef idx="0">
- <a:srgbClr val="000000">
<a:alpha val="0"/>
</a:srgbClr>
</a:fillRef>
- <a:effectRef idx="0">
<a:scrgbClr r="0" b="0" g="0"/>
</a:effectRef>
<a:fontRef idx="none"/>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:shape w14:anchorId="1E26F6A8" id="Shape 258" path="m,l5930891,e"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y

JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQDTFvccKQIAAM8EAAAOAAAAZHJzL2Uyb0RvYy54bWysVE2P0zAQvSPxHyzfadKyqdqo6R5YLRcE
K3b5Aa4/mkiObdlu0v57xpOPloI4IHpIx/bMm/dmPN49nltNOulDY01Fl4ucEmm4FY05VvTH2/OH
DSUhMiOYtkZW9CIDfdy/f7frXSlXtrZaSE8AxISydxWtY3RllgVey5aFhXXSwKGyvmURlv6YCc96
QG91tsrzddZbL5y3XIYAu0/DId0jvlKSx29KBRmJrihwi/j1+D2kb7bfsfLomasbPtJg/8CiZY2B
pDPUE4uMnHzzG1TbcG+DVXHBbZtZpRouUQOoWeZ3al5r5iRqgeIEN5cp/D9Y/rV78aQRFV0V0CrD
WmgS5iVpA8rTu1CC16t78eMqgJm0npVv0z+oIGcs6WUuqTxHwmGz2G7Wy4eCEg5nD0W+KRJmdg3m
pxA/S4tArPsS4tARMVmsnix+NpPpoa9/7ahjMcUldskkfWLyMd9sl9il1nbyzeJpvKMO1K6n2tx6
TQhkkgm+gwcYKQ0Km1PD5q04bRKLbbFKxWBw1b0RSCZY3YjnRuvEBy++/KQ96RhcWca5NHE91uwX
T29PRgy11AYypz4NnUErXrRMgNp8lwoaDL0YtAd/PMz4Of5GeHRNMQrIzFH5QPIPUcmVaVezgSsO
E4geE2AxRqTkKXEa72H5iDuMJLwZMKTTYALWHIS0rIlzvIHnBHnfqE3mwYoL3lQsCEwN8hgnPI3l
7RrLdn2H9j8BAAD//wMAUEsDBBQABgAIAAAAIQBM1K1i3AAAAAYBAAAPAAAAZHJzL2Rvd25yZXYu
eG1sTM4xT8MwEAXgHYn/YB0SC2odKhqaEKdCSEwsUBDt6MZHHDU+R7abpv+eY6Lj6T29+6r15Hox
YoidJwX38wwEUuNNR62Cr8/X2QpETJqM7j2hgjNGWNfXV5UujT/RB46b1AoeoVhqBTaloZQyNhad
jnM/IHH244PTic/QShP0icddLxdZlkunO+IPVg/4YrE5bI5Owehi2hbj+ftg33dYyPZtdbcNSt3e
TM9PIBJO6b8Mf3ymQ82mvT+SiaJXsGB4UlDkIDgtHpZLEHuu5Y8g60pe8utfAAAA//8DAFBLAQIt
ABQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAAAAAAAAAAAAAAAAAAABbQ29udGVudF9UeXBlc10u
eG1sUEsBAi0AFAAGAAgAAAAhADj9If/WAAAAlAEAAAsAAAAAAAAAAAAAAAAALwEAAF9yZWxzLy5y
ZWxzUEsBAi0AFAAGAAgAAAAhANMW9xwpAgAAzwQAAA4AAAAAAAAAAAAAAAAALgIAAGRycy9lMm9I
b2MueG1sUEsBAi0AFAAGAAgAAAAhAEzUrWLcAAAABgEAAA8AAAAAAAAAAAAAAAAAgwQAAGRycy9k
b3ducmV2LnhtbFBLBQYAAAAABAAEAPMAAACMBQAAAAA= " coordsize="5930891,45085"
style="position:absolute;margin-left:1.4pt;margin-top:4.8pt;width:471.35pt;height:3.55pt;z-index:251667456;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:text;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-relative:margin;mso-height-relative:margin;v-text-anchor:top" o:spid="_x0000_s1026" filled="f"
strokecolor="#70ad47 [3209]">
<v:stroke endcap="round"/>
<v:path textboxrect="0,0,5930891,45085" arrowok="t"/>
</v:shape>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
</w:p>
- <w:p w:rsidP="000B613A" w:rsidRDefault="005B7D45" w:rsidR="005B7D45" w14:textId="77777777" w14:paraId="6A4FA665" w:rsidRPr="00E75889">
- <w:pPr>
<w:pStyle w:val="ListParagraph"/>
<w:keepNext/>
<w:keepLines/>
- <w:numPr>
<w:ilvl w:val="0"/>
<w:numId w:val="21"/>
</w:numPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="220" w:before="0"/>
<w:ind w:right="0" w:left="426"/>
<w:jc w:val="left"/>
<w:outlineLvl w:val="1"/>
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:caps/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00570F43">
- <w:rPr>
<w:noProof/>
</w:rPr>
- <mc:AlternateContent>
- <mc:Choice Requires="wps">
- <w:drawing>
- <wp:anchor wp14:editId="33D7026D" wp14:anchorId="120A6525" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251685888" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0"/>
- <wp:positionH relativeFrom="column">
<wp:posOffset>16815</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>208915</wp:posOffset>
</wp:positionV>
<wp:extent cx="2711450" cy="0"/>
<wp:effectExtent r="31750" b="19050" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Straight Connector 8" id="8"/>
<wp:cNvGraphicFramePr/>

```
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
  - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
    - <wps:wsp>
        <wps:cNvCnPr/>
      - <wps:spPr>
        - <a:xfrm flipV="1">
            <a:off y="0" x="0"/>
            <a:ext cx="2711450" cy="0"/>
          </a:xfrm>
        - <a:prstGeom prst="line">
            <a:avLst/>
          </a:prstGeom>
          <a:noFill/>
        - <a:ln w="6350" cap="flat" algn="ctr" cmpd="sng">
          - <a:solidFill>
              <a:srgbClr val="70AD47"/>
            </a:solidFill>
            <a:prstDash val="solid"/>
            <a:miter lim="800000"/>
          </a:ln>
          <a:effectLst/>
        </wps:spPr>
        <wps:bodyPr/>
      </wps:wsp>
    </a:graphicData>
  </a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
    <wp14:pctWidth>0</wp14:pctWidth>
  </wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
    <wp14:pctHeight>0</wp14:pctHeight>
  </wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
  - <w:pict>
    - <v:line w14:anchorId="6767DB0B" id="Straight Connector 8" strokeweight=".5pt"
      o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
      90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
      0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
      OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
      SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
      JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
      bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
      JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
      22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
      OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
      IQBXcjFEzwEAAH4DAAAOAAAAZHJzL2Uyb0RvYy54bWysU01v2zAMvQ/ofxB0X+xkXVMYcYohQXsZ
      tgDddmdkyRagL1BqnPz7UbIbtNttmA+CKFKPeo/Pm4ezNewkMWrvWr5c1JxJJ3ynXd/ynz8eP95z
      FhO4Dox3suUXGfnD9ubDZgyNXPnBm04iIxAXmzG0fEgpNFUVxSAtxIUP0lFSebSQKMS+6hBGQrem
      WtX1XTV67AJ6IWOk0/2U5NuCr5QU6btSUSZmWk5vS2XFsh7zWm030PQIYdBifgb8wyssaEdNr1B7
      SMBeUP8FZbVAH71KC+Ft5ZXSQhYOxGZZ/8HmeYAgCxcSJ4arTPH/wYpvpwMy3bWcBuXA0oieE4Lu
      h8R23jkS0CO7zzqNITZUvnMHnKMYDphJnxVapowOv8gCRQYixs5F5ctVZXlOTNDhar1c3n6mYYjX
      XDVBZKiAMT1Jb1netNxolwWABk5fY6K2VPpako+df9TGlCEax8aW330qyEBWUgYSNbGByEXXcwam
      J4+KhAUxeqO7fDvjROyPO4PsBOSTdf1lf7vOlKnbu7Lceg9xmOpKanKQ1YlsbLQlHev8zbeNy+iy
      GHEmkGWchMu7o+8uRc8qRzTk0nQ2ZHbR25j2b3+b7W8AAAD//wMAUEsDBBQABgAIAAAAIQCa3wYq
      2QAAAAcBAAAPAAAAZHJzL2Rvd25yZXYueG1sTI5NT8JAEIbvJv6HzZB4MbClKJHaLTEmnjy1CFyX
      7tA2dGeb7rbUf+8YD3Kc92uedDvZVozY+8aRguUiAoFUOtNQpeBr9zF/AeGDJqNbR6jgGz1ss/u7
      VCfGXSnHsQiV4BHyiVZQh9AlUvqyRqv9wnVI7J1db3Xgs6+k6fWVx20r4yhaS6sb4g+17vC9xvJS
      DJYxhnPnP5/zfDgUy+O4Iyr3jyulHmbT2yuIgFP4L8MvPjNAxkwnN4SqI1xxUsIo3INh+ijcs
      nP4EmaXylj/7AQAA//8DAFBLAQItABQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAAAAAAAAAAAAA
      AAAAAABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAGAAgAAAAhADj9If/WAAAAlAEAAAsAAAAA
      AAAAAAAAAAAALwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAGAAgAAAAhAFdyMUTPAQAAfgMAAA4AAAA
      AAAAAAAAAAAALgIAAGRycy9lMm9Eb2MueG1sUEsBAi0AFAAGAAgAAAAhAJrfBirZAAAABwEAAA8A
      AAAAAAAAAAAAAAAAKQQAAGRycy9kb3ducmV2LnhtbFBLBQYAAAAABAAEAPMAAAAvBQAAAAA= "
      style="position:absolute;flip:y;z-index:251685888;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-
      height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-
      distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:text;mso-position-
      vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-
      relative:margin;mso-height-relative:margin" o:spid="_x0000_s1026" strokecolor="#70ad47" to="214.8pt,16.45pt"
      from="1.3pt,16.45pt">
        <v:stroke joinstyle="miter"/>
      </v:line>
    </w:pict>
  </mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:r w:rsidRPr="00E75889">
  - <w:rPr>
      <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
      <w:b/>
```

```
                    <w:caps/>
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                </w:rPr>
                <w:t>INTRODUCTION</w:t>
            </w:r>
        </w:p>
    - <w:p w:rsidP="005B7D45" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="0CAF5ED7">
        - <w:pPr>
            - <w:sectPr w:rsidR="00DF7D5C" w:rsidSect="00033A39">
                    <w:headerReference r:id="rId20" w:type="default"/>
                    <w:footerReference r:id="rId21" w:type="default"/>
                    <w:headerReference r:id="rId22" w:type="first"/>
                    <w:footerReference r:id="rId23" w:type="first"/>
                    <w:pgSz w:w="12240" w:h="15840" w:code="1"/>
                    <w:pgMar w:right="1238" w:left="1440" w:gutter="0" w:footer="576" w:header="0" w:bottom="936" w:top="720"/>
                    <w:pgNumType w:start="93"/>
                    <w:cols w:space="708"/>
                    <w:titlePg/>
                    <w:docGrid w:linePitch="360"/>
                </w:sectPr>
            </w:pPr>
        </w:p>
    - <w:p w:rsidP="001A448E" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="3ED61208">
        - <w:pPr>
                <w:spacing w:lineRule="auto" w:line="250" w:after="0" w:before="0"/>
                <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
            </w:pPr>
        - <w:r w:rsidRPr="00570F43">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>Metabolic syndrome (MetS) has become a glob</w:t>
            </w:r>
        - <w:r>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t xml:space="preserve">al health </w:t>
        - <w:r w:rsidRPr="00570F43">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>issue [</w:t>
        - <w:hyperlink w:anchor="_References" w:history="1">
            - <w:r w:rsidRPr="00C16198">
                - <w:rPr>
                        <w:rStyle w:val="Hyperlink"/>
                        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                <w:t>1</w:t>
        - <w:r w:rsidRPr="00570F43">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>]. According to the International Diabetes Federation (IDF), approximately a quarter of the world’s adult population may have the
                    MetS [</w:t>
        - <w:hyperlink w:anchor="_References" w:history="1">
```

```
- <w:r w:rsidRPr="00C16198">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>2</w:t>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00570F43">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">]. MetS </w:t>
</w:r>
- <w:r w:rsidRPr="00695689">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>is</w:t>
</w:r>
- <w:r w:rsidRPr="00570F43">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> identified as an aggregation of prevalent metabolic, biochemical, physiological, and clinical disorders related to the risk of progression to cardiovascular diseases and type 2 diabetes mellitus [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>3</w:t>
    </w:r>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00A65FF9">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
      <w:u w:val="none"/>
    </w:rPr>
    <w:t>–</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>5</w:t>
    </w:r>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00570F43">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>]. Current MetS definitions include hyperglycemia, dyslipidemia, hypertension, and visceral </w:t>
</w:r>
- <w:r w:rsidRPr="00570F43">
```

```
- <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:color w:val="auto"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t>(abdominal or central) obesity as diagnosis criteria [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>1</w:t>
    </w:r>
  </w:hyperlink>
- <w:r w:rsidRPr="00A65FF9">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
      <w:u w:val="none"/>
    </w:rPr>
    <w:t>–</w:t>
  </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>6</w:t>
    </w:r>
  </w:hyperlink>
- <w:r w:rsidRPr="00570F43">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>]. Colorectal cancer (CRC) is a multistep process (stepwise model) of carcinogenesis. This process results from the progressive accumulation of genetic mutations and epigenetic alterations that activate oncogenes and inactivate tumor suppressor genes to substitute normal epithelial cells for adenocarcinomas [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>7</w:t>
    </w:r>
  </w:hyperlink>
- <w:r w:rsidRPr="00A65FF9">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
      <w:u w:val="none"/>
    </w:rPr>
    <w:t>–</w:t>
  </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00C16198">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
```

```
            <w:t>10</w:t>
        </w:r>
    </w:hyperlink>
- <w:r>
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">]. Colorectal adenomas are </w:t>
    </w:r>
- <w:r w:rsidRPr="00570F43">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>recognized as the precursor lesions for CRC [</w:t>
    </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
    - <w:r w:rsidRPr="00C16198">
        - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>11</w:t>
        </w:r>
    </w:hyperlink>
- <w:r w:rsidRPr="00570F43">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">]. CRC is a malignancy characterized by high incidence </w:t>
    </w:r>
- <w:r w:rsidRPr="00570F43">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>
            <w:lastRenderedPageBreak/>
        <w:t>and mortality rates [</w:t>
    </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
    - <w:r w:rsidRPr="00C16198">
        - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>12</w:t>
        </w:r>
    </w:hyperlink>
- <w:r w:rsidRPr="00570F43">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>].</w:t>
    </w:r>
- <w:r w:rsidRPr="00BD718D">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve"> </w:t>
    </w:r>
- <w:r w:rsidRPr="00C90FBC">
    - <w:rPr>
```

```
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>Moreover, CRC is the third prevailing cancer in men and the second in women worldwide. Therefore, 746,000 incident cases among men (10% of all new cancer cases in men) were estimated in 2012 and 614,000 new cases within women (9.2% of all incident cancer cases in women) [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="begin"/>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"pgpEbL7D","properties":{"formattedCitation":"\\super 13\\nosupersub{}","plainCitation":"13","noteIndex":0},"citationItems":[{"id":280,"uris":["http://zotero.org/users/2724931/items/R9XH6B8N"],"uri":["http://zotero.org/users/2724931/items/R9XH6B8N"],"itemData":{"id":280,"type":"article-journal","title":"Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012","container-title":"International Journal of Cancer","page":"E359-E386","volume":"136","issue":"5","source":"CrossRef","DOI":"10.1002/ijc.29210","ISSN":"00207136","shortTitle":"Cancer incidence and mortality worldwide","language":"en","author":[{"family":"Ferlay","given":"Jacques"},{"family":"Soerjomataram","given":"Isabelle"},{"family":"Dikshit","given":"Rajesh"},{"family":"Eser","given":"Sultan"},{"family":"Mathers","given":"Colin"},{"family":"Rebelo","given":"Marise"},{"family":"Parkin","given":"Donald Maxwell"},{"family":"Forman","given":"David"},{"family":"Bray","given":"Freddie"}],"issued":{"date-parts":[["2015",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>13</w:t>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="end"/>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:color w:val="auto"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t>]. In the same year, 373,640 deaths were recorded, making it the fourth cause of mortality by cancer worldwide within men (8% of all cancer deaths in men) and 320,300 deaths among women making it the third cause of death by cancer (9% of all cancer deaths in women) [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
```

```
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                    <w:fldChar w:fldCharType="begin"/>
                </w:r>
            - <w:r w:rsidRPr="00F2237F">
                - <w:rPr>
                        <w:rStyle w:val="Hyperlink"/>
                        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                    <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NIDfSfVB","properties":
                        {"formattedCitation":"\\super 13\\nosupersub{}","plainCitation":"13","noteIndex":0},"citationItems":[{"id":280,"uris":
                        ["http://zotero.org/users/2724931/items/R9XH6B8N"],"uri":["http://zotero.org/users/2724931/items/R9XH6B8N"],"itemData":
                        {"id":280,"type":"article-journal","title":"Cancer incidence and mortality worldwide: Sources, methods and major patterns in
                        GLOBOCAN 2012: Globocan 2012","container-title":"International Journal of Cancer","page":"E359-
                        E386","volume":"136","issue":"5","source":"CrossRef","DOI":"10.1002/ijc.29210","ISSN":"00207136","shortTitle":"Cancer
                        incidence and mortality worldwide","language":"en","author":[{"family":"Ferlay","given":"Jacques"},
                        {"family":"Soerjomataram","given":"Isabelle"},{"family":"Dikshit","given":"Rajesh"},{"family":"Eser","given":"Sultan"},
                        {"family":"Mathers","given":"Colin"},{"family":"Rebelo","given":"Marise"},{"family":"Parkin","given":"Donald Maxwell"},
                        {"family":"Forman","given":"David"},{"family":"Bray","given":"Freddie"}],"issued":{"date-parts":
                        [["2015",3,1]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
                </w:r>
            - <w:r w:rsidRPr="00F2237F">
                - <w:rPr>
                        <w:rStyle w:val="Hyperlink"/>
                        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                    <w:fldChar w:fldCharType="separate"/>
                </w:r>
            - <w:r w:rsidRPr="00F2237F">
                - <w:rPr>
                        <w:rStyle w:val="Hyperlink"/>
                        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                    <w:t>13</w:t>
                </w:r>
            - <w:r w:rsidRPr="00F2237F">
                - <w:rPr>
                        <w:rStyle w:val="Hyperlink"/>
                        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                        <w:sz w:val="18"/>
                        <w:szCs w:val="18"/>
                    </w:rPr>
                    <w:fldChar w:fldCharType="end"/>
                </w:r>
            </w:hyperlink>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>].</w:t>
            </w:r>
        </w:p>
    - <w:p w:rsidP="001A448E" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="357E9207">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="250" w:after="0" w:before="0"/>
            <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
            </w:pPr>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:color w:val="auto"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>This high incidence and mortality could be attributed to various risk factors [</w:t>
            </w:r>
        </w:r>
```

```
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ErA5NXGL","properties":
        {"formattedCitation":"\\super 14\\nosupersub{}","plainCitation":"14","noteIndex":0},"citationItems":[{"id":195,"uris":
        ["http://zotero.org/users/2724931/items/UD2UMRQX"],"uri":
        ["http://zotero.org/users/2724931/items/UD2UMRQX"],"itemData":{"id":195,"type":"article-journal","title":"Molecular
        Pathways Involved in Colorectal Cancer: Implications for Disease Behavior and Prevention","container-title":"International
        Journal of Molecular Sciences","page":"16365-16385","volume":"14","issue":"8","source":"PubMed
        Central","abstract":"Research conducted during the past 30 years has increased our understanding of the mechanisms involved in
        colorectal cancer initiation and development. The findings have demonstrated the existence of at least three pathways:
        chromosomal instability, microsatellite instability and CpG island methylator phenotype. Importantly, new studies have shown
        that inflammation and microRNAs contribute to colorectal carcinogenesis. Recent data have demonstrated that several genetic
        and epigenetic changes are important in determining patient prognosis and survival. Furthermore, some of these mechanisms are
        related to patients' response to drugs, such as aspirin, which could be used for both chemoprevention and treatment in specific
        settings. Thus, in the near future, we could be able to predict disease behavior based on molecular markers found on tumors, and
        direct the best treatment options for patients.","DOI":"10.3390/ijms140816365","ISSN":"1422-0067","note":"PMID: 23965959
        \nPMCID: PMC3759916","shortTitle":"Molecular Pathways Involved in Colorectal Cancer","journalAbbreviation":"Int J Mol
        Sci","author":[{"family":"Colussi","given":"Dora"},{"family":"Brandi","given":"Giovanni"},
        {"family":"Bazzoli","given":"Franco"},{"family":"Ricciardiello","given":"Luigi"}],"issued":{"date-parts":
        [["2013",8,7]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="separate"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>14</w:t>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="end"/>
    </w:r>
  </w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>]. The increasingly aging population, male gender, and ethnicity are linked with a higher risk of developing this malignancy [</w:t>
  </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
```

```
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"N0Wsdpkn","properties":
      {"formattedCitation":"\\super 15\\nosupersub{}","plainCitation":"15","noteIndex":0},"citationItems":[{"id":301,"uris":
      ["http://zotero.org/users/2724931/items/XHU3TIVV"],"uri":["http://zotero.org/users/2724931/items/XHU3TIVV"],"itemData":
      {"id":301,"type":"article-journal","title":"Colorectal Cancer Screening","container-title":"Advances in Colorectal
      Neoplasia","page":"487-502","volume":"97","issue":"3","DOI":"10.1016/j.suc.2017.01.001","ISSN":"0039-
      6109","journalAbbreviation":"Surgical Clinics of North America","author":[{"family":"Moore","given":"Jesse Samuel"},
      {"family":"Aulet","given":"Tess Hannah"}],"issued":{"date-parts":[["2017",6]]}}}],"schema":"https://github.com/citation-style-
      language/schema/raw/master/csl-citation.json"} </w:instrText>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>15</w:t>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="end"/>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>], along with a family history of CRC [</w:t>
  </w:r>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"G4qFL7bZ","properties":
      {"formattedCitation":"\\super 16,17\\nosupersub{}","plainCitation":"16,17","noteIndex":0},"citationItems":[{"id":115,"uris":
      ["http://zotero.org/users/2724931/items/2CTJ5J54"],"uri":["http://zotero.org/users/2724931/items/2CTJ5J54"],"itemData":
      {"id":115,"type":"chapter","title":"1 - Epidemiology and Risk Factors of Colorectal Cancer A2 - Gearhart, Susan L.","container-
      title":"Early Diagnosis and Treatment of Cancer Series: Colorectal Cancer","publisher":"W.B. Saunders","publisher-
      place":"Saint Louis","page":"1-11","event-place":"Saint
      Louis","URL":"http://www.sciencedirect.com/science/article/pii/B9781416046868500063","ISBN":"978-1-4160-
      4686-8","note":"DOI: 10.1016/B978-1-4160-4686-8.50006-3","author":[{"family":"Chu","given":"Kathryn M."}],"editor":
      [{"family":"Ahuja","given":"Nita"}],"issued":{"date-parts":[["2011"]]}}},{"id":193,"uris":
      ["http://zotero.org/users/2724931/items/AK62QPK6"],"uri":["http://zotero.org/users/2724931/items/AK62QPK6"],"itemData":
      {"id":193,"type":"article-journal","title":"Meta-analyses of colorectal cancer risk factors","container-title":"Cancer Causes &
```

Control","page":"1207-1222","volume":"24","issue":"6","abstract":"Demographic, behavioral, and environmental factors have been associated with increased risk of colorectal cancer (CRC). We reviewed the published evidence and explored associations between risk factors and CRC incidence.","DOI":"10.1007/s10552-013-0201-5","ISSN":"1573-7225","journalAbbreviation":"Cancer Causes & Control","author":[{"family":"Johnson","given":"Constance M."},{"family":"Wei","given":"Caimiao"},{"family":"Ensor","given":"Joe E."},{"family":"Smolenski","given":"Derek J."},{"family":"Amos","given":"Christopher I."},{"family":"Levin","given":"Bernard"},{"family":"Berry","given":"Donald A."}],"issued":{"date-parts":[["2013"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>

</w:r>

<w:r w:rsidRPr="00F2237F">

<w:rPr>

<w:rStyle w:val="Hyperlink"/>

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>

<w:sz w:val="18"/>

<w:szCs w:val="18"/>

</w:rPr>

<w:fldChar w:fldCharType="separate"/>

</w:r>

<w:r w:rsidRPr="00F2237F">

<w:rPr>

<w:rStyle w:val="Hyperlink"/>

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>

<w:sz w:val="18"/>

<w:szCs w:val="18"/>

</w:rPr>

<w:t>16, 17</w:t>

</w:r>

<w:r w:rsidRPr="00F2237F">

<w:rPr>

<w:rStyle w:val="Hyperlink"/>

</w:rPr>

<w:fldChar w:fldCharType="end"/>

</w:r>

</w:hyperlink>

<w:r w:rsidRPr="00C90FBC">

<w:rPr>

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>

<w:color w:val="auto"/>

<w:sz w:val="18"/>

<w:szCs w:val="18"/>

</w:rPr>

<w:t>], inherited genetic predispositions (Lynch syndrome, familial adenomatous polyposis, etc.) [</w:t>

</w:r>

<w:hyperlink w:anchor="_References" w:history="1">

<w:r w:rsidRPr="00F2237F">

<w:rPr>

<w:rStyle w:val="Hyperlink"/>

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>

<w:sz w:val="18"/>

<w:szCs w:val="18"/>

</w:rPr>

<w:fldChar w:fldCharType="begin"/>

</w:r>

<w:r w:rsidRPr="00F2237F">

<w:rPr>

<w:rStyle w:val="Hyperlink"/>

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>

<w:sz w:val="18"/>

<w:szCs w:val="18"/>

</w:rPr>

<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2515jrC6","properties":{"formattedCitation":"\\super 18\\uc0\\u8211{}20\\nosupersub{}","plainCitation":"18–20","noteIndex":0},"citationItems":[{"id":95,"uris":["http://zotero.org/users/2724931/items/7XGE2M55"],"uri":["http://zotero.org/users/2724931/items/7XGE2M55"],"itemData":{"id":95,"type":"article-journal","title":"Colorectal Cancer: Epidemiology, Disease Mechanisms and Interventions to Reduce Onset and Mortality","container-title":"Clinical Colorectal Cancer","page":"195-203","volume":"15","issue":"3","source":"ScienceDirect","abstract":"Colorectal cancer (CRC) is a multifactorial disease resulting from lifestyle, genetic, and environmental factors. There are hereditary and non-hereditary CRC types; however, the majority are non-hereditary and mainly caused by somatic mutations in response to environmental factors. In past years, researchers have focused their attention on the mechanisms behind these factors and the methods of improving disease prevention and treatment. Improving the awareness of the population with regard to the benefits of a healthy lifestyle, including a balanced diet associated with exercise, could globally reduce CRC risk. The present review aims to address the current knowledge on CRC, taking into consideration the common molecular alterations upon different environmental and non-environmental factors, current and promising treatment interventions, and how all these factors may interact to positively or negatively influence CRC risk.","DOI":"10.1016/j.clcc.2016.02.008","ISSN":"1533-0028","shortTitle":"Colorectal Cancer","journalAbbreviation":"Clinical Colorectal Cancer","author":[{"family":"Aran","given":"Veronica"},{"family":"Victorino","given":"Ana Paula"},{"family":"Thuler","given":"Luiz Claudio"},{"family":"Ferreira","given":"Carlos Gil"}],"issued":{"date-parts":[["2016",9]]}}},{"id":22,"uris":["http://zotero.org/users/2724931/items/C59IRSMA"],"uri":["http://zotero.org/users/2724931/items/C59IRSMA"],"itemData":{"id":22,"type":"chapter","title":"Molecular Parameters for Prognostic and Predictive Assessment in Colorectal Cancer","container-title":"Rectal Cancer","publisher":"Springer Milan","publisher-place":"Milano","page":"41-62","source":"CrossRef","event-place":"Milano","URL":"http://link.springer.com/10.1007/978-88-470-2670-4_4","ISBN":"978-88-470-2669-8","note":"DOI: 10.1007/978-88-470-2670-4_4","editor":[{"family":"Manzini","given":"Nicolò","non-dropping-particle":"de"}],"author":

```
[{"family":"Carrer","given":"Alessandro"},{"family":"Giacca","given":"Massimo"},
{"family":"Giacca","given":"Mauro"}],"issued":{"date-parts":[["2013"]]},"accessed":{"date-parts":[["2017",1,30]]}}},
{"id":194,"uris":["http://zotero.org/users/2724931/items/JP29WN6X"],"uri":
["http://zotero.org/users/2724931/items/JP29WN6X"],"itemData":{"id":194,"type":"chapter","title":"Chapter 17 - Colorectal
Cancer A2 - Silverman, Paul M.","container-title":"Oncologic Imaging: A Multidisciplinary Approach","publisher":"W.B.
Saunders","publisher-place":"Philadelphia","page":"267-286","event-
place":"Philadelphia","URL":"http://www.sciencedirect.com/science/article/pii/B9781437722321000176","ISBN":"978-1-4377-
2232-1","note":"DOI: 10.1016/B978-1-4377-2232-1.00017-6","author":[{"family":"Tan","given":"Cher Heng"},
{"family":"Das","given":"Prajnan"},{"family":"Silberfein","given":"Eric J."},{"family":"Rodriguez-Bigas","given":"Miguel"},
{"family":"Iyer","given":"Revathy B."}],"issued":{"date-parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"} </w:instrText>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="separate"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>18</w:t>
    </w:r>
  - <w:r w:rsidRPr="00FB2242">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
        <w:u w:val="none"/>
      </w:rPr>
      <w:t>–</w:t>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>20</w:t>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="end"/>
    </w:r>
  </w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>] and inflammatory bowel diseases (Crohn’s disease, Ulcerative Colitis, etc.) [</w:t>
  </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
```

<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qWR5NiT7","properties":{"formattedCitation":"\\super 7,14,18,21\\nosupersub{}","plainCitation":"7,14,18,21","noteIndex":0},"citationItems":[{"id":134,"uris":["http://zotero.org/users/2724931/items/HGWP99MM"],"uri":["http://zotero.org/users/2724931/items/HGWP99MM"],"itemData":{"id":134,"type":"article-journal","title":"COLORECTAL CANCER","container-title":"Nature reviews. Disease primers","page":"15065","volume":"1","source":"PubMed Central","abstract":"Colorectal cancer had a low incidence several decades ago. However, it has become a predominant cancer and now accounts for approximately 10% of cancer-related mortality in western countries. The ‘rise’ of colorectal cancer in developed countries can be attributed to the increasingly ageing population, unfavourable modern dietary habits and an increase in risk factors such as smoking, low physical exercise and obesity. New treatments for primary and metastatic colorectal cancer have emerged, providing additional options for patients; these treatments include laparoscopic surgery for primary disease, more-aggressive resection of metastatic disease (such as liver and pulmonary metastases), radiotherapy for rectal cancer and neoadjuvant and palliative chemotherapies. However, these new treatment options have had limited impact on cure rates and long-term survival. For these reasons, and the recognition that colorectal cancer is long preceded by a polypoid precursor, screening programmes have gained momentum. This Primer provides an overview of the current state of art knowledge on the epidemiology and mechanisms of colorectal cancer, as well as on diagnosis and treatment.","DOI":"10.1038/nrdp.2015.65","ISSN":"2056-676X","note":"PMID: 27189416\nPMCID: PMC4874655","journalAbbreviation":"Nat Rev Dis Primers","author":[{"family":"Kuipers","given":"Ernst J."},{"family":"Grady","given":"William M."},{"family":"Lieberman","given":"David"},{"family":"Seufferlein","given":"Thomas"},{"family":"Sung","given":"Joseph J."},{"family":"Boelens","given":"Petra G."},{"family":"Velde","given":"Cornelis J. H.","non-dropping-particle":"van de"},{"family":"Watanabe","given":"Toshiaki"}],"issued":{"date-parts":[["2015",11,5]]}}},{"id":195,"uris":["http://zotero.org/users/2724931/items/UD2UMRQX"],"uri":["http://zotero.org/users/2724931/items/UD2UMRQX"],"itemData":{"id":195,"type":"article-journal","title":"Molecular Pathways Involved in Colorectal Cancer: Implications for Disease Behavior and Prevention","container-title":"International Journal of Molecular Sciences","page":"16365-16385","volume":"14","issue":"8","source":"PubMed Central","abstract":"Research conducted during the past 30 years has increased our understanding of the mechanisms involved in colorectal cancer initiation and development. The findings have demonstrated the existence of at least three pathways: chromosomal instability, microsatellite instability and CpG island methylator phenotype. Importantly, new studies have shown that inflammation and microRNAs contribute to colorectal carcinogenesis. Recent data have demonstrated that several genetic and epigenetic changes are important in determining patient prognosis and survival. Furthermore, some of these mechanisms are related to patients’ response to drugs, such as aspirin, which could be used for both chemoprevention and treatment in specific settings. Thus, in the near future, we could be able to predict disease behavior based on molecular markers found on tumors, and direct the best treatment options for patients.","DOI":"10.3390/ijms140816365","ISSN":"1422-0067","note":"PMID: 23965959\nPMCID: PMC3759916","shortTitle":"Molecular Pathways Involved in Colorectal Cancer","journalAbbreviation":"Int J Mol Sci","author":[{"family":"Colussi","given":"Dora"},{"family":"Brandi","given":"Giovanni"},{"family":"Bazzoli","given":"Franco"},{"family":"Ricciardiello","given":"Luigi"}],"issued":{"date-parts":[["2013",8,7]]}}},{"id":95,"uris":["http://zotero.org/users/2724931/items/7XGE2M55"],"uri":["http://zotero.org/users/2724931/items/7XGE2M55"],"itemData":{"id":95,"type":"article-journal","title":"Colorectal Cancer: Epidemiology, Disease Mechanisms and Interventions to Reduce Onset and Mortality","container-title":"Clinical Colorectal Cancer","page":"195-203","volume":"15","issue":"3","source":"ScienceDirect","abstract":"Colorectal cancer (CRC) is a multifactorial disease resulting from lifestyle, genetic, and environmental factors. There are hereditary and non-hereditary CRC types; however, the majority are non-hereditary and mainly caused by somatic mutations in response to environmental factors. In past years, researchers have focused their attention on the mechanisms behind these factors and the methods of improving disease prevention and treatment. Improving the awareness of the population with regard to the benefits of a healthy lifestyle, including a balanced diet associated with exercise, could globally reduce CRC risk. The present review aims to address the current knowledge on CRC, taking into consideration the common molecular alterations upon different environmental and non-environmental factors, current and promising treatment interventions, and how all these factors may interact to positively or negatively influence CRC risk.","DOI":"10.1016/j.clcc.2016.02.008","ISSN":"1533-0028","shortTitle":"Colorectal Cancer","journalAbbreviation":"Clinical Colorectal Cancer","author":[{"family":"Aran","given":"Veronica"},{"family":"Victorino","given":"Ana Paula"},{"family":"Thuler","given":"Luiz Claudio"},{"family":"Ferreira","given":"Carlos Gil"}],"issued":{"date-parts":[["2016",9]]}}},{"id":82,"uris":["http://zotero.org/users/2724931/items/5J22AIMV"],"uri":["http://zotero.org/users/2724931/items/5J22AIMV"],"itemData":{"id":82,"type":"article-journal","title":"Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies","container-title":"Clinical Gastroenterology and Hepatology","page":"639-645","volume":"10","issue":"6","source":"www.cghjournal.org","abstract":"Patients with ulcerative colitis (UC) have an increased risk of developing colorectal\ncancer (CRC). Studies examining the magnitude of this association have yielded conflicting\nresults. We performed a meta-analysis of population-based cohort studies to determine\nthe risk of CRC in patients with UC.","DOI":"10.1016/j.cgh.2012.01.010","ISSN":"1542-3565, 1542-7714","shortTitle":"Risk of Colorectal Cancer in Patients With Ulcerative Colitis","journalAbbreviation":"Clinical Gastroenterology and Hepatology","language":"English","author":[{"family":"Jess","given":"Tine"},{"family":"Rungoe","given":"Christine"},{"family":"Peyrin–Biroulet","given":"Laurent"}],"issued":{"date-parts":[["2012",6,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
<w:r w:rsidRPr="00F2237F">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
<w:r w:rsidRPr="00F2237F">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>

```
            <w:t>7, 14, 18, 21</w:t>
        </w:r>
    - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:fldChar w:fldCharType="end"/>
    </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>]. Other environmental and lifestyle-related risk factors are as well linked with CRC, including dietary habits [</w:t>
</w:r>
- <w:r w:rsidRPr="009A0F49">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="begin"/>
</w:r>
- <w:r w:rsidRPr="009A0F49">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
    </w:rPr>
    <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"jFJyUyAc","properties":
        {"formattedCitation":"\\super 22\\uc0\\u8211{}24\\nosupersub{}","plainCitation":"22–24","noteIndex":0},"citationItems":
        [{"id":133,"uris":["http://zotero.org/users/2724931/items/2QTXS5K4"],"uri":
        ["http://zotero.org/users/2724931/items/2QTXS5K4"],"itemData":{"id":133,"type":"article-journal","title":"Dietary patterns and risk
        of colorectal adenoma: a systematic review and meta-analysis of observational studies","container-title":"Journal of Human Nutrition
        and Dietetics","page":"757-767","volume":"29","issue":"6","abstract":"Background\n\nCurrent evidence suggests that dietary patterns
        may play an important role in colorectal cancer risk. The present study aimed to perform a systematic review and meta-analysis of
        observational studies exploring the association between dietary patterns and colorectal adenomas (a precancerous
        condition).\n\n\nMethods\n\nPubmed and EMBASE electronic databases were systematically searched to retrieve eligible studies.
        Only studies exploring the risk or association with colorectal adenomas for the highest versus lowest category of exposure to a
        posteriori dietary patterns were included in the quantitative analysis. Random-effects models were applied to calculate relative risks
        (RRs) of colorectal adenomas for high adherence to healthy or unhealthy dietary patterns. Statistical heterogeneity and publication
        bias were explored.\n\n\nResults\n\nTwelve studies were reviewed. Three studies explored a priori dietary patterns using scores
        identifying adherence to the Mediterranean, Paleolithic and Dietary Approaches to Stop Hypertension (DASH) diet and reported an
        association with decreased colorectal adenoma risk. Two studies tested the association with colorectal adenomas between a posteriori
        dietary patterns showing lower odds of disease related to plant-based compared to meat-based dietary patterns. Seven studies
        identified 23 a posteriori dietary patterns and the analysis revealed that higher adherence to healthy and unhealthy dietary patterns was
        significantly associated risk of colorectal adenomas (RR = 0.81, 95% confidence interval = 0.71, 0.94 and RR = 1.24, 95% confidence
        interval = 1.13, 1.35, respectively) with no evidence of heterogeneity or publication bias.\n\n\nConclusions\n\nThe results of this
        systematic review and meta-analysis indicate that dietary patterns may be associated with the risk of colorectal
        adenomas.","DOI":"10.1111/jhn.12395","ISSN":"1365-277X","journalAbbreviation":"J Hum Nutr Diet","author":
        [{"family":"Godos","given":"J."},{"family":"Bella","given":"F."},{"family":"Torrisi","given":"A."},
        {"family":"Sciacca","given":"S."},{"family":"Galvano","given":"F."},{"family":"Grosso","given":"G."}],"issued":{"date-parts":
        [["2016",12,1]]}},{"id":114,"uris":["http://zotero.org/users/2724931/items/C8IRHHIG"],"uri":
        ["http://zotero.org/users/2724931/items/C8IRHHIG"],"itemData":{"id":114,"type":"article-journal","title":"Dietary legume
        consumption reduces risk of colorectal cancer: evidence from a meta-analysis of cohort studies","container-title":"Scientific
        Reports","page":"8797","volume":"5","source":"www.nature.com","abstract":"Previous epidemiological studies on the relation
        between dietary legume consumption and risk of colorectal cancer (CRC) remain controversial. We conducted a meta-analysis based
        on prospective cohort studies to investigate the association between dietary legume consumption and risk of
        CRC.","DOI":"10.1038/srep08797","ISSN":"2045-2322","shortTitle":"Dietary legume consumption reduces risk of colorectal
        cancer","language":"en","author":[{"family":"Zhu","given":"Beibei"},{"family":"Sun","given":"Yu"},{"family":"Qi","given":"Lu"},
        {"family":"Zhong","given":"Rong"},{"family":"Miao","given":"Xiaoping"}],"issued":{"date-parts":[["2015",3,5]]}}},
        {"id":131,"uris":["http://zotero.org/users/2724931/items/786RFCKF"],"uri":
        ["http://zotero.org/users/2724931/items/786RFCKF"],"itemData":{"id":131,"type":"article-journal","title":"Foods and beverages and
        colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR
        Continuous Update Project.","container-title":"Annals of oncology : official journal of the European Society for Medical
        Oncology","abstract":"Objective: As part of the World Cancer Research Fund International Continuous Update Project, we updated
        the systematic review and meta-analysis of prospective studies to quantify the dose-response between foods and beverages intake and
        colorectal cancer risk. Data Sources: PubMed and several databases up to May 31 st 2015. Study selection: Prospective studies
        reporting adjusted relative risk estimates for the association of specific food groups and beverages and risk of colorectal, colon and
        rectal cancer. Data synthesis: Dose-response meta-analyses using random effect models to estimate summary relative risks (RRs).
        Results: Results: 400 individual study estimates from 111 unique cohort studies were included. Overall, the risk increase of colorectal
        cancer is 12% for each 100g/day increase of red and processed meat intake (95%CI=4-21%, I2 =70%, pheterogeneity (ph)<0.01) and
        7% for 10 g/day increase of ethanol intake in alcoholic drinks (95%CI=5-9%, I2 =25%, ph = 0.21). Colorectal cancer risk decrease in
        17% for each 90g/day increase of whole grains (95%CI=11-21%, I2 =0%, ph = 0.30, 6 studies). For each 400 g/day increase of dairy
```

products intake (95%CI=10-17%, I2 =18%, ph = 0.27, 10 studies). Inverse associations were also observed for vegetables intake (RR per 100 g/day =0.98 (95%CI=0.96-0.99, I2 =0%, ph = 0.48, 11 studies) and for fish intake (RR for 100g/day=0.89(95%CI=0.80-0.99, I2 =0%, ph = 0.52, 11 studies), that were weak for vegetables and driven by one study for fish. Intakes of fruits, coffee, tea, cheese, poultry and legumes were not associated with colorectal cancer risk. Conclusions: Our results reinforce the evidence that high intake of red and processed meat and alcohol increase the risk of colorectal cancer. Milk and whole grains may have a protective role against colorectal cancer. The evidence for vegetables and fish was less convincing.","DOI":"10.1093/annonc/mdx171","ISSN":"1569-8041 0923-7534","note":"PMID: 28407090","journalAbbreviation":"Ann Oncol","language":"eng","author": [{"family":"Vieira","given":"A. R."},{"family":"Abar","given":"L."},{"family":"Chan","given":"Dsm"}, {"family":"Vingeliene","given":"S."},{"family":"Polemiti","given":"E."},{"family":"Stevens","given":"C."}, {"family":"Greenwood","given":"D."},{"family":"Norat","given":"T."}],"issued":{"date-parts": [["2017",4,12]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
<w:r w:rsidRPr="009A0F49">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
<w:r w:rsidRPr="009A0F49">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>22–24</w:t>
</w:r>
<w:r w:rsidRPr="009A0F49">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
<w:r w:rsidRPr="00C90FBC">
<w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>], physical activity [</w:t>
</w:r>
<w:hyperlink w:anchor="_References" w:history="1">
<w:r w:rsidRPr="00F2237F">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="begin"/>
</w:r>
<w:r w:rsidRPr="00F2237F">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"X2cG7I0Q","properties": {"formattedCitation":"\\super 25\\nosupersub{}","plainCitation":"25","noteIndex":0},"citationItems":[{"id":113,"uris": ["http://zotero.org/users/2724931/items/348EDKUN"],"uri":["http://zotero.org/users/2724931/items/348EDKUN"],"itemData": {"id":113,"type":"article-journal","title":"Association between physical activity and colorectal cancer risk and prognosis: A meta-analysis","container-title":"Cancer Treatment and Research Communications","page":"62-69","volume":"9","abstract":"Abstract\nReverse correlation has been frequently reported between physical activity (PA) and colorectal cancer (CRC) risk and mortality in numerous prospective studies. But the contradictive results make the conclusion elusive. Here we aim to cover the effects of pre-diagnosis in CRC incidence, pre- and post-diagnosis with CRC prognosis and overall mortality. With the eligible prospective studies up to 2015, the associations of pre-diagnosis or post-diagnosis PA with CRC risk, CRC prognosis, or all-cause mortality in the modes of exerciser Vs. non-exerciser and highest PA Vs. lowest PA were investigated by combing the hazard ratios (HRs) in random effects. We also tested the effect of single study on the summary estimates using influence-analysis. Publication bias was evaluated by Egger's and Begg's test. Compared with low pre-diagnosis PA group, the high PA group displayed a reduced risk (HR: 0.78 0.66–0.92) to develop CRC. Our findings also showed that both pre- and post-diagnosis PA were significantly associated with better CRC-specific prognosis and reduced risk of overall mortality in both exerciser Vs. non-exerciser and high PA Vs. low PA modes. With the most updated prospective studies, our systematic meta-analysis confirmed the beneficial effects of PA to CRC incidence and prognosis.","DOI":"10.1016/j.ctarc.2016.07.002","ISSN":"2468-2942","journalAbbreviation":"Cancer Treatment and Research</w:instrText>
</w:r>

Communications","author":[{"family":"Zhou","given":"Xiao-Yi"},{"family":"Yan","given":"Lei"},
{"family":"Wang","given":"Li-Li"},{"family":"Wang","given":"Jun"}],"issued":{"date-parts":
[["2016"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>25</w:t>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>], smoking [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="begin"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gdq06VHO","properties":
{"formattedCitation":"\\super 9,26\\nosupersub{}","plainCitation":"9,26","noteIndex":0},"citationItems":[{"id":199,"uris":
["http://zotero.org/users/2724931/items/DNH95VZT"],"uri":["http://zotero.org/users/2724931/items/DNH95VZT"],"itemData":
{"id":199,"type":"article-journal","title":"Colon cancer","container-title":"Critical Reviews in
Oncology/Hematology","page":"106-133","volume":"74","issue":"2","abstract":"Colon cancer is one of the leading tumours in
the world and it is considered among the big killers, together with lung, prostate and breast cancer. In the recent years very
important advances occurred in the field of treatment of this frequent disease: adjuvant chemotherapy was demonstrated to be
effective, chiefly in stage III patients, and surgery was optimized in order to achieve the best results with a low morbidity.
Several new target-oriented drugs are under evaluation and some of them (cetuximab and bevacizumab) have already exhibited a
good activity/efficacy, mainly in combination with chemotherapy. The development of updated recommendations for the best
management of these patients is crucial in order to obtain the best results, not only in clinical research but also in every-day
practice. This report summarizes the most important achievements in this field and provides the readers useful suggestions for
their professional practice.","DOI":"10.1016/j.critrevonc.2010.01.010","ISSN":"1040-8428","journalAbbreviation":"Critical
Reviews in Oncology/Hematology","author":[{"family":"Labianca","given":"Roberto"},{"family":"Beretta","given":"Giordano
D."},{"family":"Kildani","given":"Basem"},{"family":"Milesi","given":"Laura"},{"family":"Merlin","given":"Federica"},
{"family":"Mosconi","given":"Stefania"},{"family":"Pessi","given":"M. Adelaide"},{"family":"Prochilo","given":"Tiziana"},
{"family":"Quadri","given":"Antonello"},{"family":"Gatta","given":"Gemma"},{"family":"Braud","given":"Filippo","non-
dropping-particle":"de"},{"family":"Wils","given":"Jacques"}],"issued":{"date-parts":[["2010",5]]}}},{"id":112,"uris":
["http://zotero.org/users/2724931/items/NAI5BBRR"],"uri":["http://zotero.org/users/2724931/items/NAI5BBRR"],"itemData":
{"id":112,"type":"article-journal","title":"Cigarette Smoking and the Risk of Colorectal Cancer: A Meta-analysis of Prospective
Cohort Studies","container-title":"Clinical Gastroenterology and Hepatology","page":"682-
688.e5","volume":"7","issue":"6","abstract":"Background & Aims\nSmoking has been implicated in many malignant
diseases, but its association with colorectal cancer (CRC) is controversial. We quantitatively evaluated the relation between
smoking and incidence of CRC in a meta-analysis of cohort studies.\nMethods\nFull publications of prospective cohort studies

were identified in MEDLINE and EMBASE from 1950 to 2008. Subjects were classified as current smokers, former smokers, or never smokers. The quantity of smoking was assessed by number of cigarettes per day, years of smoking, and pack-years. The reported relative risks of CRC were pooled by random-effects model. Sensitivity analysis was conducted, and publication bias was evaluated.\nResults\nA total of 1,463,796 subjects were recruited in 28 prospective cohorts from America, Europe, and Asia, with median follow-up of 13 years (range, 4–30 years). Current smokers showed a modestly higher risk of CRC (relative risk [RR], 1.20; 95% confidence interval [CI], 1.10–1.30) than never smokers. The risk of CRC among male smokers (RR, 1.38; 95% CI, 1.22–1.56) was more significant than among female smokers (RR, 1.06; 95% CI, 0.95–1.19). Rectal cancer was more closely related to smoking (RR, 1.36; 95% CI, 1.15–1.61) than colonic cancer. Former smokers still carried a higher CRC risk than never smokers. The increased risk of CRC was related to cigarettes per day, longer years of smoking, or larger pack-years.\nConclusions\nSmoking was associated with a significantly increased risk of CRC. The associated risk was higher for men and for rectal cancers. The association of tobacco consumption and CRC risk appeared to be dose-related.","DOI":"10.1016/j.cgh.2009.02.016","ISSN":"1542-3565","journalAbbreviation":"Clinical Gastroenterology and Hepatology","author":[{"family":"Tsoi","given":"Kelvin K.F."},{"family":"Pau","given":"Carol Y.Y."},{"family":"Wu","given":"William K.K."},{"family":"Chan","given":"Francis K.L."},{"family":"Griffiths","given":"Sian"},{"family":"Sung","given":"Joseph J.Y."}],"issued":{"date-parts":[["2009",6]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>

```
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>9, 26</w:t>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>], type 2 diabetes mellitus [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"6Rv1D5wJ","properties":{"formattedCitation":"\\super 27\\nosupersub{}","plainCitation":"27","noteIndex":0},"citationItems":[{"id":184,"uris":["http://zotero.org/users/2724931/items/UESI3VJU"],"uri":["http://zotero.org/users/2724931/items/UESI3VJU"],"itemData":{"id":184,"type":"article-journal","title":"Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation","container-title":"Scientific Reports","page":"46527","volume":"7","abstract":"Type 2 diabetes mellitus (T2DM) is associated with greater risk for colorectal cancer (CRC). The age of onset of T2DM is decreasing worldwide. An increased CRC risk in young T2DM patients could be relevant for the age at which to initiate CRC screening. We report on CRC risk in T2DM patients with attention to age of diagnosis. We used pharmacy data (from 1998 to 2010) from the PHARMO Database Network linked to the Eindhoven Cancer Registry. Multivariable time-dependent Cox regression analyses were conducted to calculate hazard ratios (HR) for developing CRC comparing T2DM with non-T2DM. During 2,599,925 years of follow-up, 394 CRC cases among 41,716 diabetes patients
```

(mean age 64.0 yr, 48% men) and 1,939 CRC cases among 325,054 non-diabetic patients (mean age 51.2 yr, 46% men) were identified. Diabetes was associated with an increased CRC risk in both men and women (HR 1.3, 95% CI 1.2–1.5), particularly in the first 6 months after T2DM diagnosis and pronounced in the proximal colon. This risk was even higher in men younger than 55 years (HR 2.0, 95% CI 1.0–3.8). T2DM was associated with a time-varying and subsite-specific increased CRC risk, which was even higher in men aged <55 years.","DOI":"10.1038/srep46527","ISSN":"2045-2322","journalAbbreviation":"Scientific Reports","author":[{"family":"Kort","given":"Sander","dropping-particle":"de"},{"family":"Masclee","given":"Ad A. M."},{"family":"Sanduleanu","given":"Silvia"},{"family":"Weijenberg","given":"Matty P."},{"family":"Herk-Sukel","given":"Myrthe P. P.","dropping-particle":"van"},{"family":"Oldenhof","given":"Nico J. J."},{"family":"Bergh","given":"Joop P. W.","dropping-particle":"van den"},{"family":"Haak","given":"Harm R."},{"family":"Janssen-Heijnen","given":"Maryska L."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

```
                </w:instrText>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
              </w:rPr>
              <w:fldChar w:fldCharType="separate"/>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
              </w:rPr>
              <w:t>27</w:t>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
              </w:rPr>
              <w:fldChar w:fldCharType="end"/>
            </w:r>
        </w:hyperlink>
    - <w:r w:rsidRPr="00C90FBC">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t>], and metabolic syndrome [</w:t>
        </w:r>
    - <w:hyperlink w:anchor="_References" w:history="1">
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
              </w:rPr>
              <w:fldChar w:fldCharType="begin"/>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
              </w:rPr>
              <w:
```

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"DXlULFJS","properties":{"formattedCitation":"\\super 28\\nosupersub{}","plainCitation":"28","noteIndex":0},"citationItems":[{"id":297,"uris":["http://zotero.org/users/2724931/items/E5G7NVFR"],"uri":["http://zotero.org/users/2724931/items/E5G7NVFR"],"itemData":{"id":297,"type":"article-journal","title":"Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.","container-title":"Endocrine","page":"634-647","volume":"44","issue":"3","abstract":"We performed a systematic review and meta-analysis of the empirical evidence on the association of metabolic syndrome and its components with colorectal cancer incidence and mortality. A systematic literature search of multiple electronic databases was conducted and complemented by cross-referencing to identify studies published before 31 October 2012. Every included study was to report risk estimates with 95 % confidence intervals for the association between metabolic syndrome and colorectal cancer (incidence or mortality). Core items of identified studies were independently extracted by two reviewers, and results were summarized by standard methods of meta-analysis. We identified 17 studies, which reported on 49 data sets with 11,462 cancer cases. Metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality in both men (RR: 1.33, 95 % CI 1.18-1.50, and 1.36, 1.25-1.48, respectively) and women (RR: 1.41, 1.18-1.70, and 1.16, 1.03-1.30, respectively). The risk estimates changed little depending on type of study (cohort vs non cohort), populations (US, Europe, Asia), cancer site (colon and rectum), or definition of the syndrome. The risk estimates for any single factor of the syndrome were significant for higher values of BMI/waist (RR: 1.19, 95 % CI 1.10-1.28), dysglycemia (RR: 1.29, 1.11-1.49), and higher blood pressure (RR:

1.09, 1.01-1.18). Dysglycemia and/or higher BMI/waist explained most of the risk associated with metabolic syndrome. Metabolic syndrome is associated with an increased risk of colorectal cancer incidence and mortality in both sexes. The risk conveyed by the full syndrome is not superior to the sum of its parts.","DOI":"10.1007/s12020-013-9939-5","ISSN":"1559-0100 1355-008X","note":"PMID: 23546613","journalAbbreviation":"Endocrine","language":"eng","author": [{"family":"Esposito","given":"Katherine"},{"family":"Chiodini","given":"Paolo"},{"family":"Capuano","given":"Annalisa"}, {"family":"Bellastella","given":"Giuseppe"},{"family":"Maiorino","given":"Maria Ida"}, {"family":"Rafaniello","given":"Concetta"},{"family":"Panagiotakos","given":"Demosthenes B."}, {"family":"Giugliano","given":"Dario"}],"issued":{"date-parts":[["2013",12]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>

</w:r>

- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
    <w:rStyle w:val="Hyperlink"/>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
    <w:rStyle w:val="Hyperlink"/>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t>28</w:t>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
    <w:rStyle w:val="Hyperlink"/>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:color w:val="auto"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t>]. This latter has been suggested to be associated with risk of developing colorectal neoplasia (CRN) including colorectal adenoma (CRA) and CRC in several epidemiological studies that endeavored to address this issue, though the results were inconsistent [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="begin"/>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
    <w:rStyle w:val="Hyperlink"/>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"QNcXyrBs","properties": {"formattedCitation":"\\super 28\\uc0\\u8211{}30\\nosupersub{}","plainCitation":"28–30","noteIndex":0},"citationItems": [{"id":297,"uris":["http://zotero.org/users/2724931/items/E5G7NVFR"],"uri": ["http://zotero.org/users/2724931/items/E5G7NVFR"],"itemData":{"id":297,"type":"article-journal","title":"Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.","container-title":"Endocrine","page":"634-647","volume":"44","issue":"3","abstract":"We performed a systematic review and meta-analysis of the empirical evidence on the association of metabolic syndrome and its components with colorectal cancer incidence and mortality. A systematic literature search of multiple electronic databases was conducted and complemented by cross-referencing to identify studies published before 31 October 2012. Every included study was to report risk estimates with 95 % confidence intervals for the association between metabolic syndrome and colorectal cancer (incidence or mortality). Core items of identified studies were independently extracted by two reviewers, and results were summarized by standard methods of meta-analysis. We identified 17 studies, which reported on 49 data sets with 11,462 cancer cases. Metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality in both men (RR: 1.33, 95 % CI 1.18-1.50, and 1.36, 1.25-1.48, respectively) and women (RR: 1.41, 1.18-1.70, and 1.16, 1.03-1.30, respectively). The risk estimates changed little depending on type of study (cohort vs non cohort), populations (US, Europe, Asia), cancer site (colon and rectum), or definition of the syndrome. The risk estimates for any single factor of the syndrome were significant for higher values of BMI/waist (RR: 1.19, 95 % CI 1.10-1.28), dysglycemia (RR: 1.29, 1.11-1.49), and higher blood pressure (RR: 1.09, 1.01-1.18). Dysglycemia and/or

higher BMI/waist explained most of the risk associated with metabolic syndrome. Metabolic syndrome is associated with an increased risk of colorectal cancer incidence and mortality in both sexes. The risk conveyed by the full syndrome is not superior to the sum of its parts.","DOI":"10.1007/s12020-013-9939-5","ISSN":"1559-0100 1355-008X","note":"PMID: 23546613","journalAbbreviation":"Endocrine","language":"eng","author":[{"family":"Esposito","given":"Katherine"},{"family":"Chiodini","given":"Paolo"},{"family":"Capuano","given":"Annalisa"},{"family":"Bellastella","given":"Giuseppe"},{"family":"Maiorino","given":"Maria Ida"},{"family":"Rafaniello","given":"Concetta"},{"family":"Panagiotakos","given":"Demosthenes B."},{"family":"Giugliano","given":"Dario"}],"issued":{"date-parts":[["2013",12]]}},{"id":252,"uris":["http://zotero.org/users/2724931/items/STQDJB38"],"uri":["http://zotero.org/users/2724931/items/STQDJB38"],"itemData":{"id":252,"type":"article-journal","title":"Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can)","container-title":"Cancer","page":"2398-2407","volume":"117","issue":"11","abstract":"BACKGROUND:: The metabolic syndrome (MetS) has been related to an increased risk of colorectal cancer, but the modest size of previous studies precluded detailed characterization of the role of individual MetS factors and their interaction on risk. \nMETHODS:: In the Metabolic Syndrome and Cancer Project (Me-Can), data on body mass index (BMI), blood pressure, and blood levels of glucose, cholesterol, and triglycerides were available for 578,700 men and women. The mean age of participants at baseline was 44 years, and the mean follow-up was 12 years. Relative risks (RR) of colorectal cancer per 1 standard deviation increment in Z score of factors and for a combined MetS score, were calculated from Cox regression models, including adjustment for potential confounders.\nRESULTS:: During follow-up, 2834 men and 1861 women were diagnosed with colorectal cancer. The RR of colorectal cancer for the MetS score was 1.25 (95% confidence interval [CI], 1.18-1.32) in men, and 1.14 (95% CI, 1.06-1.22) in women. Significant associations also were observed in men for BMI (RR, 1.07; 95% CI, 1.02-1.13), blood pressure (RR, 1.10; 95% CI, 1.02-1.18), and triglycerides (RR, 1.17; 95% CI, 1.06-1.28) and, in women, for BMI (RR, 1.08; 95% CI, 1.01-1.15). There was no significant positive interaction between the metabolic factors on risk.\nCONCLUSIONS:: The combination of metabolic factors and some separate factors was related to an increased risk of colorectal cancer, but there was no interaction between metabolic factors. Cancer 2011;. © 2010 American Cancer Society.","DOI":"10.1002/cncr.25772","ISSN":"1097-0142","journalAbbreviation":"Cancer","author":[{"family":"Stocks","given":"Tanja"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Bjørge","given":"Tone"},{"family":"Ulmer","given":"Hanno"},{"family":"Manjer","given":"Jonas"},{"family":"Almquist","given":"Martin"},{"family":"Concin","given":"Hans"},{"family":"Engeland","given":"Anders"},{"family":"Hallmans","given":"Göran"},{"family":"Nagel","given":"Gabriele"},{"family":"Tretli","given":"Steinar"},{"family":"Veierød","given":"Marit B."},{"family":"Jonsson","given":"Håkan"},{"family":"Stattin","given":"Pär"},{"literal":"for the Metabolic Syndrome Cancer Project (Me-Can) Group"}],"issued":{"date-parts":[["2011",6,1]]}},{"id":149,"uris":["http://zotero.org/users/2724931/items/NE2556PD"],"uri":["http://zotero.org/users/2724931/items/NE2556PD"],"itemData":{"id":149,"type":"article-journal","title":"The Association between Metabolic Syndrome and Colorectal Neoplasm: Systemic review and Meta-analysis","container-title":"Journal of clinical gastroenterology","page":"33-44","volume":"47","issue":"1","source":"PubMed Central","abstract":"Background\nThere has been constant speculation about the association between metabolic syndrome (MetS) and colorectal neoplasia (CN); however, the published results are conflicting. The aims of this study are to systematic search, and assess literature to determine the available evidence on the association between these two conditions.\n\nMethods\nMeta-analysis was conducted based on relevant studies identified through a systematic literature review from PubMed, OvidSP and Cochrane database during January 1980 to July 2011. A combined analysis was performed, followed by a subgroup analyses stratified by the study design, type of colorectal lesions and gender. Publication bias was assessed using the Begg's and Egger's tests and visual inspection of funnel plot.\n\nResults\nEighteen studies were included in the final analysis. Overall, MetS was associated with 34% increase in the risk of CN (summary RR - 1.34, 95% CI 1.24–1.44). The association between MetS and CN was found to be statistically significant in separate analysis for both case-control studies (summary RR -1.58, 95% CI 1.44–1.79) and cohort studies (summary RR – 1.21, 95% CI 1.13–1.29). The association remained significant when analyses were restricted by type of colorectal lesions (colorectal cancer: RR – 1.30, 95% CI 1.18–1.43; colorectal adenoma: RR – 1.37, 95% CI 1.26–1.49). Further subgroup analysis by gender showed significant association between MetS and CN in both male and female population.\n\nConclusion\nOur meta-analysis showed significant association between presence of MetS and CN. These results may help in identifying high risk individuals at early stage that might benefit from targeted CRC screening intervention.","DOI":"10.1097/MCG.0b013e3182688c15","ISSN":"0192-0790","note":"PMID: 23090040\nPMCID: PMC3518571","shortTitle":"The Association between Metabolic Syndrome and Colorectal Neoplasm","journalAbbreviation":"J Clin Gastroenterol","author":[{"family":"Jinjuvadia","given":"Raxitkumar"},{"family":"Lohia","given":"Prateek"},{"family":"Jinjuvadia","given":"Chetna"},{"family":"Montoya","given":"Sergio"},{"family":"Liangpunsakul","given":"Suthat"}],"issued":{"date-parts":[["2013",1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>

```
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>28</w:t>
</w:r>
- <w:r w:rsidRPr="00DC120B">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
      <w:u w:val="none"/>
    </w:rPr>
```

```
                <w:t>–</w:t>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>30</w:t>
        </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:fldChar w:fldCharType="end"/>
        </w:r>
    </w:hyperlink>
- <w:r w:rsidRPr="00C90FBC">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>]. In addition, the implication of each metabolic condition comprising the MetS in the carcinogenesis process remains ambiguous. We aimed to tackle those issues in our meta-analysis focusing especially on the study of the effect of each component of the MetS on developing both CRA and CRC.</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="000B613A" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="53B4D735" w:rsidRPr="000B613A">
    - <w:pPr>
        <w:pStyle w:val="ListParagraph"/>
        <w:keepNext/>
        <w:keepLines/>
    - <w:numPr>
        <w:ilvl w:val="0"/>
        <w:numId w:val="21"/>
    </w:numPr>
    <w:spacing w:lineRule="auto" w:line="259" w:after="220" w:before="200"/>
    <w:ind w:right="-29" w:left="567"/>
    <w:jc w:val="left"/>
    <w:outlineLvl w:val="1"/>
    - <w:rPr>
        <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
        <w:b/>
        <w:caps/>
        <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
    </w:rPr>
    </w:pPr>
- <w:r w:rsidRPr="002233CE">
    - <w:rPr>
        <w:noProof/>
    </w:rPr>
    - <mc:AlternateContent>
        - <mc:Choice Requires="wps">
            - <w:drawing>
                - <wp:anchor wp14:editId="08DBCC59" wp14:anchorId="4AED3374" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251687936" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
                    <wp:simplePos y="0" x="0"/>
                - <wp:positionH relativeFrom="column">
                    <wp:posOffset>172085</wp:posOffset>
                </wp:positionH>
                - <wp:positionV relativeFrom="paragraph">
                    <wp:posOffset>345135</wp:posOffset>
                </wp:positionV>
                <wp:extent cx="2711450" cy="0"/>
                <wp:effectExtent r="31750" b="19050" t="0" l="0"/>
                <wp:wrapNone/>
                <wp:docPr id="7" name="Straight Connector 7"/>
                <wp:cNvGraphicFramePr/>
                - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
                    - <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
                        - <wps:wsp>
                            <wps:cNvCnPr/>
                        - <wps:spPr>
                            - <a:xfrm flipV="1">
                                <a:off y="0" x="0"/>
```

<a:ext cx="2711450" cy="0"/>
</a:xfrm>
- <a:prstGeom prst="line">
<a:avLst/>
</a:prstGeom>
<a:ln/>
</wps:spPr>
- <wps:style>
- <a:lnRef idx="1">
<a:schemeClr val="accent6"/>
</a:lnRef>
- <a:fillRef idx="0">
<a:schemeClr val="accent6"/>
</a:fillRef>
- <a:effectRef idx="0">
<a:schemeClr val="accent6"/>
</a:effectRef>
- <a:fontRef idx="minor">
<a:schemeClr val="tx1"/>
</a:fontRef>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:line w14:anchorId="689D31CE" id="Straight Connector 7" strokeweight=".5pt"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQCnljArxAEAANQDAAAOAAAAZHJzL2Uyb0RvYy54bWysU02P0zAQvSPxHyzfaZIKtihquoeu4IKg
YoG71xk3lvylsWnSf8/YSQMChATiYsUz897Me57s7ydr2AUwau863mxqzsBJ32t37vjnT29evOYs
JuF6YbyDjl8h8vvD82f7MbSw9YM3PSAjEhfbMXR8SCm0VRXlAFbEjQ/gKKk8WpHoiueqRzESuzXV
tq7vqtFjH9BLiJGiD3OSHwq/UiDTB6UiJGY6TrOlcmI5n/JZHfaiPaMIg5bLGOIfprBCO2q6Uj2I
JNhX1L9QWS3RR6/SRnpbeaW0hKKB1DT1T2oeBxGgaCFzYlhtiv+PVr6/nJDpvuM7zpyw9ESPCYU+
D4kdvXNkoEe2yz6NIbZUfnQnXG4xnDCLnhRapowOX2gFig0kjE3F5evqMkyJSQpud03z8hU9hrzl
qpkiUwWM6S14y/JHx4122QDRisu7mKgtld5Kcti4HMuTzbOUr3Q1MCc/giJt1HOeqmwVHA2yi6B9
EFKCS3dZG9EaR9UZprQxK7Au3f8IXOozFMrG/Q14RZTO3qUVbLXz+LvuaWqWkdVcf3Ng1p0tePL9
tbxSsYZWpyhc1jzv5o/3Av/+Mx6+AQAA//8DAFBLAwQUAAYACAAAACEAhAzkQ+AAAAAIAQAADwAA
AGRycy9kb3ducmV2LnhtbEyP3UrDQBCF7wXfYRnBm9JuWpNWYjZFBJEi9afmATbJmASzsyG7aVef
3hEv9HLOOZz5TrYNphdHHF1nScFyEYFAqmzdUaOgeLufX4NwXlOte0uo4BMdbPPzs0yntT3RKx4P
vhFcQi7VClrvh1RKV7VotFvYAYm9dzsa7fkcG1mP+sTlpperKFpLozviD60e8K7F6uMwGQW7zdVX
eAlDkzwVxe559vrYGhMfg/8Lwg8/okDNTaSeqnegVrDZLTipI4hgE+CjLP
5P8B+TcAAAD//wMAUEsBAi0AFAAGAAgAAAAhALaDOJL+AAAA4QEAABMAAAAAAAAAAAAAAAAAAAAAA
AFtDb250ZW50X1R5cGVzXS54bWxQSwECLQAUAAYACAAAACEAOP0h/9YAAACUAQAACwAAAAAAAAAA
AAAAAAAvAQAAX3JlbHMvLnJlbHNQSwECLQAUAAYACAAAACEAp5YwK8QBAADUAwAADgAAAAAAAAAA
AAAAAAAuAgAAZHJzL2Uyb0RvYy54bWxQSwECLQAUAAYACAAAACEAhAzkQ+AAAAAIAQAADwAAAAAA
AAAAAAAAAAAeBAAAZHJzL2Rvd25yZXYueG1sUEsFBgAAAAAEAAQA8wAAACsFAAAAAA== "
style="position:absolute;flip:y;z-index:251687936;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:text;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-relative:margin;mso-height-relative:margin" o:spid="_x0000_s1026" strokecolor="#70ad47 [3209]"
to="227.05pt,27.2pt" from="13.55pt,27.2pt">
<v:stroke joinstyle="miter"/>
</v:line>
</w:pict>
</mc:Fallback>
</mc:AlternateContent>
</w:r>
- <w:r w:rsidRPr="000B613A">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:caps/>

```
                    <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
                </w:rPr>
                <w:t>MateriAl and Methods</w:t>
            </w:r>
        </w:p>
- <w:p w:rsidP="000B613A" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="5BB0DCBA"
    w:rsidRPr="000732DD">
    - <w:pPr>
            <w:pStyle w:val="Heading3"/>
        - <w:numPr>
                <w:ilvl w:val="1"/>
                <w:numId w:val="21"/>
            </w:numPr>
            <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
            <w:ind w:right="-29" w:left="567"/>
            <w:jc w:val="left"/>
        - <w:rPr>
                <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="000000"/>
                <w:sz w:val="20"/>
                <w:szCs w:val="22"/>
            </w:rPr>
        </w:pPr>
    - <w:r w:rsidRPr="000732DD">
        - <w:rPr>
                <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="000000"/>
                <w:sz w:val="20"/>
                <w:szCs w:val="22"/>
            </w:rPr>
            <w:t>Search strategy</w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="001D3AD1" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="2B10A88F">
    - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="250" w:after="120" w:before="120"/>
            <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
        </w:pPr>
    - <w:r w:rsidRPr="00E07084">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>A systematic literature search was carried out on the PubMed database for relevant studies examining the impact of any single component of MetS, i.e. (hypertension, hyperglycemia, dyslipidemia, and visceral obesity) on CRA and/or CRC incidence. Solely full English studies published up to June 2018 were considered and no population limitation was applied. The following Medical subject headings key terms were used: “triglycerides”, “</w:t>
        </w:r>
    - <w:r>
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve">HDL cholesterol”, “high-density </w:t>
        </w:r>
    - <w:r w:rsidRPr="00E07084">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>lipoprotein cholesterol”, “</w:t>
        </w:r>
    - <w:r w:rsidRPr="00695689">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:noProof/>
```

```
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>hyperglycaemia</w:t>
        </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">", </w:t>
    </w:r>
    - <w:r w:rsidRPr="00E07084">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>"hyperglycemia", "waist circumference", and "hypertension", in combination with "colorectal neoplasms", and "metabolic
            syndrome".</w:t>
    </w:r>
</w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="391F3963"
w:rsidRPr="000732DD">
    - <w:pPr>
        <w:pStyle w:val="Heading3"/>
        - <w:numPr>
            <w:ilvl w:val="1"/>
            <w:numId w:val="21"/>
        </w:numPr>
        <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
        <w:ind w:right="-29" w:left="567"/>
        <w:jc w:val="left"/>
        - <w:rPr>
            <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
            <w:b/>
            <w:bCs/>
            <w:color w:val="000000"/>
            <w:sz w:val="20"/>
            <w:szCs w:val="22"/>
        </w:rPr>
    </w:pPr>
    - <w:r w:rsidRPr="000732DD">
        - <w:rPr>
            <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
            <w:b/>
            <w:bCs/>
            <w:color w:val="000000"/>
            <w:sz w:val="20"/>
            <w:szCs w:val="22"/>
        </w:rPr>
        <w:t>Study selection</w:t>
    </w:r>
</w:p>
- <w:p w:rsidP="004F395F" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="7DE950B8">
    - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="250" w:after="80" w:before="80"/>
        <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
    </w:pPr>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">The inclusion criteria used to determine the eligibility of any individual retrieved study were as follows: a full
            English </w:t>
    </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
```

```
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t xml:space="preserve">published article, the study design was a cohort, case-control, or cross-sectional; CRA and/or CRC incidence as the outcome; the study must provide adequate data to estimate risk ratios (RR) and their 95% confidence intervals (CI) of CRA and/or CRC incidence among individuals with MetS and at least one of these parameters (high-density lipoprotein-cholesterol (HDL-C) concentrations, triglycerides (TG) values, fasting blood glucose levels (FBG), blood pressure (BP), and waist circumference measurements (WC)); the study must provide the MetS definition(s) used for diagnosis. Articles not published as full text such as case reports, letters, comments, editorials, news were excluded. In addition, review articles, meta-analyses, articles not published in English, and studies dealing with organisms other than humans or in vitro studies were also rejected. We examined titles, abstracts, and full texts to assess the studies relevance and to exclude studies unrelated to the topic. Relevant articles were subsequently examined based on the full text. Articles with inappropriate exposures or outcomes, with missing or inappropriate data, </w:t>
</w:r>
- <w:r w:rsidR="004F395F">
  - <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t xml:space="preserve">and </w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>stud</w:t>
</w:r>
- <w:r w:rsidR="004F395F">
  - <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>ies dealing with cancer biology or</w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t xml:space="preserve"> genetics were left out as well. Two authors (S.E and Y.T) independently performed the literature search and study selection, any disagreement found was resolved by returning to the author (M.B.K) who made the final decision.</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="7ACAA72A" w:rsidRPr="000732DD">
  - <w:pPr>
<w:pStyle w:val="Heading3"/>
  - <w:numPr>
<w:ilvl w:val="1"/>
<w:numId w:val="21"/>
</w:numPr>
<w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
<w:ind w:right="-29" w:left="567"/>
<w:jc w:val="left"/>
  - <w:rPr>
<w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000"/>
<w:sz w:val="20"/>
<w:szCs w:val="22"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="000732DD">
  - <w:rPr>
<w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000"/>
<w:sz w:val="20"/>
<w:szCs w:val="22"/>
</w:rPr>
<w:t>Data extraction and study quality assessment</w:t>
```

```
        </w:r>
    </w:p>
- <w:p w:rsidP="00B62C01" w:rsidRDefault="00DF7D5C" w:rsidR="00B62C01" w14:textId="77777777" w14:paraId="4B7BEE11">
    - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="250" w:after="0" w:before="80"/>
        <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
      - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
    </w:pPr>
    - <w:r w:rsidRPr="00466D76">
      - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>Data extraction was independently undertaken by (S.E and Y.T). Relevant data extracted from each included study involved the first author's name, the year of publication, the study location, the number of subjects, the type of the lesion, the number of events, characteristics of the studied population, and the definition of MetS used.</w:t>
    </w:r>
</w:p>
- <w:p w:rsidP="00B62C01" w:rsidRDefault="00DF7D5C" w:rsidR="00B62C01" w14:textId="77777777" w14:paraId="6C68ED19"
  w:rsidRPr="00466D76">
    - <w:pPr>
        <w:spacing w:lineRule="auto" w:line="250" w:after="80" w:before="0"/>
        <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
      - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
    </w:pPr>
    - <w:r w:rsidRPr="00466D76">
      - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>The meta-analysis was performed in conformity with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [</w:t>
    </w:r>
    - <w:hyperlink w:anchor="_References" w:history="1">
      - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:fldChar w:fldCharType="begin" w:fldLock="1"/>
      - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Yk0kUN8F","properties":
            {"formattedCitation":"\\super 31\\nosupersub{}","plainCitation":"31","noteIndex":0},"citationItems":[{"id":268,"uris":
            ["http://zotero.org/users/2724931/items/5UA8M5AE"],"uri":["http://zotero.org/users/2724931/items/5UA8M5AE"],"itemData":
            {"id":268,"type":"article-journal","title":"Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA
            Statement","container-title":"PLOS Medicine","page":"e1000097","volume":"6","issue":"7","source":"PLoS
            Journals","DOI":"10.1371/journal.pmed.1000097","ISSN":"1549-1676","shortTitle":"Preferred Reporting Items for Systematic
            Reviews and Meta-Analyses","journalAbbreviation":"PLOS Medicine","author":[{"family":"Moher","given":"David"},
            {"family":"Liberati","given":"Alessandro"},{"family":"Tetzlaff","given":"Jennifer"},{"family":"Altman","given":"Douglas G."},
            {"family":"Group","given":"The PRISMA"}],"issued":{"date-parts":[["2009",7,21]]}}}],"schema":"https://github.com/citation-
            style-language/schema/raw/master/csl-citation.json"} </w:instrText>
      - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
```

```
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>31</w:t>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00466D76">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>]. The methodological quality of the included studies was evaluated according to The Newcastle-Ottawa Scale (NOS) [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="begin"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WdKT7eO5","properties":
{"formattedCitation":"\\super 32\\nosupersub{}","plainCitation":"32","noteIndex":0},"citationItems":[{"id":751,"uris":
["http://zotero.org/users/2724931/items/G8TS9V3H"],"uri":["http://zotero.org/users/2724931/items/G8TS9V3H"],"itemData":
{"id":751,"type":"webpage","title":"The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in
meta-analyses","container-title":"Ottawa Hospital Research Institute","abstract":"Nonrandomised studies, including case-control
and cohort studies, can be challenging to implement and conduct. Assessment of the quality of such studies is essential for a
proper understanding of nonrandomised studies. The Newcastle-Ottawa Scale (NOS) is an ongoing collaboration between the
Universities of Newcastle, Australia and Ottawa, Canada. It was developed to assess the quality of nonrandomised studies with
its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-
analytic results. A 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the
study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-
control or cohort studies respectively. The goal of this project is to develop an instrument providing an easy and convenient tool
for quality assessment of nonrandomised studies to be used in a systematic review.\n\nThe face/content validity of the NOS has
been established based on a critical review of the items by several experts in the field who evaluated its clarity and completeness
for the specific task of assessing the quality of studies to be used in a meta-analysis. Also, the NOS has been refined based on
experience using it in several projects, in particular, a project assessing the association of CHD with hormone replacement
therapy in postmenopausal women and a project assessing the association of connective tissue disease with silicone breast
implants.\n\nThe evaluation of the NOS is currently in progress. Its content validity and inter-rater reliability have been
established. Its criterion validity with comparisons to more comprehensive but cumbersome scales and its intra-rater reliability
are currently being examined. An assessment plan is being formulated for evaluating its construct validity with consideration of
the theoretical relationship of the NOS to external criteria and the internal structure of the NOS
components.","URL":"http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp","author":
[{"family":"Wells","given":"GA"},{"family":"Shea","given":"B"},{"family":"O'Connell","given":"D"},
{"family":"Peterson","given":"J"},{"family":"Welch","given":"V"},{"family":"Losos","given":"M"},
{"family":"Tugwell","given":"P"}],"accessed":{"date-parts":[["2018",8,18]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
```

```
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="separate"/>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>32</w:t>
            </w:r>
        - <w:r w:rsidRPr="00F2237F">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="end"/>
            </w:r>
        </w:hyperlink>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>]. The NOS is a tool for assessing the quality of non-randomized studies which allocates a maximum of nine stars for each study on certain criteria including quality assessment of selection, comparability, exposure, and outcome.</w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="105CB9A4">
    - <w:pPr>
            <w:pStyle w:val="Heading3"/>
        - <w:numPr>
                <w:ilvl w:val="1"/>
                <w:numId w:val="21"/>
            </w:numPr>
            <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
            <w:ind w:right="-29" w:left="567"/>
            <w:jc w:val="left"/>
        - <w:rPr>
                <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="000000"/>
                <w:sz w:val="20"/>
                <w:szCs w:val="22"/>
            </w:rPr>
        </w:pPr>
    - <w:r w:rsidRPr="000732DD">
        - <w:rPr>
                <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
                <w:b/>
                <w:bCs/>
                <w:color w:val="000000"/>
                <w:sz w:val="20"/>
                <w:szCs w:val="22"/>
            </w:rPr>
            <w:t>Summary measures</w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="00B62C01" w:rsidRDefault="00B62C01" w:rsidR="00B62C01" w14:textId="77777777" w14:paraId="504A8F3C">
    - <w:pPr>
            <w:spacing w:after="120" w:before="120"/>
            <w:ind w:left="255"/>
        </w:pPr>
    - <w:r w:rsidRPr="00B62C01">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
```

```
<w:t xml:space="preserve">Mantel-Haenszel statistical method was used for dichotomous data. Risk ratios (RR) with their 95% confidence intervals were estimated. The fixed-effects meta-analysis model was used when no evidence of statistical heterogeneity was observed and random-effects meta-analysis model was applied when statistical heterogeneity was detected. The fixed-effects model </w:t>
</w:r>
- <w:r w:rsidRPr="00B62C01">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:lastRenderedPageBreak/>
    <w:t xml:space="preserve">assumes that only the chance is </w:t>
</w:r>
- <w:r w:rsidRPr="00B62C01">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>responsible</w:t>
</w:r>
- <w:r w:rsidRPr="00B62C01">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> for the differences between study results whilst </w:t>
</w:r>
- <w:r w:rsidRPr="00B62C01">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>the random</w:t>
</w:r>
- <w:r>
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>-</w:t>
</w:r>
- <w:r w:rsidRPr="00423094">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="00B62C01">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>effects meta-analysis model allows for the variations across studies of the effects being estimated and presumes that there is a distribution of these effects [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00B62C01">
    - <w:rPr>
```

```
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="begin"/>
            </w:r>
        - <w:r w:rsidRPr="00B62C01">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"koSYqJtI","properties":
                    {"formattedCitation":"\\super 33\\nosupersub{}","plainCitation":"33","noteIndex":0},"citationItems":[{"id":239,"uris":
                    ["http://zotero.org/users/2724931/items/29DLFVEG"],"uri":["http://zotero.org/users/2724931/items/29DLFVEG"],"itemData":
                    {"id":239,"type":"article-journal","title":"A basic introduction to fixed-effect and random-effects models for meta-
                    analysis","container-title":"Research Synthesis Methods","page":"97-111","volume":"1","issue":"2","abstract":"There are two
                    popular statistical models for meta-analysis, the fixed-effect model and the random-effects model. The fact that these two models
                    employ similar sets of formulas to compute statistics, and sometimes yield similar estimates for the various parameters, may lead
                    people to believe that the models are interchangeable. In fact, though, the models represent fundamentally different assumptions
                    about the data. The selection of the appropriate model is important to ensure that the various statistics are estimated correctly.
                    Additionally, and more fundamentally, the model serves to place the analysis in context. It provides a framework for the goals of
                    the analysis as well as for the interpretation of the statistics. In this paper we explain the key assumptions of each model, and then
                    outline the differences between the models. We conclude with a discussion of factors to consider when choosing between the two
                    models. Copyright © 2010 John Wiley & Sons, Ltd.","DOI":"10.1002/jrsm.12","ISSN":"1759-
                    2887","journalAbbreviation":"Res. Synth. Method","author":[{"family":"Borenstein","given":"Michael"},
                    {"family":"Hedges","given":"Larry V."},{"family":"Higgins","given":"Julian P.T."},{"family":"Rothstein","given":"Hannah
                    R."}],"issued":{"date-parts":[["2010",4,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-
                    citation.json"} </w:instrText>
            </w:r>
        - <w:r w:rsidRPr="00B62C01">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="separate"/>
            </w:r>
        - <w:r w:rsidRPr="00B62C01">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>33</w:t>
            </w:r>
        - <w:r w:rsidRPr="00B62C01">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="end"/>
            </w:r>
        </w:hyperlink>
    - <w:r w:rsidRPr="00B62C01">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>].</w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="5765D5A6" w:rsidRPr="000732DD">
    - <w:pPr>
            <w:pStyle w:val="Heading3"/>
        - <w:numPr>
                <w:ilvl w:val="1"/>
                <w:numId w:val="21"/>
            </w:numPr>
        </w:pPr>
        <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
        <w:ind w:right="-29" w:left="567"/>
        <w:jc w:val="left"/>
```

```
- <w:rPr>
    <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
    <w:b/>
    <w:bCs/>
    <w:color w:val="000000"/>
    <w:sz w:val="20"/>
    <w:szCs w:val="22"/>
  </w:rPr>
</w:pPr>
- <w:r w:rsidRPr="000732DD">
  - <w:rPr>
      <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
      <w:b/>
      <w:bCs/>
      <w:color w:val="000000"/>
      <w:sz w:val="20"/>
      <w:szCs w:val="22"/>
    </w:rPr>
    <w:t>Synthesis of results</w:t>
  </w:r>
</w:p>
- <w:p w:rsidP="003F1502" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="78C22DDF" w:rsidRPr="00466D76">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="250" w:after="80" w:before="0"/>
      <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>Tau-squared (Tau</w:t>
    </w:r>
  </w:r>
  - <w:r w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
        <w:vertAlign w:val="superscript"/>
      </w:rPr>
      <w:t>2</w:t>
    </w:r>
  - <w:r w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>) was obtained to estimate the between-study variance in the random effect model. Z-test of the null hypothesis, with no effect, was also obtained. Chi-squared test (Chi</w:t>
  </w:r>
  - <w:r w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
        <w:vertAlign w:val="superscript"/>
      </w:rPr>
      <w:t>2</w:t>
    </w:r>
  - <w:r w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
```

```
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>), which assesses whether observed differences in results are compatible</w:t>
        </w:r>
    - <w:r>
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve"> </w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>with chance alone, was measured to assess heterogeneity. A (</w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:i/>
                <w:iCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>P</</w:t>
        </w:r>
    - <w:r>
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:i/>
                <w:iCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve"> </w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>≤</w:t>
        </w:r>
    - <w:r>
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve"> </w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>0.05) was considered to indicate statistical significance. Besides, heterogeneity was assessed with the </w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
```

```
            <w:bCs/>
            <w:i/>
            <w:iCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>I</w:t>
    </w:r>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:i/>
            <w:iCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
            <w:vertAlign w:val="superscript"/>
        </w:rPr>
        <w:t>2</w:t>
    </w:r>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve"> statistic, which unlike the Chi</w:t>
    </w:r>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
            <w:vertAlign w:val="superscript"/>
        </w:rPr>
        <w:t>2</w:t>
    </w:r>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve> test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than
        sampling error [</w:t>
    </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
    - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:fldChar w:fldCharType="begin"/>
    </w:r>
    - <w:r w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WCQ2YQvT","properties":
            {"formattedCitation":"\\super 34,35\\nosupersub{}","plainCitation":"34,35","noteIndex":0},"citationItems":[{"id":274,"uris":
            ["http://zotero.org/users/2724931/items/5I4QCEPE"],"uri":["http://zotero.org/users/2724931/items/5I4QCEPE"],"itemData":
            {"id":274,"type":"article-journal","title":"Measuring inconsistency in meta-analyses","container-
            title":"BMJ","page":"557","volume":"327","issue":"7414","abstract":"Cochrane Reviews have recently started including the
            quantity I2 to help readers assess the consistency of the results of studies in meta-analyses. What does this new quantity mean,
            and why is assessment of heterogeneity so important to clinical practice? Systematic reviews and meta-analyses can provide
            convincing and reliable evidence relevant to many aspects of medicine and health care.1 Their value is especially clear when the
            results of the studies they include show clinically important effects of similar magnitude. However, the conclusions are less clear
            when the included studies have differing results. In an attempt to establish whether studies are consistent, reports of meta-
            analyses commonly present a statistical test of heterogeneity. The test seeks to determine whether there are genuine differences
```

underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity). However, the test is susceptible to the number of trials included in the meta-analysis. We have developed a new quantity, I2, which we believe gives a better measure of the consistency between trials in a meta-analysis. Assessment of the consistency of effects across studies is an essential part of meta-analysis. Unless we know how consistent the results of studies are, we cannot determine the generalisability of the findings of the meta-analysis. Indeed, several hierarchical systems for grading evidence state that the results of studies must be consistent or homogeneous to obtain the highest grading.2–4 Tests for heterogeneity are commonly used to decide on methods for combining studies and for concluding consistency or inconsistency of findings.5 6 But what does the test achieve in practice, and how should the resulting P values be interpreted? A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect. The usual test statistic …","DOI":"10.1136/bmj.327.7414.557","journalAbbreviation":"BMJ","author":[{"family":"Higgins","given":"Julian P T"},{"family":"Thompson","given":"Simon G"},{"family":"Deeks","given":"Jonathan J"},{"family":"Altman","given":"Douglas G"}],"issued":{"date-parts":[["2003",9,4]]}},{"id":273,"uris":["http://zotero.org/users/2724931/items/4DBAKQKA"],"uri":["http://zotero.org/users/2724931/items/4DBAKQKA"],"itemData":{"id":273,"type":"article-journal","title":"Quantifying heterogeneity in a meta-analysis","container-title":"Statistics in Medicine","page":"1539-1558","volume":"21","issue":"11","abstract":"The extent of heterogeneity in a meta-analysis partly determines the difficulty in drawing overall conclusions. This extent may be measured by estimating a between-study variance, but interpretation is then specific to a particular treatment effect metric. A test for the existence of heterogeneity exists, but depends on the number of studies in the meta-analysis. We develop measures of the impact of heterogeneity on a meta-analysis, from mathematical criteria, that are independent of the number of studies and the treatment effect metric. We derive and propose three suitable statistics: H is the square root of the

```
</w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:instrText>χ</w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:instrText xml:space="preserve">
```

2 heterogeneity statistic divided by its degrees of freedom; R is the ratio of the standard error of the underlying mean from a random effects meta-analysis to the standard error of a fixed effect meta-analytic estimate, and I2 is a transformation of H that describes the proportion of total variation in study estimates that is due to heterogeneity. We discuss interpretation, interval estimates and other properties of these measures and examine them in five example data sets showing different amounts of heterogeneity. We conclude that H and I2, which can usually be calculated for published meta-analyses, are particularly useful summaries of the impact of heterogeneity. One or both should be presented in published meta-analyses in preference to the test for heterogeneity. Copyright © 2002 John Wiley & Sons, Ltd.","DOI":"10.1002/sim.1186","ISSN":"1097-0258","journalAbbreviation":"Statist. Med.","author":[{"family":"Higgins","given":"Julian P. T."},{"family":"Thompson","given":"Simon G."}],"issued":{"date-parts":[["2002",6,15]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

```
</w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>34, 35</w:t>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
```

```
            </w:rPr>
            <w:t xml:space="preserve">]. </w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:i/>
            <w:iCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t>I</w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:i/>
            <w:iCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
            <w:vertAlign w:val="superscript"/>
          </w:rPr>
          <w:t>2</w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t xml:space="preserve"> values were interpreted as follows: 0-40% inconsistency may not be important, 40-70% may represent moderate heterogeneity,</w:t>
        </w:r>
    - <w:r w:rsidR="00E84C10">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t> and</w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t> ≥ 70% may represent considerable heterogeneity.</w:t>
        </w:r>
    </w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="4C66CBC8" w:rsidRPr="000732DD">
    - <w:pPr>
        <w:pStyle w:val="Heading3"/>
        - <w:numPr>
            <w:ilvl w:val="1"/>
            <w:numId w:val="21"/>
          </w:numPr>
        <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
        <w:ind w:right="-29" w:left="567"/>
        <w:jc w:val="left"/>
        - <w:rPr>
            <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
            <w:b/>
            <w:bCs/>
            <w:color w:val="000000"/>
            <w:sz w:val="20"/>
            <w:szCs w:val="22"/>
          </w:rPr>
        </w:pPr>
    - <w:r w:rsidRPr="000732DD">
        - <w:rPr>
```

```
                    <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
                    <w:b/>
                    <w:bCs/>
                    <w:color w:val="000000"/>
                    <w:sz w:val="20"/>
                    <w:szCs w:val="22"/>
                </w:rPr>
                <w:t>Publication bias</w:t>
            </w:r>
        </w:p>
    - <w:p w:rsidP="00D94EBD" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="1EA49698"
    w:rsidRPr="00466D76">
        - <w:pPr>
            <w:spacing w:lineRule="auto" w:line="250" w:after="80" w:before="0"/>
            <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
          - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
        </w:pPr>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve">Publication bias was assessed by a visual investigation of a potential asymmetry of funnel plots. </w:t>
        </w:r>
    - <w:r w:rsidRPr="00B07E60">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:noProof/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>Egger</w:t>
        </w:r>
    - <w:r w:rsidR="00B07E60">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:noProof/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>’s</w:t>
        </w:r>
    - <w:r w:rsidRPr="00B07E60">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:noProof/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve"> regression</w:t>
        </w:r>
    - <w:r w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:t xml:space="preserve"> test </w:t>
        </w:r>
    - <w:r w:rsidR="00D94EBD" w:rsidRPr="00466D76">
        - <w:rPr>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:bCs/>
                <w:color w:val="auto"/>
                <w:sz w:val="18"/>
```

```
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t>[</w:t>
        </w:r>
      - <w:hyperlink w:anchor="_References" w:history="1">
        - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
          - <w:rPr>
              <w:rStyle w:val="Hyperlink"/>
              <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
              <w:sz w:val="18"/>
              <w:szCs w:val="18"/>
            </w:rPr>
            <w:fldChar w:fldCharType="begin"/>
          </w:r>
        - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
          - <w:rPr>
              <w:rStyle w:val="Hyperlink"/>
              <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
              <w:sz w:val="18"/>
              <w:szCs w:val="18"/>
            </w:rPr>
            <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mQ6cbSxJ","properties":
              {"formattedCitation":"\\super 36\\nosupersub{}","plainCitation":"36","noteIndex":0},"citationItems":[{"id":717,"uris":
              ["http://zotero.org/users/2724931/items/X7ZTGGZL"],"uri":["http://zotero.org/users/2724931/items/X7ZTGGZL"],"itemData":
              {"id":717,"type":"article-journal","title":"Bias in meta-analysis detected by a simple, graphical test.","container-title":"BMJ :
              British Medical Journal","page":"629-634","volume":"315","issue":"7109","source":"PubMed Central","abstract":"OBJECTIVE:
              Funnel plots (plots of effect estimates against sample size) may be useful to detect bias in meta-analyses that were later
              contradicted by large trials. We examined whether a simple test of asymmetry of funnel plots predicts discordance of results
              when meta-analyses are compared to large trials, and we assessed the prevalence of bias in published meta-analyses. DESIGN:
              Medline search to identify pairs consisting of a meta-analysis and a single large trial (concordance of results was assumed if
              effects were in the same direction and the meta-analytic estimate was within 30% of the trial); analysis of funnel plots from 37
              meta-analyses identified from a hand search of four leading general medicine journals 1993-6 and 38 meta-analyses from the
              second 1996 issue of the Cochrane Database of Systematic Reviews. MAIN OUTCOME MEASURE: Degree of funnel plot
              asymmetry as measured by the intercept from regression of standard normal deviates against precision. RESULTS: In the eight
              pairs of meta-analysis and large trial that were identified (five from cardiovascular medicine, one from diabetic medicine, one
              from geriatric medicine, one from perinatal medicine) there were four concordant and four discordant pairs. In all cases
              discordance was due to meta-analyses showing larger effects. Funnel plot asymmetry was present in three out of four discordant
              pairs but in none of concordant pairs. In 14 (38%) journal meta-analyses and 5 (13%) Cochrane reviews, funnel plot asymmetry
              indicated that there was bias. CONCLUSIONS: A simple analysis of funnel plots provides a useful test for the likely presence of
              bias in meta-analyses, but as the capacity to detect bias will be limited when meta-analyses are based on a limited number of
              small trials the results from such analyses should be treated with considerable caution.","ISSN":"0959-8138","note":"PMID:
              9310563\nPMCID: PMC2127453","journalAbbreviation":"BMJ","author":[{"family":"Egger","given":"M."},{"family":"Davey
              Smith","given":"G."},{"family":"Schneider","given":"M."},{"family":"Minder","given":"C."}],"issued":{"date-parts":
              [["1997",9,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
          </w:r>
        - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
          - <w:rPr>
              <w:rStyle w:val="Hyperlink"/>
              <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
              <w:sz w:val="18"/>
              <w:szCs w:val="18"/>
            </w:rPr>
            <w:fldChar w:fldCharType="separate"/>
          </w:r>
        - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
          - <w:rPr>
              <w:rStyle w:val="Hyperlink"/>
              <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
              <w:sz w:val="18"/>
              <w:szCs w:val="18"/>
            </w:rPr>
            <w:t>36</w:t>
          </w:r>
        - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
          - <w:rPr>
              <w:rStyle w:val="Hyperlink"/>
              <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
              <w:sz w:val="18"/>
              <w:szCs w:val="18"/>
            </w:rPr>
            <w:fldChar w:fldCharType="end"/>
          </w:r>
        </w:hyperlink>
      - <w:r w:rsidR="00D94EBD" w:rsidRPR="00466D76">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t>]</w:t>
```

```
</w:r>
- <w:r w:rsidR="00D94EBD">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> </w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">and </w:t>
</w:r>
- <w:r w:rsidRPr="00B07E60">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>Begg</w:t>
</w:r>
- <w:r w:rsidR="00B07E60">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>’s</w:t>
</w:r>
- <w:r w:rsidRPr="00B07E60">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:noProof/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> rank</w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> correlation test </w:t>
</w:r>
- <w:r w:rsidR="00D94EBD" w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>[</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
```

```
            <w:fldChar w:fldCharType="begin"/>
        </w:r>
    - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mOr5xMbJ","properties":
            {"formattedCitation":"\\super 37\\nosupersub{}","plainCitation":"37","noteIndex":0},"citationItems":[{"id":720,"uris":
            ["http://zotero.org/users/2724931/items/7SZUTVK8"],"uri":["http://zotero.org/users/2724931/items/7SZUTVK8"],"itemData":
            {"id":720,"type":"article-journal","title":"Operating Characteristics of a Rank Correlation Test for Publication Bias","container-
            title":"Biometrics","page":"1088-1101","volume":"50","issue":"4","abstract":"An adjusted rank correlation test is proposed as a
            technique for identifying publication bias in a meta-analysis, and its operating characteristics are evaluated via simulations. The
            test statistic is a direct statistical analogue of the popular \"funnel-graph.\" The number of component studies in the meta-
            analysis, the nature of the selection mechanism, the range of variances of the effect size estimates, and the true underlying effect
            size are all observed to be influential in determining the power of the test. The test is fairly powerful for large meta-analyses with
            75 component studies, but has only moderate power for meta-analyses with 25 component studies. However, in many of the
            configurations in which there is low power, there is also relatively little bias in the summary effect size estimate. Nonetheless, the
            test must be interpreted with caution in small meta-analyses. In particular, bias cannot be ruled out if the test is not significant.
            The proposed technique has potential utility as an exploratory tool for meta-analysts, as a formal procedure to complement the
            funnel-graph.","DOI":"10.2307/2533446","ISSN":"0006341X, 15410420","author":[{"family":"Begg","given":"Colin B."},
            {"family":"Mazumdar","given":"Madhuchhanda"}],"issued":{"date-parts":[["1994"]]}}},"schema":"https://github.com/citation-
            style-language/schema/raw/master/csl-citation.json"} </w:instrText>
        </w:r>
    - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:fldChar w:fldCharType="separate"/>
        </w:r>
    - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:t>37</w:t>
        </w:r>
    - <w:r w:rsidR="00D94EBD" w:rsidRPr="00F2237F">
        - <w:rPr>
            <w:rStyle w:val="Hyperlink"/>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
          </w:rPr>
          <w:fldChar w:fldCharType="end"/>
        </w:r>
    </w:hyperlink>
- <w:r w:rsidR="00D94EBD" w:rsidRPr="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>]</w:t>
  </w:r>
- <w:r w:rsidR="00D94EBD">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t xml:space="preserve"> </w:t>
  </w:r>
- <w:r w:rsidR="00466D76">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:bCs/>
        <w:color w:val="auto"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
```

```
<w:t>for funnel plot asymmetry were performed afterward to investigate the small study effect and publication bias. The results were adjusted to publication bias using the trim and fill method [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ysWA9dKq","properties":{"formattedCitation":"\\super 38\\nosupersub{}","plainCitation":"38","noteIndex":0},"citationItems":[{"id":730,"uris":["http://zotero.org/users/2724931/items/6YE7FD9Q"],"uri":["http://zotero.org/users/2724931/items/6YE7FD9Q"],"itemData":{"id":730,"type":"article-journal","title":"Trim and Fill: A Simple Funnel-Plot–Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis","container-title":"Biometrics","page":"455-463","volume":"56","issue":"2","abstract":"Summary. We study recently developed nonparametric methods for estimating the number of missing studies that might exist in a meta-analysis and the effect that these studies might have had on its outcome. These are simple rank-based data augmentation techniques, which formalize the use of funnel plots. We show that they provide effective and relatively powerful tests for evaluating the existence of such publication bias. After adjusting for missing studies, we find that the point estimate of the overall effect size is approximately correct and coverage of the effect size confidence intervals is substantially improved, in many cases recovering the nominal confidence levels entirely. We illustrate the trim and fill method on existing meta-analyses of studies in clinical trials and psychometrics.","DOI":"10.1111/j.0006-341X.2000.00455.x","ISSN":"0006-341X","journalAbbreviation":"Biometrics","author":[{"literal":"Duval Sue"},{"literal":"Tweedie Richard"}],"issued":{"date-parts":[["2004",5,24]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="separate"/>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>38</w:t>
  </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="end"/>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPR="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>].</w:t>
  </w:r>
</w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="2B31FE04" w:rsidRPR="000732DD">
  - <w:pPr>
      <w:pStyle w:val="Heading3"/>
    - <w:numPr>
        <w:ilvl w:val="1"/>
        <w:numId w:val="21"/>
```

```
</w:numPr>
<w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
<w:ind w:right="-29" w:left="567"/>
<w:jc w:val="left"/>
- <w:rPr>
<w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000"/>
<w:sz w:val="20"/>
<w:szCs w:val="22"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="000732DD">
- <w:rPr>
<w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
<w:b/>
<w:bCs/>
<w:color w:val="000000"/>
<w:sz w:val="20"/>
<w:szCs w:val="22"/>
</w:rPr>
<w:t>Additional analyses</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00335B6D" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="37EAAD28"
w:rsidRPr="00874C1B">
- <w:pPr>
<w:pStyle w:val="Heading4"/>
- <w:numPr>
<w:ilvl w:val="2"/>
<w:numId w:val="21"/>
</w:numPr>
<w:spacing w:after="120" w:before="120"/>
<w:ind w:right="-29" w:left="709" w:hanging="426"/>
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:bCs/>
<w:i w:val="0"/>
<w:iCs w:val="0"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00874C1B">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:bCs/>
<w:i w:val="0"/>
<w:iCs w:val="0"/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>Sensitivity and subgroup analyses</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="003B60C7" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="410198DE">
- <w:pPr>
<w:spacing w:lineRule="auto" w:line="250" w:after="0" w:before="0"/>
<w:ind w:right="-29" w:left="245" w:firstLine="0"/>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00466D76">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>With the aim of evaluating the influence of each study on the risk estimates and the heterogeneity, we carried out sensitivity analyses by e</w:t>
```

```
</w:r>
- <w:r>
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">xcluding one dataset at a time. </w:t></w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">A pre-specified subgroup analyses according to study design (cohort, case-control, and cross-sectional), gender (men and women), MetS definition (NCEP-ATP III, IDF, the harmonized definition, and other definitions), study location (Asia, Europe, North America), </w:t></w:t>
</w:r>
- <w:r w:rsidR="003B57F8">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve">and </w:t></w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>cancer site (colon or rectal cancer) were performed in order to explore heterogeneity and differences between subgroups. The NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) definition was considered as the conventional</w:t>
</w:r>
- <w:r>
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t xml:space="preserve"> definition for MetS diagnosis. </w:t></w:t>
</w:r>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>Review Manager 5.3 program [</w:t></w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin" w:fldLock="1"/>
    </w:r>
  - <w:r w:rsidRPr="00F2237F">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
```

```
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HV6THFhk","properties":
  {"formattedCitation":"\\super 39\\nosupersub{}","plainCitation":"39","noteIndex":0},"citationItems":[{"id":240,"uris":
  ["http://zotero.org/users/2724931/items/ACAT2LHF"],"uri":["http://zotero.org/users/2724931/items/ACAT2LHF"],"itemData":
  {"id":240,"type":"book","title":"Review Manager (RevMan)","publisher":"Copenhagen: The Nordic Cochrane Centre, The
  Cochrane Collaboration","version":"5.3","issued":{"date-parts":[["2014"]]}}}],"schema":"https://github.com/citation-style-
  language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="separate"/>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>39</w:t>
  </w:r>
- <w:r w:rsidRPr="00F2237F">
  - <w:rPr>
      <w:rStyle w:val="Hyperlink"/>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:fldChar w:fldCharType="end"/>
  </w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00466D76">
  - <w:rPr>
      <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
      <w:bCs/>
      <w:color w:val="auto"/>
      <w:sz w:val="18"/>
      <w:szCs w:val="18"/>
    </w:rPr>
    <w:t>] was used for the meta-analysis, subgroup and sensitivity analyses. Publication bias analyses, test for identifying potential outliers
      and influential studies [</w:t>
</w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
  - <w:r w:rsidRPr="006C2F63">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:fldChar w:fldCharType="begin"/>
    </w:r>
  - <w:r w:rsidRPr="006C2F63">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2feFhusU","properties":
        {"formattedCitation":"\\super 40\\nosupersub{}","plainCitation":"40","noteIndex":0},"citationItems":[{"id":724,"uris":
        ["http://zotero.org/users/2724931/items/YXRXLX22"],"uri":["http://zotero.org/users/2724931/items/YXRXLX22"],"itemData":
        {"id":724,"type":"article-journal","title":"Outlier and influence diagnostics for meta-analysis","container-title":"Research
        Synthesis Methods","page":"112-125","volume":"1","issue":"2","abstract":"Abstract The presence of outliers and influential
        cases may affect the validity and robustness of the conclusions from a meta-analysis. While researchers generally agree that it is
        necessary to examine outlier and influential case diagnostics when conducting a meta-analysis, limited studies have addressed
        how to obtain such diagnostic measures in the context of a meta-analysis. The present paper extends standard diagnostic
        procedures developed for linear regression analyses to the meta-analytic fixed- and random/mixed-effects models. Three
        examples are used to illustrate the usefulness of these procedures in various research settings. Issues related to these diagnostic
        procedures in meta-analysis are also discussed. Copyright ? 2010 John Wiley & Sons,
        Ltd.","DOI":"10.1002/jrsm.11","ISSN":"1759-2879","journalAbbreviation":"Research Synthesis Methods","author":
        [{"literal":"Viechtbauer Wolfgang"},{"literal":"Cheung Mike W.-L."}],"issued":{"date-parts":
        [["2010",10,4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
    </w:r>
  - <w:r w:rsidRPr="006C2F63">
    - <w:rPr>
        <w:rStyle w:val="Hyperlink"/>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
```

```
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="separate"/>
            </w:r>
        - <w:r w:rsidRPr="006C2F63">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:t>40</w:t>
            </w:r>
        - <w:r w:rsidRPr="006C2F63">
            - <w:rPr>
                    <w:rStyle w:val="Hyperlink"/>
                    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                    <w:sz w:val="18"/>
                    <w:szCs w:val="18"/>
                </w:rPr>
                <w:fldChar w:fldCharType="end"/>
            </w:r>
    </w:hyperlink>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">] and </w:t>
    </w:r>
- <w:r w:rsidR="003B60C7">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t xml:space="preserve">Baujat plots (which illustrates </w:t>
    </w:r>
- <w:r w:rsidRPr="00466D76">
    - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
            <w:bCs/>
            <w:color w:val="auto"/>
            <w:sz w:val="18"/>
            <w:szCs w:val="18"/>
        </w:rPr>
        <w:t>studies that may contribute to overall heterogeneity) [</w:t>
    </w:r>
- <w:hyperlink w:anchor="_References" w:history="1">
    - <w:r w:rsidRPr="006C2F63">
        - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:fldChar w:fldCharType="begin"/>
        </w:r>
    - <w:r w:rsidRPr="006C2F63">
        - <w:rPr>
                <w:rStyle w:val="Hyperlink"/>
                <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
                <w:sz w:val="18"/>
                <w:szCs w:val="18"/>
            </w:rPr>
            <w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"OcbvypcV","properties":
                {"formattedCitation":"\\super 41\\nosupersub{}","plainCitation":"41","noteIndex":0},"citationItems":[{"id":726,"uris":
                ["http://zotero.org/users/2724931/items/W9DGEJY4"],"uri":["http://zotero.org/users/2724931/items/W9DGEJY4"],"itemData":
                {"id":726,"type":"article-journal","title":"A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials","container-title":"Statistics in Medicine","page":"2641-2652","volume":"21","issue":"18","abstract":"Abstract Heterogeneity can be a major component of meta-analyses and by virtue of that fact warrants investigation. Classic analysis methods, such as meta-regression, are used to explore the sources of heterogeneity. However, it may be difficult to apply such a method in complex cases or in the absence of an a priori hypothesis. This paper presents a graphical method to identify trials, groups of trials or groups of patients that are sources of heterogeneity. The contribution of these trials to the overall result can also be evaluated with this method. Each trial is represented by a dot on a 2D graph. The X-axis represents the contribution of the trial to the overall Cochran Q-test for heterogeneity. The Y-axis
```

represents the influence of the trial, defined as the standardized squared difference between the treatment effects estimated with and without the trial. This approach has been applied to data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) comprising 10850 patients in 65 randomized trials. The graphical method allowed us to identify trials that contributed considerably to the overall heterogeneity and had a strong influence on the overall result. It also provided useful information for the interpretation of heterogeneity in this meta-analysis. The proposed graphical method identifies trials that account for most of the heterogeneity without having to explore all possible sources of heterogeneity by subgroup analyses. This method can also be applied to identify types of patients that explain heterogeneity in the treatment effect. Copyright ? 2002 John Wiley & Sons, Ltd.","DOI":"10.1002/sim.1221","ISSN":"0277-6715","journalAbbreviation":"Statistics in Medicine","author":[{"literal":"Baujat Bertrand"},{"literal":"Mahé Cédric"},{"literal":"Pignon Jean-Pierre"},{"literal":"Hill Catherine"}],"issued":{"date-parts":[["2002",9,10]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

```
</w:instrText>
</w:r>
<w:r w:rsidRPr="006C2F63">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
<w:r w:rsidRPr="006C2F63">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>41</w:t>
</w:r>
<w:r w:rsidRPr="006C2F63">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
<w:r w:rsidRPr="00466D76">
<w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>] were conducted with R program (version 3.5.0) [</w:t>
</w:r>
<w:hyperlink w:anchor="_References" w:history="1">
<w:r w:rsidRPr="006C2F63">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="begin"/>
</w:r>
<w:r w:rsidRPr="006C2F63">
<w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:instrText xml:space="preserve"> ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WQieeZVw","properties":{"formattedCitation":"\\super 42,43\\nosupersub{}","plainCitation":"42,43","noteIndex":0},"citationItems":[{"id":739,"uris":["http://zotero.org/users/2724931/items/S2Q5V9MF"],"uri":["http://zotero.org/users/2724931/items/S2Q5V9MF"],"itemData":{"id":739,"type":"book","title":"R: A Language and Environment for Statistical Computing","publisher":"R Foundation for Statistical Computing","publisher-place":"Vienna, Austria","event-place":"Vienna, Austria","URL":"https://www.R-project.org/","author":[{"family":"R Core Team","given":""}],"issued":{"date-parts":[["2018"]]}}},{"id":740,"uris":["http://zotero.org/users/2724931/items/64SKTGNC"],"uri":["http://zotero.org/users/2724931/items/64SKTGNC"],"itemData":{"id":740,"type":"article-journal","title":"Conducting Meta-Analyses in R with the metafor Package","container-title":"Journal of Statistical Software; Vol 1, Issue 3 (2010)","abstract":"The metafor package provides functions for conducting meta-analyses in R . The package includes functions for fitting the meta-analytic fixed- and random-effects models and allows for the inclusion of moderators variables (study-level covariates) in these models. Meta-regression analyses with continuous and categorical moderators can be conducted in this way. Functions for the Mantel-Haenszel and Peto's one-step method for meta-analyses of 2 x 2 table data are also available. Finally, the package provides various plot functions (for example, for forest, funnel, and radial plots) and functions for assessing the model fit, for obtaining case diagnostics, and for tests of publication bias.","URL":"https://www.jstatsoft.org/v036/i03","author":
```

[{"family":"Viechtbauer","given":"Wolfgang"}],"issued":{"date-parts":[["2010",8,5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} </w:instrText>
</w:r>
- <w:r w:rsidRPr="006C2F63">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="separate"/>
</w:r>
- <w:r w:rsidRPr="006C2F63">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>42, 43</w:t>
</w:r>
- <w:r w:rsidRPr="006C2F63">
- <w:rPr>
<w:rStyle w:val="Hyperlink"/>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
</w:hyperlink>
- <w:r w:rsidRPr="00466D76">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
<w:bCs/>
<w:color w:val="auto"/>
<w:sz w:val="18"/>
<w:szCs w:val="18"/>
</w:rPr>
<w:t>].</w:t>
</w:r>
</w:p>
- <w:p w:rsidP="00D34FE2" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="75526578" w:rsidRPr="006169F2">
- <w:pPr>
<w:keepNext/>
<w:keepLines/>
- <w:numPr>
<w:ilvl w:val="0"/>
<w:numId w:val="21"/>
</w:numPr>
<w:spacing w:lineRule="auto" w:line="259" w:after="220" w:before="240"/>
<w:ind w:right="-29" w:left="567"/>
<w:jc w:val="left"/>
<w:outlineLvl w:val="1"/>
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:caps/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
</w:rPr>
</w:pPr>
- <w:r w:rsidRPr="00E75896">
- <w:rPr>
<w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:caps/>
<w:noProof/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
</w:rPr>
- <mc:AlternateContent>
- <mc:Choice Requires="wps">
- <w:drawing>
- <wp:anchor wp14:editId="41FAA748" wp14:anchorId="733B38B0" allowOverlap="1" layoutInCell="1" locked="0" behindDoc="0" relativeHeight="251688960" simplePos="0" distR="114300" distL="114300" distB="0" distT="0">
<wp:simplePos y="0" x="0" />
- <wp:positionH relativeFrom="column">
<wp:posOffset>172085</wp:posOffset>
</wp:positionH>
- <wp:positionV relativeFrom="paragraph">
<wp:posOffset>359740</wp:posOffset>
</wp:positionV>

<wp:extent cx="2711450" cy="0"/>
<wp:effectExtent r="31750" b="19050" t="0" l="0"/>
<wp:wrapNone/>
<wp:docPr name="Straight Connector 9" id="9"/>
<wp:cNvGraphicFramePr/>
- <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
- <a:graphicData uri="http://schemas.microsoft.com/office/word/2010/wordprocessingShape">
- <wps:wsp>
<wps:cNvCnPr/>
- <wps:spPr>
- <a:xfrm flipV="1">
<a:off y="0" x="0"/>
<a:ext cx="2711450" cy="0"/>
</a:xfrm>
- <a:prstGeom prst="line">
<a:avLst/>
</a:prstGeom>
<a:ln/>
</wps:spPr>
- <wps:style>
- <a:lnRef idx="1">
<a:schemeClr val="accent6"/>
</a:lnRef>
- <a:fillRef idx="0">
<a:schemeClr val="accent6"/>
</a:fillRef>
- <a:effectRef idx="0">
<a:schemeClr val="accent6"/>
</a:effectRef>
- <a:fontRef idx="minor">
<a:schemeClr val="tx1"/>
</a:fontRef>
</wps:style>
<wps:bodyPr/>
</wps:wsp>
</a:graphicData>
</a:graphic>
- <wp14:sizeRelH relativeFrom="margin">
<wp14:pctWidth>0</wp14:pctWidth>
</wp14:sizeRelH>
- <wp14:sizeRelV relativeFrom="margin">
<wp14:pctHeight>0</wp14:pctHeight>
</wp14:sizeRelV>
</wp:anchor>
</w:drawing>
</mc:Choice>
- <mc:Fallback>
- <w:pict>
- <v:line w14:anchorId="7386C9EF" id="Straight Connector 9" strokeweight=".5pt"
o:gfxdata="UEsDBBQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAW0NvbnRlbnRfVHlwZXNdLnhtbJSRQU7DM
90jcwfIWJU67QAgl6YK0S0CoHGBkTxKLZGx5TGhvj5O2G0SRWNoz/78nu9wcxkFMGNg6quQqL6RA
0s5Y6ir5vt9lD1JwBDIwOMJKHpHlpr69KfdHjyxSmriSfYz+USnWPY7AufNIadK6MEJMx9ApD/oD
OlTrorhX2lFEilmcO2RdNtjC5xDF9pCuTyYBB5bi6bQ4syoJ3g9WQ0ymaiLzg5KdCXlKLjvcW893
SUOqXwnz5DrgnHtJTxOsQfEKIT7DmDSUCaxw7Rqn8787ZsmRM9e2VmPeBN4uqYvTtW7jvijg9N/y
JsXecLq0q+WD6m8AAAD//wMAUEsDBBQABgAIAAAAIQA4/SH/1gAAAJQBAAALAAAAX3JlbHMvLnJl
bHOkkMFqwzAMhu+DvYPRfXGawxijTi+j0GvpHsDYimMaW0Yy2fr2M4PBMnrbUb/Q94l/f/hMi1qR
JVI2sOt6UJgd+ZiDgffL8ekFlFSbvV0oo4EbChzGx4f9GRdb25HMsYhqlCwG5lrLq9biZkxWOiqY
22YiTra2kYMu1l1tQD30/bPm3wwYN0x18gb45AdQl1tp5j/sFB2T0FQ7R0nTNEV3j6o9feQzro1i
OWA14Fm+Q8a1a8+Bvu/d/dMb2JY5uiPbhG/ktn4cqGU/er3pcvwCAAD//wMAUEsDBBQABgAIAAAA
IQBrY64MxQEAANQDAAAOAAAAZHJzL2Uyb0RvYy54bWysU02P0zAQvSPxHyzfaZIKFjZquoeu4IKg
YhfuXmfcWPKXxqZJ/z1jJw0IEBKIixXPzHsz73myu5usYWfAqL3reLOpOQMnfa/dqeOfH9++eMNZ
TML1wngHHb9A5Hf75892Y2hh6wdvekBGJC62Y+j4kFJoqyrKAayIGx/AUVJ5tCLRFU9Vj2Ikdmuq
bV3fVKPHPqCXECNF7+ck3xd+pUCmj0pFSMx0nGZL5cRyPuWz2u9Ee0IRBi2XMcQ/TGGFdtR0pboX
SbCvqH+hslqij16ljfS28kppCUUDqWnqn9Q8DCJA0ULmxLDaFP8frfxwPiLTfcdvOXPC0hM9JBT6
NCR28M6RgR7ZbfZpDLGl8oM74nKL4YhZ9KTQMmV0+EIrUGwgYWwqLl9Wl2FKTFJw+7ppXr6ix5DX
XDVTZKqAMb0Db1n+6LjRLhsgWnF+HxO1pdJrSQ4bl2N5snmW8pUuBubkJ1CkjXrOU5WtgoNBdha0
D0JKcOkmayNa46g6w5Q2ZgXWpfsfgUt12Hn/XPU3NMrKa668OzLqzBU++
v5RXKtbQ6hSFy5rn3fzxXuDff8b9NwAAAP//AwBQSwMEFAAGAAgAAAAhACCvDZTgAAAACAEAAA8A
AABkcnMvZG93bnJldi54bWxMj91Kw0AQhe8F32EZwZtiN61NIzGbIoJIEX/a5gE22TEJZmdDdtNG
n94RL/Ryzjmc+U62mWwnjjj41pGCxTwCgVQ501KtoDg8XN2A8EGT0Z0jVPCJHjb5+VmmU+NOtMPj
PtSCS8inWkETQp9K6asGrfZz1yOx9+4GqwOfQy3NoE9cbju5jKK1tLol/tDoHu8brD72o1WwTa6/
prepr+OXoti+zh6fZuNzqdTlxXR3CyLgFP7C8IPP6JAzU+lGMl50CpbJgpMK4nUCgv1VvGKh/BVk
nsn/A/JvAAAA//8DAFBLAQItABQABgAIAAAAIQC2gziS/gAAAOEBAAATAAAAAAAAAAAAAAAAAAAA
AABbQ29udGVudF9UeXBlc10ueG1sUEsBAi0AFAAGAAgAAAAhADj9If/WAAAAlAEAAAsAAAAAAAAA
AAAAAAAALwEAAF9yZWxzLy5yZWxzUEsBAi0AFAAGAAgAAAAhAGtjrgzFAQAA1AMAAA4AAAAAAAAA
AAAAAAAALgIAAGRycy9lMm9Eb2MueG1sUEsBAi0AFAAGAAgAAAAhACCvDZTgAAAACAEAAA8AAAAA
AAAAAAAAAAAAHwQAAGRycy9kb3ducmV2LnhtbFBLBQYAAAAABAAEAPMAAAAsBQAAAAA= "
style="position:absolute;flip:y;z-index:251688960;visibility:visible;mso-wrap-style:square;mso-width-percent:0;mso-height-percent:0;mso-wrap-distance-left:9pt;mso-wrap-distance-top:0;mso-wrap-distance-right:9pt;mso-wrap-distance-bottom:0;mso-position-horizontal:absolute;mso-position-horizontal-relative:text;mso-position-vertical:absolute;mso-position-vertical-relative:text;mso-width-percent:0;mso-height-percent:0;mso-width-

```
relative:margin;mso-height-relative:margin" o:spid="_x0000_s1026" strokecolor="#70ad47 [3209]"
to="227.05pt,28.35pt" from="13.55pt,28.35pt">
            <v:stroke joinstyle="miter"/>
          </v:line>
        </w:pict>
      </mc:Fallback>
    </mc:AlternateContent>
  </w:r>
- <w:r w:rsidRPr="006169F2">
  - <w:rPr>
      <w:rFonts w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
      <w:b/>
      <w:caps/>
      <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
    </w:rPr>
    <w:t>Results</w:t>
  </w:r>
</w:p>
- <w:p w:rsidP="00335B6D" w:rsidRDefault="00DF7D5C" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="750BB137"
w:rsidRPr="000732DD">
  - <w:pPr>
      <w:pStyle w:val="Heading3"/>
    - <w:numPr>
        <w:ilvl w:val="1"/>
        <w:numId w:val="21"/>
      </w:numPr>
      <w:spacing w:lineRule="auto" w:line="240" w:after="120" w:before="160"/>
      <w:ind w:right="-29" w:left="567"/>
      <w:jc w:val="left"/>
    - <w:rPr>
        <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
        <w:b/>
        <w:bCs/>
        <w:color w:val="000000"/>
        <w:sz w:val="20"/>
        <w:szCs w:val="22"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="000732DD">
    - <w:rPr>
        <w:rFonts w:cs="Calibri" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT" w:eastAsia="Calibri"/>
        <w:b/>
        <w:bCs/>
        <w:color w:val="000000"/>
        <w:sz w:val="20"/>
        <w:szCs w:val="22"/>
      </w:rPr>
      <w:t>Study selection</w:t>
    </w:r>
</w:p>
- <w:p w:rsidP="00B62C01" w:rsidRDefault="0054084E" w:rsidR="00DF7D5C" w14:textId="77777777" w14:paraId="5C9A784D">
  - <w:pPr>
      <w:spacing w:lineRule="auto" w:line="250" w:after="80" w:before="80"/>
      <w:ind w:right="-29" w:left="245" w:firstLine="0"/>
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
    </w:pPr>
  - <w:r w:rsidRPr="004C130F">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t>The process of study selection is demonstrated in the flow</w:t>
    </w:r>
  - <w:r w:rsidR="00B62C01">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
      <w:t xml:space="preserve"> </w:t>
    </w:r>
  - <w:r w:rsidR="00DF7D5C" w:rsidRPr="004C130F">
    - <w:rPr>
        <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
        <w:sz w:val="18"/>
        <w:szCs w:val="18"/>
      </w:rPr>
```

```
<w:t>diagram (Figure 1). In order to determine their eligibility for inclusion, 292 articles were initially identified through the database search, and their titles and abstracts were reviewed afterward. Consequently, 198 studies were excluded consisting of non-full text articles (reviews, case reports, editorials, news, letters to editors, comments, etc.) as well as studies irrelevant to the topic in question</w:t>
</w:r>
- <w:r w:rsidR="00DF7D5C">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t xml:space="preserve">. Subsequently, 94 publications </w:t>
</w:r>
- <w:r w:rsidR="00DF7D5C" w:rsidRPr="004C130F">
  - <w:rPr>
    <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Leelawadee UI Semilight" w:ascii="Leelawadee UI Semilight"/>
    <w:sz w:val="18"/>
    <w:szCs w:val="18"/>
  </w:rPr>
  <w:t>were considered relevant to the topic and were carefully examined through an intensive reading to determine ultimately the pertinent studies to include in our meta-analysis. Eventually, 31 articles discussing the correlation between the MetS and its components and CRN (CRA and CRC) were included.</w:t>
</w:r>
</w:p>
- <w:p w:rsidR="00740E76" w:rsidRDefault="00740E76" w14:textId="77777777" w14:paraId="2D05FC6A">
  - <w:pPr>
    <w:keepNext/>
    <w:spacing w:lineRule="auto" w:line="250" w:after="120" w:before="120"/>
    <w:ind w:right="0" w:left="288" w:firstLine="0"/>
  </w:pPr>
  - <w:r w:rsidRPr="000815A6">
    - <w:rPr>
      <w:noProof/>
    </w:rPr>
    - <w:drawing>
      - <wp:inline wp14:editId="68A0637B" wp14:anchorId="47F04BFF" distR="0" distL="0" distB="0" distT="0">
        <wp:extent cx="2861945" cy="3367682"/>
        <wp:effectExtent r="14605" b="23495" t="19050" l="19050"/>
        <wp:docPr name="Picture 17" id="17"/>
        - <wp:cNvGraphicFramePr>
          <a:graphicFrameLocks noChangeAspect="1" xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main"/>
        </wp:cNvGraphicFramePr>
        - <a:graphic xmlns:a="http://schemas.openxmlformats.org/drawingml/2006/main">
          - <a:graphicData uri="http://schemas.openxmlformats.org/drawingml/2006/picture">
            - <pic:pic xmlns:pic="http://schemas.openxmlformats.org/drawingml/2006/picture">
              - <pic:nvPicPr>
                <pic:cNvPr name="Flow diagram of study selection.png" id="2"/>
                <pic:cNvPicPr/>
              </pic:nvPicPr>
              - <pic:blipFill>
                - <a:blip r:embed="rId24">
                  - <a:extLst>
                    - <a:ext uri="{28A0092B-C50C-407E-A947-70E740481C1C}">
                      <a14:useLocalDpi val="0"
                        xmlns:a14="http://schemas.microsoft.com/office/drawing/2010/main"/>
                    </a:ext>
                  </a:extLst>
                </a:blip>
                - <a:stretch>
                  <a:fillRect/>
                </a:stretch>
              </pic:blipFill>
              - <pic:spPr>
                - <a:xfrm>
                  <a:off y="0" x="0"/>
                  <a:ext cx="2861945" cy="3367682"/>
                </a:xfrm>
                - <a:prstGeom prst="rect">
                  <a:avLst/>
                </a:prstGeom>
                - <a:ln w="9525">
                  - <a:solidFill>
                    - <a:schemeClr val="accent6">
                      <a:lumMod val="75000"/>
                    </a:schemeClr>
                  </a:solidFill>
                </a:ln>
              </pic:spPr>
            </pic:pic>
          </a:graphicData>
        </a:graphic>
      </wp:inline>
```

```
            </w:drawing>
        </w:r>
    </w:p>
- <w:p w:rsidP="003F1502" w:rsidRDefault="00740E76" w:rsidR="00740E76" w14:textId="67086965" w14:paraId="59B12B33">
    - <w:pPr>
            <w:pStyle w:val="Caption"/>
            <w:spacing w:after="120"/>
            <w:ind w:firstLine="278"/>
            <w:jc w:val="left"/>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
    </w:pPr>
    - <w:r w:rsidRPr="009D107C">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:b/>
            <w:bCs/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
        <w:t xml:space="preserve">Figure </w:t>
    </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:b/>
            <w:bCs/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
        <w:fldChar w:fldCharType="begin"/>
    </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:b/>
            <w:bCs/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
        <w:instrText xml:space="preserve"> SEQ Figure \* ARABIC </w:instrText>
    </w:r>
    - <w:r>
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:b/>
            <w:bCs/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
        <w:fldChar w:fldCharType="separate"/>
    - <w:r w:rsidR="005C6966">
        - <w:rPr>
            <w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
            <w:b/>
            <w:bCs/>
            <w:i w:val="0"/>
            <w:iCs w:val="0"/>
            <w:noProof/>
            <w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
            <w:sz w:val="16"/>
            <w:szCs w:val="16"/>
        </w:rPr>
```

<w:t>1</w:t>
</w:r>
- <w:r>
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:bCs/>
<w:i w:val="0"/>
<w:iCs w:val="0"/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
<w:fldChar w:fldCharType="end"/>
</w:r>
- <w:r w:rsidRPr="009D107C">
- <w:rPr>
<w:rFonts w:cs="Leelawadee UI Semilight" w:hAnsi="Tw Cen MT" w:ascii="Tw Cen MT"/>
<w:b/>
<w:bCs/>
<w:i w:val="0"/>
<w:iCs w:val="0"/>
<w:color w:val="385623" w:themeShade="80" w:themeColor="accent6"/>
<w:sz w:val="16"/>
<w:szCs w:val="16"/>
</w:rPr>
:
</w:r>

Flowchart of study selection

</w:p>

Study characteristics

Table 1 summarizes the characteristics of the included studies. The meta-analysis consisted of eight cohort studies [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"BWNiQSGe","properties":{"formattedCitation":"\\super 44\\uc0\\u8211{}51\\nosupersub{}","plainCitation":"44–51","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease (NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P < 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-

735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":693,"uris":["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUND: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype. METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer. RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},{"family":"Kroenke","given":"Candyce H"},

{"family":"Simon","given":"Michael"},{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}},{"id":692,"uris":["http://zotero.org/users/2724931/items/FETAPZNU"],"uri":["http://zotero.org/users/2724931/items/FETAPZNU"],"itemData":{"id":692,"type":"article-journal","title":"Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General Population in Korea Using the National Health Insurance Service–National Sample Cohort","container-title":"Diseases of the Colon & Rectum","volume":"60","issue":"11","abstract":"BACKGROUND: BACKGROUND:In Korea, the incidence of colorectal cancer has increased and obesity is on a rising trend because of a Westernized lifestyle in men.\nOBJECTIVE: OBJECTIVE:The purpose of this study was to evaluate the relationship between metabolic health status, as well as BMI, and the incidence of colorectal cancer.\nDESIGN: DESIGN:This was a prospective cohort study.\nSETTINGS: SETTINGS:The study was conducted with the National Health Insurance Service–National Sample Cohort.\nPATIENTS: PATIENTS:A total of 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 y).\nMAIN OUTCOME MEASURES: MAIN OUTCOME MEASURES:Demographic, anthropometric, and laboratory data at baseline were collected and categorized. The presence of diabetes mellitus, hypertension, and dyslipidemia was defined using the criteria of previous studies. The incidence of colorectal cancer was also defined according to the International Classification of Disease, 10th Revision, codes and the claim data on endoscopy with biopsy.\nRESULTS: RESULTS:During the follow-up, 5108 new cases of colorectal cancer occurred. Being underweight (<18.5

kg/m2) reduced the risk for colorectal cancer among women (adjusted HR = 0.646 (95% CI, 0.484–0.863)), whereas high BMI significantly increased the risk in men and in the elderly. Obesity (≥25

kg/m2), diabetes mellitus, and hypertension were identified as risk factors for colorectal cancer in men but not for women. Although metabolically unhealthy nonobese men had a higher risk for colorectal cancer than metabolically healthy nonobese men (adjusted HR = 1.114 (95% CI, 1.004–1.236)), the risk was lower than that in the obese men.\nLIMITATIONS: LIMITATIONS:The study population consisted of people who underwent health examinations, thus there could be selection bias.\nCONCLUSIONS: CONCLUSIONS:In Korean adults, obesity contributes to the incidence of colorectal cancer with a sex difference. Nonobese but metabolically unhealthy men are considered to be a high-risk group for colorectal cancer, but obesity itself is more important in colorectal carcinogenesis. See Video Abstract at http://links.lww.com/DCR/A475.","URL":"https://journals.lww.com/dcrjournal/Fulltext/2017/11000/Association_Among_Obesity,_Metabolic_Health,_and_the.3706","author":[{"family":"Shin","given":"Cheol Min"},{"family":"Han","given":"Kyungdo"},{"family":"Lee","given":"Dong Ho"},{"family":"Choi","given":"Yoon Jin"},{"family":"Kim","given":"Nayoung"},{"family":"Park","given":"Young Soo"},{"family":"Yoon","given":"Hyuk"}],"issued":{"date-parts":[["2017"]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology & Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":"BACKGROUND AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
–
51
], 13 case-control studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3sRthwBl","properties":{"formattedCitation":"\\super 52\\uc0\\u8211{}64\\nosupersub{}","plainCitation":"52–64","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},{"family":"Son","given":"Hee Jung"},{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":[["2016",12,1]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3′-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND:

Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol

Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}},{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with

⩾

3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}},{"id":140,"uris":["http://zotero.org/users/2724931/items/XN37VDV8"],"uri":["http://zotero.org/users/2724931/items/XN37VDV8"],"itemData":{"id":140,"type":"article-journal","title":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-Sectional, Case–Control Study","container-title":"The American Journal of Gastroenterology","page":"178-187","volume":"105","issue":"1","source":"www.nature.com","abstract":"OBJECTIVES: Colorectal adenoma is known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue (VAT) area measured by abdominal computed tomography (CT) has not been documented clearly. In addition, the relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity and colorectal adenoma, has not been studied extensively. The aim of this study was to examine VAT area and insulin resistance as risk factors of colorectal adenoma.\nMETHODS: A cross-sectional, case–control study was conducted in Koreans that presented for health check-ups. Subjects underwent various laboratory tests, abdominal CT, and colonoscopy. VAT, subcutaneous adipose tissue (SAT), and homeostatic metabolic assessment (HOMA) index were evaluated as potential risk factors of colorectal adenoma in 2,244 age-

and sex-matched subjects.\nRESULTS: According to univariate analysis, the prevalences of smoking, hypertension, metabolic syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and VAT and SAT areas were significantly different in the two groups. According to the multivariate analysis adjusted for multiple confounders, VAT area was independently associated with the risk of colorectal adenoma (odds ratio (OR)=3.09, 95% confidence interval (CI): 2.19–4.36, highest quintile vs. lowest quintile). Mean HOMA index was higher in the adenoma group than in the control group (OR=1.99, 95% CI: 1.35–2.92, highest vs. lowest quintile).\nCONCLUSIONS: Visceral obesity was found to be an independent risk factor of colorectal adenoma, and insulin resistance was associated with the presence of colorectal adenoma.","DOI":"10.1038/ajg.2009.541","ISSN":"0002-9270","shortTitle":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma","journalAbbreviation":"Am J Gastroenterol","language":"en","author":[{"family":"Kang","given":"Hyoun Woo"},{"family":"Kim","given":"Donghee"},{"family":"Kim","given":"Hwa Jung"},{"family":"Kim","given":"Chung Hyeon"},{"family":"Kim","given":"Young Sun"},{"family":"Park","given":"Min Jung"},{"family":"Kim","given":"Joo Sung"},{"family":"Cho","given":"Sang-Heon"},{"family":"Sung","given":"Myung-Whun"},{"family":"Jung","given":"Hyun Chae"},{"family":"Lee","given":"Hyo-Suk"},{"family":"Song","given":"In Sung"}],"issued":{"date-parts":[["2009",9,15]]}}},{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":713,"uris":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"uri":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"itemData":{"id":713,"type":"article-journal","title":"Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing Colorectal Tumors","page":"6","source":"Zotero","language":"en","author":[{"family":"Harima","given":"Satoko"},{"family":"Hashimoto","given":"Shinichi"},{"family":"Shibata","given":"Hiroaki"},{"family":"Matsunaga","given":"Takaharu"},{"family":"Tanabe","given":"Ryo"},{"family":"Terai","given":"Shuji"},{"family":"Sakaida","given":"Isao"}],"issued":{"date-parts":[["2013"]]}}},{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in

a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
52
–
64
], and ten cross-sectional studies as well [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zxivCORl","properties":{"formattedCitation":"\\super 65\\uc0\\u8211{}74\\nosupersub{}","plainCitation":"65–74","noteIndex":0},"citationItems":[{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectomy is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":152,"uris":["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"1406-1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702

without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the 40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}},{"id":116,"uris":["http://zotero.org/users/2724931/items/3DEUV37V"],"uri":["http://zotero.org/users/2724931/items/3DEUV37V"],"itemData":{"id":116,"type":"article-journal","title":"Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.","container-title":"Journal of gastroenterology and hepatology","page":"562-567","volume":"25","issue":"3","abstract":"BACKGROUND AND AIMS: Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver. This investigation was initiated to determine whether NAFLD has a relationship to colorectal adenomatous polyps. METHODS: We examined the 2917 participants who underwent a routine colonoscopy at Kangbuk Samsung Hospital in 2007. We divided the 2917 subjects into the adenomatous polyp group (n = 556) and the normal group (n = 2361). Anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal ultrasonographs were assessed. RESULTS: The prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03-1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. CONCLUSION: NAFLD was associated with colorectal adenomatous polyps. Further studies are needed to confirm whether NAFLD is a predictor for the development of colorectal adenomatous polyps and cancer.","DOI":"10.1111/j.1440-1746.2009.06117.x","ISSN":"1440-1746 0815-9319","note":"PMID: 20074156","journalAbbreviation":"J Gastroenterol Hepatol","language":"eng","author":[{"family":"Hwang","given":"Sang Tae"},{"family":"Cho","given":"Yong Kyun"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Park","given":"Dong Il"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Won","given":"Kyoung Hee"},{"family":"Jin","given":"Wook"}],"issued":{"date-parts":[["2010",3]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":

["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}},{"id":694,"uris":["http://zotero.org/users/2724931/items/BLYUFTHV"],"uri":["http://zotero.org/users/2724931/items/BLYUFTHV"],"itemData":{"id":694,"type":"article-journal","title":"Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean","container-title":"Medicine","page":"e5453","volume":"95","issue":"49","archive":"PMC","archive_location":"PMC5265996","abstract":"Co
of red meat and alcohol are known risk factors for colorectal cancer, but associations for dietary fat remain unclear. We investigated the associations of dietary fat, protein, and energy intake with prevalence of colorectal adenoma. We performed a prospective cross-sectional study on asymptomatic persons who underwent a screening colonoscopy at a single center during a routine health check-up from May to December 2011. Dietary data were obtained via a validated Food Frequency Questionnaire (FFQ), assisted by a registered dietician. We also obtained information on alcohol consumption and smoking status, and measured metabolic syndrome markers including abdominal circumference, blood pressure, fasting glucose, serum triglyceride and high-density lipoprotein cholesterol. We calculated odds ratio (OR) and 95% confidence interval (CI) to evaluate the associations using the polytomous logistic regression models. As a secondary analysis, we also conducted a matched analysis, matched by age and sex (557 cases and 557 non-cases). The study sample included 557 cases (406 males and 151 females) with histopathologically confirmed colorectal adenoma, and 1157 controls (650 males and 507 females). The proportion of advanced adenoma was 28.1% of men and 18.5% of female, respectively. Although vegetable protein intake was inversely associated with the prevalence of colorectal adenoma, further adjustment for potential confounding factors attenuated the association, resulting in no significant associations. There were no significant associations between dietary fat intake and colorectal adenoma in energy-adjusted models. For vegetable protein in women, the OR for the comparison of those in the highest tertile with those in the lowest tertile was 0.47 (95% CI 0.25–0.91, P for trend = 0.07) after adjustment for total energy intake. However, after controlling for metabolic syndrome markers, body mass index, smoking status, alcohol consumption, and family history of colorectal adenoma, which were all significantly high in the colorectal adenoma patients group, the association became attenuated (OR 0.54, 95% CI 0.27–1.11, P for trend = 0.13). In conclusion, we did not observe the significant associations for intakes of total energy, total, animal and vegetable fats, and total, animal and vegetable proteins in relation to colorectal adenoma prevalence.","DOI":"10.1097/MD.0000000000005453","ISSN":"0025-7974","author":[{"family":"Yang","given":"Sun Young"},{"family":"Kim","given":"Young Sun"},{"family":"Lee","given":"Jung Eun"},{"family":"Seol","given":"Jueun"},{"family":"Song","given":"Ji Hyun"},{"family":"Chung","given":"Goh Eun"},{"family":"Yim","given":"Jeong Yoon"},{"family":"Lim","given":"Sun Hee"},{"family":"Kim","given":"Joo Sung"}],"editor":[{"family":"Elrazek.","given":"Abd Elrazek Abd"}],"issued":{"date-parts":[["2016",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
65
–
74
]. With the exception of ten studies, where five were carried out in European populations [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"A5LiXXtd","properties":{"formattedCitation":"\\super 47,52,55,56,58\\nosupersub{}","plainCitation":"47,52,55,56,58","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}},{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID:

22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with

⩾

3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

47, 52, 55, 56, 58

] and five in northern American populations [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zpfcCLDm","properties":{"formattedCitation":"\\super 48,49,51,62,64\\nosupersub{}","plainCitation":"48,49,51,62,64","noteIndex":0},"citationItems":[{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations

with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471 \nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":693,"uris":["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUND: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype. METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer. RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},{"family":"Kroenke","given":"Candyce H"},{"family":"Simon","given":"Michael"},{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}},{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology & Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":"BACKGROU
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},

{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
48, 49, 51, 62, 64
], the remaining
were conducted in Asian populations. CRA was the outcome in 14 studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sTZ5ErLB","properties":{"formattedCitation":"\\super 44,46\\uc0\\u8211{}50,52\\uc0\\u8211{}58,66\\nosupersub{}","plainCitation":"44,46–50,52–58,66","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal

of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":693,"uris":["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUND: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype. METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer. RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},{"family":"Kroenke","given":"Candyce H"},{"family":"Simon","given":"Michael"},{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}},{"id":692,"uris":["http://zotero.org/users/2724931/items/FETAPZNU"],"uri":["http://zotero.org/users/2724931/items/FETAPZNU"],"itemData":{"id":692,"type":"article-journal","title":"Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General Population in Korea Using the National Health Insurance Service–National Sample Cohort","container-title":"Diseases of the Colon & Rectum","volume":"60","issue":"11","abstract":"BACKGROUND: BACKGROUND:In Korea, the incidence of colorectal cancer has increased and obesity is on a rising trend because of a Westernized lifestyle in men.\nOBJECTIVE: OBJECTIVE:The purpose of this study was to evaluate the relationship between metabolic health status, as well as BMI, and the incidence of colorectal cancer.\nDESIGN: DESIGN:This was a prospective cohort study.\nSETTINGS: SETTINGS:The study was conducted with the National Health Insurance Service–National Sample Cohort.\nPATIENTS: PATIENTS:A total of 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 y).\nMAIN OUTCOME MEASURES: MAIN OUTCOME MEASURES:Demographic, anthropometric, and laboratory data at baseline were collected and categorized. The presence of diabetes mellitus, hypertension, and dyslipidemia was defined using the criteria of previous studies. The incidence of colorectal cancer was also defined according to the International Classification of Disease, 10th Revision, codes and the claim data on endoscopy with biopsy.\nRESULTS: RESULTS:During the follow-up, 5108 new cases of colorectal cancer occurred. Being underweight (<18.5

kg/m2) reduced the risk for colorectal cancer among women (adjusted HR = 0.646 (95% CI, 0.484–0.863)), whereas high BMI significantly increased the risk in men and in the elderly. Obesity (≥25

kg/m2), diabetes mellitus, and hypertension were identified as risk factors for colorectal cancer in men but not for women. Although metabolically unhealthy nonobese men had a higher risk for colorectal cancer than metabolically healthy nonobese men (adjusted HR = 1.114 (95% CI, 1.004–1.236)), the risk was lower than that in the obese men.\nLIMITATIONS: LIMITATIONS:The study population consisted of people who underwent health examinations, thus there could be selection bias.\nCONCLUSIONS: CONCLUSIONS:In Korean adults, obesity contributes to the incidence of colorectal cancer with a sex difference. Nonobese but metabolically unhealthy men are considered to be a high-risk group for colorectal cancer, but obesity itself is more important in colorectal carcinogenesis. See Video Abstract at http://links.lww.com/DCR/A475.","URL":"https://journals.lww.com/dcrjournal/Fulltext/2017/11000/Association_Among_Obesity_3706","author":[{"family":"Shin","given":"Cheol Min"},{"family":"Han","given":"Kyungdo"},{"family":"Lee","given":"Dong Ho"},{"family":"Choi","given":"Yoon Jin"},{"family":"Kim","given":"Nayoung"},{"family":"Park","given":"Young Soo"},{"family":"Yoon","given":"Hyuk"}],"issued":{"date-parts":[["2017"]]}}},{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},{"family":"Son","given":"Hee Jung"},

{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":[["2016",12,1]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic

Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B."},"non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}},{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with
⩾
3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}},{"id":152,"uris":["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"1406-1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine

tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
4
4, 46
–
50, 52–58, 66
], whereas 19 studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"1SssHDL5","properties":{"formattedCitation":"\\super 44\\uc0\\u8211{}46,51,59\\uc0\\u8211{}65,67\\uc0\\u8211{}74\\nosupersub{}","plainCitation":"44–46,51,59–65,67–74","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease (NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P < 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma

including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":140,"uris":["http://zotero.org/users/2724931/items/XN37VDV8"],"uri":["http://zotero.org/users/2724931/items/XN37VDV8"],"itemData":{"id":140,"type":"article-journal","title":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-Sectional, Case–Control Study","container-title":"The American Journal of Gastroenterology","page":"178-187","volume":"105","issue":"1","source":"www.nature.com","abstract":"OBJECTIVES: Colorectal adenoma is known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue (VAT) area measured by abdominal computed tomography (CT) has not been documented clearly. In addition, the relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity and colorectal adenoma, has not been studied extensively. The aim of this study was to examine VAT area and insulin resistance as risk factors of colorectal adenoma.\nMETHODS: A cross-sectional, case–control study was conducted in Koreans that presented for health check-ups. Subjects underwent various laboratory tests, abdominal CT, and colonoscopy. VAT, subcutaneous adipose tissue (SAT), and homeostatic metabolic assessment (HOMA) index were evaluated as potential risk factors of colorectal adenoma in 2,244 age- and sex-matched subjects.\nRESULTS: According to univariate analysis, the prevalences of smoking, hypertension, metabolic syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and VAT and SAT areas were significantly different in the two groups. According to the multivariate analysis adjusted for multiple confounders, VAT area was independently associated with the risk of colorectal adenoma (odds ratio (OR)=3.09, 95% confidence interval (CI): 2.19–4.36, highest quintile vs. lowest quintile). Mean HOMA index was higher in the adenoma group than in the control group (OR=1.99, 95% CI: 1.35–2.92, highest vs. lowest quintile).\nCONCLUSIONS: Visceral obesity was found to be an independent risk factor of colorectal adenoma, and insulin resistance was associated with the presence of colorectal adenoma.","DOI":"10.1038/ajg.2009.541","ISSN":"0002-9270","shortTitle":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma","journalAbbreviation":"Am J Gastroenterol","language":"en","author":[{"family":"Kang","given":"Hyoun Woo"},{"family":"Kim","given":"Donghee"},{"family":"Kim","given":"Hwa Jung"},{"family":"Kim","given":"Chung Hyeon"},{"family":"Kim","given":"Young Sun"},{"family":"Park","given":"Min Jung"},{"family":"Kim","given":"Joo Sung"},{"family":"Cho","given":"Sang-Heon"},{"family":"Sung","given":"Myung-Whun"},{"family":"Jung","given":"Hyun Chae"},{"family":"Lee","given":"Hyo-Suk"},{"family":"Song","given":"In Sung"}],"issued":{"date-parts":[["2009",9,15]]}}},{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":713,"uris":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"uri":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"itemData":{"id":713,"type":"article-journal","title":"Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing Colorectal Tumors","page":"6","source":"Zotero","language":"en","author":[{"family":"Harima","given":"Satoko"},{"family":"Hashimoto","given":"Shinichi"},{"family":"Shibata","given":"Hiroaki"},{"family":"Matsunaga","given":"Takaharu"},{"family":"Tanabe","given":"Ryo"},{"family":"Terai","given":"Shuji"},

{"family":"Sakaida","given":"Isao"}],"issued":{"date-parts":[["2013"]]}}},{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology &
Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":"BACKGROU
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectomy is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":

["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the 40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}},{"id":116,"uris":["http://zotero.org/users/2724931/items/3DEUV37V"],"uri":["http://zotero.org/users/2724931/items/3DEUV37V"],"itemData":{"id":116,"type":"article-journal","title":"Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.","container-title":"Journal of gastroenterology and hepatology","page":"562-567","volume":"25","issue":"3","abstract":"BACKGROUND AND AIMS: Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver. This investigation was initiated to determine whether NAFLD has a relationship to colorectal adenomatous polyps. METHODS: We examined the 2917 participants who underwent a routine colonoscopy at Kangbuk Samsung Hospital in 2007. We divided the 2917 subjects into the adenomatous polyp group (n = 556) and the normal group (n = 2361). Anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal ultrasonographs were assessed. RESULTS: The prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03-1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. CONCLUSION: NAFLD was associated with colorectal adenomatous polyps. Further studies are needed to confirm whether NAFLD is a predictor for the development of colorectal adenomatous polyps and cancer.","DOI":"10.1111/j.1440-1746.2009.06117.x","ISSN":"1440-1746 0815-9319","note":"PMID: 20074156","journalAbbreviation":"J Gastroenterol Hepatol","language":"eng","author":[{"family":"Hwang","given":"Sang Tae"},{"family":"Cho","given":"Yong Kyun"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Park","given":"Dong Il"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Won","given":"Kyoung Hee"},{"family":"Jin","given":"Wook"}],"issued":{"date-parts":[["2010",3]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and

fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}},{"id":694,"uris":["http://zotero.org/users/2724931/items/BLYUFTHV"],"uri":["http://zotero.org/users/2724931/items/BLYUFTHV"],"itemData":{"id":694,"type":"article-journal","title":"Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean","container-title":"Medicine","page":"e5453","volume":"95","issue":"49","archive":"PMC","archive_location":"PMC5265996","abstract":"Co of red meat and alcohol are known risk factors for colorectal cancer, but associations for dietary fat remain unclear. We investigated the associations of dietary fat, protein, and energy intake with prevalence of colorectal adenoma. We performed a prospective cross-sectional study on asymptomatic persons who underwent a screening colonoscopy at a single center during a routine health check-up from May to December 2011. Dietary data were obtained via a validated Food Frequency Questionnaire (FFQ), assisted by a registered dietician. We also obtained information on alcohol consumption and smoking status, and measured metabolic syndrome markers including abdominal circumference, blood pressure, fasting glucose, serum triglyceride and high-density lipoprotein cholesterol. We calculated odds ratio (OR) and 95% confidence interval (CI) to evaluate the associations using the polytomous logistic regression models. As a secondary analysis, we also conducted a matched analysis, matched by age and sex (557 cases and 557 non-cases). The study sample included 557 cases (406 males and 151 females) with histopathologically confirmed colorectal adenoma, and 1157 controls (650 males and 507 females). The proportion of advanced adenoma was 28.1% of men and 18.5% of female, respectively. Although vegetable protein intake was inversely associated with the prevalence of colorectal adenoma, further adjustment for potential confounding factors attenuated the association, resulting in no significant associations. There were no significant associations between dietary fat intake and colorectal adenoma in energy-adjusted models. For vegetable protein in women, the OR for the comparison of those in the highest tertile with those in the lowest tertile was 0.47 (95% CI 0.25–0.91, P for trend = 0.07) after adjustment for total energy intake. However, after controlling for metabolic syndrome markers, body mass index, smoking status, alcohol consumption, and family history of colorectal adenoma, which were all significantly high in the colorectal adenoma patients group, the association became attenuated (OR 0.54, 95% CI 0.27–1.11, P for trend = 0.13). In conclusion, we did not observe the significant associations for intakes of total energy, total, animal and vegetable fats, and total, animal and vegetable proteins in relation to colorectal adenoma prevalence.","DOI":"10.1097/MD.0000000000005453","ISSN":"0025-7974","author":[{"family":"Yang","given":"Sun Young"},{"family":"Kim","given":"Young Sun"},{"family":"Lee","given":"Jung Eun"},{"family":"Seol","given":"Jueun"},{"family":"Song","given":"Ji Hyun"},{"family":"Chung","given":"Goh Eun"},{"family":"Yim","given":"Jeong Yoon"},{"family":"Lim","given":"Sun Hee"},{"family":"Kim","given":"Joo Sung"}],"editor":[{"family":"Elrazek.","given":"Abd Elrazek Abd"}],"issued":{"date-parts":[["2016",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
–
46, 51, 59
–
65, 67
–
74
] reported data on CRC incidence. The NCEP-ATPIII definition was utilized in 14 studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9P189WOF","properties":{"formattedCitation":"\\super 44\\uc0\\u8211{}46,48,49,55,56,59,67,69\\uc0\\u8211{}71,73,74\\nosupersub{}","plainCitation":"44–46,48,49,55,56,59,67,69–71,73,74","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease

(NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P < 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":693,"uris":["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUND: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype. METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer. RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},{"family":"Kroenke","given":"Candyce H"},{"family":"Simon","given":"Michael"},{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}},{"id":119,"uris":

["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":140,"uris":["http://zotero.org/users/2724931/items/XN37VDV8"],"uri":["http://zotero.org/users/2724931/items/XN37VDV8"],"itemData":{"id":140,"type":"article-journal","title":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-Sectional, Case–Control Study","container-title":"The American Journal of Gastroenterology","page":"178-187","volume":"105","issue":"1","source":"www.nature.com","abstract":"OBJECTIVES: Colorectal adenoma is known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue (VAT) area measured by abdominal computed tomography (CT) has not been documented clearly. In addition, the relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity and colorectal adenoma, has not been studied extensively. The aim of this study was to examine VAT area and insulin resistance as risk factors of colorectal adenoma.\nMETHODS: A cross-sectional, case–control study was conducted in Koreans that presented for health check-ups. Subjects underwent various laboratory tests, abdominal CT, and colonoscopy. VAT, subcutaneous adipose tissue (SAT), and homeostatic metabolic assessment (HOMA) index were evaluated as potential risk factors of colorectal adenoma in 2,244 age- and sex-matched subjects.\nRESULTS: According to univariate analysis, the prevalences of smoking, hypertension, metabolic syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and VAT and SAT areas were significantly different in the two groups. According to the multivariate analysis adjusted for multiple confounders, VAT area was independently associated with the risk of colorectal adenoma (odds ratio (OR)=3.09, 95% confidence interval (CI): 2.19–4.36, highest quintile vs. lowest quintile). Mean HOMA index was higher in the adenoma group than in the control group (OR=1.99, 95% CI: 1.35–2.92, highest vs. lowest quintile).\nCONCLUSIONS: Visceral obesity was found to be an independent risk factor of colorectal adenoma, and insulin resistance was associated with the presence of colorectal adenoma.","DOI":"10.1038/ajg.2009.541","ISSN":"0002-9270","shortTitle":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma","journalAbbreviation":"Am J Gastroenterol","language":"en","author":[{"family":"Kang","given":"Hyoun Woo"},{"family":"Kim","given":"Donghee"},{"family":"Kim","given":"Hwa Jung"},{"family":"Kim","given":"Chung Hyeon"},{"family":"Kim","given":"Young Sun"},{"family":"Park","given":"Min Jung"},{"family":"Kim","given":"Joo Sung"},{"family":"Cho","given":"Sang-Heon"},{"family":"Sung","given":"Myung-Whun"},{"family":"Jung","given":"Hyun Chae"},{"family":"Lee","given":"Hyo-Suk"},{"family":"Song","given":"In Sung"}],"issued":{"date-parts":[["2009",9,15]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a

vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the 40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}},{"id":116,"uris":["http://zotero.org/users/2724931/items/3DEUV37V"],"uri":["http://zotero.org/users/2724931/items/3DEUV37V"],"itemData":{"id":116,"type":"article-journal","title":"Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.","container-title":"Journal of gastroenterology and hepatology","page":"562-567","volume":"25","issue":"3","abstract":"BACKGROUND AND AIMS: Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver. This investigation was initiated to determine whether NAFLD has a relationship to colorectal adenomatous polyps. METHODS: We examined the 2917 participants who underwent a routine colonoscopy at Kangbuk Samsung Hospital in 2007. We divided the 2917 subjects into the adenomatous polyp group (n = 556) and the normal group (n = 2361). Anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal ultrasonographs were assessed. RESULTS: The prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03-1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. CONCLUSION: NAFLD was associated with colorectal adenomatous polyps. Further studies are needed to confirm whether NAFLD is a predictor for the development of colorectal adenomatous polyps and cancer.","DOI":"10.1111/j.1440-1746.2009.06117.x","ISSN":"1440-1746 0815-9319","note":"PMID: 20074156","journalAbbreviation":"J Gastroenterol Hepatol","language":"eng","author":[{"family":"Hwang","given":"Sang Tae"},{"family":"Cho","given":"Yong Kyun"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Park","given":"Dong Il"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Won","given":"Kyoung Hee"},{"family":"Jin","given":"Wook"}],"issued":{"date-parts":[["2010",3]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}},{"id":694,"uris":["http://zotero.org/users/2724931/items/BLYUFTHV"],"uri":["http://zotero.org/users/2724931/items/BLYUFTHV"],"itemData":{"id":694,"type":"article-journal","title":"Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean","container-title":"Medicine","page":"e5453","volume":"95","issue":"49","archive":"PMC","archive_location":"PMC5265996","abstract":"C
of red meat and alcohol are known risk factors for colorectal cancer, but associations for dietary fat remain unclear. We investigated the associations of dietary fat, protein, and energy intake with prevalence of colorectal adenoma. We performed a prospective cross-sectional study on asymptomatic persons who underwent a screening colonoscopy at a single center during a routine health check-up from May to December 2011. Dietary data were obtained via a validated Food Frequency Questionnaire (FFQ), assisted by a registered dietician. We also obtained information on alcohol consumption and smoking status, and measured metabolic syndrome markers including abdominal circumference, blood pressure, fasting glucose, serum triglyceride and high-density lipoprotein cholesterol. We calculated odds ratio (OR) and 95% confidence interval (CI) to evaluate the associations using the polytomous logistic regression models. As a secondary analysis, we also conducted a matched analysis, matched by age and sex (557 cases and 557 non-cases). The study sample included 557 cases (406 males and 151 females) with histopathologically confirmed colorectal adenoma, and 1157 controls (650 males and 507 females). The proportion of advanced adenoma was 28.1% of men and 18.5% of female, respectively. Although vegetable protein intake was inversely associated with the prevalence of colorectal adenoma, further adjustment for potential confounding factors attenuated the association, resulting in no significant associations. There were no significant associations between dietary fat intake and colorectal adenoma in energy-adjusted models. For vegetable protein in women, the OR for the comparison of those in the highest tertile with those in the lowest tertile was 0.47 (95% CI 0.25–0.91, P for trend = 0.07) after adjustment for total energy intake. However, after controlling

for metabolic syndrome markers, body mass index, smoking status, alcohol consumption, and family history of colorectal adenoma, which were all significantly high in the colorectal adenoma patients group, the association became attenuated (OR 0.54, 95% CI 0.27–1.11, P for trend = 0.13). In conclusion, we did not observe the significant associations for intakes of total energy, total, animal and vegetable fats, and total, animal and vegetable proteins in relation to colorectal adenoma prevalence.","DOI":"10.1097/MD.0000000000005453","ISSN":"0025-7974","author":[{"family":"Yang","given":"Sun Young"},{"family":"Kim","given":"Young Sun"},{"family":"Lee","given":"Jung Eun"},{"family":"Seol","given":"Jueun"},{"family":"Song","given":"Ji Hyun"},{"family":"Chung","given":"Goh Eun"},{"family":"Yim","given":"Jeong Yoon"},{"family":"Lim","given":"Sun Hee"},{"family":"Kim","given":"Joo Sung"}],"editor":[{"family":"Elrazek.","given":"Abd Elrazek Abd"}],"issued":{"date-parts":[["2016",12]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
–
46, 48, 49, 55, 56, 59, 67, 69
–
71, 73, 74
], four applied the IDF definition for the diagnosis of individuals with MetS [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Jaa4YECK","properties":{"formattedCitation":"\\super 56,58,63,72\\nosupersub{}","plainCitation":"56,58,63,72","noteIndex":0},"citationItems":[{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with
⩾
3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic

abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
56, 58, 63, 72

], while two studies used the harmonized definition [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LyTcVTIz","properties":{"formattedCitation":"\\super 56,68 \\nosupersub{}","plainCitation":"56,68","noteIndex":0},"citationItems":[{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal

adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
56, 68
], and 13 studies employed other definitions [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"OOg8KNfs","properties":{"formattedCitation":"\\super 47,50\\uc0\\u8211{}54,57,60\\uc0\\u8211{}62,64\\uc0\\u8211{}66\\nosupersub{}","plainCitation":"47,50–54,57,60–62,64–66","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}},{"id":692,"uris":["http://zotero.org/users/2724931/items/FETAPZNU"],"uri":["http://zotero.org/users/2724931/items/FETAPZNU"],"itemData":{"id":692,"type":"article-journal","title":"Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General Population in Korea Using the National Health Insurance Service–National Sample Cohort","container-title":"Diseases of the Colon & Rectum","volume":"60","issue":"11","abstract":"BACKGROUND: BACKGROUND:In Korea, the incidence of colorectal cancer has increased and obesity is on a rising trend because of a Westernized lifestyle in men.\nOBJECTIVE: OBJECTIVE:The purpose of this study was to evaluate the relationship between metabolic health status, as well as BMI, and the incidence of colorectal cancer.\nDESIGN: DESIGN:This was a prospective cohort study.\nSETTINGS: SETTINGS:The study was conducted with the National Health Insurance Service–National Sample Cohort.\nPATIENTS: PATIENTS:A total of 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 y).\nMAIN OUTCOME MEASURES: MAIN

OUTCOME MEASURES:Demographic, anthropometric, and laboratory data at baseline were collected and categorized. The presence of diabetes mellitus, hypertension, and dyslipidemia was defined using the criteria of previous studies. The incidence of colorectal cancer was also defined according to the International Classification of Disease, 10th Revision, codes and the claim data on endoscopy with biopsy.\nRESULTS: RESULTS:During the follow-up, 5108 new cases of colorectal cancer occurred. Being underweight (<18.5

kg/m2) reduced the risk for colorectal cancer among women (adjusted HR = 0.646 (95% CI, 0.484–0.863)), whereas high BMI significantly increased the risk in men and in the elderly. Obesity (≥25

kg/m2), diabetes mellitus, and hypertension were identified as risk factors for colorectal cancer in men but not for women. Although metabolically unhealthy nonobese men had a higher risk for colorectal cancer than metabolically healthy nonobese men (adjusted HR = 1.114 (95% CI, 1.004–1.236)), the risk was lower than that in the obese men.\nLIMITATIONS: LIMITATIONS:The study population consisted of people who underwent health examinations, thus there could be selection bias.\nCONCLUSIONS: CONCLUSIONS:In Korean adults, obesity contributes to the incidence of colorectal cancer with a sex difference. Nonobese but metabolically unhealthy men are considered to be a high-risk group for colorectal cancer, but obesity itself is more important in colorectal carcinogenesis. See Video Abstract at http://links.lww.com/DCR/A475.","URL":"https://journals.lww.com/dcrjournal/Fulltext/2017/11000/Association_Among_Obesity 3706","author":[{"family":"Shin","given":"Cheol Min"},{"family":"Han","given":"Kyungdo"},{"family":"Lee","given":"Dong Ho"},{"family":"Choi","given":"Yoon Jin"},{"family":"Kim","given":"Nayoung"},{"family":"Park","given":"Young Soo"},{"family":"Yoon","given":"Hyuk"}],"issued":{"date-parts":[["2017"]]}},{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},{"family":"Son","given":"Hee Jung"},{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":[["2016",12,1]]}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}},{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":713,"uris":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"uri":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"itemData":{"id":713,"type":"article-journal","title":"Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing Colorectal Tumors","page":"6","source":"Zotero","language":"en","author":[{"family":"Harima","given":"Satoko"},{"family":"Hashimoto","given":"Shinichi"},{"family":"Shibata","given":"Hiroaki"},{"family":"Matsunaga","given":"Takaharu"},{"family":"Tanabe","given":"Ryo"},{"family":"Terai","given":"Shuji"},{"family":"Sakaida","given":"Isao"}],"issued":{"date-parts":[["2013"]]}}},{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology &
Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":"BACKGROU
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial

regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectomy is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":152,"uris":["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"1406-1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
47, 50
–
54, 57, 60
–
62, 64
–
66
]. According to the NOS scales, the included cohort studies scored an average of eight stars, the case-control studies were awarded an average of 7.85 stars, while the cross-sectional studies were al
located an average of 7.6 stars.

Synthesis of results

Hyperglycemia and colorectal neoplasms

To examine the association between FBG and CRA, data from nine studies comprising 11 datasets were pooled
.
Compared to individuals with normal FBG levels, patients with high FBG values (hyperglycemia) were more susceptible to developing CRA (RR
=
1.33; 95% CI 1.14-1.54;
I
2
=
92%) (Table 2, Figure 2). There was no evidence of significant publication bias with Begg
’s
test (
P
=
0.5423), contrarily to Egger
’s
test (
P
=

0.0232). None of the subgroups modified the risk estimate. The adjusted summary RR on publication bias was decreased by the trim and fill method to 1.28 (95% CI 1.11-1.46).

The Baujat plot indicated that the dataset (Kim 2012 AA / NCEP-ATP III) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"PKTxyOh2","properties":{"formattedCitation":"\\super 46 \\nosupersub{}","plainCitation":"46","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

46

] contributed to the overall heterogeneity and the dataset (Hu 2011 CRA / NCEP-ATP III) contributed to the overall result (Figure 3). The risk estimates for the relationship between FBG levels and CRC were consistent with those expressed by the previous analysis concerning CRA. A summary RR of 1.35 (95% CI 1.23-1.47;

$I^2 = 59\%$) was found (Supplementary Figure 1.1), suggesting, therefore, a strong effect of hyperglycemia on both outcomes. There was no evidence of funnel plot asymmetry ($P = 0.2792$ with the Begg's test and $P = 0.2360$ with the Egger's test). The pooled analysis result was influenced by study type, study location, and gender. Cohort studies showed a higher association with a summary RR of 1.41 (95% CI 1.08-1.84; $I^2 = 81\%$) than case-control studies (RR = 1.33; 95% CI 1.25-1.41; $I^2 = 0\%$). Similarly, the association between hyperglycemia and CRC observed within Asian populations was stronger (RR = 1.42; 95% CI 1.21-1.67; $I^2 = 78\%$) compared to Europeans (RR = 1.30; 95% CI 1.20-1.41; $I^2 = 0\%$). When stratified by gender, a stronger association between high FBG and CRC risk was noticed for women (RR = 1.63; 95% CI 1.18-2.26; $I^2 = 86\%$) than men (RR = 1.34; 95% CI 1.24-1.45; $I^2 = 30\%$) (Supplementary Table 3). The trim and fill method reduced the summary RR to 1.29 (95% CI 1.17-1.43). Sensitivity

analysis and the Baujat plot showed that the dataset (Lin 2014 CRC / NCEP-ATP III (W)) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"AfzmPPFv","properties":{"formattedCitation":"\\super 44 \\nosupersub{}","plainCitation":"44","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
] contributed to the overall heterogeneity (RR
=
1.30; 95% CI 1.22-1.38;
I
2
=
18%), and it was considered as an influential study (Supplementary Figur
e 1.2, Supplementary Table 1.3).

Hypertension and colorectal neoplasms

Using a random-effects meta-analysis model, due to evidence of heterogeneity, in 17 studies with 23 datasets involving 38,510 participants, high BP was associated with an increase in CRA incidence (RR
=
1.26; 95% CI 1.17-1.36;
I
2
=
82%) (Supplementary Figure 2.1).

There was no evidence of significant publication bias with Begg
’s
test (
P
=
0.1715), contrarily to Egger
’s
test (
P
=
0.0213). Subgroup analyses revealed that study type and MetS definitions slightly modified the risk estimates (Supplementary Table 2.1). The conventional definition showed a stronger significant positive association (RR
=
1.31; 95% CI 1.18-1.46;
I
2
=
88%) compared with studies using unconventional definitions (RR
=
1.20; 95% CI 1.06-1.35;
I
2
=
68%). The adjusted effect size to publication bias decreased with the trim and fill method (RR
=
1.17; 95% CI 1.08-1.26). One study [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Zyxk7ukT","properties":{"formattedCitation":"\\super 45 \\nosupersub{}","plainCitation":"45","noteIndex":0},"citationItems":[{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease (NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P

< 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

45

] contributed to overall heterogeneity and was considered potentially influential (Supplementary Figure 2.2).

Comparing individuals with and without hypertension, the summary of RR of 13 studies with 24 datasets including 615,867 participants of which 12,570 cases of a confirmed diagnosis of CRC showed an increased risk of developing this malignancy by 28% (RR = 1.28; 95% CI 1.20-1.37; I^2 = 66%) (Supplementary Figure 2.3). There was no evidence of funnel plot asymmetry in Begg's test (P = 0.6062) or in Egger's test (P = 0.5381).

This analysis was subdivided according to study type, study location, MetS definition, gender, and cancer site. All the strata considerably changed the risk estimate (Supplementary Table 2.1). A stronger relationship between CRC risk and high BP was found in cohort studies (RR = 1.37; 95% CI 1.31-1.43; I^2 = 41%) than non-cohort studies (RR=1.23; 95% CI 1.12-1.35; I^2 = 68%). A similar pattern was noticed for studies conducted in Asian populations (RR = 1.43; 95% CI 1.32-1.56; I^2 = 60%) compared with (RR = 1.18; 95% CI 1.11-1.24; I^2 = 36%) for studies carried out in European countries. This association was more significant for colon cancer (RR = 1.29; 95% CI 1.14-1.45; I^2 = 76%) than rectal cancer (RR = 1.23; 95% CI 1.04-1.45; I^2 = 71%) and among men (RR = 1.22; 95% CI 1.08-1.38; I^2 = 59%) while a modest relationship was observed among women (RR = 1.12; 95% CI 1.02-1.22; I^2 =

12%). No study met the criteria as an influential study, however, the Baujat plot revealed that the dataset (Jeon 2014 RC / Other) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nFpRU2vD","properties":{"formattedCitation":"\\super 54 \\nosupersub{}","plainCitation":"54","noteIndex":0},"citationItems":[{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3 ′ -UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3 ′ -UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3 ′ -UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 54
] contributed to overall heterogeneity and result (Supplementary Figure 2.4).

Table SEQ Table * ARABIC 1 : Characteristics of included studies

Cohort studies	
Cohort/study center	
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	
Taipei Veterans General Hospital	
The Women’s Health Initiative (WHI)	
The National Cancer Center	
The Women’s Health Initiative (WHI)	
The First Affiliated Hospital of Wenzhou Medical University	

The Scarborough Hospital, General and Birchmount Sites, The North Toronto Endoscopy Clinic, and The Intestinal Health Institute, Markham, Ontario	7	Other	227 CC / 28573	183 RC/ 28573	689 CC / 689	404 RC / 404	CC, RC	
The National Health Insurance Service–National Sample Cohort	9	NCEP-ATP III	216 / 1522		347 / 407		CRA	
Case-control studies	7	NCEP-ATP III	81 CRC / 4821	65 CC / 4821	460 / 377		CRC	
Cohort/study center	7	NCEP-ATP III	1771 CRA / 6438	1292 CC / 6438	146 RC / 6438	264 CC / 400	186 RC / 400	CRA, AA
The European Prospective Investigation into Cancer and Nutrition Study (23 centers from 10 European countries)	8	NCEP-ATP III	114 CRC / 5068	88 CC / 5068	1122 / 1122		CRA, CRC	
The Department of Gastroenterology and Hepatology at the Tel Aviv Medical Center	8	NCEP-ATP III	1500 CRA / 2315	446 CRC / 2315	250 / 250		CRC, CC	
Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine	9	Other	383 CRA / 1534	99 AA / 1534			CRA, CC, RC	
CHA Bundang Medical Center Seongnam	9	Other	5108 / 408931				CRC, CC	
Seoul National University Hospital Healthcare System Gangnam Center								
Saint Savvas Cancer hospital and Alexandra General hospital in Athens								

Lesion type
CC, RC
CRA
CRA
CC, RC
CRA
CRC
Follow up
1985 - 1988
01/01/2003-
31/12/2010
1993 - 1998
04/2007- 04/2009
1993 - 1998
10/2007 -12/2011
2009 - 2014
2003 - 2008
Follow up
1999 - 2003
2010 - 2015
04/2009 - 03/2012
06/2004 -01/2009
01/2006 -12/2007
12/2009 -12/2010
Country
Finland
Taiwan
The USA
Korea
The USA
China
Canada
Korea
Country
European countries
Israel
Japan
Korea
South Korea
Greece
Author, year [ref]
Bowers
et al.
2006 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"G6jQFyq2","properties":{"formattedCitation":"\\super 47\\nosupersub{}","plainCitation":"47","noteIndex":0},"citationItems":[{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
47
]
Huang
et al.
2013 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"V1RL94Tn","properties":{"formattedCitation":"\\super 45\\nosupersub{}","plainCitation":"45","noteIndex":0},"citationItems":[{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of

Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease (NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P < 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

45

]

Kabat et al. 2012 [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0CvqQ14L","properties":{"formattedCitation":"\\super 48\\nosupersub{}","plainCitation":"48","noteIndex":0},"citationItems":[{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

48

]

Kim et al. 2012 [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7EIl9Jl5","properties":{"formattedCitation":"\\super 46\\nosupersub{}","plainCitation":"46","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},

{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},
{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum
Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},
{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},
{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":
[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46
]
Liang
et al.
2017 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Yzztyzck","properties":{"formattedCitation":"\\super
49\\nosupersub{}","plainCitation":"49","noteIndex":0},"citationItems":[{"id":693,"uris":
["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":
["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-
journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal
women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American
Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-
161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUNI
The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have
explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight
individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who
were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype.
METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample
included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the
Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or
none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting
glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to
estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer.
RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal
cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A
metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight
women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps
taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-
9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},
{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},
{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},
{"family":"Kroenke","given":"Candyce H"},{"family":"Simon","given":"Michael"},
{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},
{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}}],"schema":"https://github.com/citation-
style-language/schema/raw/master/csl-citation.json"}
49
]
Lin
et al.
2014 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J3w2VZpo","properties":{"formattedCitation":"\\super
44\\nosupersub{}","plainCitation":"44","noteIndex":0},"citationItems":[{"id":123,"uris":
["http://zotero.org/users/2724931/items/33PI99M5"],"uri":
["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-
journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a
large study","container-title":"Molecular Biology Reports","page":"2989-
2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a
strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was
to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and
determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and
945 females) who underwent a routine colonoscopy according to international colorectal cancer screening
guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by
ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of
CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in
the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at
sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal
adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate
analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05).
After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for
CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid
carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD.
(ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?
term=zheng+minghua&rank=1)."","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-
4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},
{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},
{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-
Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},
{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":
[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
]
Shapero
et al.
2017 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0XBMu8Y6","properties":
{"formattedCitation":"\\super 51\\nosupersub{}","plainCitation":"51","noteIndex":0},"citationItems":

[{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":
["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-
journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian
Community-Based Study","container-title":"Canadian Journal of Gastroenterology &
Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":'
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic
syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects
undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia
(HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and
histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30)
and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses
included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL,
DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each
colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese
females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia,
significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations
thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese.
CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian
population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":
[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},
{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},
{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":
[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
51

]

Shin
et al.
2017

[

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ayHItPd8","properties":{"formattedCitation":"\\super
50\\nosupersub{}","plainCitation":"50","noteIndex":0},"citationItems":[{"id":692,"uris":
["http://zotero.org/users/2724931/items/FETAPZNU"],"uri":
["http://zotero.org/users/2724931/items/FETAPZNU"],"itemData":{"id":692,"type":"article-
journal","title":"Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General
Population in Korea Using the National Health Insurance Service–National Sample Cohort","container-
title":"Diseases of the Colon & Rectum","volume":"60","issue":"11","abstract":"BACKGROUND:
BACKGROUND:In Korea, the incidence of colorectal cancer has increased and obesity is on a rising trend
because of a Westernized lifestyle in men.\nOBJECTIVE: OBJECTIVE:The purpose of this study was to evaluate
the relationship between metabolic health status, as well as BMI, and the incidence of colorectal
cancer.\nDESIGN: DESIGN:This was a prospective cohort study.\nSETTINGS: SETTINGS:The study was
conducted with the National Health Insurance Service–National Sample Cohort.\nPATIENTS: PATIENTS:A total
of 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 y).\nMAIN
OUTCOME MEASURES: MAIN OUTCOME MEASURES:Demographic, anthropometric, and laboratory data
at baseline were collected and categorized. The presence of diabetes mellitus, hypertension, and dyslipidemia was
defined using the criteria of previous studies. The incidence of colorectal cancer was also defined according to the
International Classification of Disease, 10th Revision, codes and the claim data on endoscopy with
biopsy.\nRESULTS: RESULTS:During the follow-up, 5108 new cases of colorectal cancer occurred. Being
underweight (<18.5

kg/m2) reduced the risk for colorectal cancer among women (adjusted HR = 0.646 (95% CI, 0.484–0.863)),
whereas high BMI significantly increased the risk in men and in the elderly. Obesity (≥25

kg/m2), diabetes mellitus, and hypertension were identified as risk factors for colorectal cancer in men but not for
women. Although metabolically unhealthy nonobese men had a higher risk for colorectal cancer than
metabolically healthy nonobese men (adjusted HR = 1.114 (95% CI, 1.004–1.236)), the risk was lower than that in
the obese men.\nLIMITATIONS: LIMITATIONS:The study population consisted of people who underwent
health examinations, thus there could be selection bias.\nCONCLUSIONS: CONCLUSIONS:In Korean adults,
obesity contributes to the incidence of colorectal cancer with a sex difference. Nonobese but metabolically
unhealthy men are considered to be a high-risk group for colorectal cancer, but obesity itself is more important in
colorectal carcinogenesis. See Video Abstract at
http://links.lww.com/DCR/A475.","URL":"https://journals.lww.com/dcrjournal/Fulltext/2017/11000/Association_
3706","author":[{"family":"Shin","given":"Cheol Min"},{"family":"Han","given":"Kyungdo"},
{"family":"Lee","given":"Dong Ho"},{"family":"Choi","given":"Yoon Jin"},
{"family":"Kim","given":"Nayoung"},{"family":"Park","given":"Young Soo"},
{"family":"Yoon","given":"Hyuk"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-
style-language/schema/raw/master/csl-citation.json"}
50

]

Author, year [ref]
Aleksandrova
et al
.
2011 [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5FvVqt6Q","properties":{"formattedCitation":"\\super
56\\nosupersub{}","plainCitation":"56","noteIndex":0},"citationItems":[{"id":146,"uris":
["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":
["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-
journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective
Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention
Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related
to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent
international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what

extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
56
]
Fliss-Isakov et al. 2017 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3y7dcYbe","properties":{"formattedCitation":"\\super 60\\nosupersub{}","plainCitation":"60","noteIndex":0},"citationItems":[{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss-Isakov Naomi"},{"literal":"Zelber-Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
60
]
Harima et al. 2013 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"epCxdcM9","properties":{"formattedCitation":"\\super 61\\nosupersub{}","plainCitation":"61","noteIndex":0},"citationItems":[{"id":713,"uris":

["http://zotero.org/users/2724931/items/LV3SB6ZM"],"uri":
["http://zotero.org/users/2724931/items/LV3SB6ZM"],"itemData":{"id":713,"type":"article-
journal","title":"Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing
Colorectal Tumors","page":"6","source":"Zotero","language":"en","author":
[{"family":"Harima","given":"Satoko"},{"family":"Hashimoto","given":"Shinichi"},
{"family":"Shibata","given":"Hiroaki"},{"family":"Matsunaga","given":"Takaharu"},
{"family":"Tanabe","given":"Ryo"},{"family":"Terai","given":"Shuji"},
{"family":"Sakaida","given":"Isao"}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-
style-language/schema/raw/master/csl-citation.json"}
61
]
Jeon
et al
.
2014 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"IW4DvtgH","properties":
{"formattedCitation":"\\super 54\\nosupersub{}","plainCitation":"54","noteIndex":0},"citationItems":
[{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":
["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-
journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in
determining the risk of colorectal cancer in Koreans","container-title":"BMC
Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO
Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in
cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three
VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850
participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF
polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and
gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs)
of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p =
0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-
environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008).
CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS.
ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-
881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-
881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong
Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},
{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},
{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},

{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":
[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
54
]
Kang
et al
.
2009 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Pjccav8R","properties":{"formattedCitation":"\\super
59\\nosupersub{}","plainCitation":"59","noteIndex":0},"citationItems":[{"id":140,"uris":
["http://zotero.org/users/2724931/items/XN37VDV8"],"uri":
["http://zotero.org/users/2724931/items/XN37VDV8"],"itemData":{"id":140,"type":"article-
journal","title":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-
Sectional, Case–Control Study","container-title":"The American Journal of Gastroenterology","page":"178-
187","volume":"105","issue":"1","source":"www.nature.com","abstract":"OBJECTIVES: Colorectal adenoma is
known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue
(VAT) area measured by abdominal computed tomography (CT) has not been documented clearly. In addition, the
relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity
and colorectal adenoma, has not been studied extensively. The aim of this study was to examine VAT area and
insulin resistance as risk factors of colorectal adenoma.\nMETHODS: A cross-sectional, case–control study was
conducted in Koreans that presented for health check-ups. Subjects underwent various laboratory tests, abdominal
CT, and colonoscopy. VAT, subcutaneous adipose tissue (SAT), and homeostatic metabolic assessment (HOMA)
index were evaluated as potential risk factors of colorectal adenoma in 2,244 age- and sex-matched
subjects.\nRESULTS: According to univariate analysis, the prevalences of smoking, hypertension, metabolic
syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control
group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and
VAT and SAT areas were significantly different in the two groups. According to the multivariate analysis adjusted
for multiple confounders, VAT area was independently associated with the risk of colorectal adenoma (odds ratio
(OR)=3.09, 95% confidence interval (CI): 2.19–4.36, highest quintile vs. lowest quintile). Mean HOMA index
was higher in the adenoma group than in the control group (OR=1.99, 95% CI: 1.35–2.92, highest vs. lowest
quintile).\nCONCLUSIONS: Visceral obesity was found to be an independent risk factor of colorectal adenoma,
and insulin resistance was associated with the presence of colorectal
adenoma.","DOI":"10.1038/ajg.2009.541","ISSN":"0002-9270","shortTitle":"Visceral Obesity and Insulin
Resistance as Risk Factors for Colorectal Adenoma","journalAbbreviation":"Am J
Gastroenterol","language":"en","author":[{"family":"Kang","given":"Hyoun Woo"},
{"family":"Kim","given":"Donghee"},{"family":"Kim","given":"Hwa Jung"},{"family":"Kim","given":"Chung
Hyeon"},{"family":"Kim","given":"Young Sun"},{"family":"Park","given":"Min Jung"},
{"family":"Kim","given":"Joo Sung"},{"family":"Cho","given":"Sang-Heon"},
{"family":"Sung","given":"Myung-Whun"},{"family":"Jung","given":"Hyun Chae"},
{"family":"Lee","given":"Hyo-Suk"},{"family":"Song","given":"In Sung"}],"issued":{"date-parts":
[["2009",9,15]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
59
]
Kontou
et al
.
2012 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"kP9wMM29","properties":
{"formattedCitation":"\\super 55\\nosupersub{}","plainCitation":"55","noteIndex":0},"citationItems":
[{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":
["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-
journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-
control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect
of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250
patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls.
Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75),
while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III]
National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02,
2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer
(3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI
0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer.
Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI
0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-
1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":
[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},
{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},
{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},
{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":
[["2012",7]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
55
]
Outpatient gastroenterology clinic
Two Self Defense Forces (SDF) hospitals
Six Italian areas and in Canton Vaud, Switzerland
Center for Health Promotion of the Samsung Medical Center in Seoul
The Department of Gastroenterological Su
rgery, Peking University People’
s Hospital
The Northern Sweden Health and Disease Cohort
CLUE II cohort
Cross-sectional studies
Cohort/study center

Healthcare Center of Konkuk University Medical Center in Seoul
Healthcare Center of Konkuk University Medical Center in Seoul
Shin Kong Wu Ho-Su Memorial Hospital
The Kangbuk Samsung Hospital, College of Medicine at Sungkyunkwan University
Total Healthcare Center of Kangbuk Samsung Hospital
The Center for Health Promotion, Samsung Medical Center in Seoul
The Dongguk University Ilsan Hospital Medical Screening Center, Seoul
The Health Promotion Center of Asan Medical Center Seoul
Tohuku Central Hospital for Public School Teachers, Yamagata
Seoul National University Hospital Healthcare System Gangnam Center
AA
advanced adenoma,
CC
colon cancer,
CRA
colorectal adenoma,
CRC
colorectal cancer,
IDF
International Diabetes Foundation,
MetS
metabolic syndrome,
NCEP-ATP III
National Cholesterol Education Program-Adult Treatment Panel III,
RC
rectal cancer,
RNETs
rectal neuroendocrine tumors.
8
8
8
8
9
7
8
Quality score
8
7
8
8
8
8
8
7
7
7
Other
IDF
IDF
Other
Other
Other
Other
MetS definition
NCEP-ATP III
Other
NCEP-ATP III
NCEP-ATP III
Other
NCEP-ATP III
NCEP-ATP III
IDF
Harmonized
NCEP-ATP III
167 / 612
756 / 1751
1378 CC / 4661
878 RC / 4661
102 / 52583
507 / 507
306 / 595
132 / 392
№
events /
№
total
339 / 1761
1258 / 3368
397 / 3106
556 / 2917
101 / 57819
731 / 2531

154 / 714
53 / 200
261 / 963
406 M / 1056
151 W / 658
CRA
CRA
CC, RC
RNETs
CRC
CRC
CRA
Lesion type
CRA
CRA
CRA
CRA
RNETs
CRA
CRA
CRA
CRA
CRA
2007 - 2009
01/1995 -03/2002
1992 - 2001
01/2002 -12/2012
01/2002 -03/2007
1985 - 1996
1989 - 2000
Follow up
09/2005 -03/2009
01/2011 -12/2011
10/2004 -04/2006
2007
2010 - 2011
03/2004 -12/2005
07/2005 -12/2012
10/2005 -12/2005
06/2008 -01/2010
5/2011 - 12/2011
The USA
Japan
Italy and Switzerland
Korea
China
Sweden
The USA
Country
Korea
Korea
Taiwan
Korea
Korea
Korea
Korea
Korea
Japan
Korea
Lipka
et al.
2013 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"r9NQtsMu","properties":{"formattedCitation":"\\super 62\\nosupersub{}","plainCitation":"62","noteIndex":0},"citationItems":[{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
62
]
Morita

et al
.
2005 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"KUzFhdMf","properties":{"formattedCitation":"\\super 63\\nosupersub{}","plainCitation":"63","noteIndex":0},"citationItems":[{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
63
]
Pelluchi
et al
.
2010 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"1MkNHp3N","properties":{"formattedCitation":"\\super 58\\nosupersub{}","plainCitation":"58","noteIndex":0},"citationItems":[{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with
⩾
3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
58
]
Pyo
et al.
2016 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sOFF4Ytb","properties":{"formattedCitation":"\\super 53\\nosupersub{}","plainCitation":"53","noteIndex":0},"citationItems":[{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},

{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},
{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},
{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},
{"family":"Son","given":"Hee Jung"},{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":
[["2016",12,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
53
]
Shen
et al
.
2010 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7lqQ1YnS","properties":{"formattedCitation":"\\super
57\\nosupersub{}","plainCitation":"57","noteIndex":0},"citationItems":[{"id":144,"uris":
["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":
["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-
journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal
carcinoma","container-title":"ANZ Journal of Surgery","page":"331-
336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot
of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study
aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507
cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to
establish the database. The patients with colorectal cancer were divided into two groups based on the presence of
MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox
proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype,
differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The
existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence
of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in
the control group. MS is one of the important elements that can independently influence the survival (odds ratio
(OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival
compared with other parameters. Conclusion: There is a close relationship between MS and colorectal
carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma.
Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the
cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":
[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},
{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},
{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":
[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
57
]
Stocks
et al.
2008 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8d18v7SC","properties":{"formattedCitation":"\\super
52\\nosupersub{}","plainCitation":"52","noteIndex":0},"citationItems":[{"id":704,"uris":
["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":
["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-
journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective
study","container-title":"International Journal Of
Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":
[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},
{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},
{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":
[["2007",9,18]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
52
]
Tsilidis
et al
.
2010 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5C5aoWZm","properties":
{"formattedCitation":"\\super 64\\nosupersub{}","plainCitation":"64","noteIndex":0},"citationItems":
[{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":
["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-
journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-
title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed
Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in
several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association
between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control
study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative
sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants
in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor
binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and
triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height
and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was
measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome
components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at
baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the
metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00;
95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that
components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes
mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-
5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes

Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
64
]
Author, year [ref]
Hong
et al
.
2010 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Ur3KYndV","properties":{"formattedCitation":"\\super 70\\nosupersub{}","plainCitation":"70","noteIndex":0},"citationItems":[{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the 40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
70
]
Hong
et al
.
2015 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"lrbZ495J","properties":{"formattedCitation":"\\super 65\\nosupersub{}","plainCitation":"65","noteIndex":0},"citationItems":[{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
65
]
Hu
et al
.
2011 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"P9fd6pHI","properties":{"formattedCitation":"\\super 69\\nosupersub{}","plainCitation":"69","noteIndex":0},"citationItems":[{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-

journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
69
]
Hwang et al.
2010 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nDY0SWiE","properties":{"formattedCitation":"\\super 71\\nosupersub{}","plainCitation":"71","noteIndex":0},"citationItems":[{"id":116,"uris":["http://zotero.org/users/2724931/items/3DEUV37V"],"uri":["http://zotero.org/users/2724931/items/3DEUV37V"],"itemData":{"id":116,"type":"article-journal","title":"Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.","container-title":"Journal of gastroenterology and hepatology","page":"562-567","volume":"25","issue":"3","abstract":"BACKGROUND AND AIMS: Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver. This investigation was initiated to determine whether NAFLD has a relationship to colorectal adenomatous polyps. METHODS: We examined the 2917 participants who underwent a routine colonoscopy at Kangbuk Samsung Hospital in 2007. We divided the 2917 subjects into the adenomatous polyp group (n = 556) and the normal group (n = 2361). Anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal ultrasonographs were assessed. RESULTS: The prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03-1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. CONCLUSION: NAFLD was associated with colorectal adenomatous polyps. Further studies are needed to confirm whether NAFLD is a predictor for the development of colorectal adenomatous polyps and cancer.","DOI":"10.1111/j.1440-1746.2009.06117.x","ISSN":"1440-1746 0815-9319","note":"PMID: 20074156","journalAbbreviation":"J Gastroenterol Hepatol","language":"eng","author":[{"family":"Hwang","given":"Sang Tae"},{"family":"Cho","given":"Yong Kyun"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Park","given":"Dong Il"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Won","given":"Kyoung Hee"},{"family":"Jin","given":"Wook"}],"issued":{"date-parts":[["2010",3]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
71
]
Jung et al.
2014 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5bJsyUZq","properties":{"formattedCitation":"\\super 66\\nosupersub{}","plainCitation":"66","noteIndex":0},"citationItems":[{"id":152,"uris":["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"1406-1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
66
]
Kim et al.
2007 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uPLJzFpo","properties":{"formattedCitation":"\\super 73\\nosupersub{}","plainCitation":"73","noteIndex":0},"citationItems":[{"id":386,"uris":

["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
73
]
Lee et al.
2014 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"vyUbkw7c","properties":{"formattedCitation":"\\super 67\\nosupersub{}","plainCitation":"67","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
67
]
Oh et al.
2008 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"iuswu51g","properties":{"formattedCitation":"\\super 72\\nosupersub{}","plainCitation":"72","noteIndex":0},"citationItems":[{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
72
]
Sato et al.
2011 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Mq6w4xYx","properties":{"formattedCitation":"\\super 68\\nosupersub{}","plainCitation":"68","noteIndex":0},"citationItems":[{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving

individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
68
]
Yang
et al.
2016 [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"b6c2NtqR","properties":{"formattedCitation":"\\super 74\\nosupersub{}","plainCitation":"74","noteIndex":0},"citationItems":[{"id":694,"uris":["http://zotero.org/users/2724931/items/BLYUFTHV"],"uri":["http://zotero.org/users/2724931/items/BLYUFTHV"],"itemData":{"id":694,"type":"article-journal","title":"Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean","container-title":"Medicine","page":"e5453","volume":"95","issue":"49","archive":"PMC","archive_location":"PMC5265996"
of red meat and alcohol are known risk factors for colorectal cancer, but associations for dietary fat remain unclear. We investigated the associations of dietary fat, protein, and energy intake with prevalence of colorectal adenoma. We performed a prospective cross-sectional study on asymptomatic persons who underwent a screening colonoscopy at a single center during a routine health check-up from May to December 2011. Dietary data were obtained via a validated Food Frequency Questionnaire (FFQ), assisted by a registered dietician. We also obtained information on alcohol consumption and smoking status, and measured metabolic syndrome markers including abdominal circumference, blood pressure, fasting glucose, serum triglyceride and high-density lipoprotein cholesterol. We calculated odds ratio (OR) and 95% confidence interval (CI) to evaluate the associations using the polytomous logistic regression models. As a secondary analysis, we also conducted a matched analysis, matched by age and sex (557 cases and 557 non-cases). The study sample included 557 cases (406 males and 151 females) with histopathologically confirmed colorectal adenoma, and 1157 controls (650 males and 507 females). The proportion of advanced adenoma was 28.1% of men and 18.5% of female, respectively. Although vegetable protein intake was inversely associated with the prevalence of colorectal adenoma, further adjustment for potential confounding factors attenuated the association, resulting in no significant associations. There were no significant associations between dietary fat intake and colorectal adenoma in energy-adjusted models. For vegetable protein in women, the OR for the comparison of those in the highest tertile with those in the lowest tertile was 0.47 (95% CI 0.25–0.91, P for trend = 0.07) after adjustment for total energy intake. However, after controlling for metabolic syndrome markers, body mass index, smoking status, alcohol consumption, and family history of colorectal adenoma, which were all significantly high in the colorectal adenoma patients group, the association became attenuated (OR 0.54, 95% CI 0.27–1.11, P for trend = 0.13). In conclusion, we did not observe the significant associations for intakes of total energy, total, animal and vegetable fats, and total, animal and vegetable proteins in relation to colorectal adenoma prevalence.","DOI":"10.1097/MD.0000000000005453","ISSN":"0025-7974","author":[{"family":"Yang","given":"Sun Young"},{"family":"Kim","given":"Young Sun"},{"family":"Lee","given":"Jung Eun"},{"family":"Seol","given":"Jueun"},{"family":"Song","given":"Ji Hyun"},{"family":"Chung","given":"Goh Eun"},{"family":"Yim","given":"Jeong Yoon"},{"family":"Lim","given":"Sun Hee"},{"family":"Kim","given":"Joo Sung"}],"editor":[{"family":"Elrazek.","given":"Abd Elrazek Abd"}],"issued":{"date-parts":[["2016",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
74
]

Table
SEQ Table * ARABIC
2
:
Summary of results

Outcome	№ of studies (datasets) ref	Model	RR [95% CI]	Z-test (P value)	Heterogeneity	Publication bias (P value)	Tau 2	Chi 2 (P

value)
I
2
(%)
Begg’s test
Egger’s test
Hyperglycemia and CRN risk
CRA
9 (11) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mAoldjsx","properties":{"formattedCitation":"\\super 44,46,63\\uc0\\u8211{}65,68,69,72,73\\nosupersub{}","plainCitation":"44,46,63–65,68,69,72,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes

mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)

60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

44, 46, 63

–

65, 68, 69, 72, 73

]

RE

1.33 [1.14-1.54]

3.75

(

P

= 0.0002)

0.05

123.99, df = 10

(

P

< 0.00001)

92

0.5423

0.0232

CRC

7 (14) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"p5v8EW0x","properties":{"formattedCitation":"\\super 44,46,48,52,54,56,57\\nosupersub {}","plainCitation":"44,46,48,52,54,56,57","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at

sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGR
Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C
>
T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},

{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},
{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},
{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},
{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":
["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-
journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal
carcinoma","container-title":"ANZ Journal of Surgery","page":"331-
336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot
of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study
aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507
cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to
establish the database. The patients with colorectal cancer were divided into two groups based on the presence of
MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox
proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype,
differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The
existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence
of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in
the control group. MS is one of the important elements that can independently influence the survival (odds ratio
(OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival
compared with other parameters. Conclusion: There is a close relationship between MS and colorectal
carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma.
Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the
cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":
[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},
{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},
{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":
[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 48, 52, 54, 56, 57
]
RE
1.35 [1.23-1.47]
6.61
(
P
< 0.00001)
0.01
31.66, df = 13
(
P
= 0.003)
59
0.2792
0.2360
Hypertension and CRN risk
CRA
17 (23) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZWjDNnUq","properties":
{"formattedCitation":"\\super 44\\uc0\\u8211{}46,51,59\\uc0\\u8211{}64,67\\uc0\\u8211{}69,71\\uc0\\u8211{}
74\\nosupersub{}","plainCitation":"44–46,51,59–64,67–69,71–74","noteIndex":0},"citationItems":
[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":
["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-
journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a
large study","container-title":"Molecular Biology Reports","page":"2989-
2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a
strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was
to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and
determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and
945 females) who underwent a routine colonoscopy according to international colorectal cancer screening
guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by
ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of
CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in
the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at
sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal
adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate
analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05).
After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for
CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid
carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD.
(ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?
term=zheng+minghua&rank=1)."","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-
4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},
{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},
{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-
Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},

{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":122,"uris":["http://zotero.org/users/2724931/items/K9AVA46D"],"uri":["http://zotero.org/users/2724931/items/K9AVA46D"],"itemData":{"id":122,"type":"article-journal","title":"Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy.","container-title":"Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland","page":"830-835","volume":"15","issue":"7","abstract":"AIM: The study aimed to determine whether nonalcoholic fatty liver disease (NAFLD) is an independent risk factor of adenoma after negative baseline colonoscopy. METHOD: A retrospective cohort study was conducted on 1522 health-check individuals who underwent two consecutive colonoscopies at Taipei Veterans General Hospital between 2003 and 2010. Those developing an adenoma after an initial negative baseline colonoscopy (adenoma group) were compared with those in whom the second colonoscopy was negative (nonadenoma group). Anthropometric measurements, biochemical tests and the presence of NAFLD were compared between the two groups. RESULTS: The adenoma group had a higher prevalence of NAFLD than the nonadenoma group (55.6% vs 38.8%; P < 0.05). On multivariate logistic regression analysis, NAFLD was an independent risk factor (OR = 1.45, 95% CI: 1.07-1.98) for adenoma formation after a negative baseline colonoscopy. The risk of colorectal adenoma increased when NAFLD patients had other morbidities including metabolic syndrome, hypertension or smoking (OR = 2.85, 4.03 and 4.17). CONCLUSION: NAFLD is an independent risk factor for colorectal adenoma formation after a negative baseline colonoscopy. The risk is higher in individuals with NAFLD and other comorbidities, such as hypertension, smoking or metabolic syndrome.","DOI":"10.1111/codi.12172","ISSN":"1463-1318 1462-8910","note":"PMID: 23398678","journalAbbreviation":"Colorectal Dis","language":"eng","author":[{"family":"Huang","given":"K.-W."},{"family":"Leu","given":"H.-B."},{"family":"Wang","given":"Y.-J."},{"family":"Luo","given":"J.-C."},{"family":"Lin","given":"H.-C."},{"family":"Lee","given":"F.-Y."},{"family":"Chan","given":"W.-L."},{"family":"Lin","given":"J.-K."},{"family":"Chang","given":"F.-Y."}],"issued":{"date-parts":[["2013",7]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":140,"uris":["http://zotero.org/users/2724931/items/XN37VDV8"],"uri":["http://zotero.org/users/2724931/items/XN37VDV8"],"itemData":{"id":140,"type":"article-journal","title":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-Sectional, Case–Control Study","container-title":"The American Journal of Gastroenterology","page":"178-187","volume":"105","issue":"1","source":"www.nature.com","abstract":"OBJECTIVES: Colorectal adenoma is known to be associated with obesity, but the association between colorectal adenoma and visceral adipose tissue (VAT) area measured by abdominal computed tomography (CT) has not been documented clearly. In addition, the

relationship between insulin resistance and colorectal adenomas, which underlies the mechanism that links obesity and colorectal adenoma, has not been studied extensively. The aim of this study was to examine VAT area and insulin resistance as risk factors of colorectal adenoma.\nMETHODS: A cross-sectional, case–control study was conducted in Koreans that presented for health check-ups. Subjects underwent various laboratory tests, abdominal CT, and colonoscopy. VAT, subcutaneous adipose tissue (SAT), and homeostatic metabolic assessment (HOMA) index were evaluated as potential risk factors of colorectal adenoma in 2,244 age- and sex-matched subjects.\nRESULTS: According to univariate analysis, the prevalences of smoking, hypertension, metabolic syndrome, and family history of colorectal cancer were higher in the adenoma group than in the normal control group. In addition, body mass index, waist circumference, triglyceride, high-density lipoprotein cholesterol, and VAT and SAT areas were significantly different in the two groups. According to the multivariate analysis adjusted for multiple confounders, VAT area was independently associated with the risk of colorectal adenoma (odds ratio (OR)=3.09, 95% confidence interval (CI): 2.19–4.36, highest quintile vs. lowest quintile). Mean HOMA index was higher in the adenoma group than in the control group (OR=1.99, 95% CI: 1.35–2.92, highest vs. lowest quintile).\nCONCLUSIONS: Visceral obesity was found to be an independent risk factor of colorectal adenoma, and insulin resistance was associated with the presence of colorectal adenoma.","DOI":"10.1038/ajg.2009.541","ISSN":"0002-9270","shortTitle":"Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma","journalAbbreviation":"Am J Gastroenterol","language":"en","author":[{"family":"Kang","given":"Hyoun Woo"},{"family":"Kim","given":"Donghee"},{"family":"Kim","given":"Hwa Jung"},{"family":"Kim","given":"Chung Hyeon"},{"family":"Kim","given":"Young Sun"},{"family":"Park","given":"Min Jung"},{"family":"Kim","given":"Joo Sung"},{"family":"Cho","given":"Sang-Heon"},{"family":"Sung","given":"Myung-Whun"},{"family":"Jung","given":"Hyun Chae"},{"family":"Lee","given":"Hyo-Suk"},{"family":"Song","given":"In Sung"}],"issued":{"date-parts":[["2009",9,15]]}}},{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":713,"uris":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"uri":["http://zotero.org/users/2724931/items/LV3SB6ZM"],"itemData":{"id":713,"type":"article-journal","title":"Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing Colorectal Tumors","page":"6","source":"Zotero","language":"en","author":[{"family":"Harima","given":"Satoko"},{"family":"Hashimoto","given":"Shinichi"},{"family":"Shibata","given":"Hiroaki"},{"family":"Matsunaga","given":"Takaharu"},{"family":"Tanabe","given":"Ryo"},{"family":"Terai","given":"Shuji"},{"family":"Sakaida","given":"Isao"}],"issued":{"date-parts":[["2013"]]}}},{"id":701,"uris":["http://zotero.org/users/2724931/items/XUEP2NAY"],"uri":["http://zotero.org/users/2724931/items/XUEP2NAY"],"itemData":{"id":701,"type":"article-journal","title":"Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital","container-title":"Journal of Gastrointestinal Cancer","page":"270-276","volume":"44","issue":"3","abstract":"We studied a racially diverse population and the relationship with colorectal adenomas (CA) further looking for risks related to BMI and metabolic factors.","DOI":"10.1007/s12029-013-9476-8","ISSN":"1941-6636","journalAbbreviation":"Journal of Gastrointestinal Cancer","author":[{"family":"Lipka","given":"Seth"},{"family":"Zheng","given":"Xi Emily"},{"family":"Hurtado-Cordovi","given":"Jorge"},{"family":"Singh","given":"Jaspreet"},{"family":"Levine","given":"Evan"},{"family":"Vlacancich","given":"Raymond"},{"family":"Krishnamachari","given":"Bhuma"},{"family":"Jung","given":"Min-Kyung"},{"family":"Fu","given":"Shuang"},{"family":"Takeshige","given":"Umeko"},{"family":"Avezbakiyev","given":"Boris"},{"family":"Li","given":"Ting"},{"family":"Iqbal","given":"Javed"},{"family":"Rizvon","given":"Kaleem"},{"family":"Mustacchia","given":"Paul"}],"issued":{"date-parts":[["2013",9,1]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal

obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":
[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},
{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},
{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":
[["2005",4]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":
["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-
journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology & Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":'
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":
[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},
{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},
{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":
[["2017"]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":
["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-
journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-
1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-
2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":
[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},
{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":
["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":
["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-
journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-
303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},
{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},
{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":
["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-
journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-
108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)
60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},
{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":116,"uris":
["http://zotero.org/users/2724931/items/3DEUV37V"],"uri":

["http://zotero.org/users/2724931/items/3DEUV37V"],"itemData":{"id":116,"type":"article-journal","title":"Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.","container-title":"Journal of gastroenterology and hepatology","page":"562-567","volume":"25","issue":"3","abstract":"BACKGROUND AND AIMS: Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver. This investigation was initiated to determine whether NAFLD has a relationship to colorectal adenomatous polyps. METHODS: We examined the 2917 participants who underwent a routine colonoscopy at Kangbuk Samsung Hospital in 2007. We divided the 2917 subjects into the adenomatous polyp group (n = 556) and the normal group (n = 2361). Anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal ultrasonographs were assessed. RESULTS: The prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03-1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. CONCLUSION: NAFLD was associated with colorectal adenomatous polyps. Further studies are needed to confirm whether NAFLD is a predictor for the development of colorectal adenomatous polyps and cancer.","DOI":"10.1111/j.1440-1746.2009.06117.x","ISSN":"1440-1746 0815-9319","note":"PMID: 20074156","journalAbbreviation":"J Gastroenterol Hepatol","language":"eng","author":[{"family":"Hwang","given":"Sang Tae"},{"family":"Cho","given":"Yong Kyun"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Park","given":"Dong Il"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Won","given":"Kyoung Hee"},{"family":"Jin","given":"Wook"}],"issued":{"date-parts":[["2010",3]]}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}},{"id":694,"uris":["http://zotero.org/users/2724931/items/BLYUFTHV"],"uri":["http://zotero.org/users/2724931/items/BLYUFTHV"],"itemData":{"id":694,"type":"article-journal","title":"Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean","container-title":"Medicine","page":"e5453","volume":"95","issue":"49","archive":"PMC","archive_location":"PMC5265996'
of red meat and alcohol are known risk factors for colorectal cancer, but associations for dietary fat remain unclear. We investigated the associations of dietary fat, protein, and energy intake with prevalence of colorectal adenoma. We performed a prospective cross-sectional study on asymptomatic persons who underwent a screening colonoscopy at a single center during a routine health check-up from May to December 2011. Dietary data were obtained via a validated Food Frequency Questionnaire (FFQ), assisted by a registered dietician. We also obtained information on alcohol consumption and smoking status, and measured metabolic syndrome markers including abdominal circumference, blood pressure, fasting glucose, serum triglyceride and high-density lipoprotein cholesterol. We calculated odds ratio (OR) and 95% confidence interval (CI) to evaluate the associations using the polytomous logistic regression models. As a secondary analysis, we also conducted a matched analysis, matched by age and sex (557 cases and 557 non-cases). The study sample included 557 cases (406 males and 151 females) with histopathologically confirmed colorectal adenoma, and 1157 controls (650 males and 507 females). The proportion of advanced adenoma was 28.1% of men and 18.5% of female, respectively. Although vegetable protein intake was inversely associated with the prevalence of colorectal adenoma, further adjustment for potential confounding factors attenuated the association, resulting in no significant associations. There were no significant associations between dietary fat intake and colorectal adenoma in energy-adjusted models. For vegetable protein in women, the OR for the comparison of those in the highest tertile with those in the lowest tertile was 0.47 (95% CI 0.25–0.91, P for trend = 0.07) after adjustment for total energy intake. However, after controlling for metabolic syndrome markers, body mass index, smoking status, alcohol consumption, and family history of colorectal adenoma, which were all significantly high in the colorectal adenoma patients group, the association became attenuated (OR 0.54, 95% CI 0.27–1.11, P for trend = 0.13). In conclusion, we did not observe the significant associations for intakes of total energy, total, animal and vegetable fats, and total, animal and vegetable proteins in relation to colorectal adenoma prevalence.","DOI":"10.1097/MD.0000000000005453","ISSN":"0025-

7974","author":[{"family":"Yang","given":"Sun Young"},{"family":"Kim","given":"Young Sun"},{"family":"Lee","given":"Jung Eun"},{"family":"Seol","given":"Jueun"},{"family":"Song","given":"Ji Hyun"},{"family":"Chung","given":"Goh Eun"},{"family":"Yim","given":"Jeong Yoon"},{"family":"Lim","given":"Sun Hee"},{"family":"Kim","given":"Joo Sung"}],"editor":[{"family":"Elrazek.","given":"Abd Elrazek Abd"}],"issued":{"date-parts":[["2016",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

44

–

46, 51, 59

–

64, 67

–

69, 71

–

74

]

RE

1.26 [1.17-1.36]

5.79

(

P

< 0.00001)

0.02

120.97, df = 22

(

P

< 0.00001)

82

0.1715

0.0213

CRC

13 (24) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"REKpz5NJ","properties":{"formattedCitation":"\\super 44,46,47,49,50,52\\uc0\\u8211{}58,66\\nosupersub{}","plainCitation":"44,46,47,49,50,52–58,66","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal

adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}}},{"id":693,"uris":["http://zotero.org/users/2724931/items/8F2B2BVX"],"uri":["http://zotero.org/users/2724931/items/8F2B2BVX"],"itemData":{"id":693,"type":"article-journal","title":"Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"155-161","volume":"26","issue":"2","archive":"PMC","archive_location":"PMC5301805","abstract":"BACKGROUND: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype. METHODS: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5–<25 kg/m(2). Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer. RESULTS: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02–2.18) compared to those who were metabolically healthy. CONCLUSIONS: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women. IMPACT: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.","DOI":"10.1158/1055-9965.EPI-16-0761","ISSN":"1055-9965","author":[{"family":"Liang","given":"Xiaoyun"},{"family":"Margolis","given":"Karen L"},{"family":"Hendryx","given":"Michael"},{"family":"Rohan","given":"Thomas"},{"family":"Groessl","given":"Erik J"},{"family":"Thomson","given":"Cynthia A"},{"family":"Kroenke","given":"Candyce H"},{"family":"Simon","given":"Michael"},{"family":"Lane","given":"Dorothy"},{"family":"Stefanick","given":"Marcia"},{"family":"Luo","given":"Juhua"}],"issued":{"date-parts":[["2017",2]]}}},{"id":692,"uris":["http://zotero.org/users/2724931/items/FETAPZNU"],"uri":["http://zotero.org/users/2724931/items/FETAPZNU"],"itemData":{"id":692,"type":"article-journal","title":"Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General Population in Korea Using the National Health Insurance Service–National Sample Cohort","container-title":"Diseases of the Colon & Rectum","volume":"60","issue":"11","abstract":"BACKGROUND: BACKGROUND:In Korea, the incidence of colorectal cancer has increased and obesity is on a rising trend because of a Westernized lifestyle in men.\nOBJECTIVE: OBJECTIVE:The purpose of this study was to evaluate the relationship between metabolic health status, as well as BMI, and the incidence of colorectal cancer.\nDESIGN: DESIGN:This was a prospective cohort study.\nSETTINGS: SETTINGS:The study was conducted with the National Health Insurance Service–National Sample Cohort.\nPATIENTS: PATIENTS:A total of 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 y).\nMAIN OUTCOME MEASURES: MAIN OUTCOME MEASURES:Demographic, anthropometric, and laboratory data at baseline were collected and categorized. The presence of diabetes mellitus, hypertension, and dyslipidemia was defined using the criteria of previous studies. The incidence of colorectal cancer was also defined according to the International Classification of Disease, 10th Revision, codes and the claim data on endoscopy with biopsy.\nRESULTS: RESULTS:During the follow-up, 5108 new cases of colorectal cancer occurred. Being underweight (<18.5

kg/m2) reduced the risk for colorectal cancer among women (adjusted HR = 0.646 (95% CI, 0.484–0.863)), whereas high BMI significantly increased the risk in men and in the elderly. Obesity (≥25

kg/m2), diabetes mellitus, and hypertension were identified as risk factors for colorectal cancer in men but not for women. Although metabolically unhealthy nonobese men had a higher risk for colorectal cancer than metabolically healthy nonobese men (adjusted HR = 1.114 (95% CI, 1.004–1.236)), the risk was lower than that in the obese men.\nLIMITATIONS: LIMITATIONS:The study population consisted of people who underwent health examinations, thus there could be selection bias.\nCONCLUSIONS: CONCLUSIONS:In Korean adults, obesity contributes to the incidence of colorectal cancer with a sex difference. Nonobese but metabolically unhealthy men are considered to be a high-risk group for colorectal cancer, but obesity itself is more important in colorectal carcinogenesis. See Video Abstract at http://links.lww.com/DCR/A475.","URL":"https://journals.lww.com/dcrjournal/Fulltext/2017/11000/Association_3706","author":[{"family":"Shin","given":"Cheol Min"},{"family":"Han","given":"Kyungdo"},{"family":"Lee","given":"Dong Ho"},{"family":"Choi","given":"Yoon Jin"},{"family":"Kim","given":"Nayoung"},{"family":"Park","given":"Young Soo"},{"family":"Yoon","given":"Hyuk"}],"issued":{"date-parts":[["2017"]]}},{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},{"family":"Son","given":"Hee Jung"},{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":[["2016",12,1]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3

′

-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3

′

-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3

′

-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study

aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}},{"id":142,"uris":["http://zotero.org/users/2724931/items/6XNHFT4N"],"uri":["http://zotero.org/users/2724931/items/6XNHFT4N"],"itemData":{"id":142,"type":"article-journal","title":"Metabolic syndrome is associated with colorectal cancer in men","container-title":"European Journal of Cancer","page":"1866-1872","volume":"46","issue":"10","abstract":"Aim of the study\nWe assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.\nMethods\nWe analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.\nResults\nWith reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with
⩾
3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.\nConclusion\nThis study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.","DOI":"10.1016/j.ejca.2010.03.010","ISSN":"0959-8049","journalAbbreviation":"European Journal of Cancer","author":[{"family":"Pelucchi","given":"Claudio"},{"family":"Negri","given":"Eva"},{"family":"Talamini","given":"Renato"},{"family":"Levi","given":"Fabio"},{"family":"Giacosa","given":"Attilio"},{"family":"Crispo","given":"Anna"},{"family":"Bidoli","given":"Ettore"},{"family":"Montella","given":"Maurizio"},{"family":"Franceschi","given":"Silvia"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2010",7]]}}},{"id":152,"uris":["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology","page":"1406-1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 47, 49, 50, 52
–
58, 66
]
RE
1.28 [1.20-1.37]
7.51
(
P
< 0.00001)
0.01
67.35, df = 23
(

P
< 0.00001)
66
0.6062
0.5381
AA
3 (3) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E9aVCv1N","properties":{"formattedCitation":"\\super 46,51,67\\nosupersub{}","plainCitation":"46,51,67","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology & Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":'AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia. Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 51, 67
]
FE
1.43 [1.14-1.79]
3.13
(
P
= 0.002)
NA
0.48, df = 2
(
P
= 0.79)

0
Hypertriglyceridemia and CRN risk
CRA
9 (12) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Y0Dk6ld0","properties":{"formattedCitation":"\\super 44,46,63\\uc0\\u8211{}65,67\\uc0\\u8211{}69,73\\nosupersub{}","plainCitation":"44,46,63–65,67–69,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},

{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},

{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

44, 46, 63

–

65, 67

–

69, 73

]

RE

1.30 [1.13-1.49]

3.76

(

P

= 0.0002)

0.05

137.65, df = 11

(

P

< 0.00001)

92

0.5452

0.0518

CRC

6 (12) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"iQPZO9Kw","properties":{"formattedCitation":"\\super 44,46,54,56,57,66\\nosupersub {}","plainCitation":"44,46,54,56,57,66","noteIndex":0},"citationItems":[{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},

{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},
{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":
["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-
journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in
determining the risk of colorectal cancer in Koreans","container-title":"BMC
Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO
Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in
cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three
VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850
participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF
polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and
gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs)
of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p =
0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-
environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008).
CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS.
ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-
881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-
881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong
Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},
{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},
{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},
{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":152,"uris":
["http://zotero.org/users/2724931/items/2S89J5KW"],"uri":
["http://zotero.org/users/2724931/items/2S89J5KW"],"itemData":{"id":152,"type":"article-journal","title":"Risk
factors associated with rectal neuroendocrine tumors: a cross-sectional study.","container-title":"Cancer
epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research,
cosponsored by the American Society of Preventive Oncology","page":"1406-
1413","volume":"23","issue":"7","abstract":"BACKGROUND: The incidence of rectal neuroendocrine tumors
(NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known

about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population. METHODS: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression. RESULTS: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14-0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06-4.15), male gender (OR, 1.92; 95% CI, 1.15-3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01-2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10-3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (>/=150 mg/dL), and higher homeostasis model assessment of insulin resistance (>/=2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis. CONCLUSIONS: Young age (<50 years), male gender, alcohol drinking, and a low","DOI":"10.1158/1055-9965.EPI-14-0132","ISSN":"1538-7755 1055-9965","note":"PMID: 24813818","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","language":"eng","author":[{"family":"Jung","given":"Yoon Suk"},{"family":"Yun","given":"Kyung Eun"},{"family":"Chang","given":"Yoosoo"},{"family":"Ryu","given":"Seungho"},{"family":"Park","given":"Jung Ho"},{"family":"Kim","given":"Hong Joo"},{"family":"Cho","given":"Yong Kyun"},{"family":"Sohn","given":"Chong Il"},{"family":"Jeon","given":"Woo Kyu"},{"family":"Kim","given":"Byung Ik"},{"family":"Park","given":"Dong Il"}],"issued":{"date-parts":[["2014",7]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence

of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 54, 56, 57, 66
]
RE
1.14 [1.01-1.28]
2.10
(
P
= 0.04)
0.03
49.46, df = 11
(
P
< 0.00001)
78
0.3108
0.7347
AA
2 (2) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"4U4tMUz4","properties":{"formattedCitation":"\\super 46,67\\nosupersub{}","plainCitation":"46,67","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 67
]
FE
2.12 [1.62-2.77]
5.46
(
P
< 0.00001)
NA
0.56, df = 1
(
P
= 0.45)

0
Visceral Obesity and CRN risk
CRA
10 (13) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9J0cdb28","properties":{"formattedCitation":"\\super 46,60,63,65,67\\uc0\\u8211{}70,72,73\\nosupersub{}","plainCitation":"46,60,63,65,67–70,72,73","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},

{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the

40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

46, 60, 63, 65, 67

–

70, 72, 73

]

RE

1.30 [1.19-1.42]

5.72

(

P

< 0.00001)

0.01

37.58, df = 12

(

P

= 0.0002)

68

0.7650

0.6954

CRC

4 (12) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"W4t7iJcm","properties":{"formattedCitation":"\\super 46,53,55,56\\nosupersub{}","plainCitation":"46,53,55,56","noteIndex":0},"citationItems":[{"id":250,"uris":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"uri":["http://zotero.org/users/2724931/items/QHPCVRZ8"],"itemData":{"id":250,"type":"article-journal","title":"Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center","container-title":"Journal of Gastroenterology","page":"1112-1121","volume":"51","issue":"12","abstract":"Rectal neuroendocrine tumor (NET) is the most common NET in Asia. The risk factors associated with rectal NETs are unclear because of the overall low incidence rate of these tumors and the associated difficulty in conducting large epidemiological studies on rare cases. The aim of this study was to exploit the benefits of big data analytics to assess the risk factors associated with rectal NET.","DOI":"10.1007/s00535-016-1198-9","ISSN":"1435-5922","journalAbbreviation":"Journal of Gastroenterology","author":[{"family":"Pyo","given":"Jeung Hui"},{"family":"Hong","given":"Sung Noh"},{"family":"Min","given":"Byung-Hoon"},{"family":"Lee","given":"Jun Haeng"},{"family":"Chang","given":"Dong Kyung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae Jun"},{"family":"Choi","given":"Sun Kyu"},{"family":"Jung","given":"Sin-Ho"},

{"family":"Son","given":"Hee Jung"},{"family":"Kim","given":"Young-Ho"}],"issued":{"date-parts":[["2016",12,1]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":119,"uris":["http://zotero.org/users/2724931/items/S9F263MP"],"uri":["http://zotero.org/users/2724931/items/S9F263MP"],"itemData":{"id":119,"type":"article-journal","title":"Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study.","container-title":"Angiology","page":"390-396","volume":"63","issue":"5","abstract":"The effect of Mediterranean diet on colorectal cancer, in the presence of the metabolic syndrome, was evaluated in 250 patients with first developed cancer (63 +/- 12 years, 59% males) and 250 age-gender-matched controls. Adherence to the Mediterranean diet was evaluated with the modified-MedDietScore (theoretical range 0-75), while assessment of the metabolic syndrome (MetS) was based on the third Adult Treatment Panel ([ATP III] National Cholesterol Education Program) criteria. Presence of MetS (1.66, 95% confidence interval [CI] 1.02, 2.69), age (4.25, 95% CI 2.33, 7.77), smoking (1.85, 95% CI 1.27, 2.70), and family history of colorectal cancer (3.37, 95% CI 1.69, 6.75) had a detrimental effect, whereas adherence to the Mediterranean diet (0.88, 95% CI 0.84, 0.92) and body mass index (0.93, 95%CI 0.89, 0.98) had a protective role regarding colorectal cancer. Mediterranean diet had the same effect in relation to colorectal cancer, in both participants with (0.84, 95% CI 0.76, 0.93) and without MetS (0.89, 95% CI 0.85, 0.94).","DOI":"10.1177/0003319711421164","ISSN":"1940-1574 0003-3197","note":"PMID: 22267847","journalAbbreviation":"Angiology","language":"eng","author":[{"family":"Kontou","given":"Niki"},{"family":"Psaltopoulou","given":"Theodora"},{"family":"Soupos","given":"Nick"},{"family":"Polychronopoulos","given":"Evangelos"},{"family":"Xinopoulos","given":"Dimitrios"},{"family":"Linos","given":"Athena"},{"family":"Panagiotakos","given":"Demosthenes B."}],"issued":{"date-parts":[["2012",7]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},

{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 53, 55, 56
]
RE
1.18 [1.07-1.31]
3.30
(
P
= 0.0010)
0.02
39.40, df = 11
(
P
< 0.0001)
72
0.8406
0.9420
AA
3 (3) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NC57P0lE","properties":{"formattedCitation":"\\super
46,67,70\\nosupersub{}","plainCitation":"46,67,70","noteIndex":0},"citationItems":[{"id":121,"uris":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-
journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-
title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE:
Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal
neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon,
including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess
the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the
National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667
polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated
using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride
levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated
with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal
adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon
adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and
adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum.
CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including
advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-
5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":
[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},
{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},
{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum
Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},
{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},
{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":
[["2012",5]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":
["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-
journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in
Asians","container-title":"Digestive Diseases and Sciences","page":"1025-
1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet
protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of
colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-
2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":
[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min
Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun
Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},
{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":145,"uris":
["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":
["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-
journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49
years of age","container-title":"Gastrointestinal Endoscopy","page":"480-
489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal
neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence
and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults
offered to subjects of a health care provider that offers screening services as part of an employer-provided
wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of
age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in
subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with
increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced
adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased
significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the
40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and
older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal

obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 67, 70
]
RE
1.21 [0.74-1.96]
0.77
(
P
= 0.44)
0.12
5.83, df = 2
(
P
= 0.05)
66
Low HDL-Cholesterol and CRN risk
CRA
7 (10) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"yc9KFo1X","properties":{"formattedCitation":"\\super 44,46,63,67\\uc0\\u8211{}69,73\\nosupersub{}","plainCitation":"44,46,63,67–69,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":

[["2012",5]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 63, 67
–

69, 73
]
RE
1.02 [0.92-1.12]
0.31
(
P
= 0.75)
0.01
34.52, df = 9
(
P
< 0.0001)
74
0.7275
0.0548
CRC
5 (12) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NHmQ96A6","properties":{"formattedCitation":"\\super 44,46,47,54,56\\nosupersub {}","plainCitation":"44,46,47,54,56","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":702,"uris":["http://zotero.org/users/2724931/items/YE8JCYJA"],"uri":["http://zotero.org/users/2724931/items/YE8JCYJA"],"itemData":{"id":702,"type":"article-journal","title":"A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers","container-title":"American Journal of Epidemiology","page":"652-664","volume":"164","issue":"7","abstract":"Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)2) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon (n = 227), rectal (n = 183), and colorectal (n = 410) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-

Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85; p-trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index ≥25 kg/m2, and HDL cholesterol level <40 mg/dl (<1.55 mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.","DOI":"10.1093/aje/kwj253","ISSN":"0002-9262","journalAbbreviation":"American Journal of Epidemiology","author":[{"family":"Bowers","given":"Katherine"},{"family":"Albanes","given":"Demetrius"},{"family":"Limburg","given":"Paul"},{"family":"Pietinen","given":"Pirjo"},{"family":"Taylor","given":"Phil R."},{"family":"Virtamo","given":"Jarmo"},{"family":"Stolzenberg-Solomon","given":"Rachael"}],"issued":{"date-parts":[["2006",10,1]]}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3

′

-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3

′

-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3

′

-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective

Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 47, 54, 56
]
RE
1.13 [0.93-1.37]
1.26
(
P
= 0.21)
0.10
102.94, df = 11
(
P
< 0.00001)
89
0.7373
0.8443
AA
2 (2) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EQDOJC2W","properties":{"formattedCitation":"\\super 46,67\\nosupersub{}","plainCitation":"46,67","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":

[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},
{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},
{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum
Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},
{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},
{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":
[["2012",5]]}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":
["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-
journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in
Asians","container-title":"Digestive Diseases and Sciences","page":"1025-
1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet
protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of
colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-
2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":
[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min
Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun
Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},
{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":
[["2014"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 67

]
FE
1.18 [0.84-1.66]
0.95
(
P
= 0.34)
NA
0.84, df = 1
(
P
= 0.36)
0

AA
advanced adenoma,
CRA
colorectal adenoma,
CRC
colorectal cancer,
df
degree of freedom,
FE
fixed-effects,
HDL
high-density lipoprotein,
NA
not applicable,
RE
random-effects,
RR
risk ratio.

Hypertriglyceridemia and colorectal neoplasms

In a pooled analysis of nine studies comprising 12 datasets, a summary RR of 1.30 (95% CI 1.13-1.49) was found (Supplementary Figure 3.1), with evidence of considerable heterogeneity (
I
2
=
92%), suggesting that individuals with elevated levels of triglycerides are more prone to developing CRA than individuals with normal levels. The results of Begg
’s
and Egger
’s
tests revealed no sign of funnel plot asymmetry (
P
=
0.5452 and
P
=
0.0518 respe
ctively).

A stratified analysis by MetS definitions found a higher significant positive association with CRA risk in studies using the conventional definition (RR
=
1.44; 95% CI 1.18-1.75;
I
2
=
95%) compared to a non-significant modest increase of CRA incidence when using unconventional definitions (RR
=
1.07; 95% CI 0.96-1.19;

I
2
=
11%) (Supplementary Table 3.1). The Baujat plot illustrated that the dataset (Kim 2012 AA / NCEP-ATP III)
[
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"30FauoEJ","properties":{"formattedCitation":"\\super 46\\nosupersub {}","plainCitation":"46","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46
] contributed to overall heterogeneity (Supplementary Figure 3.2).
A modest relationship between hypertriglyceridemia and risk of CRC was noticed in a meta-analysis of six studies with 12 datasets involving 73,856 participants (RR
=
1.14; 95% CI 1.01-1.28;
I
2
=
78%) (Supplementary Figure 3.3). Begg's test (
P
=
0.5452) and Egger's test (
P
=
0.0518) suggested no evidence of a small study effect. All the strata considerably influenced the risk estimate.
Significant positive associations were noticed in cohort studies (RR
=
1.33; 95% CI 1.15-1.54;
I
2
=
60%), studies considering the conventional MetS definition (RR
=
1.21; 95% CI 1.08-1.35;
I
2
=
64%), and among men (RR
=
1.16; 95% CI 1.05-1.28;
I
2
=
0%), while a non-significant increase of CRC incidence was noticed in non-cohort studies (RR
=
1.04; 95% CI 0.91-1.20;
I
2
=
71%), in studies utilizing unconventional MetS definitions (RR
=
1.01; 95% CI 0.73-1.38;
I
2
=
86%), and among women (RR
=
1.10; 95% CI 0.97-1.25;
I
2
=

0%).
Sensitivity analysis revealed that two datasets (Kim 2012 CC / NCEP-ATP III) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"YUgMBWto","properties":{"formattedCitation":"\\super 46 \\nosupersub{}","plainCitation":"46","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46
] and (Jeon 2014 CC / Other) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"OC2BiJfH","properties":{"formattedCitation":"\\super 54 \\nosupersub{}","plainCitation":"54","noteIndex":0},"citationItems":[{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

54

] modified the heterogeneity estimat
ion (Supplementary Table 3.3). H
owever, one study contributed to overall heterogeneity and res
ult according to the Baujat plot
(Supplementary Figure 3.4).
There was a remarkable difference in the magnitude of the risk estimates about the involvement of high values of triglycerides with CRA and CRC.
Visceral obesity and colorectal neoplasms
Ten studies with 13 datasets on visceral obesity and CRA
incidence were available for the analysis.
The combined
RRs for patients with versus without central obesity was 1.30 (95% CI 1.19-1.42,
I
2
=
68%) (Supplementary Figure 4.1), suggesting a positive significant association. There was no evidence of small study effect or publication bias (
P
=
0.7650 with Begg's test and
P
=
0.6954 with Egger's test). MetS definition influenced the effect estimate. A significant association was found in studies considering the conventional MetS definition (RR
=
1.23; 95% CI 1.07-1.42;
I
2
=
71%), however, the result for the unconventional definitions was stronger (RR
=
1.35; 95% CI 1.20-1.52;
I
2
=
63%) (Supplementary Table 4.1). The Baujat plot illustrated that two studies [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NLqDsaZS","properties":{"formattedCitation":"\\super 60,68 \\nosupersub{}","plainCitation":"60,68","noteIndex":0},"citationItems":[{"id":690,"uris":["http://zotero.org/users/2724931/items/VY8D9VHF"],"uri":["http://zotero.org/users/2724931/items/VY8D9VHF"],"itemData":{"id":690,"type":"article-journal","title":"Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps","container-title":"Obesity","page":"S72-S80","volume":"25","issue":"S2","abstract":"Objective Prevention of colorectal cancer (CRC) by colonoscopy is recommended according to age and personal/familial history. Metabolic alterations are associated with colorectal adenomas, but data are scarce regarding serrated polyps and advanced polyps. The aim of this study was to evaluate the association between metabolic alterations and colorectal polyp type and advanced polyps. Methods A case?control study was conducted among consecutive subjects, 40 to 70 years old, who underwent screening/diagnostic colonoscopy from 2010 to 2015. Subjects who were treated for diabetes, who had a family/personal history of CRC, and who were at high risk for CRC were excluded. Participants underwent anthropometric, laboratory, and ultrasonographic evaluations and a medical and lifestyle interview. Polyps were histologically classified as adenomatous or serrated polyps and divided into advanced and non?advanced categories. Results The study included 828 participants (58.4?±?6.6 years, 50.4% men). Abdominal obesity (odds ratio [OR]?=?1.67, 95% CI: 1.20?2.30), hypertension (OR?=?1.47, 95% CI: 1.03?2.09), and a high glycosylated hemoglobin percentage (HbA1c%) (OR?=?1.57, 95% CI: 1.06?2.34) were independently associated with colorectal adenomas, whereas a high triglyceride to high?density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR?=?2.31, 95% CI: 1.32?4.03). A combination of three metabolic alterations was strongly associated with colorectal polyps. Conclusions Abdominal obesity, hypertension, and a high HbA1c% are independently associated with adenomas, whereas a high TG/HDL ratio is associated with serrated polyps. These parameters are easily accessible in clinical practice and may help define high?risk groups for CRC.","DOI":"10.1002/oby.22001","ISSN":"1930-7381","journalAbbreviation":"Obesity","author":[{"literal":"Fliss
-
Isakov Naomi"},{"literal":"Zelber
-
Sagi Shira"},{"literal":"Webb Muriel"},{"literal":"Halpern Zamir"},{"literal":"Shibolet Oren"},{"literal":"Kariv Revital"}],"issued":{"date-parts":[["2017",10,31]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with

adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
60, 68
] contributed on the overall result, and one study [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3v7xvye4","properties":{"formattedCitation":"\\super 67\\nosupersub {}","plainCitation":"67","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
67
] comprised of two datasets one contributed to the overall heterogeneity and the other on overall result (Supplementary Figure 4.2). This positive statistically significant association was similarly observed in four studies with 12 datasets on the relationship between WC and CRC (RR
=
1.18; 95% CI 1.07-1.31;
I
2
=
72%) (Supplementary Figure 4.3). Neither Begg’s test (
P
=
0.8406) nor Egger’s test (
P
=
0.9420) have shown statistical significance for publication bias. MetS definition and cancer site modified the pooled risk ratio. A higher risk estimate, but not statistically significant was observed in studies using unconventional MetS definitions (RR=1.26; 95% CI 0.99-1.60;
I
2
=
85%) than studies applying the conventional definition (RR
=
1.14; 95% CI 1.05-1.25;
I
2
=
43%).

804545
3412186
0
0
173990
8078801

Figure
SEQ Figure * ARABIC
2
:
Association between FBG and CRA formation: (a) Forest plot; (b) Funnel plot.
AA
advanced adenomas,
CI
confidence interval,
CRA
colorectal adenoma,
FBG
fasting blood glucose,
IDF
International Diabetes Foundation,
M
men,
M-H

Mantel-Haenszel,
NCEP-ATP III
National Cholesterol Education Program-Adult Treatment Panel III, W women.

0
0

Figure
SEQ Figure * ARABIC
2
:
Association between FBG and CRA formation: (a) Forest plot; (b) Funnel plot.
AA
advanced adenomas,
CI
confidence interval,
CRA
colorectal adenoma,
FBG
fasting blood glucose,
IDF
International Diabetes Foundation,
M
men,
M-H
Mantel-
Haenszel
,
NCEP-ATP III
National Cholesterol Education Program-Adult Treatment Panel III, W women.

Figure
SEQ Figure * ARABIC
3
:
Additional analyses for the association between FBG and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. One simulated negative study was added (hollow circle) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR slightly decreased from (1.33; 95% CI 1.14-1.54) in the initial analysis to (1.28; 95% CI 1.11-1.46) after adjustment. (b) Baujat plot: indicates that the 1st dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Kim 2012 AA / NCEP-ATP III)) has contributed to the overall heterogeneity and the 6th dataset (which corresponds to (Hu 2011 CRA / NCEP-ATP III)) contributed on the overall result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.

A stratified analysis by cancer site yielded a stronger association between high waist circumference and colon cancer (RR
=
1.31; 95% CI 1.12-1.52;
I
2
=
83%) than rectal cancer (RR
=
1.11; 95% CI 1.00-1.22;
I
2
=
0%). The adjusted
RR on publication bias was increased to 1.25 (95% CI 1.13-1.38). Following the sensitivity analysis, one dataset (Aleksandrova 2011 CC / IDF (M)) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cTwPDSFa","properties":{"formattedCitation":"\\super 56 \\nosupersub{}","plainCitation":"56","noteIndex":0},"citationItems":[{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},

{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},
{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},
{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},
{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},
{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},
{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
56
] significantly modified the heterogeneity evaluation, (RR = 1.15; 95% CI 1.09-1.22;
I
2
= 28%) after its exclusion (Supplementary Table 4.3). The same dataset contributed to overall heterogeneity and was considered potentially influential (Supplementary Figure 4.4).

Low HDL-C and colorectal neoplasms

Seven studies, including ten datasets, have reported data about the relationship between CRA risk and low values of HDL-C. A non-significant positive association was found in a weighted analysis of individuals with normal levels of HDL-C against individuals with low HDL-C (RR
=
1.02; 95% CI 0.92-1.12;
I
2
=
74%) (Supplementary Figure 5.1).

Table
SEQ Table * ARABIC
3
:
Subgroup analyses results of the association between hyperglycemia and colorectal neoplasms

Subgroup	№ of studies (datasets) ref	Model	RR [95% CI]	Z-test (P value)	Heterogeneity Tau 2	Chi 2 (P value)	I 2 (%)
Hyperglycemia and colorectal adenomas							
All studies	9 (11) [	ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"842J3gRg","properties":{"formattedCitation":"\\super 44,46,63\\uc0\\u8211{}65,68,69,72,73\\nosupersub{}","plainCitation":"44,46,63–65,68,69,72,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},						

{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom

is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-

Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},
{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":
[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 63
–
65, 68, 69, 72, 73
]
RE
1.33 [1.14-1.54]
3.75 (
P
= 0.0002)
0.05
123.99, df = 10
(
P
< 0.00001)
92
Study type
Cohort
2 (4) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CWvZzEf4","properties":
{"formattedCitation":"\\super 44,46\\nosupersub{}","plainCitation":"44,46","noteIndex":0},"citationItems":
[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-
journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-
title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE:
Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal
neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon,
including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess
the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the
National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667
polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated
using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride
levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated
with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal
adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon
adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and
adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum.
CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including
advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-
5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":
[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},
{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},
{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum
Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},
{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},
{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":
[["2012",5]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":
["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-
journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a
large study","container-title":"Molecular Biology Reports","page":"2989-
2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a
strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was
to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and
determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and
945 females) who underwent a routine colonoscopy according to international colorectal cancer screening
guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by
ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of
CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in
the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at
sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal
adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate
analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05).
After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for
CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid
carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD.
(ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?
term=zheng+minghua&rank=1)."","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-
4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},
{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},
{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-
Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},
{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":
[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46
]
RE
1.27 [1.03-1.56]
2.25 (
P
= 0.02)

0.04
49.54, df = 3
(
P
< 0.00001)
94
Non-cohort
7 (7) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NaZmIS6y","properties":{"formattedCitation":"\\super 63\\uc0\\u8211{}65,68,69,72,73\\nosupersub{}","plainCitation":"63–65,68,69,72,73","noteIndex":0},"citationItems":[{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":118,"uris":

["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":
["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-
journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma
in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-
303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between
metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin
resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic
syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment
insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving
individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to
males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three
groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was
defined by a combination of any three of the following components: central obesity (waist circumference >/= 90
cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg);
elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and
elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and
insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist
circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively).
Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001).
However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate
that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-
3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp
Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},
{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},
{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":
["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-
journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal
Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the
Formosan Medical Association","page":"100-
108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)
60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},
{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-
Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":137,"uris":
["http://zotero.org/users/2724931/items/566MKVT3"],"uri":
["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-
journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of
Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim:
Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral
obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults
(male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic
computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of
CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous
adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and
percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic
syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking,
metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT
(P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate
analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for
those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic
syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate
analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are
needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-
1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},
{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},
{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-
Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae
Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":
[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":
["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is
Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and
Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol
Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},
{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang
Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},
{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-
Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},
{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":
[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
63
–
65, 68, 69, 72, 73
]
RE
1.35 [1.12-1.63]
3.20 (
P
= 0.001)
0.05
35.49, df = 6
(
P
< 0.00001)

83
Cross-sectional
5 (5) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"vKJrGcpw","properties":{"formattedCitation":"\\super 65,68,69,72,73\\nosupersub{}","plainCitation":"65,68,69,72,73","noteIndex":0},"citationItems":[{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":118,"uris":["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was

defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 65, 68, 69, 72, 73

]

RE

1.37 [1.13-1.67]

3.21 (

P

= 0.001)

0.03

18.57, df = 4

(

P

= 0.0010)

78

Case-control

2 (2) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2B4WEtc6","properties":{"formattedCitation":"\\super 63,64\\nosupersub{}","plainCitation":"63,64","noteIndex":0},"citationItems":[{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":[["2005",4]]}}},{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 63, 64

]

FE
1.39 [0.74-2.64]
1.02 (
P
= 0.31)
0.19
8.36, df = 1 (
P
= 0.004)
88
Study location
Asia
8 (10) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ednawrA9","properties":{"formattedCitation":"\\super 44,46,63,65,68,69,72,73\\nosupersub {}","plainCitation":"44,46,63,65,68,69,72,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":708,"uris":["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately

increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":
[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},
{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},
{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":
[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":
["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical Science","page":"1288-
1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom
is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL
ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":
[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":118,"uris":
["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":
["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},
{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":
["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-
108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)
60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},
{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":137,"uris":
["http://zotero.org/users/2724931/items/566MKVT3"],"uri":
["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are

needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 63, 65, 68, 69, 72, 73
]
RE
1.29 [1.11-1.50]
3.35 (
P
= 0.0008)
0.05
117.99, df = 9
(
P
< 0.00001)
92
North America
1 (1) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"1TZFYGOZ","properties":{"formattedCitation":"\\super 64\\nosupersub{}","plainCitation":"64","noteIndex":0},"citationItems":[{"id":362,"uris":["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
64
]
RE
1.98 [1.30-3.00]
3.20 (
P
= 0.001)
NA
NA
NA
MetS definition
Conventional
4 (6) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"VgcbE5YN","properties":{"formattedCitation":"\\super 44,46,69,73\\nosupersub{}","plainCitation":"44,46,69,73","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was

to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}},{"id":386,"uris":["http://zotero.org/users/2724931/items/FP3DWZMH"],"uri":["http://zotero.org/users/2724931/items/FP3DWZMH"],"itemData":{"id":386,"type":"article-journal","title":"Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?","container-title":"Cancer Epidemiology and Prevention Biomarkers","page":"1543-1546","volume":"16","issue":"8","journalAbbreviation":"Cancer Epidemiol Biomarkers Prev","author":[{"family":"Kim","given":"Jeong Hwan"},{"family":"Lim","given":"Yun Jeong"},{"family":"Kim","given":"Young-Ho"},{"family":"Sung","given":"In-Kyung"},{"family":"Shim","given":"Sang Goon"},{"family":"Oh","given":"Sung-Ook"},{"family":"Park","given":"Sin-Sil"},{"family":"Yang","given":"Sun"},{"family":"Son","given":"Hee Jung"},{"family":"Rhee","given":"Poong-Lyul"},{"family":"Kim","given":"Jae J."},{"family":"Rhee","given":"Jong Chul"},{"family":"Choi","given":"Yoon-Ho"}],"issued":{"date-parts":[["2007",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 69, 73
]
RE
1.35 [1.11-1.64]
3.01 (
P
= 0.003)
0.05
86.30, df = 5
(
P
< 0.00001)
94
Unconventional
5 (5) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Zr0YH6Cd","properties":{"formattedCitation":"\\super 63\\uc0\\u8211{}65,68,72\\nosupersub{}","plainCitation":"63

–65,68,72","noteIndex":0},"citationItems":[{"id":362,"uris":
["http://zotero.org/users/2724931/items/83RDVNWE"],"uri":
["http://zotero.org/users/2724931/items/83RDVNWE"],"itemData":{"id":362,"type":"article-
journal","title":"Metabolic syndrome components and colorectal adenoma in the CLUE II cohort","container-
title":"Cancer causes & control : CCC","page":"1-10","volume":"21","issue":"1","source":"PubMed
Central","abstract":"Background\nMetabolic syndrome components have been associated with colorectal cancer in
several studies; however, the evidence for colorectal adenomas is limited. Thus, we evaluated the association
between markers of the metabolic syndrome with colorectal adenoma development in a nested case-control
study.\n\nMethods\nColorectal adenoma cases (n= 132) and matched controls who had had a negative
sigmoidoscopy or a colonoscopy (n=260) were identified between baseline in 1989 and 2000 among participants
in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor
binding protein-1, glycosylated hemoglobin, total cholesterol, high density lipoprotein-cholesterol, and
triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height
and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was
measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome
components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at
baseline.\n\nResults\nNo statistically significant associations with adenomas were observed for the markers of the
metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00;
95% CI, 1.70 – 37.67), albeit based on small numbers.\n\nConclusion\nOur findings do not support that
components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes
mellitus warranting medical treatment.","DOI":"10.1007/s10552-009-9428-6","ISSN":"0957-
5243","note":"PMID: 19774471\nPMCID: PMC3010872","journalAbbreviation":"Cancer Causes
Control","author":[{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Brancati","given":"Frederick L"},
{"family":"Pollak","given":"Michael N"},{"family":"Rifai","given":"Nader"},{"family":"Clipp","given":"Sandra
L"},{"family":"Hoffman-Bolton","given":"Judy"},{"family":"Helzlsouer","given":"Kathy J"},
{"family":"Platz","given":"Elizabeth A"}],"issued":{"date-parts":[["2010",1]]}}},{"id":708,"uris":
["http://zotero.org/users/2724931/items/VNR6N7NX"],"uri":
["http://zotero.org/users/2724931/items/VNR6N7NX"],"itemData":{"id":708,"type":"article-journal","title":"The
Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense
Forces Health Study","page":"5","volume":"6","issue":"4","source":"Zotero","abstract":"The metabolic syndrome,
a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for
cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for
colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and
colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls
with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self
Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal
obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered
HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic
blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist
circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made
for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately
increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds
ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI
1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and
was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to
be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and
type 2 diabetes.","journalAbbreviation":"APJCP","language":"en","author":
[{"family":"Morita","given":"Takako"},{"family":"Tabata","given":"Shinji"},
{"family":"Mineshita","given":"Masamichi"},{"family":"Mizoue","given":"Tetsuya"},
{"family":"Moore","given":"Malcolm A"},{"family":"Kono","given":"Suminori"}],"issued":{"date-parts":
[["2005",4]]}}},{"id":255,"uris":["http://zotero.org/users/2724931/items/7IV5ACIY"],"uri":
["http://zotero.org/users/2724931/items/7IV5ACIY"],"itemData":{"id":255,"type":"article-journal","title":"The
Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases","container-title":"Journal of Korean Medical
Science","page":"1288-
1294","volume":"30","issue":"9","archive":"PMC","archive_location":"PMC4553676","abstract":"Cholecystectom
is associated with an increased risk of colorectal cancer, but little is known about the relationship between
gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk
factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study,
we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and
identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic
individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and
colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was
significantly higher than that in the control group (32.1% vs. 26.8%; P = 0.032, 35.8% vs. 26.9%; P = 0.020). A
multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted
odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14;
95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI,
0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with
increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to
gallbladder polyps, especially those ≥ 5 mm. GRAPHICAL
ABSTRACT:","DOI":"10.3346/jkms.2015.30.9.1288","ISSN":"1011-8934","author":
[{"family":"Hong","given":"Sung Noh"},{"family":"Lee","given":"Tae Yoon"},{"family":"Yun","given":"Sung-
Cheol"}],"issued":{"date-parts":[["2015",9]]}}},{"id":118,"uris":
["http://zotero.org/users/2724931/items/TSAINUMV"],"uri":
["http://zotero.org/users/2724931/items/TSAINUMV"],"itemData":{"id":118,"type":"article-
journal","title":"Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma
in Japanese males.","container-title":"The Tohoku journal of experimental medicine","page":"297-
303","volume":"223","issue":"4","abstract":"Many previous reports have documented a relationship between
metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin
resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic
syndrome components and insulin resistance with adenoma, we investigated homeostasis model assessment
insulin resistance (HOMA-IR) in individuals with adenoma. A cross-sectional study was conducted involving
individuals who underwent scheduled health examinations using total colonoscopy. Restricting the subjects to

males, 261 with adenoma and 702 without adenoma were investigated. HOMA-IR was categorized into three groups: normal (< 1.6), intermediate (>/= 1.6 - < 2.5), and insulin resistance (2.5 </=). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >/= 90 cm); elevated blood pressure (systolic blood pressure >/= 130 mmHg and/or diastolic blood pressure 85 mmHg); elevated fasting plasma glucose (>/= 100 mg/dL); reduced high-density lipoprotein-cholesterol (< 40 mg/dL); and elevated triglyceride (>/= 150 mg/dL). Multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P trend = 0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. Our data indicate that an increased level of HOMA-IR is a risk factor for colorectal adenoma in Japanese males.","ISSN":"1349-3329 0040-8727","note":"PMID: 21478654","journalAbbreviation":"Tohoku J Exp Med","language":"eng","author":[{"family":"Sato","given":"Takeshi"},{"family":"Takeda","given":"Hiroaki"},{"family":"Sasaki","given":"Yu"},{"family":"Kawata","given":"Sumio"}],"issued":{"date-parts":[["2011",4]]}}},{"id":137,"uris":["http://zotero.org/users/2724931/items/566MKVT3"],"uri":["http://zotero.org/users/2724931/items/566MKVT3"],"itemData":{"id":137,"type":"article-journal","title":"Visceral obesity as a risk factor for colorectal neoplasm","container-title":"Journal of Gastroenterology and Hepatology","page":"411-417","volume":"23","issue":"3","abstract":"Background and Aim: Obesity as a risk factor for colorectal neoplasm (CRN) is controversial. In the present study, we evaluated visceral obesity as a risk factor for CRN. Methods: We prospectively enrolled 200 consecutive, asymptomatic adults (male : female = 133:67, mean age, 50.9 ± 8.5 years) undergoing both colonoscopy and abdominopelvic computed tomography (CT) scan for routine health evaluations. The presence or absence and the characteristics of CRN were determined during colonoscopy. The amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue was measured by an abdominopelvic CT scan. Body mass index, waist circumference, and percentage of body fat were measured. Blood pressure and other blood markers for assessing the metabolic syndrome were also investigated. Results: Of the 200 patients, 53 (26.5%) had CRN. Old age, smoking, metabolic syndrome, and a high fasting plasma glucose level were associated with an increased risk of CRN. VAT (P < 0.01) and waist circumference (P = 0.01) were significantly higher in those with CRN. A multivariate analysis of the risks of CRN showed an odds ratio of 4.07 (95% confidence interval: 1.01–16.43, P = 0.03) for those with VAT over 136.61 cm2 relative to those with VAT under 67.23 cm2. Waist circumference, metabolic syndrome, and fasting plasma glucose levels were not independent risk factors for CRN in the multivariate analysis. Conclusion: Increased VAT is an independent risk factor for CRN. Further large scale studies are needed to clarify the causal relationship between VAT and CRN.","DOI":"10.1111/j.1440-1746.2007.05125.x","ISSN":"1440-1746","author":[{"family":"Oh","given":"Tae-Hoon"},{"family":"Byeon","given":"Jeong-Sik"},{"family":"Myung","given":"Seung-Jae"},{"family":"Yang","given":"Suk-Kyun"},{"family":"Choi","given":"Kwi-Sook"},{"family":"Chung","given":"Jun-Won"},{"family":"Kim","given":"Benjamin"},{"family":"Lee","given":"Don"},{"family":"Byun","given":"Jae Ho"},{"family":"Jang","given":"Se Jin"},{"family":"Kim","given":"Jin-Ho"}],"issued":{"date-parts":[["2008",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
63
–
65, 68, 72
]
RE
1.30 [1.01-1.67]
2.04 (
P
= 0.04)
0.06
25.61, df = 4
(
P
< 0.0001)
84
Hyperglycemia and colorectal cancer
All studies
7 (14) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9zH9ZO8A","properties":{"formattedCitation":"\\super 44,46,48,52,54,56,57\\nosupersub {}","plainCitation":"44,46,48,52,54,56,57","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal

adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},

{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},
{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},
{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":
["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-
journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal
carcinoma","container-title":"ANZ Journal of Surgery","page":"331-
336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot
of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study
aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507
cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to
establish the database. The patients with colorectal cancer were divided into two groups based on the presence of
MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox
proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype,
differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The
existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence
of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in
the control group. MS is one of the important elements that can independently influence the survival (odds ratio
(OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival
compared with other parameters. Conclusion: There is a close relationship between MS and colorectal
carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma.
Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the
cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":
[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},
{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},
{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":
[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 48, 52, 54, 56, 57

]
RE
1.35 [1.23-1.47]
6.61
(
P
< 0.00001)
0.01
31.66, df = 13
(
P
= 0.003)
59
Study type
Cohort
3 (6) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8Q2wtCs4","properties":{"formattedCitation":"\\super
44,46,48\\nosupersub{}","plainCitation":"44,46,48","noteIndex":0},"citationItems":[{"id":123,"uris":
["http://zotero.org/users/2724931/items/33PI99M5"],"uri":
["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-
journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a
large study","container-title":"Molecular Biology Reports","page":"2989-
2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a
strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was
to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and
determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and
945 females) who underwent a routine colonoscopy according to international colorectal cancer screening
guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by
ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of
CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in
the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at
sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal
adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate
analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05).
After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for
CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid
carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD.
(ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?
term=zheng+minghua&rank=1)."."DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-
4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},
{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},
{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-
Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},
{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-
journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-

title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46, 48
]
RE
1.41 [1.08-1.84]
2.49
(
P
= 0.01)
0.08
26.39, df = 5
(
P
< 0.0001)
81
Case-control
4 (8) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H3957dYA","properties":{"formattedCitation":"\\super 52,54,56,57\\nosupersub{}","plainCitation":"52,54,56,57","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
'
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC

Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO
Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer

Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 52, 54, 56, 57
]
FE
1.33 [1.25-1.41]
8.92
(
P
< 0.00001)
NA
5.72, df = 7 (
P
= 0.57)
0
Study location
Asia
4 (7) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wrTfwK0t","properties":{"formattedCitation":"\\super 44,46,54,57\\nosupersub{}","plainCitation":"44,46,54,57","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for

CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 44, 46, 54, 57

]

RE

1.42 [1.21-1.67]

4.18

(

P

< 0.0001)

0.03

27.26, df = 6

(

P

= 0.0001)

78

Europe

2 (4) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"82WzyCTE","properties":{"formattedCitation":"\\super 52,56\\nosupersub{}","plainCitation":"52,56","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal

cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 52, 56

]

FE

1.30 [1.20-1.41]

6.52

(

P

< 0.00001)

NA

3.45, df = 4 (

P

= 0.49)

0

North America

1 (2) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3dxf0P11","properties":{"formattedCitation":"\\super 48\\nosupersub{}","plainCitation":"48","noteIndex":0},"citationItems":[{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 48

]

RE

1.21 [0.83-1.77]

1.00 (

P

= 0.32)
0.02
1.30, df = 1 (
P
= 0.25)
23
MetS definition
Conventional
4 (10) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UXrMKays","properties":{"formattedCitation":"\\super 44,46,48,56\\nosupersub {}","plainCitation":"44,46,48,56","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)","page":"326-332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological

mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 44, 46, 48, 56
]
RE
1.33 [1.18-1.51]
4.50
(
P
< 0.00001)
0.02
28.42, df = 9
(
P
= 0.0008)
68
Unconventional
3 (4) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"SWMLHN8h","properties":{"formattedCitation":"\\super 52,54,57\\nosupersub{}","plainCitation":"52,54,57","noteIndex":0},"citationItems":[{"id":704,"uris":["http://zotero.org/users/2724931/items/S5H49BBF"],"uri":["http://zotero.org/users/2724931/items/S5H49BBF"],"itemData":{"id":704,"type":"article-journal","title":"Components of the metabolic syndrome and colorectal cancer risk; a prospective study","container-title":"International Journal Of Obesity","page":"304","volume":"32","journalAbbreviation":"International Journal Of Obesity","author":[{"family":"Stocks","given":"T"},{"family":"Lukanova","given":"A"},{"family":"Johansson","given":"M"},{"family":"Rinaldi","given":"S"},{"family":"Palmqvist","given":"R"},{"family":"Hallmans","given":"G"},{"family":"Kaaks","given":"R"},{"family":"Stattin","given":"P"}],"issued":{"date-parts":[["2007",9,18]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3

′

-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3

′

-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3

′

-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":144,"uris":["http://zotero.org/users/2724931/items/R3KQJIJK"],"uri":["http://zotero.org/users/2724931/items/R3KQJIJK"],"itemData":{"id":144,"type":"article-journal","title":"Clinical study on the correlation between metabolic syndrome and colorectal carcinoma","container-title":"ANZ Journal of Surgery","page":"331-336","volume":"80","issue":"5","abstract":"Background: Although metabolic syndrome (MS) has received a lot of attention in recent years, the correlation between MS and colorectal carcinoma is still not very clear. This study aims at exploring the relationship between MS and colorectal carcinoma. Methods: Data was collected from 507 cases of colorectal carcinoma and 507 cases of healthy patients between January 2002 and March 2007 to establish the database. The patients with colorectal cancer were divided into two groups based on the presence of MS. Multivariate analysis of these data for the overall survival and recurrence was performed with the Cox proportional hazard model. Variables examined by multivariate analysis were sex , age, location, histotype, differentiation, tumour, node, metastasis (TNM) stage, the number of lymph nodes detected, etc. Results: The existence of MS in the colorectal carcinoma group was clearly more than that in the control group. The existence of two to four types of abnormal metabolic diseases was significantly more in the colorectal cancer group than in the control group. MS is one of the important elements that can independently influence the survival (odds ratio (OR) = 1.501, 95% confidence interval (CI) = 1.057–2.131) and have the highest risk with worse survival compared with other parameters. Conclusion: There is a close relationship between MS and colorectal carcinoma, and MS is a significantly independent element that influences the survival of the colorectal carcinoma. Decreasing the incidence of MS maybe play a role in improving therapeutic efficacy and prognosis of the

cancer.","DOI":"10.1111/j.1445-2197.2009.05084.x","ISSN":"1445-2197","author":[{"family":"Shen","given":"Zhanlong"},{"family":"Wang","given":"Shan"},{"family":"Ye","given":"Yingjiang"},{"family":"Yin","given":"Mujun"},{"family":"Yang","given":"Xiaodong"},{"family":"Jiang","given":"Kewei"},{"family":"Liu","given":"Yan"}],"issued":{"date-parts":[["2010",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 52, 54, 57

]

FE

1.37 [1.25-1.51]

6.72

(

P

< 0.00001)

NA

2.63, df = 3 (

P

= 0.45)

0

Gender

Men

2 (3) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wKwiuRiX","properties":{"formattedCitation":"\\super 44,56\\nosupersub{}","plainCitation":"44,56","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},

{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},
{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},
{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},
{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},
{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 56
]
FE
1.34 [1.24-1.45]
3.14 (
P
= 0.002)
NA
2.85, df = 2 (
P
= 0.24)
30
Women
2 (3) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"VfvcuJcz","properties":{"formattedCitation":"\\super
44,56\\nosupersub{}","plainCitation":"44,56","noteIndex":0},"citationItems":[{"id":123,"uris":
["http://zotero.org/users/2724931/items/33PI99M5"],"uri":
["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-
journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a
large study","container-title":"Molecular Biology Reports","page":"2989-
2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a
strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was
to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and
determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and
945 females) who underwent a routine colonoscopy according to international colorectal cancer screening
guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by
ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of
CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in
the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at
sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal
adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate
analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05).
After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for
CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid
carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD.
(ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?
term=zheng+minghua&rank=1)."","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-
4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},
{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},
{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-
Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},
{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":
["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":
["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-
journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective
Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention
Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related
to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent
international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what
extent the MetS components individually account for such an association. We addressed these issues in a nested
case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density
sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined
according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III
(NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among
individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer,
whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal
cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with
colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII,
but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall,
these associations were stronger in women than in men. However, the association between MetS and colorectal
cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide
risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data
suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals
at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer
Prev Res; 4(11); 1873–83. ©2011 AACR."","DOI":"10.1158/1940-6207.CAPR-11-
0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":
[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},
{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},
{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B."},"non-dropping-

particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},
{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},
{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},
{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},
{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},
{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},
{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},
{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},
{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},
{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},
{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},
{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},
{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},
{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},
{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},
{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},
{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},
{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":
[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 56

]

RE

1.63 [1.18-2.26]

2.95 (

P

= 0.003)

0.07

14.26, df = 2

(

P

= 0.0008)

86

Cancer site

Colon

4 (5) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EQFIWyye","properties":
{"formattedCitation":"\\super 46,48,54,56\\nosupersub
{}","plainCitation":"46,48,54,56","noteIndex":0},"citationItems":[{"id":121,"uris":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":
["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-
journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-
title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE:
Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal
neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon,
including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess
the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the
National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667
polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated
using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride
levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated
with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal
adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon
adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and
adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum.
CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including
advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-
5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":
[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},
{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},
{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum
Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},
{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},
{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":
[["2012",5]]}}},{"id":700,"uris":["http://zotero.org/users/2724931/items/CSEQKLIG"],"uri":
["http://zotero.org/users/2724931/items/CSEQKLIG"],"itemData":{"id":700,"type":"article-journal","title":"A
Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal
Women","container-title":"European journal of cancer prevention : the official journal of the European Cancer
Prevention Organisation (ECP)","page":"326-
332","volume":"21","issue":"4","archive":"PMC","archive_location":"PMC5759970","abstract":"The metabolic
syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other
related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is
associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic
syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated
measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at
baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and
95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81
incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic
syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and
colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of
serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the
baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of
colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological

mechanism underlying these associations remains to be clarified.","DOI":"10.1097/CEJ.0b013e32834dbc81","ISSN":"0959-8278","author":[{"family":"Kabat","given":"Geoffrey C"},{"family":"Kim","given":"Mimi Y"},{"family":"Peters","given":"Ulrike"},{"family":"Stefanick","given":"Marcia"},{"family":"Hou","given":"Lifang"},{"family":"Wactawski-Wende","given":"Jean"},{"family":"Messina","given":"Catherine"},{"family":"Shikany","given":"James M"},{"family":"Rohan","given":"Thomas E"}],"issued":{"date-parts":[["2012",7]]}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density

sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 46, 48, 54, 56

]

FE

1.36 [1.25-1.47]

7.17

(

P

< 0.00001)

NA

2.45, df = 4 (

P

= 0.65)

0

Rectal

3 (4) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WfmCBuwM","properties":{"formattedCitation":"\\super 46,54,56\\nosupersub{}","plainCitation":"46,54,56","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3

′

-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGRO Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′

-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′

-UTR polymorphisms (1451C

>

T [rs3025040], 1612G

>

A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},{"id":146,"uris":["http://zotero.org/users/2724931/items/9WXARXXK"],"uri":["http://zotero.org/users/2724931/items/9WXARXXK"],"itemData":{"id":146,"type":"article-journal","title":"Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study","container-title":"Cancer Prevention Research","page":"1873","volume":"4","issue":"11","abstract":"Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide

risk information beyond these components (likelihood ratio test P = 0.10 for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.","DOI":"10.1158/1940-6207.CAPR-11-0218","journalAbbreviation":"Cancer Prev Res (Phila)","author":[{"family":"Aleksandrova","given":"Krasimira"},{"family":"Boeing","given":"Heiner"},{"family":"Jenab","given":"Mazda"},{"family":"Bas Bueno-de-Mesquita","given":"H."},{"family":"Jansen","given":"Eugene"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Fedirko","given":"Veronika"},{"family":"Rinaldi","given":"Sabina"},{"family":"Romieu","given":"Isabelle"},{"family":"Riboli","given":"Elio"},{"family":"Romaguera","given":"Dora"},{"family":"Overvad","given":"Kim"},{"family":"Østergaard","given":"Jane Nautrup"},{"family":"Olsen","given":"Anja"},{"family":"Tjønneland","given":"Anne"},{"family":"Boutron-Ruault","given":"Marie-Christine"},{"family":"Clavel-Chapelon","given":"Françoise"},{"family":"Morois","given":"Sophie"},{"family":"Masala","given":"Giovanna"},{"family":"Agnoli","given":"Claudia"},{"family":"Panico","given":"Salvatore"},{"family":"Tumino","given":"Rosario"},{"family":"Vineis","given":"Paolo"},{"family":"Kaaks","given":"Rudolf"},{"family":"Lukanova","given":"Annekatrin"},{"family":"Trichopoulou","given":"Antonia"},{"family":"Naska","given":"Androniki"},{"family":"Bamia","given":"Christina"},{"family":"Peeters","given":"Petra H."},{"family":"Rodríguez","given":"Laudina"},{"family":"Buckland","given":"Genevieve"},{"family":"Sánchez","given":"María-José"},{"family":"Dorronsoro","given":"Miren"},{"family":"Huerta","given":"Jose-María"},{"family":"Barricarte","given":"Aurelio"},{"family":"Hallmans","given":"Göran"},{"family":"Palmqvist","given":"Richard"},{"family":"Khaw","given":"Kay-Tee"},{"family":"Wareham","given":"Nicholas"},{"family":"Allen","given":"Naomi E."},{"family":"Tsilidis","given":"Konstantinos K"},{"family":"Pischon","given":"Tobias"}],"issued":{"date-parts":[["2011",11,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
46, 54, 56
]
FE
1.32 [1.18-1.49]
4.64
(
P
< 0.00001)
NA
3.70, df = 3 (
P
= 0.30)
19
Colorectal adenomas versus colorectal cancer
CRA
2 (4) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"TK4zM80H","properties":{"formattedCitation":"\\super 44,46\\nosupersub{}","plainCitation":"44,46","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride

levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} 44, 46

]

RE

1.27 [1.03-1.56]

2.25 (

P

= 0.02)

0.04

49.54, df = 3

(

P

< 0.00001)

94

CRC

2 (4) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0wkerqMp","properties":{"formattedCitation":"\\super 44,46\\nosupersub{}","plainCitation":"44,46","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},

{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46
]
RE
1.50 [1.06-2.12]
2.30 (
P
= 0.02)
0.10
25.40, df = 3
(
P
< 0.0001)
88
CRA
colorectal adenoma,
CRC
colorectal cancer,
df
degree of freedom,
FE
fixed-effects,
MetS
metabolic syndrome,
NA
not applicable,
RE
random-effects,
RR
risk ratio.
There was no evidence of significant publication bias with Begg
’s
test (
P
=
0.7275) and with Egger’s test (
P
=
0.0548). The result slightly
decreased
after adjusting to publication bias via the trim and fill
method to 1.00 (95% CI 0.92-1.09)
.
Two
studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"20uWHvnX","properties":{"formattedCitation":"\\super 44,69 \\nosupersub{}","plainCitation":"44,69","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},{"id":390,"uris":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"uri":["http://zotero.org/users/2724931/items/9BZ8ICKP"],"itemData":{"id":390,"type":"article-journal","title":"Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy","container-title":"Journal of the Formosan Medical Association","page":"100-108","volume":"110","issue":"2","source":"CrossRef","DOI":"10.1016/S0929-6646(11)60016-8","ISSN":"09296646","language":"en","author":[{"family":"Hu","given":"Nien-Chih"},{"family":"Chen","given":"Jong-Dar"},{"family":"Lin","given":"Yu-Min"},{"family":"Chang","given":"Jun-Yih"},{"family":"Chen","given":"Yu-Hung"}],"issued":{"date-parts":[["2011",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 69
] contributed
to

overall heterogeneity and result and one study [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"pqFDVpBd","properties":{"formattedCitation":"\\super 67 \\nosupersub{}","plainCitation":"67","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
67
] contributed to the overall heterogeneity according to the Baujat plot. One study was considered potentially influential [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Zonj7H9R","properties":{"formattedCitation":"\\super 44 \\nosupersub{}","plainCitation":"44","noteIndex":0},"citationItems":[{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations. Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1).","DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44
] (Supplementary Figure 5.2).
Consistently, our results suggest a statistically non-significant increase for HDL-C on CRC incidence. The summary of RR was 1.13; 95% CI 0.93-1.37;
I
2
=
89%) in five studies with 12 datasets comparing patients with low HDL-C levels and individuals with normal val ues (Supplementary Figure 5.3).
No evidence of the small study effect or publication bias was found (Begg's test
P
=
0.7373) and (Egger's test
P
=
0.8443). The study type, study location, and cancer site influenced the risk estimate (Supplementary Table 5.1). The adjusted RR for publication bias increased to 1.18 (95% CI 0.79-1.43) by the trim and fill method. The Baujat plot illustrated that the dataset (Jeon 2014 RC / Other) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"lTZ8wv5I","properties":{"formattedCitation":"\\super 54\\nosupersub{}","plainCitation":"54","noteIndex":0},"citationItems":[{"id":125,"uris":["http://zotero.org/users/2724931/items/ENWMID8V"],"uri":["http://zotero.org/users/2724931/items/ENWMID8V"],"itemData":{"id":125,"type":"article-journal","title":"Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans","container-title":"BMC Cancer","page":"881","volume":"14","archive":"PMC","archive_location":"PMC4289193","abstract":"BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3
′
-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3
′
-UTR polymorphisms (1451C
>
T [rs3025040], 1612G
>
A [rs10434], and 1725G

>

A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C

>

T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G

>

A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C

>

T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p <

.001) whereas the combination of VEGF 1725G

>

A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C

>

T and 1725G

>

A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS. ELECTRONIC SUPPLEMENTARY MATERIAL: The online version of this article (doi:10.1186/1471-2407-14-881) contains supplementary material, which is available to authorized users.","DOI":"10.1186/1471-2407-14-881","ISSN":"1471-2407","author":[{"family":"Jeon","given":"Young Joo"},{"family":"Kim","given":"Jong Woo"},{"family":"Park","given":"Hye Mi"},{"family":"Jang","given":"Hyo Geun"},{"family":"Kim","given":"Jung O"},{"family":"Oh","given":"Jisu"},{"family":"Chong","given":"So Young"},{"family":"Kwon","given":"Sung Won"},{"family":"Kim","given":"Eo Jin"},{"family":"Oh","given":"Doyeun"},{"family":"Kim","given":"Nam Keun"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
54
] contributed
to
overall heterogeneity and result (Supplementary Figure 5.4).
Advanced adenomas and components of the MetS
Four studies [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZMNCOAPK","properties":{"formattedCitation":"\\super 46,51,67,70\\nosupersub{}","plainCitation":"46,51,67,70","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":689,"uris":["http://zotero.org/users/2724931/items/WPUBA46Z"],"uri":["http://zotero.org/users/2724931/items/WPUBA46Z"],"itemData":{"id":689,"type":"article-journal","title":"Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study","container-title":"Canadian Journal of Gastroenterology & Hepatology","page":"8750967","volume":"2017","archive":"PMC","archive_location":"PMC5525097","abstract":"BACKGROU
AND AIMS: Obesity is a risk factor for colorectal neoplasia. We examined the influence of obesity and metabolic syndrome (MetS) on prevalence of neoplasia at screening colonoscopy. METHODS: We evaluated 2020 subjects undergoing first screening colonoscopy. Body mass index (BMI) was calculated at enrolment. Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) were identified. Details of colonoscopy, polypectomy, and histology were recorded. Odds for adenomas (A) and advanced adenomas (ADV) in overweight (BMI 25.1–30) and obese (BMI > 30) subjects were assessed by multinomial regression, adjusted for covariates. Analyses included relationships between HL, HT, DM, age, tobacco usage, and neoplasia.

Discriminatory power of HT, HL, DM, and BMI for neoplasia was assessed by binary logistic regression. Odds were calculated for neoplasia in each colonic segment related to BMI. RESULTS: A and ADV were commoner in overweight and obese males, obese females, older subjects, and smokers. HL, HT, and DM were associated with increased odds for neoplasia, significantly for A with hypertension. BMI alone predicted neoplasia as well as HT, HL, DM, or combinations thereof. All segments of the colon were affected. Multiple polyps were particularly prevalent in the obese. CONCLUSIONS: Obesity and MetS are risk factors for colonic neoplasia in a Canadian population.","DOI":"10.1155/2017/8750967","ISSN":"2291-2789","author":[{"family":"Shapero","given":"Theodore F"},{"family":"Chen","given":"Grant I"},{"family":"Devlin","given":"Tim"},{"family":"Gibbs","given":"Alison"},{"family":"Murray","given":"Iain C"},{"family":"Tran","given":"Stanley"},{"family":"Weigensberg","given":"Corey"}],"issued":{"date-parts":[["2017"]]}}},{"id":150,"uris":["http://zotero.org/users/2724931/items/HXJHWUI6"],"uri":["http://zotero.org/users/2724931/items/HXJHWUI6"],"itemData":{"id":150,"type":"article-journal","title":"Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians","container-title":"Digestive Diseases and Sciences","page":"1025-1035","volume":"59","issue":"5","abstract":"Although epidemiologic and animal studies suggest a vegetarian diet protects against the development of colorectal cancer, the relationship between vegetarian diet and incidence of colorectal adenoma is not yet conclusive, especially for Asians.","DOI":"10.1007/s10620-013-2974-5","ISSN":"1573-2568","journalAbbreviation":"Digestive Diseases and Sciences","author":[{"family":"Lee","given":"Chang Geun"},{"family":"Hahn","given":"Suk Jae"},{"family":"Song","given":"Min Keun"},{"family":"Lee","given":"Jun Kyu"},{"family":"Kim","given":"Jae Hak"},{"family":"Lim","given":"Yun Jeong"},{"family":"Koh","given":"Moon-Soo"},{"family":"Lee","given":"Jin Ho"},{"family":"Kang","given":"Hyoun Woo"}],"issued":{"date-parts":[["2014"]]}}},{"id":145,"uris":["http://zotero.org/users/2724931/items/FX77VBWZ"],"uri":["http://zotero.org/users/2724931/items/FX77VBWZ"],"itemData":{"id":145,"type":"article-journal","title":"Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age","container-title":"Gastrointestinal Endoscopy","page":"480-489","volume":"72","issue":"3","abstract":"Background\nA paucity of information exists regarding colorectal neoplasm in asymptomatic, average-risk individuals 40 to 49 years of age.\nObjective\nTo evaluate the prevalence and risk factors of colorectal neoplasms in those in their 40s.\nDesign\nCross-sectional study.\nSetting\nResults offered to subjects of a health care provider that offers screening services as part of an employer-provided wellness program.\nPatients\nA consecutive series of 1761 asymptomatic, average-risk screenees 40 to 59 years of age.\nIntervention\nFirst screening colonoscopy.\nResults\nThe prevalence of overall colorectal neoplasm in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with increasing age (13.7%, 20.2%, 21.0%, and 23.8%, respectively; P < .001). The prevalence of advanced adenomas in subjects of ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years increased significantly with age (1.9%, 3.0%, 3.2%, and 5.9%, respectively; P = .004). Multivariate analysis of data from the 40- to 49-year age group identified an increased risk of colorectal neoplasm associated with ages 45 years and older (odds ratio [OR], 1.68; 95% CI, 1.20-2.35), male sex (OR, 1.76; 95% CI, 1.15-2.69), presence of abdominal obesity (OR, 1.57; 95% CI, 1.12-2.21), and metabolic syndrome (OR, 1.56; 95% CI, 1.03-2.35), whereas for advanced adenomas, abdominal obesity (OR, 2.37; 95% CI, 1.06-5.27) and metabolic syndrome (OR, 2.83; 95% CI, 1.23-6.53) were the independent risk factors.\nLimitations\nSingle-center study and the cohort composed of ethnic Korean subjects who lived in the same geographic region.\nConclusion\nIn average-risk individuals 40 to 49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasm.","DOI":"10.1016/j.gie.2010.06.022","ISSN":"0016-5107","journalAbbreviation":"Gastrointestinal Endoscopy","author":[{"family":"Hong","given":"Sung Noh"},{"family":"Kim","given":"Jeong Hwan"},{"family":"Choe","given":"Won Hyeok"},{"family":"Han","given":"Hye Seung"},{"family":"Sung","given":"In Kyung"},{"family":"Park","given":"Hyung Seok"},{"family":"Shim","given":"Chan Sup"}],"issued":{"date-parts":[["2010",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

46, 51, 67, 70

] provided data on the correlation between advanced colorectal adenoma (AA) and components of the MetS. Our results showed that only hypertriglyceridemia and hypertension seem to significantly increase the AA incidence (Table 2).

Colorectal adenomas versus colorectal cancer

We performed an analysis with the purpose of comparing the effect estimates for the different metabolic factors between CRA and CRC using only studies that reported both outcomes. Two studies [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aj6skd8ilb","properties":{"formattedCitation":"\\super 44,46 \\nosupersub{}","plainCitation":"44,46","noteIndex":0},"citationItems":[{"id":121,"uris":["http://zotero.org/users/2724931/items/7FAPCFIV"],"uri":["http://zotero.org/users/2724931/items/7FAPCFIV"],"itemData":{"id":121,"type":"article-journal","title":"Association of colorectal adenoma with components of metabolic syndrome.","container-title":"Cancer causes & control : CCC","page":"727-735","volume":"23","issue":"5","abstract":"PURPOSE: Recently, some studies have shown that diabetes mellitus and metabolic syndrome increase the risk of colorectal neoplasms. Although the mechanism is not known, those have been proposed to contribute to this phenomenon, including insulin resistance, oxidative stress, and adipokine production. The objective of this study was to assess the association between metabolic risk factors and colorectal neoplasm. METHODS: Study participants visited the National Cancer Center, Korea, for screening (2007-2009). A total of 1,771 diagnosed adenoma patients and 4,667 polyp-free controls were included. The association between risk factors and colorectal neoplasm was evaluated using logistic regression models. RESULTS: High waist circumference, blood pressure, and serum triglyceride levels were associated with an increased risk of colorectal adenoma. Metabolic syndrome (MS) was associated with an increased risk of adenoma (OR = 1.44, 95 % CI = 1.23-1.70). The association between MS and colorectal adenoma was observed regardless of advanced/low-risk adenoma, and multiplicity. MS affected right colon adenomas (OR = 1.50, 95 % CI = 1.22-1.85), left colon adenomas (OR = 1.36, 95 % CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95 % CI = 1.19-2.12), but was not associated with rectum. CONCLUSION: Central obesity, triglyceride level, and MS are risk factors for colorectal adenoma including advanced adenoma and multiplicity.","DOI":"10.1007/s10552-012-9942-9","ISSN":"1573-7225 0957-5243","note":"PMID: 22450737","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Kim","given":"Byung Chang"},{"family":"Shin","given":"Aesun"},{"family":"Hong","given":"Chang Won"},{"family":"Sohn","given":"Dae Kyung"},{"family":"Han","given":"Kyung Su"},{"family":"Ryu","given":"Kum Hei"},{"family":"Park","given":"Bum Joon"},{"family":"Nam","given":"Ji Hyung"},{"family":"Park","given":"Ji Won"},{"family":"Chang","given":"Hee Jin"},{"family":"Choi","given":"Hyo Seong"},{"family":"Kim","given":"Jeongseon"},{"family":"Oh","given":"Jae Hwan"}],"issued":{"date-parts":[["2012",5]]}}},{"id":123,"uris":["http://zotero.org/users/2724931/items/33PI99M5"],"uri":["http://zotero.org/users/2724931/items/33PI99M5"],"itemData":{"id":123,"type":"article-journal","title":"Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study","container-title":"Molecular Biology Reports","page":"2989-2997","volume":"41","issue":"5","abstract":"Nonalcoholic fatty liver disease (NAFLD) has been suggested to be a strong risk factor of colorectal benign adenomas and advanced neoplasms. The aim of this large cohort study was to further investigate the prevalence of colorectal malignant neoplasm (CRMN) in patients with NAFLD and determine whether association between NAFLD and CRMN exists. 2,315 community subjects (1,370 males and 945 females) who underwent a routine colonoscopy according to international colorectal cancer screening guideline were recruited. Nature of colorectal lesions determined by biopsy and NAFLD was diagnosed by ultrasound. Binary logistic regression analysis was applied to explore the related associations.

Prevalence of CRMN was 29.3 % (77/263) in patients with NAFLD, which was significantly higher than 18.0 % (369/2,052) in the control group (P < 0.05). In addition, malignant neoplasm in NAFLD group occurred more frequently at sigmoid colon than in control group (14.3 vs. 11.9 %). The incidence of highly-differentiated colorectal adenocarcinoma in NAFLD group was significantly higher than control group (62.3 vs. 9.8 %). Univariate analysis showed that NAFLD had strong association with CRMN (OR 2.043; 95 % CI 1.512–2.761; P < 0.05). After adjusting for metabolic and other confounding factors, NAFLD remained as an independent risk factor for CRMN (OR 1.868; 95 % CI 1.360–2.567; P < 0.05). NAFLD was an independent risk factor for CRMN. Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in NAFLD. (ClinicalTrials.gov number, NCT01657773, website: http://clinicaltrials.gov/ct2/show/NCT01657773?term=zheng+minghua&rank=1)."},"DOI":"10.1007/s11033-014-3157-y","ISSN":"1573-4978","journalAbbreviation":"Molecular Biology Reports","author":[{"family":"Lin","given":"Xian-Feng"},{"family":"Shi","given":"Ke-Qing"},{"family":"You","given":"Jie"},{"family":"Liu","given":"Wen-Yue"},{"family":"Luo","given":"Ying-Wan"},{"family":"Wu","given":"Fa-Ling"},{"family":"Chen","given":"Yong-Ping"},{"family":"Wong","given":"Danny Ka-Ho"},{"family":"Yuen","given":"Man-Fung"},{"family":"Zheng","given":"Ming-Hua"}],"issued":{"date-parts":[["2014"]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
44, 46

] were available for all factors except for waist circumference. Our findings displayed a stronger association between hyperglycemia, hypertriglyceridemia, and hypertension with CRC than CRA (Supplementary Tables 1.1, 2.1, and 3.1). No difference in the magnitude of the effect was observed for the association between HDL-C and both out
comes (Supplementary Table 5.1).

172085
186359
0
0

Discussion

We focused in this meta-analysis on answering the question of which condition(s) of the MetS are related to the developing of CRA and CRC since we have demonstrated the MetS association with both conditions in a previous study [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"VGhuk3hg","properties":{"formattedCitation":"\\super 75\\nosupersub{}","plainCitation":"75","noteIndex":0},"citationItems":[{"id":205,"uris":["http://zotero.org/users/2724931/items/6FGISE53"],"uri":["http://zotero.org/users/2724931/items/6FGISE53"],"itemData":{"id":205,"type":"article-journal","title":"Metabolic Syndrome and Risk of Colorectal Adenoma and Colorectal Cancer: A Meta-Analysis","container-title":"The North African Journal of Food and Nutrition Research","page":"30-43","volume":"01","issue":"02","abstract":"BACKGROUND: Growing evidence suggests that metabolic syndrome (MetS) could be linked with the incidence of colorectal adenoma and cancer (CRA and CRC). AIMS: Conducting a meta analysis to assess the association of MetS with both CRA and CRC. METHODS AND MATERIAL: Relevant studies were identified by systematically searching PubMed database for articles published in the last ten years. A random effect analysis model and Mantel-Haenszel statistical method were used to obtain pooled risk ratios (RRs) and their 95% confidence intervals (CIs) for dichotomous data. The analyses were assessed for heterogeneity and publication bias. RESULTS: 35 studies were included in the meta-analysis involving approximately 13 000 00 participants. A significant high risk for CRA was observed among patients with MetS compared to those without (RR = 1.43; 95% CI = 1.31, 1.57). The pooled RRs of CRC were 1.46 (95% CI = 1.36, 1.56). The risk estimates varied according to the type of the study (cohorts and non-cohorts), gender (men and women), MetS definition (NCEP-ATPIII, IDF, harmonized and others), populations (Asia, Europe, and the USA), and cancer location (colon and rectum). CONCLUSIONS: MetS is associated with an increased risk of CRA and CRC. The risk was higher for advanced adenomas. Taking into consideration MetS patients in the secondary prevention programs and the management of this condition in the aim of the primary prevention is highly recommended.","ISSN":"2588-1582","journalAbbreviation":"Nor. Afr. J. Food Nutr. Res","language":"English","author":[{"family":"Elharag","given":"Salah Eddine"},{"family":"Traoré","given":"Youssouf"},{"family":"Khaled","given":"Meghit Boumediene"}],"issued":{"date-parts":[["2017",10,28]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
75

]. We also aimed to determine whether these elements influence the carcinogenesis
process in its earlier or later stages. Our results suggest that individuals with hyperglycemia, hypertension, and visceral obesity, but not low values of HDL-C are associated with an increased risk of developing both CRA and CRC.

According to a recent worldwide estimate by the World Health Organization, the global prevalence of obesity has become three times as higher since 1975 [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"viuvIpJC","properties":{"formattedCitation":"\\super 76\\nosupersub{}","plainCitation":"76","noteIndex":0},"citationItems":[{"id":217,"uris":["http://zotero.org/users/2724931/items/UAY7CSIR"],"uri":["http://zotero.org/users/2724931/items/UAY7CSIR"],"itemData":{"id":217,"type":"webpage","title":"WHO | Obesity and overweight","container-title":"WHO","abstract":"Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.","URL":"http://www.who.int/mediacentre/factsheets/fs311/en/","language":"English","author":[{"family":"World Health Organization","given":""}],"issued":{"date-parts":[["2017",10]]},"accessed":{"date-parts":[["2017",11,29]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
76

]. Accordingly, in 2016, more than 13% of the world adults (above 18 years) were obese, that is more than 650 million cases. Additionally, 124 million children and adolescents (5-18 years) were considered obese in the same year [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Ypwjk1hd","properties":{"formattedCitation":"\\super 76\\nosupersub{}","plainCitation":"76","noteIndex":0},"citationItems":[{"id":217,"uris":["http://zotero.org/users/2724931/items/UAY7CSIR"],"uri":["http://zotero.org/users/2724931/items/UAY7CSIR"],"itemData":{"id":217,"type":"webpage","title":"WHO | Obesity and overweight","container-title":"WHO","abstract":"Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.","URL":"http://www.who.int/mediacentre/factsheets/fs311/en/","language":"English","author":[{"family":"World Health Organization","given":""}],"issued":{"date-parts":[["2017",10]]},"accessed":{"date-parts":[["2017",11,29]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
76

]. Subsequently, the key element in the pathogenesis of MetS is the alteration of normal visceral adipose tissue function [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dAJeBcrG","properties":{"formattedCitation":"\\super 6\\nosupersub{}","plainCitation":"6","noteIndex":0},"citationItems":[{"id":108,"uris":["http://zotero.org/users/2724931/items/96BBC78J"],"uri":["http://zotero.org/users/2724931/items/96BBC78J"],"itemData":{"id":108,"type":"chapter","title":"Pathophysiology of the Metabolic Syndrome","container-title":"The Metabolic Syndrome: Pharmacology and Clinical Aspects","publisher":"Springer Vienna","publisher-place":"Vienna","page":"17-42","event-place":"Vienna","URL":"http://dx.doi.org/10.1007/978-3-7091-1331-8_3","ISBN":"978-3-7091-1331-8","note":"DOI: 10.1007/978-3-7091-1331-8_3","author":[{"family":"Nolan","given":"John J."},{"family":"O'Gorman","given":"Donal

J."}],"editor":[{"family":"Beck-Nielsen","given":"Henning"}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
6
]. Visceral obesity regularly measured by WC has long been linked to certain types of cancer in several epidemiological studies, known also as obesity-related cancers [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JtuoNiy6","properties":{"formattedCitation":"\\super 77,78 \\nosupersub{}","plainCitation":"77,78","noteIndex":0},"citationItems":[{"id":218,"uris":["http://zotero.org/users/2724931/items/FEYRCJAE"],"uri":["http://zotero.org/users/2724931/items/FEYRCJAE"],"itemData":{"id":218,"type":"article-journal","title":"Obesity and cancer: An update of the global impact","container-title":"Cancer Epidemiology","page":"8-15","volume":"41","issue":"Supplement C","abstract":"Abstract\nIn view of the growing global obesity epidemic, this paper reviews the relation between recent trends in body mass index (BMI) and the changing profile of cancer worldwide. By examining seven selected countries, each representing a world region, a pattern of increasing BMI with region and gender-specific diversity is noted: increasing levels of BMI were most pronounced in the Middle East (Saudi Arabia), rather modest in Eastern Asia (India) and generally more rapid in females than in males. This observation translates into a disproportionate distribution of cancer attributable to high levels of BMI, ranging by sex from 4–9% in Saudi Arabia and from 0.2–1.2% in India. Overweight and obesity may also influence cancer outcomes, and hence have a varying impact on cancer survival and death in different world regions. Future challenges in cancer studies exploring the association with overweight and obesity concern the measurement of adiposity and its potentially cumulative effect over the life course. Given the limitations of BMI as an imperfect measure of body fatness, routine anthropometric data collection needs to be extended to develop more informative measures, such as waist circumference in settings where the gold standard tools remain unaffordable. Furthermore, questions surrounding the dose-response and timing of obesity and their associations with cancer remain to be answered. Improved surveillance of health risk factors including obesity as well as the scale and profile of cancer in every country of the world is urgently needed. This will enable the design of cost-effective actions to curb the growing burden of cancer related to excess body weight.","DOI":"10.1016/j.canep.2016.01.003","ISSN":"1877-7821","journalAbbreviation":"Cancer Epidemiology","author":[{"family":"Arnold","given":"Melina"},{"family":"Leitzmann","given":"Michael"},{"family":"Freisling","given":"Heinz"},{"family":"Bray","given":"Freddie"},{"family":"Romieu","given":"Isabelle"},{"family":"Renehan","given":"Andrew"},{"family":"Soerjomataram","given":"Isabelle"}],"issued":{"date-parts":[["2016",4,1]]}}},{"id":221,"uris":["http://zotero.org/users/2724931/items/JB424BQY"],"uri":["http://zotero.org/users/2724931/items/JB424BQY"],"itemData":{"id":221,"type":"article-journal","title":"Obesity and cancer: “Dangerous friendship”","container-title":"Medicina Clínica (English Edition)","page":"24-30","volume":"145","issue":"1","abstract":"Abstract\nObesity and cancer are one of the most important health problems is Spain. Between 23 and 28% of the adult population in Spain are obese, 39% are overweight and 36% have abdominal obesity. The association between obesity and type 2 diabetes mellitus, hypertension, dyslipidemia and sleep obstructive apnea is well known. On the contrary, the association between obesity and cancer is less known, because the recent evidence on it. Several prospective studies have shown during the last years the strong relationship between obesity and cancer of colon, breast in post-menopausal women, endometrial, kidney and pancreas as well as esophageal adenocarcinoma. Furthermore there is recent evidence showing that liver, gallbladder, thyroid and ovarian cancer as well as leukaemia, multiple myeloma and Hodgkin lymphomas are probably associated with obesity, yet more studies are needed. A better knowledge of the relation between cancer and obesity will allow improving the prevention strategies against cancer, a more efficient early detection, and a more suitable treatment of obesity and overweight. Although the mechanisms of carcinogenesis of obesity are not well established, avoiding overweight and obesity are considered one of the best approaches to reduce the risk of cancer. Therefore the general population must be aware that cancer is one of the most important hazards associated with the current obesity epidemic in our society.\nResumen\nObesidad y cáncer son 2 problemas sanitarios de primera magnitud en España. La obesidad afecta al 23–28% de la población adulta española, y el sobrepeso y la obesidad abdominal al 39 y 36%, respectivamente. Es bien conocida la relación entre obesidad y diabetes mellitus tipo 2, hipertensión arterial, dislipidemia, y apnea obstructiva del sueño. Menos conocida es en cambio la asociación con el cáncer, porque la evidencia es más reciente. Numerosos estudios prospectivos han demostrado en los últimos años, con un alto grado de evidencia científica, una asociación clara entre la obesidad y los cánceres de colon y recto, mama en mujeres pos-menopáusicas, endometrio, riñón, esófago y páncreas. Esta asociación es también probable con los tumores de hígado, vesícula biliar, cardias, tiroides, y hematológicos, para los que se requieren más estudios. Un mejor conocimiento de la relación entre obesidad y cáncer puede permitir mejorar las estrategias de prevención del cáncer, así como una más eficiente detección precoz, y un tratamiento más adecuado de la obesidad y el sobrepeso. Aunque los mecanismos por los cuales la obesidad induce los distintos tipos de cánceres no son suficientemente conocidos, evitar el sobrepeso y la obesidad es hoy una de las medidas más efectivas para reducir el riesgo de cáncer, por lo que es necesario concienciar a la población general sobre uno de los mayores peligros que entraña la actual epidemia de obesidad.","DOI":"10.1016/j.medcle.2014.05.011","ISSN":"2387-0206","journalAbbreviation":"Medicina Clínica (English Edition)","author":[{"family":"González Svatetz","given":"Carlos A."},{"family":"Goday Arnó","given":"Alberto"}],"issued":{"date-parts":[["2015",7,6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
77, 78
]. The relationship between WC and CRC was examined in a meta-analysis of 12 studies. The RR of CRC for the highest versus the lowest categories of WC was 1.455 (95% CI 1.327-1.569;
I
2
=
10.8%) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"bdzmP8JC","properties":{"formattedCitation":"\\super 79 \\nosupersub{}","plainCitation":"79","noteIndex":0},"citationItems":[{"id":300,"uris":["http://zotero.org/users/2724931/items/6ZCCPDUJ"],"uri":["http://zotero.org/users/2724931/items/6ZCCPDUJ"],"itemData":{"id":300,"type":"article-journal","title":"Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies","container-title":"PLOS ONE","page":"e53916","volume":"8","issue":"1","abstract":"Background Mounting evidence indicates that obesity may be associated with the risk of colorectal cancer (CRC). To conduct a systematic review of prospective studies assessing the association of obesity with the risk of CRC using meta-analysis. Methodology/Principal Findings Relevant studies were identified by a search of MEDLINE and EMBASE databases before January 2012, with no restrictions. We also reviewed reference lists from retrieved articles. We included prospective studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) for the association between general obesity [measured using body mass index (BMI)] or central obesity [measured using waist circumference (WC)] and the risk of colorectal, colon, or rectal cancer. Approximately 9, 000, 000 participants from several countries were included in this analysis. 41 studies on general obesity and 13 studies on central obesity were included in the meta-analysis. The pooled RRs of CRC for the obese vs. normal category of BMI were 1.334 (95% CI, 1.253–1.420), and the highest vs. lowest category of WC were 1.455 (95% CI, 1.327–1.596). There was heterogeneity among studies of BMI (P<0.001) but not among studies of WC (P = 0.323). Conclusions Both of general and central obesity were positively associated with the risk of CRC in this meta-analysis.","DOI":"10.1371/journal.pone.0053916","journalAbbreviation":"PLOS ONE","author":[{"family":"Ma","given":"Yanlei"},{"family":"Yang","given":"Yongzhi"},{"family":"Wang","given":"Feng"},

{"family":"Zhang","given":"Peng"},{"family":"Shi","given":"Chenzhang"},{"family":"Zou","given":"Yang"},{"family":"Qin","given":"Huanlong"}],"issued":{"date-parts":[["2013",1,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

79

]. Our results suggested an implication of WC in CRC risk with an 18% increase, lower than previous findings (43%) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"GH95hqmj","properties":{"formattedCitation":"\\super 28 \\nosupersub{}","plainCitation":"28","noteIndex":0},"citationItems":[{"id":297,"uris":["http://zotero.org/users/2724931/items/E5G7NVFR"],"uri":["http://zotero.org/users/2724931/items/E5G7NVFR"],"itemData":{"id":297,"type":"article-journal","title":"Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.","container-title":"Endocrine","page":"634-647","volume":"44","issue":"3","abstract":"We performed a systematic review and meta-analysis of the empirical evidence on the association of metabolic syndrome and its components with colorectal cancer incidence and mortality. A systematic literature search of multiple electronic databases was conducted and complemented by cross-referencing to identify studies published before 31 October 2012. Every included study was to report risk estimates with 95 % confidence intervals for the association between metabolic syndrome and colorectal cancer (incidence or mortality). Core items of identified studies were independently extracted by two reviewers, and results were summarized by standard methods of meta-analysis. We identified 17 studies, which reported on 49 data sets with 11,462 cancer cases. Metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality in both men (RR: 1.33, 95 % CI 1.18-1.50, and 1.36, 1.25-1.48, respectively) and women (RR: 1.41, 1.18-1.70, and 1.16, 1.03-1.30, respectively). The risk estimates changed little depending on type of study (cohort vs non cohort), populations (US, Europe, Asia), cancer site (colon and rectum), or definition of the syndrome. The risk estimates for any single factor of the syndrome were significant for higher values of BMI/waist (RR: 1.19, 95 % CI 1.10-1.28), dysglycemia (RR: 1.29, 1.11-1.49), and higher blood pressure (RR: 1.09, 1.01-1.18). Dysglycemia and/or higher BMI/waist explained most of the risk associated with metabolic syndrome. Metabolic syndrome is associated with an increased risk of colorectal cancer incidence and mortality in both sexes. The risk conveyed by the full syndrome is not superior to the sum of its parts.","DOI":"10.1007/s12020-013-9939-5","ISSN":"1559-0100 1355-008X","note":"PMID: 23546613","journalAbbreviation":"Endocrine","language":"eng","author":[{"family":"Esposito","given":"Katherine"},{"family":"Chiodini","given":"Paolo"},{"family":"Capuano","given":"Annalisa"},{"family":"Bellastella","given":"Giuseppe"},{"family":"Maiorino","given":"Maria Ida"},{"family":"Rafaniello","given":"Concetta"},{"family":"Panagiotakos","given":"Demosthenes B."},{"family":"Giugliano","given":"Dario"}],"issued":{"date-parts":[["2013",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

28

].

Various factors could relate obesity to CRC. A chronic low-grade inflammation is associated with obesity attributable to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, leading to cell apoptosis inhibition and cell survival promotion [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sTtLatUp","properties":{"formattedCitation":"\\super 80,81 \\nosupersub{}","plainCitation":"80,81","noteIndex":0},"citationItems":[{"id":296,"uris":["http://zotero.org/users/2724931/items/ZDVTPUWS"],"uri":["http://zotero.org/users/2724931/items/ZDVTPUWS"],"itemData":{"id":296,"type":"chapter","title":"Obesity and Cancer","container-title":"Obesity: A Practical Guide","publisher":"Springer International Publishing","publisher-place":"Cham","page":"211-220","event-place":"Cham","URL":"http://dx.doi.org/10.1007/978-3-319-19821-7_16","ISBN":"978-3-319-19821-7","note":"DOI: 10.1007/978-3-319-19821-7_16","author":[{"family":"Zhang","given":"Xiang"},{"family":"Wu","given":"William K. K."},{"family":"Yu","given":"Jun"}],"editor":[{"family":"Ahmad","given":"Shamim I."},{"family":"Imam","given":"Syed Khalid"}],"issued":{"date-parts":[["2016"]]}}},{"id":338,"uris":["http://zotero.org/users/2724931/items/WTEBWSE8"],"uri":["http://zotero.org/users/2724931/items/WTEBWSE8"],"itemData":{"id":338,"type":"article-journal","title":"How significant is the association between metabolic syndrome and prevalence of colorectal neoplasia?","container-title":"World Journal of Gastroenterology","page":"8103-8111","volume":"22","issue":"36","source":"PubMed Central","abstract":"The incidence and prevalence of metabolic syndrome (MS) and colorectal cancer (CRC) has been rising in developed countries. The association between these two diseases has been widely studied and reported. Less evidence is available about the relationship between MS and CRC precancerous lesions (adenomatous polyps, adenomas). The aim of this paper is to present an overview of our scientific understanding of that topic and its implication in clinical practice. One of the principal goals of current CRC secondary prevention efforts is to detect and remove the precancerous lesions in individuals with an average CRC risk to prevent the development of invasive cancer. MS is not currently considered a high-risk CRC factor and is therefore not included in the guidelines of organized screening programs. However, in light of growing scientific evidence, the approach to patients with MS should be changed. Metabolic risk factors for the development of adenomas and cancers are the same - obesity, impaired glucose tolerance, dyslipidemia, hypertension, cardiovascular diseases and diabetes mellitus type 2. Therefore, the key issue in the near future is the development of a simple scoring system, easy to use in clinical practice, which would identify individuals with high metabolic risk of colorectal neoplasia and would be used for individual CRC secondary prevention strategies. Currently, such scoring systems have been published based on Asian (Asia-Pacific Colorectal Screening Score; APCS) and Polish populations.","DOI":"10.3748/wjg.v22.i36.8103","ISSN":"1007-9327","note":"PMID: 27688652\nPMCID: PMC5037079","journalAbbreviation":"World J Gastroenterol","author":[{"family":"Suchanek","given":"Stepan"},{"family":"Grega","given":"Tomas"},{"family":"Ngo","given":"Ondrej"},{"family":"Vojtechova","given":"Gabriela"},{"family":"Majek","given":"Ondrej"},{"family":"Minarikova","given":"Petra"},{"family":"Brogyuk","given":"Nagyija"},{"family":"Bunganic","given":"Bohus"},{"family":"Seifert","given":"Bohumil"},{"family":"Dusek","given":"Ladislav"},{"family":"Zavoral","given":"Miroslav"}],"issued":{"date-parts":[["2016",9,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

80, 81

]. Besides, insulin resistance, which is a characteristic of the MetS, associated with hyperinsulinemia, increased secretion of insulin-like growth factor 1 (IGF1), and hyperglycemia

are

supposed to promote CRC carcinogenesis. High levels of insulin may lead to an overproduction of IGF1, causing an overstimulation of the receptors, and activation of insulin receptor substrate-1. This can activate various signal pathways, including mitogen-activated protein kinase (MAPK) and

phosphatidylinositol-3

kinase that decreases cell apoptosis and enhances cell proliferation [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"kdnxCqjn","properties":{"formattedCitation":"\\super 80\\uc0\\u8211{}84\\nosupersub{}","plainCitation":"80–84","noteIndex":0},"citationItems":[{"id":296,"uris":["http://zotero.org/users/2724931/items/ZDVTPUWS"],"uri":["http://zotero.org/users/2724931/items/ZDVTPUWS"],"itemData":{"id":296,"type":"chapter","title":"Obesity and Cancer","container-title":"Obesity: A Practical Guide","publisher":"Springer International Publishing","publisher-place":"Cham","page":"211-220","event-place":"Cham","URL":"http://dx.doi.org/10.1007/978-3-319-19821-7_16","ISBN":"978-3-319-19821-7","note":"DOI: 10.1007/978-3-319-19821-7_16","author":[{"family":"Zhang","given":"Xiang"},{"family":"Wu","given":"William K. K."},

{"family":"Yu","given":"Jun"}],"editor":[{"family":"Ahmad","given":"Shamim I."},{"family":"Imam","given":"Syed Khalid"}],"issued":{"date-parts":[["2016"]]}},{"id":338,"uris":["http://zotero.org/users/2724931/items/WTEBWSE8"],"uri":["http://zotero.org/users/2724931/items/WTEBWSE8"],"itemData":{"id":338,"type":"article-journal","title":"How significant is the association between metabolic syndrome and prevalence of colorectal neoplasia?","container-title":"World Journal of Gastroenterology","page":"8103-8111","volume":"22","issue":"36","source":"PubMed Central","abstract":"The incidence and prevalence of metabolic syndrome (MS) and colorectal cancer (CRC) has been rising in developed countries. The association between these two diseases has been widely studied and reported. Less evidence is available about the relationship between MS and CRC precancerous lesions (adenomatous polyps, adenomas). The aim of this paper is to present an overview of our scientific understanding of that topic and its implication in clinical practice. One of the principal goals of current CRC secondary prevention efforts is to detect and remove the precancerous lesions in individuals with an average CRC risk to prevent the development of invasive cancer. MS is not currently considered a high-risk CRC factor and is therefore not included in the guidelines of organized screening programs. However, in light of growing scientific evidence, the approach to patients with MS should be changed. Metabolic risk factors for the development of adenomas and cancers are the same - obesity, impaired glucose tolerance, dyslipidemia, hypertension, cardiovascular diseases and diabetes mellitus type 2. Therefore, the key issue in the near future is the development of a simple scoring system, easy to use in clinical practice, which would identify individuals with high metabolic risk of colorectal neoplasia and would be used for individual CRC secondary prevention strategies. Currently, such scoring systems have been published based on Asian (Asia-Pacific Colorectal Screening Score; APCS) and Polish populations.","DOI":"10.3748/wjg.v22.i36.8103","ISSN":"1007-9327","note":"PMID: 27688652\nPMCID: PMC5037079","journalAbbreviation":"World J Gastroenterol","author":[{"family":"Suchanek","given":"Stepan"},{"family":"Grega","given":"Tomas"},{"family":"Ngo","given":"Ondrej"},{"family":"Vojtechova","given":"Gabriela"},{"family":"Majek","given":"Ondrej"},{"family":"Minarikova","given":"Petra"},{"family":"Brogyuk","given":"Nagyija"},{"family":"Bunganic","given":"Bohus"},{"family":"Seifert","given":"Bohumil"},{"family":"Dusek","given":"Ladislav"},{"family":"Zavoral","given":"Miroslav"}],"issued":{"date-parts":[["2016",9,28]]}},{"id":155,"uris":["http://zotero.org/users/2724931/items/GGQCZFQ2"],"uri":["http://zotero.org/users/2724931/items/GGQCZFQ2"],"itemData":{"id":155,"type":"article-journal","title":"Metabolic syndrome and risk of cancer: Which link?","container-title":"Metabolism","page":"182-189","volume":"64","issue":"2","abstract":"Abstract\nMetabolic syndrome (MS) is characterized by a group of metabolic disturbances which lead to an enhanced risk of cardiovascular diseases and type 2 diabetes mellitus. MS constitutes a preoccupant issue with elevated prevalence in the western countries and is often related with cancer development. Elucidating the mechanisms linking these two pathologies is, therefore, essential to identify potential therapeutic molecular targets for cancer treatment in MS patients. The main goals of this review are, to identify the relation between MS and cancer development, handling specifically each one of the main players on this process: insulin and IGF system, estrogen, pro-inflammatory cytokines and others; and, given that colorectal cancer is one of the most prevalent types of cancer in MS patients, we intend to particularly highlight the mechanisms that promote colorectal cancer development in MS individuals. Finally, we will also focus on the clinical implications of the presented mechanisms on cancer therapy and care.","DOI":"10.1016/j.metabol.2014.10.008","ISSN":"0026-0495","journalAbbreviation":"Metabolism","author":[{"family":"Mendonça","given":"Fernando Miguel"},{"family":"Sousa","given":"Filipa Rodrigues","non-dropping-particle":"de"},{"family":"Barbosa","given":"Ana Luísa"},{"family":"Martins","given":"Sara Costa"},{"family":"Araújo","given":"Raquel Lage"},{"family":"Soares","given":"Raquel"},{"family":"Abreu","given":"Cristina"}],"issued":{"date-parts":[["2015",2]]}},{"id":141,"uris":["http://zotero.org/users/2724931/items/MSKMWXQX"],"uri":["http://zotero.org/users/2724931/items/MSKMWXQX"],"itemData":{"id":141,"type":"article-journal","title":"Metabolic syndrome and risk of subsequent colorectal cancer","container-title":"World Journal of Gastroenterology : WJG","page":"5141-5148","volume":"15","issue":"41","archive":"PMC","archive_location":"PMC2773892","abstract":"The metabolic syndrome and visceral obesity have an increasing prevalence and incidence in the general population. The actual prevalence of the metabolic syndrome is 24% in US population and between 24.6% and 30.9% in Europe. As demonstrated by many clinical trials (NAHANES III, INTERHART) the metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. In addition to cardiovascular disease, individual components of the metabolic syndrome have been linked to the development of cancer, particularly to colorectal cancer. Colorectal cancer is an important public health problem; in the year 2000 there was an estimated total of 944

717 incident cases of colorectal cancer diagnosed world-wide. This association is sustained by many epidemiological studies. Recent reports suggest that individuals with metabolic syndrome have a higher risk of colon or rectal cancer. Moreover, the clusters of metabolic syndrome components increase the risk of associated cancer. The physiopathological mechanism that links metabolic syndrome and colorectal cancer is mostly related to abdominal obesity and insulin resistance. Population and experimental studies demonstrated that hyperinsulinemia, elevated C-peptide, elevated body mass index, high levels of insulin growth factor-1, low levels of insulin growth factor binding protein-3, high leptin levels and low adiponectin levels are all involved in carcinogenesis. Understanding the pathological mechanism that links metabolic syndrome and its components to carcinogenesis has a major clinical significance and may have profound health benefits on a number of diseases including cancer, which represents a major cause of mortality and morbidity in our societies.","DOI":"10.3748/wjg.15.5141","ISSN":"1007-9327","author":[{"family":"Pais","given":"Raluca"},{"family":"Silaghi","given":"Horatiu"},{"family":"Silaghi","given":"Alina Cristina"},{"family":"Rusu","given":"Mihai Lucian"},{"family":"Dumitrascu","given":"Dan Lucian"}],"issued":{"date-parts":[["2009",11,7]]}},{"id":292,"uris":["http://zotero.org/users/2724931/items/4P5JJ2WZ"],"uri":["http://zotero.org/users/2724931/items/4P5JJ2WZ"],"itemData":{"id":292,"type":"article-journal","title":"Metabolic syndrome: a novel high-risk state for colorectal cancer.","container-title":"Cancer letters","page":"56-61","volume":"334","issue":"1","abstract":"Metabolic syndrome (MS) and related disorders, including cancer, are steadily increasing in most countries of the world. However, mechanisms underlying the link between MS and colon carcinogenesis have yet to be fully elucidated. In this review article we focus on the relationships between various individual associated conditions (obesity, dyslipidemia, diabetes mellitus type 2 and hypertension) and colon cancer development, and demonstrate probable related factors revealed by in vivo and in vitro studies. Furthermore, molecules suggested to be involved in cancer promotion are addressed, and the potential for cancer prevention by targeting these molecules is discussed.","DOI":"10.1016/j.canlet.2012.10.012","ISSN":"1872-7980 0304-3835","note":"PMID: 23085010","journalAbbreviation":"Cancer Lett","language":"eng","author":[{"family":"Ishino","given":"Kousuke"},{"family":"Mutoh","given":"Michihiro"},{"family":"Totsuka","given":"Yukari"},{"family":"Nakagama","given":"Hitoshi"}],"issued":{"date-parts":[["2013",6,28]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
80
–
84

]. Hyperglycemia is suggested to promote cancer development by way of a variety of mechanisms. A high glucose level leads to a state of an oxidative stress by increasing the production of reactive oxygen species [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ve9nNeZQ","properties":{"formattedCitation":"\\super 85 \\nosupersub{}","plainCitation":"85","noteIndex":0},"citationItems":[{"id":210,"uris":

["http://zotero.org/users/2724931/items/9THFH6PC"],"uri":["http://zotero.org/users/2724931/items/9THFH6PC"],"itemData":{"id":210,"type":"article-journal","title":"Diabetes and the risk for colorectal cancer","container-title":"Journal of Diabetes and its Complications","page":"50-55","volume":"26","issue":"1","abstract":"Abstract\nDiabetes mellitus has been reported to be associated with an increased risk for colorectal cancer. The review analyzes current epidemiological data on the association of diabetes and the risk for colorectal cancer. Hyperinsulinemia, hyperglycemia, and inflammation are suggested to play a key role in the pathophysiology of cancer in diabetes. Data regarding potential treatment-related risks, particularly in conjunction with the use of insulin and insulin analogues, are also presented. Furthermore, the impact of glycemic control and cardiorespiratory fitness on cancer prognosis is considered. Finally, the preventive potential of aspirin and other nonsteroidal anti-inflammatory drugs, and the recommendations concerning colonoscopy-screening are presented.","DOI":"10.1016/j.jdiacomp.2011.11.003","ISSN":"1056-8727","journalAbbreviation":"Journal of Diabetes and its Complications","author":[{"family":"Erbach","given":"Michael"},{"family":"Mehnert","given":"Hellmut"},{"family":"Schnell","given":"Oliver"}],"issued":{"date-parts":[["2012",1,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

85

] and enhances inflammatory pathways which lead also to a state of a chronic low-grade inflammation [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZopVyP1g","properties":{"formattedCitation":"\\super 86\\nosupersub{}","plainCitation":"86","noteIndex":0},"citationItems":[{"id":229,"uris":["http://zotero.org/users/2724931/items/4KZ2TDZ3"],"uri":["http://zotero.org/users/2724931/items/4KZ2TDZ3"],"itemData":{"id":229,"type":"article-journal","title":"Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer","container-title":"Journal of the Academy of Nutrition and Dietetics","abstract":"Abstract\nPancreatic ductal adenocarcinoma (PDAC) is among the deadliest types of cancer. The worldwide estimates of its incidence and mortality in the general population are eight cases per 100,000 person-years and seven deaths per 100,000 person-years, and they are significantly higher in the United States than in the rest of the world. The incidence of this disease in the United States is more than 50,000 new cases in 2017. Indeed, total deaths due to PDAC are projected to increase dramatically to become the second leading cause of cancer-related deaths before 2030. Considering the failure to date to efficiently treat existing PDAC, increased effort should be undertaken to prevent this disease. A better understanding of the risk factors leading to PDAC development is of utmost importance to identify and formulate preventive strategies. Large epidemiologic and cohort studies have identified risk factors for the development of PDAC, including obesity and type 2 diabetes mellitus. This review highlights the current knowledge of obesity and type 2 diabetes as risk factors for PDAC development and progression, their interplay and underlying mechanisms, and the relation to diet. Research gaps and opportunities to address this deadly disease are also outlined.","URL":"http://www.sciencedirect.com/science/article/pii/S2212267217310870","DOI":"10.1016/j.jand.2017.07.005","ISSN":"2212-2672","journalAbbreviation":"Journal of the Academy of Nutrition and Dietetics","author":[{"family":"Eibl","given":"Guido"},{"family":"Cruz-Monserrate","given":"Zobeida"},{"family":"Korc","given":"Murray"},{"family":"Petrov","given":"Maxim S."},{"family":"Goodarzi","given":"Mark O."},{"family":"Fisher","given":"William E."},{"family":"Habtezion","given":"Aida"},{"family":"Lugea","given":"Aurelia"},{"family":"Pandol","given":"Stephen J."},{"family":"Hart","given":"Phil A."},{"family":"Andersen","given":"Dana K."}],"issued":{"date-parts":[["2017",9,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

86

].

Hyperglycemia provides to cancer cells the necessary energy source which allows for cell survival and resistance to chemotherapy [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"op5cdn44","properties":{"formattedCitation":"\\super 87\\nosupersub{}","plainCitation":"87","noteIndex":0},"citationItems":[{"id":215,"uris":["http://zotero.org/users/2724931/items/SYD6W494"],"uri":["http://zotero.org/users/2724931/items/SYD6W494"],"itemData":{"id":215,"type":"article-journal","title":"Diabetes and Cancer","container-title":"Diabetes Mellitus: Associated Conditions","page":"167-185","volume":"43","issue":"1","DOI":"10.1016/j.ecl.2013.09.008","ISSN":"0889-8529","journalAbbreviation":"Endocrinology and Metabolism Clinics of North America","author":[{"family":"Zelenko","given":"Zara"},{"family":"Gallagher","given":"Emily Jane"}],"issued":{"date-parts":[["2014",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

87

] and indirectly increases cancer progression by dysregulating signaling pathways in many types of cancer (breast, lung, and prostate cancer) [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"GgMaTvaC","properties":{"formattedCitation":"\\super 88\\nosupersub{}","plainCitation":"88","noteIndex":0},"citationItems":[{"id":213,"uris":["http://zotero.org/users/2724931/items/6VL4HRV3"],"uri":["http://zotero.org/users/2724931/items/6VL4HRV3"],"itemData":{"id":213,"type":"article-journal","title":"Translating Mechanism-Based Strategies to Break the Obesity–Cancer Link: A Narrative Review","container-title":"Journal of the Academy of Nutrition and Dietetics","abstract":"Abstract\nPrevalence of obesity, an established risk factor for many cancers, has increased dramatically over the past 50 years in the United States and across the globe. Relative to normoweight cancer patients, obese cancer patients often have poorer prognoses, resistance to chemotherapies, and are more likely to develop distant metastases. Recent progress on elucidating the mechanisms underlying the obesity–cancer connection suggests that obesity exerts pleomorphic effects on pathways related to tumor development and progression and, thus, there are multiple opportunities for primary prevention and treatment of obesity-related cancers. Obesity-associated alterations, including systemic metabolism, adipose inflammation, growth factor signaling, and angiogenesis, are emerging as primary drivers of obesity-associated cancer development and progression. These obesity-associated host factors interact with the intrinsic molecular characteristics of cancer cells, facilitating several of the hallmarks of cancer. Each is considered in the context of potential preventive and therapeutic strategies to reduce the burden of obesity-related cancers. In addition, this review focuses on emerging mechanisms behind the obesity–cancer link, as well as relevant dietary interventions, including calorie restriction, intermittent fasting, low-fat diet, and ketogenic diet, that are being implemented in preclinical and clinical trials, with the ultimate goal of reducing incidence and progression of obesity-related cancers.","URL":"http://www.sciencedirect.com/science/article/pii/S2212267217313485","DOI":"10.1016/j.jand.2017.08.112","ISSN":"2212-2672","journalAbbreviation":"Journal of the Academy of Nutrition and Dietetics","author":[{"family":"Smith","given":"Laura A."},{"family":"O'Flanagan","given":"Ciara H."},{"family":"Bowers","given":"Laura W."},{"family":"Allott","given":"Emma H."},{"family":"Hursting","given":"Stephen D."}],"issued":{"date-parts":[["2017",11,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

88

]. However, hyperglycemia may be dependent on other factors like hyperinsulinemia and diet [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"hZhPtlzJ","properties":{"formattedCitation":"\\super 89\\nosupersub{}","plainCitation":"89","noteIndex":0},"citationItems":[{"id":232,"uris":["http://zotero.org/users/2724931/items/HVKIVYIE"],"uri":["http://zotero.org/users/2724931/items/HVKIVYIE"],"itemData":{"id":232,"type":"article-journal","title":"Effect of hyperglycemia on hepatocellular carcinoma development in diabetes","container-title":"Biochemical and Biophysical Research Communications","page":"344-350","volume":"463","issue":"3","abstract":"Abstract\nCompared with other cancers, diabetes mellitus is more closely associated with hepatocellular carcinoma (HCC). However, whether hyperglycemia is associated with hepatic carcinogenesis remains

uncertain. In this study, we investigate the effect of hyperglycemia on HCC development. Mice pretreated with 7,12-dimethylbenz (a) anthracene were divided into three feeding groups: normal diet (Control), high-starch diet (Starch), and high-fat diet (HFD) groups. In addition, an STZ group containing mice that were fed a normal diet and injected with streptozotosin to induce hyperglycemia was included. The STZ group demonstrated severe hyperglycemia, whereas the Starch group demonstrated mild hyperglycemia and insulin resistance. The HFD group demonstrated mild hyperglycemia and severe insulin resistance. Multiple HCC were macroscopically and histologically observed only in the HFD group. Hepatic steatosis was observed in the Starch and HFD groups, but levels of inflammatory cytokines, interleukin (IL)-6, tumor necrosis factor-
α
, and IL-1
β
, were elevated only in the HFD group. The composition of gut microbiota was similar between the Control and STZ groups. A significantly higher number of Clostridium cluster XI was detected in the feces of the HFD group than that of all other groups; it was not detectable in the Starch group. These data suggested that hyperglycemia had no effect on hepatic carcinogenesis. Different incidences of HCC between the Starch and HFD groups may be attributable to degree of insulin resistance, but diet-induced changes in gut microbiota including Clostridium cluster XI may have influenced hepatic carcinogenesis. In conclusion, in addition to the normalization of blood glucose levels, diabetics may need to control insulin resistance and diet contents to prevent HCC development.","DOI":"10.1016/j.bbrc.2015.05.066","ISSN":"0006-291X","journalAbbreviation":"Biochemical and Biophysical Research Communications","author":[{"family":"Niwa","given":"Yasuhiro"},{"family":"Ishikawa","given":"Kota"},{"family":"Ishigami","given":"Masatoshi"},{"family":"Honda","given":"Takashi"},{"family":"Achiwa","given":"Koichi"},{"family":"Izumoto","given":"Takako"},{"family":"Maekawa","given":"Ryuya"},{"family":"Hosokawa","given":"Kaori"},{"family":"Iida","given":"Atsushi"},{"family":"Seino","given":"Yusuke"},{"family":"Hamada","given":"Yoji"},{"family":"Goto","given":"Hidemi"},{"family":"Oiso","given":"Yutaka"},{"family":"Arima","given":"Hiroshi"},{"family":"Tsunekawa","given":"Shin"}],"issued":{"date-parts":[["2015",7,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
89
].
Our results indicated that hyperglycemia increases the risk by 35% for CRC. In a dose-response analysis performed by Shi et al. [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ilQy8pZc","properties":{"formattedCitation":"\\super 90\\nosupersub{}","plainCitation":"90","noteIndex":0},"citationItems":[{"id":291,"uris":["http://zotero.org/users/2724931/items/CJPDMAU2"],"uri":["http://zotero.org/users/2724931/items/CJPDMAU2"],"itemData":{"id":291,"type":"article-journal","title":"A Linear Dose-Response Relationship between Fasting Plasma Glucose and Colorectal Cancer Risk: Systematic Review and Meta-analysis","container-title":"Scientific Reports","page":"17591","volume":"5","archive":"PMC","archive_location":"PMC4665197","abstract":"For many years, the question of whether hyperglycaemia, a manifestation of prediabetes, diabetes mellitus and metabolic syndrome, is a risk factor for colorectal cancer has been intensely studied. In fact, even after the conclusion of several prospective studies, the topic is still controversial. We conducted a systematic review and meta-analysis to investigate the dose-response relationship between blood glucose concentration and the incidence of colorectal cancer. A linear (P
=
0.303 for non-linearity) dose-response relationship was observed between fasting plasma glucose (FPG) and colorectal cancer risk without significant heterogeneity. The relative risk (RR) for colorectal cancer per 20
mg/dL increase in FPG was 1.015 (95% CI: 1.012–1.019, P
=
0.000). In subgroup analyses, the pooled RRs for colon cancer (CC) and rectal cancer (RC) studies were 1.035 (95% CI 1.008–1.062, P
=
0.011) and 1.031 (95% CI: 0.189–5.628, P
=
0.972), respectively; in the analysis comparing men and women, the pooled RRs were 1.016 (95% CI: 1.012–1.020, P
=
0.000) and 1.011 (95% CI: 0.995–1.027, P
=
0.164), respectively. Sensitivity analyses using two methods showed similar results. In conclusion, there is a significant linear dose-response relationship between FPG and the incidence risk of colorectal cancer. For people with diabetes or prediabetes, controlling blood glucose might be useful to prevent colorectal cancer.","DOI":"10.1038/srep17591","ISSN":"2045-2322","author":[{"family":"Shi","given":"Jianguo"},{"family":"Xiong","given":"Lijuan"},{"family":"Li","given":"Jiaoyuan"},{"family":"Cao","given":"Heng"},{"family":"Jiang","given":"Wen"},{"family":"Liu","given":"Bo"},{"family":"Chen","given":"Xueqin"},{"family":"Liu","given":"Cheng"},{"family":"Liu","given":"Ke"},{"family":"Wang","given":"Guobin"},{"family":"Cai","given":"Kailin"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
90
], an RR of 1.015 (95% CI 1.012-1.019;
P
=
0.000) was found for each 20 mg/dl increase in blood glucose concentration which agrees with our findings. Furthermore, Esposito et al. [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Thq7NkCp","properties":{"formattedCitation":"\\super 28 \\nosupersub{}","plainCitation":"28","noteIndex":0},"citationItems":[{"id":297,"uris":["http://zotero.org/users/2724931/items/E5G7NVFR"],"uri":["http://zotero.org/users/2724931/items/E5G7NVFR"],"itemData":{"id":297,"type":"article-journal","title":"Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.","container-title":"Endocrine","page":"634-647","volume":"44","issue":"3","abstract":"We performed a systematic review and meta-analysis of the empirical evidence on the association of metabolic syndrome and its components with colorectal cancer incidence and mortality. A systematic literature search of multiple electronic databases was conducted and complemented by cross-referencing to identify studies published before 31 October 2012. Every included study was to report risk estimates with 95 % confidence intervals for the association between metabolic syndrome and colorectal cancer (incidence or mortality). Core items of identified studies were independently extracted by two reviewers, and results were summarized by standard methods of meta-analysis. We identified 17 studies, which reported on 49 data sets with 11,462 cancer cases. Metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality in both men (RR: 1.33, 95 % CI 1.18-1.50, and 1.36, 1.25-1.48, respectively) and women (RR: 1.41, 1.18-1.70, and 1.16, 1.03-1.30, respectively). The risk estimates changed little depending on type of study (cohort vs non cohort), populations (US, Europe, Asia), cancer site (colon and rectum), or definition of the syndrome. The risk estimates for any single factor of the syndrome were significant for higher values of BMI/waist (RR: 1.19, 95 % CI 1.10-1.28), dysglycemia (RR: 1.29, 1.11-1.49), and higher blood pressure (RR: 1.09, 1.01-1.18). Dysglycemia and/or higher BMI/waist explained most of the risk associated with metabolic syndrome. Metabolic syndrome is associated with an increased risk of colorectal cancer incidence and mortality in both sexes. The risk conveyed by the full syndrome is not superior to the sum of its parts.","DOI":"10.1007/s12020-013-9939-5","ISSN":"1559-0100 1355-008X","note":"PMID: 23546613","journalAbbreviation":"Endocrine","language":"eng","author":[{"family":"Esposito","given":"Katherine"},{"family":"Chiodini","given":"Paolo"},{"family":"Capuano","given":"Annalisa"},{"family":"Bellastella","given":"Giuseppe"},{"family":"Maiorino","given":"Maria Ida"},{"family":"Rafaniello","given":"Concetta"},{"family":"Panagiotakos","given":"Demosthenes B."},{"family":"Giugliano","given":"Dario"}],"issued":{"date-parts":[["2013",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

28

] noticed a 9% increase in CRC risk in patients with high blood pressure. However, 25% was the increase that we found in our meta-analysis. The mechanisms by which hypertension affects the development of cancer remain unclear. The renin-angiotensin system which is implicated in the etiology of hypertension is linked to the development of many cancers. The angiotensin II activates downstream MAPK and STAT signal pathways throughout its effect on angiotensin type 1 receptor which induces the expression of proto-oncogenes and subsequently the promotion of cell proliferation [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wk3ZSJtx","properties":{"formattedCitation":"\\super 84\\nosupersub{}","plainCitation":"84","noteIndex":0},"citationItems":[{"id":292,"uris":["http://zotero.org/users/2724931/items/4P5JJ2WZ"],"uri":["http://zotero.org/users/2724931/items/4P5JJ2WZ"],"itemData":{"id":292,"type":"article-journal","title":"Metabolic syndrome: a novel high-risk state for colorectal cancer.","container-title":"Cancer letters","page":"56-61","volume":"334","issue":"1","abstract":"Metabolic syndrome (MS) and related disorders, including cancer, are steadily increasing in most countries of the world. However, mechanisms underlying the link between MS and colon carcinogenesis have yet to be fully elucidated. In this review article we focus on the relationships between various individual associated conditions (obesity, dyslipidemia, diabetes mellitus type 2 and hypertension) and colon cancer development, and demonstrate probable related factors revealed by in vivo and in vitro studies. Furthermore, molecules suggested to be involved in cancer promotion are addressed, and the potential for cancer prevention by targeting these molecules is discussed.","DOI":"10.1016/j.canlet.2012.10.012","ISSN":"1872-7980 0304-3835","note":"PMID: 23085010","journalAbbreviation":"Cancer Lett","language":"eng","author":[{"family":"Ishino","given":"Kousuke"},{"family":"Mutoh","given":"Michihiro"},{"family":"Totsuka","given":"Yukari"},{"family":"Nakagama","given":"Hitoshi"}],"issued":{"date-parts":[["2013",6,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

84

]. Epidemiological studies have reported the association between hypertension and cancer development. Women with hypertension were at a high risk of endometrial cancer, while a history of hypertension has been related to kidney cancer [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xHgiVynf","properties":{"formattedCitation":"\\super 91\\nosupersub{}","plainCitation":"91","noteIndex":0},"citationItems":[{"id":50,"uris":["http://zotero.org/users/2724931/items/M8NRCE3R"],"uri":["http://zotero.org/users/2724931/items/M8NRCE3R"],"itemData":{"id":50,"type":"book","title":"A Quick Guide to Cancer Epidemiology","publisher":"Springer International Publishing","publisher-place":"Cham","source":"CrossRef","event-place":"Cham","URL":"http://link.springer.com/10.1007/978-3-319-05068-3","ISBN":"978-3-319-05067-6","language":"en","author":[{"family":"Boffetta","given":"Paolo"},{"family":"Boccia","given":"Stefania"},{"family":"La Vecchia","given":"Carlo"}],"issued":{"date-parts":[["2014"]]},"accessed":{"date-parts":[["2016",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

91

]. The prevalence of hypertension was higher among subjects with prostate cancer [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H5FTgAm8","properties":{"formattedCitation":"\\super 92 \\nosupersub{}","plainCitation":"92","noteIndex":0},"citationItems":[{"id":235,"uris":["http://zotero.org/users/2724931/items/HYSN7LID"],"uri":["http://zotero.org/users/2724931/items/HYSN7LID"],"itemData":{"id":235,"type":"article-journal","title":"Prostate cancer is associated with the metabolic syndrome","container-title":"Journal of Men's Health","page":"125-129","volume":"6","issue":"2","abstract":"Abstract\nObesity has been linked consistently to an increased risk of developing several malignancies, including cancers of the breast, colon, kidney, pancreas, and gallbladder. The link between obesity and the metabolic syndrome (MS) remains elusive. The objective of this study was to evaluate the prevalence of the MS and diabetes at initial diagnosis of prostate cancer and to evaluate the relationship between the components of the MS in subjects with prostate cancer. In a retrospective study, we reviewed clinical data, specifically the components of the metabolic syndrome (MS), to evaluate the prevalence of the MS and diabetes at the initial diagnosis of prostate cancer. At initial diagnosis among 1408 subjects with prostate cancer, 60% of these subjects had the MS and 29% had diabetes. Among those subjects with the MS, 38% had diabetes and 89% had hypertension. Hypertension, elevated blood glucose levels, elevated body mass index, low high density lipoproteins and high triglycerides were the leading components of the MS, while low density lipoprotein cholesterol played a lesser role. We conclude that the prevalence of the MS is high in subjects with prostate cancer.","DOI":"10.1016/j.jomh.2009.01.005","ISSN":"1875-6867","journalAbbreviation":"Journal of Men's Health","author":[{"family":"Yaturu","given":"Subhashini"},{"family":"Fort","given":"Charlton"}],"issued":{"date-parts":[["2009",6,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

92

]. Moreover, a long-term use of anti-hypertensive medication which is an indication of a long duration of hypertension increased the risk of invasive breast cancer [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"SCaHXcRp","properties":{"formattedCitation":"\\super 93 \\nosupersub{}","plainCitation":"93","noteIndex":0},"citationItems":[{"id":293,"uris":["http://zotero.org/users/2724931/items/IFV5ZPG2"],"uri":["http://zotero.org/users/2724931/items/IFV5ZPG2"],"itemData":

{"id":293,"type":"article-journal","title":"Hypertension, antihypertensive medication use, and breast cancer risk in the California Teachers Study cohort","container-title":"Cancer Causes & Control","page":"1615-1624","volume":"21","issue":"10","abstract":"We investigated the association between hypertension, antihypertensive (AH) medication use, and breast cancer in a large prospective study, the California Teachers Study (CTS).","DOI":"10.1007/s10552-010-9590-x","ISSN":"1573-7225","journalAbbreviation":"Cancer Causes & Control","author":[{"family":"Largent","given":"Joan A."},{"family":"Bernstein","given":"Leslie"},{"family":"Horn-Ross","given":"Pamela L."},{"family":"Marshall","given":"Sarah F."},{"family":"Neuhausen","given":"Susan"},{"family":"Reynolds","given":"Peggy"},{"family":"Ursin","given":"Giske"},{"family":"Zell","given":"Jason A."},{"family":"Ziogas","given":"Argyrios"},{"family":"Anton-Culver","given":"Hoda"}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
93
].
The results of the association between dyslipidemia, a condition that includes high serum TG levels and low values of HDL-C, were inconsistent. We noticed that low HDL-C levels do not have a significant effect on the CRC incidence which matched previous findings. In a meta-analysis attempting to evaluate the association between serum lipids and CRN, the pooled RR of serum HDL-C for CRC was 0.97 (95% CI 0.80-1.18;
P
=
0.77), suggesting no significant relevance [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1hiu503c8f","properties":{"formattedCitation":"\\super 94 \\nosupersub{}","plainCitation":"94","noteIndex":0},"citationItems":[{"id":287,"uris":["http://zotero.org/users/2724931/items/M2FUF3AU"],"uri":["http://zotero.org/users/2724931/items/M2FUF3AU"],"itemData":{"id":287,"type":"article-journal","title":"The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis","container-title":"Public Health Nutrition","page":"3355-3370","volume":"18","issue":"18","source":"Cambridge University Press","archive":"Cambridge Core","abstract":"AbstractObjectiveThere have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.DesignWe identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.SettingWe analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).SubjectsCRN cases (n 21 809) were identified.ResultsOverall, people with high levels of serum TAG (risk ratio (RR) =1·08; 95 % CI 1·05, 1·12, P<0·00001) and LDL-C (RR=1·07; 95 % CI 1·00, 1·14, P=0·04) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR=1·04; 95 % CI 1·01, 1·09, P=0·02), TAG (RR=1·06; 95 % CI 1·03, 1·10, P=0·0009) and LDL-C (RR=1·11; 95 % CI 1·04, 1·19, P=0·003) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.ConclusionsBoth TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.","DOI":"10.1017/S1368980015000646","ISSN":"1368-9800","author":[{"family":"Tian","given":"Yun"},{"family":"Wang","given":"Keming"},{"family":"Li","given":"Juan"},{"family":"Wang","given":"Jirong"},{"family":"Wang","given":"Zhaoxia"},{"family":"Fan","given":"Yingrui"},{"family":"Ye","given":"Ying"},{"family":"Ji","given":"Guozhong"},{"family":"Li","given":"Yi"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
94
]. Another meta-analysis presented results for high versus low concentrations of serum HDL-C and CRC risk. A random-effects model yielded a summary RR of 0.84 (95% CI 0.69, 1.02), with evidence of moderate heterogeneity (
P
=
0.059,
I
2
=
42.5 %) [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1e2l9h9ima","properties":{"formattedCitation":"\\super 95 \\nosupersub{}","plainCitation":"95","noteIndex":0},"citationItems":[{"id":288,"uris":["http://zotero.org/users/2724931/items/QR8JSJ4M"],"uri":["http://zotero.org/users/2724931/items/QR8JSJ4M"],"itemData":{"id":288,"type":"article-journal","title":"Dyslipidemia and colorectal cancer risk: a meta-analysis of prospective studies.","container-title":"Cancer causes & control : CCC","page":"257-268","volume":"26","issue":"2","abstract":"PURPOSE: The findings from epidemiologic studies of dyslipidemia and colorectal cancer risk have been conflicting. We performed a dose-response meta-analysis of published prospective studies to assess the aforementioned association. METHODS: Relevant studies that reported the association between the components of dyslipidemia (serum triglyceride, total cholesterol, and high-/low-density lipoprotein cholesterol) and colorectal cancer risk were identified by searching PubMed until the end of May 2014. We pooled the relative risks (RRs) from individual studies using a random- and fixed-effects models and performed dose-response, heterogeneity, and publication bias analyses. RESULTS: Seventeen prospective studies, including 1,987,753 individuals with 10,876 colorectal cancer events, were included in the meta-analysis. The overall pooled RR for high versus low concentrations for triglyceride (n = 9 studies) was 1.18 (95 % CI 1.04-1.34; I (2) = 47.8 %), for total cholesterol (n = 10 studies) was 1.11 (95 % CI 1.01-1.21; I (2) = 46.7 %), for high-density lipoprotein cholesterol (n = 6 studies) was 0.84 (95 % CI 0.69-1.02; I (2) = 42.5 %), and for low-density lipoprotein cholesterol (n = 3 studies) was 1.04 (95 % CI 0.60-1.81; I (2) = 82.7 %). In the dose-response analysis, the overall pooled RR was 1.01 (95 % CI 1.00-1.03; I (2) = 0 %) per 50 mg/dL of triglyceride and 1.01 (95 % CI 0.97-1.05; I (2) = 64.3 %) per 100 mg/dL of total cholesterol. CONCLUSIONS: This meta-analysis of prospective studies suggests that dyslipidemia, especially high levels of serum triglyceride and total cholesterol, is associated with an increased risk of colorectal cancer, whereas high-density lipoprotein cholesterol might associate with a decreased risk of colorectal cancer. Further studies are warranted to determine whether altering the concentrations of these metabolic variables may reduce colorectal cancer risk.","DOI":"10.1007/s10552-014-0507-y","ISSN":"1573-7225 0957-5243","note":"PMID: 25488827","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Yao","given":"Xu"},{"family":"Tian","given":"Zhong"}],"issued":{"date-parts":[["2015",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
95
].
Tian
et al
. [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"KDf2hUUE","properties":{"formattedCitation":"\\super 94 \\nosupersub{}","plainCitation":"94","noteIndex":0},"citationItems":[{"id":287,"uris":["http://zotero.org/users/2724931/items/M2FUF3AU"],"uri":["http://zotero.org/users/2724931/items/M2FUF3AU"],"itemData":{"id":287,"type":"article-journal","title":"The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis","container-title":"Public Health Nutrition","page":"3355-3370","volume":"18","issue":"18","source":"Cambridge University Press","archive":"Cambridge Core","abstract":"AbstractObjectiveThere have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.DesignWe identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.SettingWe analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).SubjectsCRN cases (n 21 809) were identified.ResultsOverall, people with high levels of serum TAG (risk ratio (RR) =1·08; 95 % CI 1·05, 1·12, P<0·00001) and LDL-C (RR=1·07; 95 % CI 1·00, 1·14, P=0·04) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR=1·04; 95 % CI 1·01, 1·09, P=0·02), TAG (RR=1·06; 95 % CI 1·03, 1·10, P=0·0009) and LDL-C (RR=1·11; 95 % CI 1·04, 1·19, P=0·003) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.ConclusionsBoth TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.","DOI":"10.1017/S1368980015000646","ISSN":"1368-9800","author":[{"family":"Tian","given":"Yun"},{"family":"Wang","given":"Keming"},{"family":"Li","given":"Juan"},{"family":"Wang","given":"Jirong"},{"family":"Wang","given":"Zhaoxia"},{"family":"Fan","given":"Yingrui"},{"family":"Ye","given":"Ying"},{"family":"Ji","given":"Guozhong"},{"family":"Li","given":"Yi"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
94
] stated that TG was associated with an increased incidence of CRA, but not CRC. Though, our results disagree with those findings. A stronger association was found among subjects with high TG values for developing CRA than for CRC in our analysis. Additionally, our results are not in line with those found by Tian et al. [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a19ssh7qc7r","properties":{"formattedCitation":"\\super 94 \\nosupersub{}","plainCitation":"94","noteIndex":0},"citationItems":[{"id":287,"uris":["http://zotero.org/users/2724931/items/M2FUF3AU"],"uri":["http://zotero.org/users/2724931/items/M2FUF3AU"],"itemData":{"id":287,"type":"article-journal","title":"The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis","container-title":"Public Health Nutrition","page":"3355-3370","volume":"18","issue":"18","source":"Cambridge University Press","archive":"Cambridge Core","abstract":"AbstractObjectiveThere have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.DesignWe identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.SettingWe analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).SubjectsCRN cases (n 21 809) were identified.ResultsOverall, people with high levels of serum TAG (risk ratio (RR) =1·08; 95 % CI 1·05, 1·12, P<0·00001) and LDL-C (RR=1·07; 95 % CI 1·00, 1·14, P=0·04) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR=1·04; 95 % CI 1·01, 1·09, P=0·02), TAG (RR=1·06; 95 % CI 1·03, 1·10, P=0·0009) and LDL-C (RR=1·11; 95 % CI 1·04, 1·19, P=0·003) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.ConclusionsBoth TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.","DOI":"10.1017/S1368980015000646","ISSN":"1368-9800","author":[{"family":"Tian","given":"Yun"},{"family":"Wang","given":"Keming"},{"family":"Li","given":"Juan"},{"family":"Wang","given":"Jirong"},{"family":"Wang","given":"Zhaoxia"},{"family":"Fan","given":"Yingrui"},{"family":"Ye","given":"Ying"},{"family":"Ji","given":"Guozhong"},{"family":"Li","given":"Yi"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
94
] (RR = 1.07; 95% CI 0.99-1.15; P = 0.10) and Esposito et al. [

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adkp6ng780","properties":{"formattedCitation":"\\super 28 \\nosupersub{}","plainCitation":"28","noteIndex":0},"citationItems":[{"id":297,"uris":["http://zotero.org/users/2724931/items/E5G7NVFR"],"uri":["http://zotero.org/users/2724931/items/E5G7NVFR"],"itemData":{"id":297,"type":"article-journal","title":"Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.","container-title":"Endocrine","page":"634-647","volume":"44","issue":"3","abstract":"We performed a systematic review and meta-analysis of the empirical evidence on the association of metabolic syndrome and its components with colorectal cancer incidence and mortality. A systematic literature search of multiple electronic databases was conducted and complemented by cross-referencing to identify studies published before 31 October 2012. Every included study was to report risk estimates with 95 % confidence intervals for the association between metabolic syndrome and colorectal cancer (incidence or mortality). Core items of identified studies were independently extracted by two reviewers, and results were summarized by standard methods of meta-analysis. We identified 17 studies, which reported on 49 data sets with 11,462 cancer cases. Metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality in both men (RR: 1.33, 95 % CI 1.18-1.50, and 1.36, 1.25-1.48, respectively) and women (RR: 1.41, 1.18-1.70, and 1.16, 1.03-1.30, respectively). The risk estimates changed little depending on type of study (cohort vs non cohort), populations (US, Europe, Asia), cancer site (colon and rectum), or definition of the syndrome. The risk estimates for any single factor of the syndrome were significant for higher values of BMI/waist (RR: 1.19, 95 % CI 1.10-1.28), dysglycemia (RR: 1.29, 1.11-1.49), and higher blood pressure (RR: 1.09, 1.01-1.18). Dysglycemia and/or higher BMI/waist explained most of the risk associated with metabolic syndrome. Metabolic syndrome is associated with an increased risk of colorectal cancer incidence and mortality in both sexes. The risk conveyed by the full syndrome is not superior to the sum of its parts.","DOI":"10.1007/s12020-013-9939-5","ISSN":"1559-0100 1355-008X","note":"PMID: 23546613","journalAbbreviation":"Endocrine","language":"eng","author":[{"family":"Esposito","given":"Katherine"},{"family":"Chiodini","given":"Paolo"},{"family":"Capuano","given":"Annalisa"},

{"family":"Bellastella","given":"Giuseppe"},{"family":"Maiorino","given":"Maria Ida"},
{"family":"Rafaniello","given":"Concetta"},{"family":"Panagiotakos","given":"Demosthenes B."},
{"family":"Giugliano","given":"Dario"}],"issued":{"date-parts":[["2013",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
28
] (RR
=
1.12; 95% CI 0.98-1.27) where a non-significant association of serum TG with CRC risk was observed, our findings suggest a positive significant relationship. By contrast, our findings support those reported by Yao and Tian. [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2m8fbati2g","properties":{"formattedCitation":"\\super 95 \\nosupersub{}","plainCitation":"95","noteIndex":0},"citationItems":[{"id":288,"uris":["http://zotero.org/users/2724931/items/QR8JSJ4M"],"uri":["http://zotero.org/users/2724931/items/QR8JSJ4M"],"itemData":{"id":288,"type":"article-journal","title":"Dyslipidemia and colorectal cancer risk: a meta-analysis of prospective studies.","container-title":"Cancer causes & control : CCC","page":"257-268","volume":"26","issue":"2","abstract":"PURPOSE: The findings from epidemiologic studies of dyslipidemia and colorectal cancer risk have been conflicting. We performed a dose-response meta-analysis of published prospective studies to assess the aforementioned association. METHODS: Relevant studies that reported the association between the components of dyslipidemia (serum triglyceride, total cholesterol, and high-/low-density lipoprotein cholesterol) and colorectal cancer risk were identified by searching PubMed until the end of May 2014. We pooled the relative risks (RRs) from individual studies using a random- and fixed-effects models and performed dose-response, heterogeneity, and publication bias analyses. RESULTS: Seventeen prospective studies, including 1,987,753 individuals with 10,876 colorectal cancer events, were included in the meta-analysis. The overall pooled RR for high versus low concentrations for triglyceride (n = 9 studies) was 1.18 (95 % CI 1.04-1.34; I (2) = 47.8 %), for total cholesterol (n = 10 studies) was 1.11 (95 % CI 1.01-1.21; I (2) = 46.7 %), for high-density lipoprotein cholesterol (n = 6 studies) was 0.84 (95 % CI 0.69-1.02; I (2) = 42.5 %), and for low-density lipoprotein cholesterol (n = 3 studies) was 1.04 (95 % CI 0.60-1.81; I (2) = 82.7 %). In the dose-response analysis, the overall pooled RR was 1.01 (95 % CI 1.00-1.03; I (2) = 0 %) per 50 mg/dL of triglyceride and 1.01 (95 % CI 0.97-1.05; I (2) = 64.3 %) per 100 mg/dL of total cholesterol. CONCLUSIONS: This meta-analysis of prospective studies suggests that dyslipidemia, especially high levels of serum triglyceride and total cholesterol, is associated with an increased risk of colorectal cancer, whereas high-density lipoprotein cholesterol might associate with a decreased risk of colorectal cancer. Further studies are warranted to determine whether altering the concentrations of these metabolic variables may reduce colorectal cancer risk.","DOI":"10.1007/s10552-014-0507-y","ISSN":"1573-7225 0957-5243","note":"PMID: 25488827","journalAbbreviation":"Cancer Causes Control","language":"eng","author":[{"family":"Yao","given":"Xu"},{"family":"Tian","given":"Zhong"}],"issued":{"date-parts":[["2015",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
95
] when assessing the implication of high levels of TG with CRC risk. Results for
high versus low concentrations of serum TG and CRC occurrence yielded a summary RR of 1.18; 95 % CI 1.04-1.34), with evidence of moderate heterogeneity (P=0.011,
I
2
=
47.8 %). A case-cohort study found that plasma triglycerides and HDL-C were unrelated to CRC risk [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2ctk926iig","properties":{"formattedCitation":"\\super 96 \\nosupersub{}","plainCitation":"96","noteIndex":0},"citationItems":[{"id":242,"uris":["http://zotero.org/users/2724931/items/E8RBN7LE"],"uri":["http://zotero.org/users/2724931/items/E8RBN7LE"],"itemData":{"id":242,"type":"article-journal","title":"Colorectal cancer risk and dyslipidemia: A case–cohort study nested in an Italian multicentre cohort","container-title":"Cancer Epidemiology","page":"144-151","volume":"38","issue":"2","source":"CrossRef","DOI":"10.1016/j.canep.2014.02.002","ISSN":"18777821","shortTitle":"Co
cancer risk and dyslipidemia","language":"en","author":[{"family":"Agnoli","given":"Claudia"},{"family":"Grioni","given":"Sara"},{"family":"Sieri","given":"Sabina"},{"family":"Sacerdote","given":"Carlotta"},{"family":"Vineis","given":"Paolo"},{"family":"Tumino","given":"Rosario"},{"family":"Giurdanella","given":"Maria Concetta"},{"family":"Pala","given":"Valeria"},{"family":"Mattiello","given":"Amalia"},{"family":"Chiodini","given":"Paolo"},{"family":"Iacoviello","given":"Licia"},{"family":"De Curtis","given":"Amalia"},{"family":"Cattaneo","given":"Leonardo"},{"family":"Duijnhoven","given":"Fränzel J.B.","non-dropping-particle":"van"},{"family":"Panico","given":"Salvatore"},{"family":"Krogh","given":"Vittorio"}],"issued":{"date-parts":[["2014",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
96
].
The biological mechanisms linking dyslipidemia to CRC pathogenesis remain unknown. Nevertheless, some hypotheses were postulated. Fat intake increases bile acids production, which are transformed in the colon to secondary bile acids. The increase in the amounts of secondary bile salts may be carcinogenic for colon cells. Additionally, the constant damage to the colonic mucosa caused by secondary bile acids promotes the proliferation of colonocytes which may leads afterward to CRC development [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rRPioCJw","properties":{"formattedCitation":"\\super 81,82,97 \\nosupersub{}","plainCitation":"81,82,97","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/users/2724931/items/GGQCZFQ2"],"uri":["http://zotero.org/users/2724931/items/GGQCZFQ2"],"itemData":{"id":155,"type":"article-journal","title":"Metabolic syndrome and risk of cancer: Which link?","container-title":"Metabolism","page":"182-189","volume":"64","issue":"2","abstract":"Abstract\nMetabolic syndrome (MS) is characterized by a group of metabolic disturbances which lead to an enhanced risk of cardiovascular diseases and type 2 diabetes mellitus. MS constitutes a preoccupant issue with elevated prevalence in the western countries and is often related with cancer development. Elucidating the mechanisms linking these two pathologies is, therefore, essential to identify potential therapeutic molecular targets for cancer treatment in MS patients. The main goals of this review are, to identify the relation between MS and cancer development, handling specifically each one of the main players on this process: insulin and IGF system, estrogen, pro-inflammatory cytokines and others; and, given that colorectal cancer is one of the most prevalent types of cancer in MS patients, we intend to particularly highlight the mechanisms that promote colorectal cancer development in MS individuals. Finally, we will also focus on the clinical implications of the presented mechanisms on cancer therapy and care.","DOI":"10.1016/j.metabol.2014.10.008","ISSN":"0026-0495","journalAbbreviation":"Metabolism","author":[{"family":"Mendonça","given":"Fernando Miguel"},{"family":"Sousa","given":"Filipa Rodrigues","non-dropping-particle":"de"},{"family":"Barbosa","given":"Ana Luísa"},{"family":"Martins","given":"Sara Costa"},{"family":"Araújo","given":"Raquel Lage"},{"family":"Soares","given":"Raquel"},{"family":"Abreu","given":"Cristina"}],"issued":{"date-parts":[["2015",2]]}},{"id":202,"uris":["http://zotero.org/users/2724931/items/TEALYR9E"],"uri":["http://zotero.org/users/2724931/items/TEALYR9E"],"itemData":{"id":202,"type":"article-journal","title":"Metabolic Syndrome and Its Association With Colorectal Cancer: A Review","container-title":"The American Journal of the Medical Sciences","page":"227-

231","volume":"341","issue":"3","abstract":"Currently, significant amount of epidemiologic evidence is present to suggest that metabolic syndrome increases the risk of developing colorectal cancer. This evidence is based on studies of the evaluate determinants of the metabolic syndrome (obesity), clinical consequences of metabolic syndrome (type 2 diabetes and hypertension) and serum component of metabolic syndrome (hypertriglyceridemia, hyperglycemia and low high-density lipoprotein cholesterol), as well as markers of hyperinsulinemia. Although the exact pathogenesis of this relationship is unknown, it seems that hyperinsulinemia may play a pivotal role in increasing CRC risk.","DOI":"10.1097/MAJ.0b013e3181df9055","ISSN":"0002-9629","author":[{"family":"Siddiqui","given":"Ali A."},{"family":"Palmer","given":"Biff F."}]},{"id":338,"uris":["http://zotero.org/users/2724931/items/WTEBWSE8"],"uri":["http://zotero.org/users/2724931/items/WTEBWSE8"],"itemData":{"id":338,"type":"article-journal","title":"How significant is the association between metabolic syndrome and prevalence of colorectal neoplasia?","container-title":"World Journal of Gastroenterology","page":"8103-8111","volume":"22","issue":"36","source":"PubMed Central","abstract":"The incidence and prevalence of metabolic syndrome (MS) and colorectal cancer (CRC) has been rising in developed countries. The association between these two diseases has been widely studied and reported. Less evidence is available about the relationship between MS and CRC precancerous lesions (adenomatous polyps, adenomas). The aim of this paper is to present an overview of our scientific understanding of that topic and its implication in clinical practice. One of the principal goals of current CRC secondary prevention efforts is to detect and remove the precancerous lesions in individuals with an average CRC risk to prevent the development of invasive cancer. MS is not currently considered a high-risk CRC factor and is therefore not included in the guidelines of organized screening programs. However, in light of growing scientific evidence, the approach to patients with MS should be changed. Metabolic risk factors for the development of adenomas and cancers are the same - obesity, impaired glucose tolerance, dyslipidemia, hypertension, cardiovascular diseases and diabetes mellitus type 2. Therefore, the key issue in the near future is the development of a simple scoring system, easy to use in clinical practice, which would identify individuals with high metabolic risk of colorectal neoplasia and would be used for individual CRC secondary prevention strategies. Currently, such scoring systems have been published based on Asian (Asia-Pacific Colorectal Screening Score; APCS) and Polish populations.","DOI":"10.3748/wjg.v22.i36.8103","ISSN":"1007-9327","note":"PMID: 27688652\nPMCID: PMC5037079","journalAbbreviation":"World J Gastroenterol","author":[{"family":"Suchanek","given":"Stepan"},{"family":"Grega","given":"Tomas"},{"family":"Ngo","given":"Ondrej"},{"family":"Vojtechova","given":"Gabriela"},{"family":"Majek","given":"Ondrej"},{"family":"Minarikova","given":"Petra"},{"family":"Brogyuk","given":"Nagyija"},{"family":"Bunganic","given":"Bohus"},{"family":"Seifert","given":"Bohumil"},{"family":"Dusek","given":"Ladislav"},{"family":"Zavoral","given":"Miroslav"}],"issued":{"date-parts":[["2016",9,28]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
81, 82, 97
]. The results of epidemiological studies on the relationship involving dyslipidemia and cancer development were also conflicting [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"o22yNjo7","properties":{"formattedCitation":"\\super 98,99 \\nosupersub{}","plainCitation":"98,99","noteIndex":0},"citationItems":[{"id":286,"uris":["http://zotero.org/users/2724931/items/2FUTC7K7"],"uri":["http://zotero.org/users/2724931/items/2FUTC7K7"],"itemData":{"id":286,"type":"chapter","title":"Insulin, Insulin Resistance, and Cancer Associations","container-title":"Insulin Resistance and Cancer: Epidemiology, Cellular and Molecular Mechanisms and Clinical Implications","publisher":"Springer New York","publisher-place":"New York, NY","page":"111-140","event-place":"New York, NY","URL":"http://dx.doi.org/10.1007/978-1-4419-9911-5_5","ISBN":"978-1-4419-9911-5","note":"DOI: 10.1007/978-1-4419-9911-5_5","author":[{"family":"Lipscombe","given":"Lorraine"}],"editor":[{"family":"Fantus","given":"I. George"}],"issued":{"date-parts":[["2011"]]}}},{"id":236,"uris":["http://zotero.org/users/2724931/items/AV69CCZF"],"uri":["http://zotero.org/users/2724931/items/AV69CCZF"],"itemData":{"id":236,"type":"article-journal","title":"The molecular mechanisms between metabolic syndrome and breast cancer","container-title":"Biochemical and Biophysical Research Communications","page":"391-395","volume":"471","issue":"4","abstract":"Abstract\nMetabolic syndrome, which is extremely common in developed and some developing countries, is a clustering of at least three of five of the following medical conditions: abdominal obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density lipoprotein levels. It has been proved that there is a strong association between metabolic syndrome and breast cancer. Metabolic syndrome could increase the risk of breast cancer and influence the prognosis of the breast cancer patients. Some characteristic of metabolic syndrome such as obesity and lack of physical exercise are all risk factors for developing breast cancer. The metabolic syndrome mainly include obesity, type 2 diabetes, hypercholesterolemia and nonalcoholic fatty liver disease, and each of them impacts the risk of breast cancer and the prognosis of the breast cancer patients in different ways. In this Review, we focus on recently uncovered aspects of the immunological and molecular mechanisms that are responsible for the development of this highly prevalent and serious disease. These studies bring new insight into the complex associations between metabolic syndrome and breast cancer and have led to the development of novel therapeutic strategies that might enable a personalized approach in the management of this disease.","DOI":"10.1016/j.bbrc.2016.02.034","ISSN":"0006-291X","journalAbbreviation":"Biochemical and Biophysical Research Communications","author":[{"family":"Chen","given":"Yi"},{"family":"Wen","given":"Ya-yuan"},{"family":"Li","given":"Zhi-rong"},{"family":"Luo","given":"Dong-lin"},{"family":"Zhang","given":"Xiao-hua"}],"issued":{"date-parts":[["2016",3,18]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
98, 99
]. A weak inverse-association, which was dependent on smoking status, was noticed in a prospective cohort study between HDL-C and lung cancer [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a19kge83o70","properties":{"formattedCitation":"\\super 100 \\nosupersub{}","plainCitation":"100","noteIndex":0},"citationItems":[{"id":227,"uris":["http://zotero.org/users/2724931/items/TYUCCQN5"],"uri":["http://zotero.org/users/2724931/items/TYUCCQN5"],"itemData":{"id":227,"type":"article-journal","title":"HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study","container-title":"Lung Cancer","page":"292-300","volume":"61","issue":"3","abstract":"Summary\nThis study examined prospectively the association of baseline plasma HDL-cholesterol levels with incidence of lung cancer in 14,547 members of the Atherosclerosis Risk in Communities (ARIC) cohort. There were 259 cases of incident lung cancer identified during follow-up from 1987 through 2000. Results of this study indicated a relatively weak inverse association of HDL-cholesterol with lung cancer that was dependent on smoking status. The hazard ratio of lung cancer incidence in relation to low HDL-cholesterol, adjusted for race, gender, exercise, alcohol consumption, body mass index, triglycerides, age, and cigarette pack-years of smoking, was 1.45 (95% confidence interval 1.10, 1.92). This association was observed among former smokers (hazard ratio: 1.77, 95% confidence interval 1.05, 2.97), but not current smokers. The number of cases among never smokers in this study was too small (n=13) for meaningful interpretation of effect estimates. Excluding cases occurring within 5 years of baseline did not appreciably change the point estimates, suggesting lack of reverse causality. The modest association of low plasma HDL-cholesterol with greater incident lung cancer observed in this study is in agreement with existing case–control studies.","DOI":"10.1016/j.lungcan.2008.01.015","ISSN":"0169-5002","journalAbbreviation":"Lung Cancer","author":[{"family":"Kucharska-Newton","given":"Anna M."},{"family":"Rosamond","given":"Wayne D."},{"family":"Schroeder","given":"Jane C."},{"family":"McNeill","given":"Ann Marie"},{"family":"Coresh","given":"Josef"},{"family":"Folsom","given":"Aaron R."}],"issued":{"date-parts":[["2008",9,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
100

]. Moreover, no correlation was observed between low HDL-C and breast cancer incidence for both the total sample and among postmenopausal women, while a modest association was noticed for premenopausal women [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1lmiiikjsn","properties":{"formattedCitation":"\\super 101 \\nosupersub{}","plainCitation":"101","noteIndex":0},"citationItems":[{"id":226,"uris":["http://zotero.org/users/2724931/items/SP8XSDDA"],"uri":["http://zotero.org/users/2724931/items/SP8XSDDA"],"itemData":{"id":226,"type":"article-journal","title":"HDL-Cholesterol and Incidence of Breast Cancer in the ARIC Cohort Study","container-title":"Annals of Epidemiology","page":"671-677","volume":"18","issue":"9","abstract":"An association of low plasma HDL-cholesterol with risk of breast cancer has been suggested by multiple studies; the evidence, however, is not conclusive. We examined the possible association of low HDL-cholesterol with incidence of breast cancer using data from the Atherosclerosis Risk in Communities Study (ARIC) cohort, a prospective study of a randomly selected sample of women and men from four U.S. communities. Among 7,575 female members of the ARIC cohort, 359 cases of incident breast cancer were ascertained during the follow-up from 1987 through 2000. In analysis adjusted for age, race, body mass index, smoking, and reproductive variables, we observed no association of low baseline HDL-cholesterol (<50mg/dL) with incident breast cancer in the total sample (hazard ratio [HR]=1.08 [95% confidence interval (CI), 0.84–1.40]) and a modest association (HR=1.67 [95% CI, 1.06–2.63]) among women who were premenopausal at baseline. No association was observed among women who were postmenopausal at baseline. Removal from analysis of the first 5 years of follow-up did not appreciably change the observed associations. Results of our study suggest that low HDL-cholesterol among premenopausal women may be a marker of increased breast cancer risk.","DOI":"10.1016/j.annepidem.2008.06.006","ISSN":"1047-2797","journalAbbreviation":"Annals of Epidemiology","author":[{"family":"Kucharska-Newton","given":"Anna M."},{"family":"Rosamond","given":"Wayne D."},{"family":"Mink","given":"Pamela J."},{"family":"Alberg","given":"Anthony J."},{"family":"Shahar","given":"Eyal"},{"family":"Folsom","given":"Aaron R."}],"issued":{"date-parts":[["2008",9,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
101
]. Similarly, a retrospective cohort study found no significant association between both HDL-C and TG with liver and breast cancer [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a12r82p64b","properties":{"formattedCitation":"\\super 102 \\nosupersub{}","plainCitation":"102","noteIndex":0},"citationItems":[{"id":237,"uris":["http://zotero.org/users/2724931/items/2QD6EPZJ"],"uri":["http://zotero.org/users/2724931/items/2QD6EPZJ"],"itemData":{"id":237,"type":"article-journal","title":"Metabolic syndrome and incidence of liver and breast cancers in Japan","container-title":"Cancer Epidemiology","page":"141-147","volume":"36","issue":"2","abstract":"Abstract\nAim of the study To clarify the relationship between the presence of metabolic syndrome and the incidence of cancer in a general Japanese population. Methods A retrospective cohort study was conducted among 8329 male and 15,386 female subjects between 1992 and 2000. The analysis used five definitions of metabolic syndrome. The information on the site-specific cancer was obtained from the population-based cancer registry. A Cox proportional hazard model was adapted for the statistical analyses. The average follow-up period was 9.1 years. Results The National Cholesterol Education Program Adult Treatment Panel III 2001 criteria of metabolic syndrome revealed that the hazard ratio of metabolic syndrome for liver cancer was 1.89 (95% confidence interval (CI) 1.11–3.22) for males, and 3.67 (CI 1.78–7.57) for females. The hazard ratio for female breast cancer was 2.87 (CI 1.67–4.94). When the analysis was limited to postmenopausal women (55 years of age or older), the ratio increased to 6.73 (CI 2.93–15.43). The NCEP-ATPIII 2001 criteria were superior to the other four proposed criteria for predicting the incidence of cancer. In the statistical model, which included all components of the metabolic syndrome and the metabolic syndrome (present or absent), high blood glucose was a significant associated factor for all sites and liver cancers, whereas the metabolic syndrome was found to be a significant associated factor for breast cancer. Conclusion Metabolic syndrome may play an important role in the incidence of breast cancer. High fasting plasma glucose level is considered to be useful as an associated factor for the incidence of all-sites and liver cancer.","DOI":"10.1016/j.canep.2011.03.007","ISSN":"1877-7821","journalAbbreviation":"Cancer Epidemiology","author":[{"family":"Osaki","given":"Yoneatsu"},{"family":"Taniguchi","given":"Shin-ichi"},{"family":"Tahara","given":"Aya"},{"family":"Okamoto","given":"Mikizo"},{"family":"Kishimoto","given":"Takuji"}],"issued":{"date-parts":[["2012",4,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
102
]. Inversely, a strong association was remarked between low HDL-C and high TG values and prostate cancer incidence [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2nco12fbpj","properties":{"formattedCitation":"\\super 92\\nosupersub{}","plainCitation":"92","noteIndex":0},"citationItems":[{"id":235,"uris":["http://zotero.org/users/2724931/items/HYSN7LID"],"uri":["http://zotero.org/users/2724931/items/HYSN7LID"],"itemData":{"id":235,"type":"article-journal","title":"Prostate cancer is associated with the metabolic syndrome","container-title":"Journal of Men's Health","page":"125-129","volume":"6","issue":"2","abstract":"Abstract\nObesity has been linked consistently to an increased risk of developing several malignancies, including cancers of the breast, colon, kidney, pancreas, and gallbladder. The link between obesity and the metabolic syndrome (MS) remains elusive. The objective of this study was to evaluate the prevalence of the MS and diabetes at initial diagnosis of prostate cancer and to evaluate the relationship between the components of the MS in subjects with prostate cancer. In a retrospective study, we reviewed clinical data, specifically the components of the metabolic syndrome (MS), to evaluate the prevalence of the MS and diabetes at the initial diagnosis of prostate cancer. At initial diagnosis among 1408 subjects with prostate cancer, 60% of these subjects had the MS and 29% had diabetes. Among those subjects with the MS, 38% had diabetes and 89% had hypertension. Hypertension, elevated blood glucose levels, elevated body mass index, low high density lipoproteins and high triglycerides were the leading components of the MS, while low density lipoprotein cholesterol played a lesser role. We conclude that the prevalence of the MS is high in subjects with prostate cancer.","DOI":"10.1016/j.jomh.2009.01.005","ISSN":"1875-6867","journalAbbreviation":"Journal of Men's Health","author":[{"family":"Yaturu","given":"Subhashini"},{"family":"Fort","given":"Charlton"}],"issued":{"date-parts":[["2009",6,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
92
]. In vitro assays showed that HDL-C does not have a role in promoting breast cancer cell proliferation, angiogenesis or metastasis [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"yFABsw1l","properties":{"formattedCitation":"\\super 103 \\nosupersub{}","plainCitation":"103","noteIndex":0},"citationItems":[{"id":228,"uris":["http://zotero.org/users/2724931/items/AW8P4A5F"],"uri":["http://zotero.org/users/2724931/items/AW8P4A5F"],"itemData":{"id":228,"type":"article-journal","title":"VLDL and LDL, but not HDL, promote breast cancer cell proliferation, metastasis and angiogenesis","container-title":"Cancer Letters","page":"130-138","volume":"388","issue":"Supplement C","abstract":"Abstract\nAbnormal lipoprotein profiles are associated with breast cancer progression. However, the mechanisms linking abnormal lipoprotein levels to breast cancer progression, especially metastasis, remain unclear. Herein, we found that L1 and L5 subfractions of LDL and VLDL, but not HDL, enhanced breast cancer cell viability. L1, L5, and VLDL also increased the in vitro tumorigenesis of breast cancer cells in anchorage-independent soft agar assay. In addition, L1, L5, and VLDL, but not HDL, increased the levels of mesenchymal markers Slug, Vimentin, and
β
-Catenin, and promoted breast cancer cell migration and invasion. L1, L5, and VLDL increased Akt Ser473 phosphorylation and promoted cell migration, which were reversed by the PI3K/Akt inhibitor wortmannin. Further in vitro angiogenesis assay and cytokine array analysis demonstrated that L1, L5, and VLDL enhanced secretion of angiogenic factors in breast cancer cells and promoted angiogenic activity. However, only VLDL reduced anchorage-dependent cell death and promoted lung metastasis in

nude mice. In summary, our data suggest that L1, L5, and especially VLDL promote breast cancer progression and metastasis through Akt-induced EMT and angiogenesis, and provide a novel mechanism of how dyslipoproteinemia promotes breast cancer progression.","DOI":"10.1016/j.canlet.2016.11.033","ISSN":"0304-3835","journalAbbreviation":"Cancer Letters","author":[{"family":"Lu","given":"Chun-Wun"},{"family":"Lo","given":"Yi-Hsuan"},{"family":"Chen","given":"Chu-Huang"},{"family":"Lin","given":"Ching-Yi"},{"family":"Tsai","given":"Chun-Hao"},{"family":"Chen","given":"Po-Jung"},{"family":"Yang","given":"Yi-Fang"},{"family":"Wang","given":"Chie-Hong"},{"family":"Tan","given":"Chun-Hsiang"},{"family":"Hou","given":"Ming-Feng"},{"family":"Yuan","given":"Shyng-Shiou F."}],"issued":{"date-parts":[["2017",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
103
].
Research concerning the effect of the MetS and its individual conditions on CRA risk is limited. Tian et al. [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a9ih6tie2r","properties":{"formattedCitation":"\\super 94\\nosupersub{}","plainCitation":"94","noteIndex":0},"citationItems":[{"id":287,"uris":["http://zotero.org/users/2724931/items/M2FUF3AU"],"uri":["http://zotero.org/users/2724931/items/M2FUF3AU"],"itemData":{"id":287,"type":"article-journal","title":"The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis","container-title":"Public Health Nutrition","page":"3355-3370","volume":"18","issue":"18","source":"Cambridge University Press","archive":"Cambridge Core","abstract":"AbstractObjectiveThere have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.DesignWe identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.SettingWe analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).SubjectsCRN cases (n 21 809) were identified.ResultsOverall, people with high levels of serum TAG (risk ratio (RR) =1·08; 95 % CI 1·05, 1·12, P<0·00001) and LDL-C (RR=1·07; 95 % CI 1·00, 1·14, P=0·04) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR=1·04; 95 % CI 1·01, 1·09, P=0·02), TAG (RR=1·06; 95 % CI 1·03, 1·10, P=0·0009) and LDL-C (RR=1·11; 95 % CI 1·04, 1·19, P=0·003) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.ConclusionsBoth TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.","DOI":"10.1017/S1368980015000646","ISSN":"1368-9800","author":[{"family":"Tian","given":"Yun"},{"family":"Wang","given":"Keming"},{"family":"Li","given":"Juan"},{"family":"Wang","given":"Jirong"},{"family":"Wang","given":"Zhaoxia"},{"family":"Fan","given":"Yingrui"},{"family":"Ye","given":"Ying"},{"family":"Ji","given":"Guozhong"},{"family":"Li","given":"Yi"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
94
] indicated that serum TG was significantly associated with the CRA formation (RR = 1.06; 95% CI 1.03-1.10; P = 0.0009; I^2 = 69%). Yet, this is lower than the 30% increase in the CRA risk observed in our analysis. The meta-analysis undertaken by Tian et al. [
ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mhcua940v","properties":{"formattedCitation":"\\super 94\\nosupersub{}","plainCitation":"94","noteIndex":0},"citationItems":[{"id":287,"uris":["http://zotero.org/users/2724931/items/M2FUF3AU"],"uri":["http://zotero.org/users/2724931/items/M2FUF3AU"],"itemData":{"id":287,"type":"article-journal","title":"The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis","container-title":"Public Health Nutrition","page":"3355-3370","volume":"18","issue":"18","source":"Cambridge University Press","archive":"Cambridge Core","abstract":"AbstractObjectiveThere have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.DesignWe identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.SettingWe analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).SubjectsCRN cases (n 21 809) were identified.ResultsOverall, people with high levels of serum TAG (risk ratio (RR) =1·08; 95 % CI 1·05, 1·12, P<0·00001) and LDL-C (RR=1·07; 95 % CI 1·00, 1·14, P=0·04) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR=1·04; 95 % CI 1·01, 1·09, P=0·02), TAG (RR=1·06; 95 % CI 1·03, 1·10, P=0·0009) and LDL-C (RR=1·11; 95 % CI 1·04, 1·19, P=0·003) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.ConclusionsBoth TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.","DOI":"10.1017/S1368980015000646","ISSN":"1368-9800","author":[{"family":"Tian","given":"Yun"},{"family":"Wang","given":"Keming"},{"family":"Li","given":"Juan"},{"family":"Wang","given":"Jirong"},{"family":"Wang","given":"Zhaoxia"},{"family":"Fan","given":"Yingrui"},{"family":"Ye","given":"Ying"},{"family":"Ji","given":"Guozhong"},{"family":"Li","given":"Yi"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}
94
] showed that the RR for CRA with serum HDL-C was 1.03 (95 % CI 0.99-1.06; P =0.12) with a moderate heterogeneity (I^2 = 43 %). Correspondingly, our analysis revealed a non-significant effect of low levels of HDL-C on CRA risk (RR = 1.02; 95% CI 0.92-1.12;

I
2
=
74%).
To the best of our knowledge, our study could be the first comprehensive meta-analysis that shed the light on the effect of each metabolic factor constituting the MetS and CRA formation in addition to their association with the risk of developing CRC. This could be of high importance, particularly to determine the implication of MetS components on CRC carcinogenesis. Future research should focus on determining whether the increased risk of CRN is attributable to the entire cluster or to every particular condition. Moreover, understanding the role of
each component and the biological mechanisms relating to those factors and CRN incidence may provide indications for colorectal cancer therapy. In general, no evidence of the small study effect or publication bias was found. Besides, the additional analyses including subgroup, influence, and sensitivity analyses were performed and the Baujat plots were constructed for all the analyses. The results showed that no dataset has contributed in a way that significantly alters the findings, apart from the exceptions mentioned, emphasizing therefore on the strength of our findings. Although, this study has certain limitations. Including case-control and cross-sectional studies may result in selection bias. Several analyses presented results with moderate or considerable heterogeneity, hence these findings should be interpreted with caution. Nevertheless, subgroup and sensitivity analyses were carried out with the aim of exploring the sources of heterogeneity.

172085
202235
0
0

Conclusions
In summary, our findings demonstrate that hyperglycemia, hypertension, hypertriglyceridemia, and central obesity are associated with a moderately increased risk of both CRA and CRC. In fact, the proportions for the augmentation of the risk oscillated between 26-33% for CRA, and between 14-35% for CRC. In general, regarding the relationship between the increased CRC risk and these conditions, the association was more noticeable in the colon than in rectal cancer and in men than women. Nonetheless, low HDL-C shows a statistically non-significant positive effect on both outcomes. Our results display stronger associations between MetS components and CRA risk compared with those of CRC. Thus, screening programs aiming to prevent CRC should take into consideration MetS patients. The management of MetS and its individual components is highly recommended. Further research should be focused on understanding the biological mechanisms underlying the relationship between MetS and CRC.

172085
208585
0
0

References
Inoue K, Maeda N, Funahashi T. Metabolic Syndrome. In: Lammert E, Zeeb M, eds.
Metabolism of Human Diseases: Organ Physiology and Pathophysiology
. Vienna: Springer Vienna; 2014:199-203.
doi:10.1007/978-3-7091-0715-7_30
The International Diabetes Federation (IDF). IDF Consensus Worldwide Definition of the Metabolic Syndrome.
https://idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-
the-metabolic-syndrome
. Published 2006. Accessed July 17, 2017.
Kaur J. A Comprehensive Review
on
Metabolic Syndrome.
Cardiol Res Pract
. 2014;2014:e943162
.
doi:10.1155/2014/943162
Sorrentino MJ. The Metabolic Syndrome. In: Sorrentino MJ, ed.
Hyperlipidemia in Primary Care: A Practical Guide to Risk Reduction
. Totowa, NJ: Humana Press; 2011:13-39
.
doi:10.1007/978-1-60327-502-6_2
LeRoith D, Vinik AI, eds.
Controversies in Treating Diabetes
. Totowa, NJ: Humana Press; 2008.
doi:10.1007/978-1-59745-572-5
Nolan JJ, O'Gorman DJ. Pathophysiology of the Metabolic Syndrome. In: Beck-Nielsen H, ed.
The Metabolic Syndrome: Pharmacology and Clinical Aspects
. Vienna: Springer Vienna; 2013:17-42.
doi:10.1007/978-3-7091-1331-8_3
Kuipers EJ, Grady WM, Lieberman D,
Seufferlein
T
,
Sung
JJ
,
Boelens
P
G,
van de Velde
CJH,
Watanabe
T
. COLORECTAL CANCER.
Nat Rev Dis Primer
. 2015;1:15065.
doi:10.1038/nrdp.2015.65
Graham DM, Coyle VM, Kennedy RD, Wilson RH. Molecular Subtypes and Personalized Therapy in Metastatic Colorectal Cancer.

Curr Colorectal Cancer Rep
. 2016;12(3):141-150.
doi:10.1007/s11888-016-0312-y
Labianca R, Beretta GD, Kildani B,
Milesi
L,
Merlin
F,
Mosconi
S,
Pessi
MA,
Prochilo
T,
Quadri
A,
Gatta
G,
de Braud
F,
Wils
J
. Colon cancer.
Crit Rev Oncol Hematol
. 2010;74(2):106-133.
doi:10.1016/j.critrevonc.2010.01.010
Vipperla K, O'Keefe SJ. Colorectal Cancer. In: Lammert E, Zeeb M, eds.
Metabolism of Human Diseases
. Vienna: Springer Vienna; 2014:149-154.
doi:10.1007/978-3-7091-0715-7_24
Jenab-Wolcott J, Giantonio B. Cancers of the Rectum and Anal Canal. In: Sepulveda AR, Lynch JP, eds.
Molecular Pathology of Neoplastic Gastrointestinal Diseases
. Vol 7. Boston, MA: Springer US; 2013:141-171.
doi:10.1007/978-1-4614-6015-2_9
Parsyan
A, Robichaud N, Meterissian S. Colorectal Cancers. In:
Parsyan
A, ed.
Translation and Its Regulation in Cancer Biology and Medicine
. Springer Netherlands; 2014:593-610.
doi:10.1007/978-94-017-9078-9_29
Ferlay J, Soerjomataram I, Dikshit R,
Eser
S,
Mathers
C,
Rebelo
M,
Parkin
DM,
Forman
D,
Bray
F
. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012.
Int J Cancer
. 2015;136(5)
:E359-E386
.
doi:10.1002/ijc.29210
Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular Pathways Involved in Colorectal Cancer:
Implications for Disease Behavior and Prevention.
Int J Mol Sci
. 2013;14(8):
16365-16385.
doi:10.3390/ijms140816365
Moore JS, Aulet TH. Colorectal Cancer Screening.
Adv Colorectal Neoplasia
. 2017;97(3):487-502.
doi:10.1016/j.suc.2017.01.001
Chu KM. 1 - Epidemiology and Risk Factors of Colorectal Cancer A2 - Gearhart, Susan L. In: Ahuja N, ed.
Early Diagnosis and Treatment of Cancer Series: Colorectal Cancer
.
Saint Louis: W.B. Saunders; 2011:1-11.
doi:10.1016/B978-1-4160-4686-8.50006-3
Johnson CM, Wei C, Ensor JE,
Smolenski
DJ,
Amos
CI,
Levin
B,

Berry
DA
. Meta-analyses of colorectal cancer risk factors.
Cancer Causes Control
. 2013;24(6):1207-1222.
doi:10.1007/s10552-013-0201-5
Aran V, Victorino AP, Thuler LC, Ferreira CG. Colorectal Cancer: Epidemiology, Disease Mechanisms
and
Interventions to Reduce Onset and Mortality.
Clin Colorectal Cancer
. 2016;15(3):195-203.
doi:10.1016/j.clcc.2016.02.008
Carrer A, Giacca M, Giacca M. Molecular Parameters for Prognostic and Predictive Assessment in Colorectal Cancer. In: de Manzini N, ed.
Rectal Cancer
. Milano: Springer Milan; 2013:41-62.
doi:10.1007/978-88-470-2670-4_4
Tan CH, Das P, Silberfein EJ, Rodriguez-Bigas M, Iyer RB. Chapter 17 - Colorectal Cancer A2 - Silverman, Paul M. In:
Oncologic Imaging: A Multidisciplinary Approach
.
Philadelphia: W.B. Saunders; 2012:267-286.
doi:10.1016/B978-1-4377-2232-1.00017-6
Jess T, Rungoe C, Peyrin–Biroulet L. Risk of Colorectal Cancer in Patients
w
ith Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies.
Clin Gastroenterol Hepatol
. 2012;
10
(6):
639-645.
doi:10.1016/j.cgh.2012.01.010
Godos
J, Bella F, Torrisi A, Sciacca S, Galvano F, Grosso G. Dietary patterns and risk of colorectal adenoma: a systematic review and meta-analysis of observational studies.
J Hum Nutr Diet
. 2016;29(6):757-767.
doi:10.1111/jhn.12395
Zhu B, Sun Y, Qi L, Zhong R, Miao X. Dietary legume consumption reduces
risk
of colorectal cancer: evidence from a meta-analysis of cohort studies.
Sci Rep
. 2015;5:8797.
doi:10.1038/srep08797
Vieira AR, Abar L, Chan D,
Vingeliene
S,
Polemiti
E,
Stevens
C,
Greenwood
D,
Norat
T
. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project.
Ann Oncol Off J Eur Soc Med Oncol
. April 2017.
doi:10.1093/annonc/mdx171
Zhou X-Y, Yan L, Wang L-L, Wang J. Association between physical activity and colorectal cancer risk
and prognosis: A meta-analysis.
Cancer Treat Res Commun
. 2016;
9:
62-69.
doi:10.1016/j.ctarc.2016.07.002
Tsoi KKF, Pau CYY, Wu WKK, Chan FKL, Griffiths S, Sung JJY. Cigarette Smoking and the Risk of Colorectal Cancer: A Meta-analysis of Prospective Cohort Studies.
Clin Gastroenterol Hepatol
.
2009;7(6):682-688.e5.
doi:10.1016/j.cgh.2009.02.016
Kort S de, Masclee AAM, Sanduleanu S,
Weijenberg
MPP,
Herk-Sukel
MP,
Oldenhof
NJJ,
Bergh
JPW,
Haak

HR,
Janssen-Heijnen
ML
. Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation.
Sci Rep
. 2017;
7:
46527.
doi:10.1038/srep46527
Esposito K, Chiodini P, Capuano A,
Bellastella
G,
Maiorino
MI,
Rafaniello
C,
Panagiotakos
DB,
Giugliano
D
. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis.
Endocrine
. 2013;
44
(3):
634-647.
doi:10.1007/s12020-013-9939-5
Stocks T, Lukanova A, Bjørge T,
Ulmer
H,
Manjer
J,
Almquist
M,
Concin
H,
Engeland
A,
Hallmans
G,
Nagel
G,
Tretli
S,
Veierød
MB,
Jonsson
H,
Stattin
P
. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can).
Cancer
. 2011;117(11):2398-2407.
doi:10.1002/cncr.25772
Jinjuvadia R, Lohia P, Jinjuvadia C, Montoya S, Liangpunsakul S. The Association between Metabolic Syndrome and Colorectal Neoplasm: Systemic review and Meta-analysis.
J Clin Gastroenterol
. 2013;47(1):33-44.
doi:10.1097/MCG.0b013e3182688c15
Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.
PLOS Med
. 2009;6(7):
e1000097.
doi:10.1371/journal.pmed.1000097
Wells G, Shea B, O'Connell D,
Peterson
J,
Welch
V,
Losos
M,
Tugwell
P
. The Newcastle-Ottawa Scale (NOS) for assessing the quality of
nonrandomised
studies in meta-analyses. Ottawa Hospital Research Institute.
http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
. Accessed August 18, 2018.

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis.
Res Synth Methods
. 2010;1(2):97-111.
doi:10.1002/jrsm.12
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses.
BMJ
. 2003;327(7414):557.
doi:10.1136/bmj.327.7414.557
Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis.
Stat Med
. 2002;21(11):1539-1558.
doi:10.1002/sim.1186
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test.
BMJ
. 1997;315(7109):629-634.
doi:10.1136/bmj.315.7109.629
Begg CB, Mazumdar M. Operating Characteristics of a Rank Correlation Test for Publication Bias.
Biometrics
. 1994;50(4):1088-1101.
doi:10.2307/2533446
Duval Sue, Tweedie Richard. Trim and Fill: A Simple Funnel-Plot–Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis.
Biometrics
. 2004;56(2):455-463.
doi:10.1111/j.0006-341X.2000.00455.x
Review Manager (RevMan)
. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration
; 2014.
https://community.cochrane.org
Viechtbauer Wolfgang, Cheung Mike W.-L. Outlier and influence diagnostics for meta-analysis.
Res Synth Methods
. 2010;1(2):112-125.
doi:10.1002/jrsm.11
Baujat Bertrand, Mahé Cédric, Pignon Jean-Pierre, Hill Catherine. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials.
Stat Med
. 2002;21(18):2641-2652.
doi:10.1002/sim.1221
R Core Team.
R: A Language and Environment for Statistical Computing
. Vienna, Austria: R Foundation for Statistical Computing
; 2018.
https://www.R-project.org/
.
Viechtbauer W. Conducting Meta-Analyses in R with the
metafor
Package.
J Stat Softw Vol 1 Issue 3
2010
. August 2010.
https://www.jstatsoft.org/v036/i03
.
Lin X-F, Shi K-Q, You J,
Liu
WY,
Luo
YW,
Wu
FL,
Chen
YP,
Chen
DKH,
Yuen
MF,
Zheng
MH
. Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study.
Mol Biol Rep
. 2014;41(5):2989-2997.
doi:10.1007/s11033-014-3157-y
Huang K-W, Leu H-B, Wang Y-J,
Luo
JC,
Lin
HC,
Lee
FY,
Chan
WL,
Lin

JK,
Chang
FY
. Patients with
nonalcoholic
fatty liver disease have
higher
risk of colorectal adenoma after negative baseline colonoscopy.
Colorectal Dis Off J Assoc Coloproctology G B Irel
. 2013;15(7):830-835.
doi:10.1111/codi.12172
Kim BC, Shin A, Hong CW,
Sohn
DK,
Han
KS,
Ryu
KH,
Park
BJ,
Nam
JH,
Park
JW,
Chang
HJ,
Choi
HS,
Kim
J,
Oh
JH
. Association of colorectal adenoma with components of metabolic syndrome.
Cancer Causes Control CCC
. 2012;23(5):727-735.
doi:10.1007/s10552-012-9942-9
Bowers K, Albanes D, Limburg P,
Pietinen
P,
Taylor
PH,
Virtamo
J,
Stolzenberg-Solomon
R
. A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers.
Am J Epidemiol
. 2006;164(7):652-664.
doi:10.1093/aje/kwj253
Kabat GC, Kim MY, Peters U,
Stefanick
M,
Hou
L,
Wactawski-Wende
J,
Messina
C,
Shikany
JM,
Rohan
TE
. A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women.
Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP
. 2012;21(4):326-332.
doi:10.1097/CEJ.0b013e32834dbc81
Liang X, Margolis KL, Hendryx M,
Rohan
T,
Groessl
EJ,
Thomson
CA,
Kroenke
CH,
Simon
M,
Lane
D,
Stefanick
M,

Luo
J
. Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women.
Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol
. 2017;26(2):155-161.
doi:10.1158/1055-9965.EPI-16-0761
Shin CM, Han K, Lee DH,
Choi
YJ,
Kim
N,
Park
YS,
Yoon
H
. Association Among Obesity, Metabolic Health, and the Risk for Colorectal Cancer in the General Population in Korea Using the National Health Insurance Service–National Sample Cohort.
Dis Colon Rectum
. 2017;60(11):
1192–1200
.
doi:10.1097/DCR.0000000000000876
Shapero TF, Chen GI, Devlin T,
Gibbs
A,
Murray
IC,
Tran
S,
Weigensberg
C
. Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study.
Can J Gastroenterol Hepatol
. 2017;2017:8750967.
doi:10.1155/2017/8750967
Stocks T, Lukanova A, Johansson M,
Rinaldi
S,
Palmqvist
R,
Hallmans
G,
Kaaks
R,
Stattin
P
. Components of the metabolic syndrome and colorectal cancer risk; a prospective study.
Int J Obes
.
2007;32:304.
doi:10.1038/sj.ijo.0803713
Pyo JH, Hong SN, Min B-H,
Lee
JH,
Chang
DK,
Rhee
PL,
Kim
JJ,
Choi
SK,
Jung
SH,
Son
HJ,
Kim
YH
. Evaluation of the risk factors associated with rectal neuroendocrine tumors: a big data analytic study from a health screening center.
J Gastroenterol
. 2016;51(12):1112-1121.
doi:10.1007/s00535-016-1198-9
Jeon YJ, Kim JW, Park HM,
Jang
HG,
Kim
JO,
Oh
J,
Chong
SY,
Kwon

SW,
Kim
EJ,
Oh
D,
Kim
NK
. Interplay between 3
′
-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans.
BMC Cancer
.
2014;14:881.
doi:10.1186/1471-2407-14-881
Kontou N, Psaltopoulou T, Soupos N,
Polychronopoulos
E,
Xinopoulos
D,
Linos
A,
Panagiotakos
DB
. Metabolic syndrome and colorectal cancer: the protective role of
Mediterranean
diet--a case-control study.
Angiology
. 2012;63(5):390-396.
doi:10.1177/0003319711421164
Aleksandrova K, Boeing H, Jenab M,
Bas Bueno-de-Mesquita
H,
Jansen
E,
van Duijnhoven
FBJ,
Fedirko
V,
Rinaldi
S,
Romieu
I,
Riboli
E,
Romaguera
D,
Overvad
K,
Østergaard
JN,
Olsen
A,
Tjønneland
A,
Boutron-Ruault
MC,
Clavel-Chapelon
F,
Morois
S,
Masala
G,
Agnoli
C,
Panico
S,
Tumino
R,
Vineis
P,
Kaaks
R,
Lukanova
A,
Trichopoulou
A,
Naska
A,
Bamia
C,
Peeters

PH,
Rodríguez
L,
Buckland
G,
Sánchez
MJ,
Dorronsoro
M,
Huerta
JM,
Barricarte
A,
Hallmans
G,
Palmqvist
R,
Khaw
KT,
Wareham
N,
Allen
NE,
Tsilidis
KK,
Pischon
T
. Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study.
Cancer Prev Res (Phila Pa)
. 2011;4(11):1873.
doi:10.1158/1940-6207.CAPR-11-0218
Shen Z, Wang S, Ye Y,
Yin
M,
Yang
X,
Jiang
K,
Liu
Y
. Clinical study on the correlation between metabolic syndrome and colorectal carcinoma.
ANZ J Surg
. 2010;80(5):331-336.
doi:10.1111/j.1445-2197.2009.05084.x
Pelucchi C, Negri E, Talamini R,
Levi
F,
Giacosa
A,
Crispo
A,
Bidoli
E,
Montella
M,
Franceschi
S,
La Vecchia
C
. Metabolic syndrome is associated with colorectal cancer in men.
Eur J Cancer
. 2010;46(10):1866-1872.
doi:10.1016/j.ejca.2010.03.010
Kang HW, Kim D, Kim HJ,
Kim
C,
Kim
YS,
Park
MJ,
Kim
JS,
Cho
SH,
Sung
MW,
Jung
HC,
Lee
HS,
Song

IS
. Visceral Obesity and Insulin Resistance as Risk Factors for Colorectal Adenoma: A Cross-Sectional, Case–Control Study.
Am J Gastroenterol
. 2009;105(1):178-187.
doi:10.1038/ajg.2009.541
F liss - Isakov Naomi, Zelber -
Sagi Shira, Webb Muriel, Halpern Zamir, Shibolet Oren, Kariv Revital. Distinct Metabolic Profiles are Associated with Colorectal Adenomas and Serrated Polyps.
Obesity
. 2017;25(S2):S72-S80
.
doi:10.1002/oby.22001
Harima S, Hashimoto S, Shibata H, Matsunaga T, Tanabe R, Terai S, Sakaida I
. Correlations between Obesity/ Metabolic Syndrome-Related Factors and Risk of Developing Colorectal Tumors.
Hepato-gastroenterology
hge
.
2013:
733-737
.
doi:10.5754/hge12895
Lipka S, Zheng XE, Hurtado-Cordovi J, Singh J, Levine E, Vlacancich R, Krishnamachari B, Jung MK, Fu S, Takeshige U, Avezbakiyev B, Li T, Iqbal J, Rizvon K, Mustacchia P
. Obesity, Metabolic Factors, and Colorectal Adenomas: a Retrospective Study in a Racially Diverse New York State Hospital.
J Gastrointest Cancer
. 2013;44(3):270-276.
doi:10.1007/s12029-013-9476-8
Morita T, Tabata S, Mineshita M, Mizoue T, Moore MA, Kono S. The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study.
APJCP
. 2005;6(4):5.
http://journal.waocp.org/?sid=Entrez:PubMed&id=pmid:16435997&key=2005.6.4.485
Tsilidis KK, Brancati FL, Pollak MN, Rifai N, Clipp SL, Hoffman-Bolton J, Helzlsouer KJ,

Platz
EA
. Metabolic syndrome components and colorectal adenoma in the CLUE II cohort.
Cancer Causes Control CCC
. 2010;21(1):1-10.
doi:10.1007/s10552-009-9428-6
Hong SN, Lee TY, Yun S-C. The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases.
J Korean Med Sci
. 2015;30(9):1288-1294.
doi:10.3346/jkms.2015.30.9.1288
Jung YS, Yun KE, Chang Y,
Ryu
S,
Park
JH,
Kim
HJ,
Cho
YK,
Sohn
I,
Jeon
WK,
Kim
BI,
Park
I
. Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study.
Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol
. 2014;23(7):1406-1413.
doi:10.1158/1055-9965.EPI-14-0132
Lee CG, Hahn SJ, Song MK,
Lee
JK,
Kim
JH,
Lim
YJ,
Koh
MS,
Lee
JH,
Kang
HW
. Vegetarianism as a Protective Factor for Colorectal Adenoma and Advanced Adenoma in Asians.
Dig Dis Sci
. 2014;59(5):1025-1035.
doi:10.1007/s10620-013-2974-5
Sato T, Takeda H, Sasaki Y, Kawata S. Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males.
Tohoku J Exp Med
. 2011;223(4):297-303.
doi:10.1620/tjem.223.297
Hu N-C, Chen J-D, Lin Y-M, Chang J-Y, Chen Y-H. Stepwise Relationship Between Components of Metabolic Syndrome and Risk of Colorectal Adenoma in a Taiwanese Population Receiving Screening Colonoscopy.
J Formos Med Assoc
. 2011;110(2):100-108.
doi:10.1016/S0929-6646(11)60016-8
Hong SN, Kim JH, Choe WH,
Han
HS,
Sung
IK,
Park
HS,
Shim
CS
. Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age.
Gastrointest Endosc
. 2010;72(3):480-489.
doi:10.1016/j.gie.2010.06.022
Hwang ST, Cho YK, Park JH,
Kim
HJ,
Park
DI,
Sohn
CI,
Jeon
WK,
Kim
BI,

Won
KH
. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps.
J Gastroenterol Hepatol
. 2010;25(3):562-567.
doi:10.1111/j.1440-1746.2009.06117.x
Oh T-H, Byeon
J-S
, Myung S-J,
Yang
SK,
Choi
KS,
Chung
JW,
Kim
B,
Lee
D,
Byun
JH,
Jang
SJ,
Kim
JH
.
Visceral obesity as a risk factor for colorectal neoplasm.
J Gastroenterol Hepatol
. 2008;23(3):411-417.
doi:10.1111/j.1440-1746.2007.05125.x
Kim JH, Lim YJ, Kim Y-H,
Sung
IK,
Shim
SG,
Oh
SO,
Park
SS,
Yang
S,
Son
HG
,
Rhee
PL,
Kim
JJ,
Rhee
JC,
Choi
YH
. Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?
Cancer Epidemiol Prev Biomark
. 2007;16(8):1543-1546.
doi:10.1158/1055-9965.EPI-07-0199
Yang SY, Kim YS, Lee JE,
Seol
J,
Song
JH,
Chung
GE,
Yim
JY,
Lim
SH,
Kim
JS
. Dietary protein and fat intake in relation to risk of colorectal adenoma in Korean. Elrazek. AEA, ed.
Medicine (Baltimore)
. 2016;95(49):e5453.
doi:10.1097/MD.0000000000005453
Elher
rag SE, Traoré Y, Khaled MB. Metabolic Syndrome and Risk of Colorectal Adenoma and Colorectal Cancer: A Meta-Analysis.
North Afr J Food Nutr Res
. 2017;01(02):30-43.
doi:10.5281/zenodo.1245604
World Health Organization. WHO | Obesity and overweight. WHO.
http://www.who.int/mediacentre/factsheets/fs311/en/
.
Published

October 2017. Accessed November 29, 2017.
Arnold M, Leitzmann M, Freisling H, Bray F, Romieu I, Renehan A, Soerjomataram I. Obesity and cancer: An update of the global impact. Cancer Epidemiol. 2016;41(Supplement C):8-15. doi:10.1016/j.canep.2016.01.003
González Svatetz CA, Goday Arnó A. Obesity and cancer: “Dangerous friendship.” Med Clínica Engl Ed. 2015;145(1):24-30. doi:10.1016/j.medcle.2014.05.011
Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, Qin H. Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies. PLOS ONE. 2013;8(1):e53916. doi:10.1371/journal.pone.0053916
Zhang X, Wu WKK, Yu J. Obesity and Cancer. In: Ahmad SI, Imam SK, eds. Obesity: A Practical Guide. Cham: Springer International Publishing; 2016:211-220. doi:10.1007/978-3-319-19821-7_16
Suchanek S, Grega T, Ngo O, Vojtechova G, Majek O, Minarikova P, Brogyuk N, Bunganic B, Seifert B, Dusek L, Zavoral M. How significant is the association between metabolic syndrome and prevalence of colorectal neoplasia? World J Gastroenterol. 2016;22(36):8103-8111. doi:10.3748/wjg.v22.i36.8103
Mendonça FM, de Sousa FR, Barbosa AL, Martins SC, Araújo RL, Soares R, Abreu C. Metabolic syndrome and risk of cancer: Which link? Metabolism. 2015;64(2):182-189. doi:10.1016/j.metabol.2014.10.008
Pais R, Silaghi H, Silaghi AC, Rusu ML, Dumitrascu DL. Metabolic syndrome and risk of subsequent colorectal cancer. World J Gastroenterol WJG. 2009;15(41):5141-5148. doi:10.3748/wjg.15.5141
Ishino K, Mutoh M, Totsuka Y, Nakagama H. Metabolic syndrome: a novel high-risk state for colorectal cancer. Cancer Lett. 2013;334(1):56-61. doi:10.1016/j.canlet.2012.10.012
Erbach M, Mehnert H, Schnell O. Diabetes and the risk for colorectal cancer.

J Diabetes Complications
. 2012;26(1):50-55.
doi:10.1016/j.jdiacomp.2011.11.003
Eibl G, Cruz-Monserrate Z, Korc M,
Petrov
MS,
Goodarzi
MO,
Fisher
WE,
Habtezion
A,
Lugea
A,
Pandol
SJ,
Hart
PA,
Andersen
DK
. Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer.
J Acad Nutr Diet
. September 2017.
doi:10.1016/j.jand.2017.07.005
Zelenko Z, Gallagher EJ. Diabetes and Cancer.
Diabetes Mellit Assoc Cond
. 2014;43(1):167-185.
doi:10.1016/j.ecl.2013.09.008
Smith LA, O'Flanagan CH, Bowers LW, Allott EH, Hursting SD. Translating Mechanism-Based Strategies to Break the Obesity−Cancer
Link: A Narrative Review.
J Acad Nutr Diet
. November 2017.
doi:10.1016/j.jand.2017.08.112
Niwa Y, Ishikawa K, Ishigami M,
Honda
T,
Achiwa
K,
Izumoto
T,
Maekawa
R,
Hosokawa
K,
Iida
A,
Seino
Y,
Hamada
Y,
Goto
H,
Oiso
Y,
Arima
H,
Tsunekawa
S
. Effect of hyperglycemia on hepatocellular carcinoma development in diabetes.
Biochem Biophys Res Commun
. 2015;463(3):344-350.
doi:10.1016/j.bbrc.2015.05.066
Shi J, Xiong L, Li J,
Cao
H,
Jiang
W,
Liu
B,
Chen
X,
Liu
C,
Liu
K,
Wang
G,
Cai
K
. A Linear Dose-Response Relationship between Fasting Plasma Glucose and Colorectal Cancer Risk: Systematic Review and Meta-analysis.

Sci Rep
. 2015;5:17591.
doi:10.1038/srep17591
Boffetta P, Boccia S, La Vecchia C.
A Quick Guide to Cancer Epidemiology
. Cham: Springer International Publishing
; 2014.
doi:10.1007/978-3-319-05068-3
Yaturu S, Fort C. Prostate cancer is associated with the metabolic syndrome.
J Mens Health
. 2009;6(2):125-129.
doi:10.1016/j.jomh.2009.01.005
Largent JA, Bernstein L, Horn-Ross PL,
Marshall
SF,
Neuhausen
S,
Reynolds
P,
Ursin
G,
Zell
JA,
Ziogas
A,
Anton-Culver
H
. Hypertension, antihypertensive medication use, and breast cancer risk in the California Teachers Study cohort.
Cancer Causes Control
. 2010;21(10):1615-1624.
doi:10.1007/s10552-010-9590-x
Tian Y, Wang K, Li J,
Wang
J,
Wang
Z,
Fan
Y,
Ye
Y,
Ji
G,
Li
Y
. The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis.
Public Health Nutr
. 2015;18(18):3355-3370.
doi:10.1017/S1368980015000646
Yao X, Tian Z. Dyslipidemia and colorectal cancer risk: a meta-analysis of prospective studies.
Cancer Causes Control CCC
. 2015;26(2):257-268.
doi:10.1007/s10552-014-0507-y
Agnoli C, Grioni S,
Sieri
S,
Sacerdote
C,
Vineis
P,
Tumino
R,
Giurdanella
MC,
Pala
V,
Mattiello
A,
Chiodini
P,
Iacoviello
L,
De Curtis
A,
Cattaneo
L,
van Duijnhoven
FGB,
Panico
S,
Krogh
V
. Colorectal cancer risk and dyslipidemia: A

case–cohort
study nested in an Italian multicentre cohort.
Cancer Epidemiol
.
2014;38(2):144-151.
doi:10.1016/j.canep.2014.02.002
Siddiqui AA, Palmer BF. Metabolic Syndrome and Its Association With Colorectal Cancer: A Review.
Am J Med Sci
. 341(3):227-231.
doi:10.1097/MAJ.0b013e3181df9055
Lipscombe L. Insulin, Insulin Resistance, and Cancer Associations. In: Fantus IG, ed.
Insulin Resistance and Cancer: Epidemiology, Cellular
and
Molecular Mechanisms and Clinical Implications
. New York, NY: Springer New York
; 2011:111-140.
doi:10.1007/978-1-4419-9911-5_5
Chen Y, Wen Y, Li Z, Luo D, Zhang X. The molecular mechanisms between metabolic syndrome and breast cancer.
Biochem Biophys Res
Commun
. 2016;471(4):391-395.
doi:10.1016/j.bbrc.2016.02.034
Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study.
Lung Cancer
. 2008;61(3):292-300.
doi:10.1016/j.lungcan.2008.01.015
Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-Cholesterol and Incidence of Breast Cancer in the ARIC Cohort Study.
Ann Epidemiol
. 2008;18(9):671-677.
doi:10.1016/j.annepidem.2008.06.006
Osaki Y, Taniguchi S, Tahara A, Okamoto M, Kishimoto T. Metabolic syndrome and incidence of liver and breast cancers in Japan.
Cancer Epidemiol
. 2012;36(2):141-147.
doi:10.1016/j.canep.2011.03.007
Lu C-W, Lo Y-H, Chen C-H,
Lin
CY,
Tsai
CH,
Chen
PJ,
Yang
YF,
Wang
CH,
Tan
CH,
Hou
MF,
Yuan
SF
. VLDL and LDL, but not HDL, promote breast cancer cell proliferation, metastasis
and
angiogenesis.
Cancer Lett
. 2017;388(Supplement C):130-138.
doi:10.1016/j.canlet.2016.11.033
315849
226822

Cite this article as
:
Elherrag S.E
,
Traoré
Y
, and Khaled M
.
B
.
Metabolic syndrome components correlation with colorectal neoplasms:
A
systematic review and a meta-analysis
.
Nor. Afr. J. Food Nutr. Res.
July – December (2018); 02 (04
):
93-110.
https://doi.org/10.5281/zenodo.
1478870

Cite this article as
:
Elherrag
S.E
,
Traoré
Y
, and Khaled M
.
B
.
Metabolic syndrome components correlation with colorectal neoplasms:
A
systematic review and a meta-analysis
.
Nor. Afr. J. Food
Nutr
. Res.
July – December (2018); 02 (04
):
93-110.
https://doi.org/10.5281/zenodo.
1478870

</w:body>
</w:document>
</pkg:xmlData>
</pkg:part>

172085
94297
171450
252730
0
0

The North African Journal of Food and Nutrition Research
.
Nor.
Afr. J. F
ood
Nutr. Res.
I
July – December 2018
I
Volume
02
I
Issue
04

172206
251581
0
0

Nor.
Afr. J. F
ood
Nutr. Res.
I
January – June 2017
I
Volume
01
I
Issue
01

67945
22581

Elherrag
et al.:
Metabolic syndrome components and colorectal neoplasms

0

Elherrag
et al.:
Metabolic syndrome components and colorectal neoplasms

PAGE * MERGEFORMAT
99
PAGE * MERGEFORMAT
93

172206
251581

0
0

Nor.
Afr. J. F
ood
Nutr. Res.
I
July – December 2018
I
Volume
02
I
Issue
04

iVBORw0KGgoAAAANSUhEUgAAAOQAAABdCAMAAAH1SwqUAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAALoUExURf////7r1/uyaPmRJfmCCfmGDvqbO/zEhv779/mOF/vGiP/9/f738PmJE/3h
w/mPGfmIFfmGEP3MmvqnUfmRJv7s2vqfQPzQoP3evv/9/P78+f7p1P3w4fmEDfzVq/ugQf748vmE
DPutWfu1bfzPofzRpPu2b/zOnPqYNf/+/v3cufqkS/7oz//+/f/+/P7hw/mFEPqIE/mGDf769f78
+v3Sp/3atfmDDP/38PmEDv3fvvy4c/mFD/7y5vu3b/mNH/mNHP79+/u/fv///v3TqPmULP3Qovu3
cP79/PmRIfy9ev706/78+P7+/v7+/fmDCvu7ePzJlP3bt/mKGPvFjP/9+v3WrfzTpfqhRPu/f/74
8PuxZv706vzLl/mZOP3XrfmZLvmLG/u7dfmGEvmHD/mIEfuwYP/9+f7buPurVvmMHPzIk/mCCv3e
u/utW/mSKfuiPfqwYfmMFvmXLv727fuuXvmOHvzKmPmSI/3Vqv7x5fqYM//58vmOHPqkSv717PqW
LfzEif/7+fmKGf3du/y6dfutXvmFDPqrVP/8+fmFDvu6cfmJF/3myvuzaPzChvunUvmDC/qUJfmJ
GP/x4/qtXv7mzv748f7z5v7t2/qoU/7w4fqrWPzHj/zUqPqcN/mQJPzJkPmJEvmJFPmGD/mVL/zV
qv7y5f3dvPmWLf/69f78+/zKlP7o0vqrWv769vqrUf7x4/zNmvzBgfmfQvuuXPy+f/qYMPmPIv/5
8/3ixv7s2fmMHfmSJ/mEC/qUK/727v737/705/u4avqdPP/48vqgQv3p1Pu9e/qnT/u+fPqvX/mO
If/8+v3Wr/qUKvqPIvy5cv7kyPqaMPuyY/uyZfqmSvqWKvqUJ/3Mmfu+f/mLF/769/mSKPzMm/7q
1fu2cPu1av7v3vqOHPuzaf7hxfqlRPqXM/zIj/3YsvqoUf3Nm/mQJfmOH/3o0/vKlf3gw/716/mM
Gv3t2/3atvzIkf7t2gAAAGfwSGwAAAD4dFJOU//
SFlzAAAh1QAAIdUBBJy0nQAABwdJREFUaEPtm7tu20gUhlWwSptncLfNFkFKPUBAIH2KrVwstnIX
wKkCB3Cz8FPsG7hym6cIkErFlkmRF9jzX+bCixRJ2NGaWn02Oef8Z4aHQ4oUyaFW+9N1NuaI4I4w
Qrta74x2gc0EpO6Nl3oVE9NDoSaPjizOWbkCgZFUEbFxgxqsQG/734WJt8BV3sLu9oQ12d8ZmzRtk
Q4T/3eptKOI7Zj00hxL1Yti2Fmqg7+jL/AqdDOTvul/t7Y9X+5fD1z61OL7fR7RUNwP7s2zWXDb2
JqbY67TlNYxHxMLhxDpR3iFML5U9dU7ZikMWhlphWt1An4P6DWbbamyF+XJxGNEoaHOkPyuO2jqB
NtBxW3a92hzT1E26bsNyf3Kyg5PmBkesrjlpS+wSYn9v3CywMEvXvY2jVccvSzZ0SB70W0XiGL+P
afUFDv7518UXSK5LkqeFWsC/HPzDikktOVtnK2a8FHBlzWRYjk9cH+ehPgykgIwYo/C0FJsITome
Vy0PQo1oHNNyYOzLlXI9HpySaynsHwB2z//ipHkGcFcJK41xsozldgzSfKmdVrwa5ThBzkmGs0w5
4VQpkYecKCVzDXDgcFJrlte1n2aAKr7bilOFUuk2uHIbuDfFpeKZKjDuV+Fp47F4n56FqICqhu1NT
ubna0L/HWoiH7h5FBLiQiLuIbyJ+GbFWNgqQqLHNNYvk2sgVmCO5roLZQFBK5MTXH2pLpVXMKH50
cRcNy5sd24a4mrLRdAFyl2v6QDPU7bqPEGEMGnTKKw/s3iKT0SFF/8el2p7M8wj60222lAyZRpn
nOakz23dDuYAcZ1rHGlHz51XONGFXN/jMjUOHvsXLjxzeHgc8ZzwWD4oIbHUGCczFpviVBnLDfm7
JJLVPucgCx0+MG0Ik9gORm4TxjlOlNImgd845zNIyZta2434D1KOGd9VnwA8PjvTlHGHZU6U8onJ
ahxohtPUONIKZxng0OGgMe7O0lJc2kENlGLgVLFUdqq8cdRF3nOkIdgeUFqDBO/Cu22x+sArEXKu0
COhWMRUcIabHZwNcTJQxqfiEuEzradINqZbJqByboh1LSewDZnS2TG8jEvExYmh4VOOXM7atqycpN
gzW2DUgVYp52G/VUU22kqlRKjKhmaUA5MNlUU3CdRr5yG5c4xuCmmphnhRsW+WLSPZ1b2dLgftJQ
DpqPysBL2ViKDxSbVXV3pIRRmY8sNSu6HkfYBTCfXMoHY4EpNbNUYrKTkWdFYMmiyC7MPR82jeHj
Fz2DYX2KbCg7G4U7P265HSzwBtuiBPckL515tDNhLaUg8DiaejUTjMbbSiJwsQphUbTlK+ny4fS
MuU0wXXrjEpZpfhr5LeAKfITNHl2mqEsATcpwPmkKTj5DXjiSaIpo5ztEwY8y5urk2QM4oyLfN8u
jw0vXLjw3Nl8Xnfd7Qt7Z8cLnv0HOHIu/OpuTWh+HXEy3KF5Tjfa0RJ3ZjsHjYA/T9wTcGuJWCOW
Fou7EViocCCwsFDciS3dcCywsEjcha2duHW4+2BhibgL3e/2Jzi+6F3pHmzvwjtXOOtOcrAK2F8i
7z7rz+6Uc+jkT/nuPp51JznSAOwvn7zbgvcjSe6y4btyU85oT7ofO3HVpeJe/ARXPiF+OcDe5LLE
XlBcWjBlZBis4PVbfXAaVs78NtEopEHK7KafmZobxrJiDz8yDIbfY9LEWOCwpe2gCieTZUIh4Tfo
C9aFNSMt9aiqudtVJ+3MVxa8ZqaVB5JTibeJ7Wu8XSAc4FF6FNKEAsTKCAeDwXa25kaVCUauBJtg
6N6HN736r+qgv/XIOxqgtGwwXHCNqj1+BzhOJyMKW9G10O24ZYs+GHDeJvaFCMBbndlx67txKeQ
8j2D4ygSSRbhaExEM8xRQUAiGmTeguuMG+IH2CUbZYGxNJsGFYT89PaPj1B7dSO+22o7vX6BgpSh
Xv9IInAn+5eYY7K++gEdvLQAPlIprQMqwL5/kyLCRVF2TP54FVxvwOh3LfSqSvB8xKdAKhPhljSp
k71PyXmYS25gPyg/ESgnlTIQaL80DPCWDsrq0SXcdBolEGxW4Nj6ajsYVYIb50KtUFZoGEZI9DV3
sv9KadLJ8nKsBfHNYpG94WAOLZRmxp0Le2sO3bJdQX4oYb8yCWNkXToZRrKGtewGFozFSi6urPK2
Ul6jP+m+taej3TYYuHD0hgHwm1lHgp2ojhULeOHpQA4sGIvjtVoWXvN63S0QS4EFvSW3MPAVQOyD
fMa1D6wsckfuu/b5oBmcMZeD137nrw9cI7CwOLz6gYUxt3zHi1hZIO4A8AupNY4QS4vEXTB/WK0v
zInVxeJu7OKhfLkulL7P58956guI5RK9KOeXEWf12lp0tL6DIuexC2eIjgn7Fy4cxWr1D26f3sHx zagSAAAAAElFTkSuQmCC
iVBORw0KGgoAAAANSUhEUgAAAVYAAADlCAIAAAHw43gtAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAAJcEhZcwAAIdUAACHVAQSctJ0AAF9vSURBVHhe7Z0HfBRFF8A3CR2pIgIKKkU/VFAh
PSQQQguE0KsUAQVsSBMFRAER6VVAsIsFe+9iRREVQVAQFRFURFJRAeCGnwvd33bnb27e7d3uUuOcm+
3z+XedNndvZtn1GU5sUN14sepp/RxODZuYnSM1737xkPv7qqETc4Tlb9g9g+mYNQiWpP5qkCf4dI9B
N4hIFZIagCgtqljUwONGwVTBr4FeJKuB2aGlips4TLj9huki34SJ15Pbpgaym2rQrTn6q0Bu+OsT
g2JVAIjsBsFQ4QkOkqOkgG7i0WQipyzF3SXMVNZHbz0XnQwwDwwDR3BqAEmEDVAHw30sRQRumX6r6rK
agBg5t5R/7peQ7FZH2g+whOF/IG0C+CXfDUpRA2kNJSX8JFCj2efVVmRX8W/VhYDTv
qH+YowZmxyRpaBLlZR/zt79+UzKbyhEIUZId6p+UgPKzEjmaXUwWR6VTY0N5ZtS/uDIiAWUUW1r4
CE8Qs6edqiMXZgnTKaP29Vl69I+fOExkjT52qo6uUTUGRc5oqqKjZURBbbS/CyKR6iGoMnL+ljAd
M+qyKpMhh8ru9Ac7YC3Bvefff/wuHmA65guOtGWprHjgufefExHQAaGZKzvrXeVv8QDTMV/mKYMR
hLRb1o5qCTVoX7MoagBgHBQSQZUCbkGPeLkVLZw3TF9JvbuZw2H2juH2jUM8fWLPu4LqkYg8aYgAd
9FbDW6EjdlCs8Cw4XQDnYdEDo2VPoGHXhn/+8eZ6QR941Ad0FBgfAXYPzI6EhV5b5qeRK
snpxT+XA4QPgiIiOMPj3lMeKF1ego8ftPdABQA2EW9Tg8p6Xn8g+Ifx1uF70cL3oV7c3oXYq3GeqvubvE
+MgvyFeiVUfpuNI9JlDPdxnbJTcv9/7H7ke1bHxZdHS4tQM6Zj02K/46deoaEn/oOaEn/LYe2frbbd9i
kPZXvHC96OF60SMrTfs2BUO7/IXlsicaOLLBHS8DH3JLccw+fiArWAMUsqwedE/puCASMtU/ZEWu
AYjqaaoBOlBEQb6h6w0HaBemYtijp7I4jVoU5ccwgeSyu4AkBXsA9UtMjXWAEX2bsJKVsfyErT
cQPkjOR80Y1ijiAcOlK2PqB/WjJWg3L9Hh/HS/FNFQD8Glm2AktBUJf2fAJ
OE6fPi18DIgyvKP+Qew2deFXrwGm1zL66+AB8MzNy9NK0YqBoNTzMQJ6omB8AxDHJ3pUVgPJH2gy
9loepKEVrYoSX14NRWJKUcz0S3VPO9Q/T3ZYA7NQBCkmBUgihxrAYryg/nli29UARMRBycNcobkb0S
WDQVuTBL6J8We+2WbyAjJbm6nr5nfSK3rO2IBsqcTH5VuzfSS7/JCVtV+vVXMBN6bHM0kg4wpWAFMh
Dvfx+PtGd8WVpT6AlKnn0YUYklw9+1Q2laFFJrenJFRBhA8hMveCrFAf9IwTl0ECCMUyfvztR+FO

XdaKqqj5BFI8ICv6VpCuxerNriciaOWegTN3dCi9m6mVw0qw4gFPKh/IilwDO7BsFFCxlhaVMCW0
RVac1ADA4kFQ1SsBagCV4Lpj5MtWoOWcFF0tmhoEDVkRF6ar31oNv9EjlB4zlWb9VasCF6+nck+9
t/69/Px8jAORZz46Exw3zLihVGyphOsS4GIGjpMYuu23bfUz6z/6+qOTl02G6x9IBZc0VVpWgaAX
PnzhmXee0S+C6Z+ROU/MQQfUAB2Qe3ZOtqgBXrkOnzEcQ4GYQTG12tXCGmz9dSv8dhvX7Y4ld8AF
MlwNQyqIgDUAqrWqhg4V3VVccL3okZVZHyrf7fgOHNCf6PPBhg/gFzZzzTY10cfMZd3UyxggdUQq
OnA3Ob+jesEKm//o8aOg/vHPH/B78tRJ+NUvWwHdVVxwvQTC9aDT8jzuE25wXYJdxoKwCPohyAPF
04SebGj+O37fQb6afL7pc0M+GvjYFoUFhRauS5i7AEVtVcq5Sus62DwZiqGJ0j1G9YyOWvj0QvKS
ZMKSCay4cO8C1jwQNY6x/QCFaaK0Uq/qWt1zI+laJpddq7840Oxa6Tw+syk+tEXR/YsArkvg3RQU
tYUJFcGTdE1K920hGo9QgCagikt/kGvGD8Y4fx/+l7zOnKmQVIGK8zw5R0EfIr6cuk+hG65+4Nfh
QwuHcF1CvoCkGmjkFeSTryZyEHlpIqsnc055iYYYusD88BqJLaPWDRzGqhYKrkuwHYFBAZp8vm0z
82QRMFSGAjRBH0ddgJiqWigMirEAQxeIUIndB/ZRsCZ3r3kIHRCEDjtRH7iYesGPLvD5FN0vdJco
wOM27AgwAsEz7UI1tFs0xdSgGB5JmETv7qCocTB/fMHDxNXjBy595wVwUAJNfHQBAIcbzLbw0D+R
teQ2dIEcB+hyteojrJQGRFv5/isYH0X1b1FZjam90qYCbswqswm6KaokSdcnW3cBxId+BNpfoqU1
PPQLHPUvOsoAKxiBaMwH6drcOghzZ54CFtT2YkP8+PLW77FYggkLA/1j+Wp4uaVoJ5RbV+3QZQXF
8yUXDs9kCW3BEgsD/WP5ajQZe23ylJGIGie9EYsARPZKoFpLwuLIUAxNWBBAAR5hodZ004ZhYeC6
lPva77+mukBtcOeXQs1QVE2yjScCAgrWhAWppNamME14qBm55gHDdUQrAO/qouilYsGTPHd4b+b9
Qgk0YUGQkAI0MYfCEYfCNOERzIgKFwauCzo0xBuaKGp5d5SnZtuRRmkpjUf0PI1BNcdfSQkH6K9A
Cynfv6XeVDNBPEfmuoShC8CnpX532xI5rbjZjXJxBtl80jVJWphCCUUnAr2vKdsvmTeYERMlCgoC
XJfgXcCAXeAmk6cRSuyRKi2rkEsTaIzoPt4RrM0yaJWCCNclfHSBYygLk2Co3AuGjuhgcQBSwSer
QYTrEsHqAgHl5RE5qPn05rwjMIi1X5B4jkhbWLheAuF6CYTrRth7ieIxj6DHTOWxNx4TKhwINvy4
ARzZOdnw+9769+BXPINa8Kmy9EuKCQyfMVw8sRAsf2E5PiWCoNKxpcUTquUblLz8PHTHXxdfP7M+
OB59/VHxoiNWVZQFiKdHPuB6QFw39TrmEwB3Lr2T+QhqdSLHNf2vEZ7ihVOH2ObP9RII1yVmfUgO
8W7n0ueWwu/n39FTgNrta6MDwIdk4pVRhN76BbTXR5HScaXhV7xHihw4fKDL2C7gyM3Lhd/7H7u/
46iO4Ji3eh78noIrDuPz7IWf6S+aIvjcDpDfDVbfXPW4W49sDb8R5rsMXJcQXYCkXJ/yz6F/ZB/B
ypdWwu+efXuwC9AQII17aDe5tC54YL362+EWteoXdtRuQHlY8eIK1gVy7RG5CwYuMnQBRBZdAJTC
t56aK198/0WvCb3QHUgXlBS4XtLgekmD6yUNrpc0uC5BVzCasCAD+NRYg2KfOVNvpGrSVc+MK8Dx
7xH92SG+XWKGgjVhQSGE6xJUF49MXjbZEAGONJ5mCyiq3H7A60WhgMI0YUEhhOsSVBdJ9GehEAEd
RigetL+T9kUjeDZXnnjjCfL1yLvr38UiZChMExYUQrguQXUxyj9HDmGrRJtlKJLa/nrkaZOPKEVA
AZqwoBDCdQmqi0lufWS+GkFqtoBiYPu1OG2m3UpeZ87AKTC5zpzpfnt3URBCAZqwoBDCdQmqiybP
fP4+uTRRIyRXk1uOULDY/1mrpAggGIHwEhRSuC5BddEE6vfXwf2kaIINZlAYth98pEyqX9cOfB79
6A3Sz5wpm0DXVywtCPkXAVyXoLpowhqDgvWWoQBP+0nRxBwHhMoy+3siq8/p5W/nxQwLwYLrElQX
TcjTWMu8/Hy9ZhoUYGr/mnUfiDiQinyNPUhemsj+BrQ6BPP1Ca4LMhpTXTSRK0Femlw5pr9lELSf
XJrIceRoIN49OVCxonhAohVGddFEr0HP+Maj+5KvJnIQeWme5NJEjmMXRLomwpMTxDviCNclqC6a
sHrkFxRQgCbCn3SjiFAZCtPEzscaUz0LhUExHtKoLprI/ggFeET2LN+/JTrsBOdfEWLOEH2sARMo
17mQGBTIPcHzYiPb/p4PEmUozCNmHzuBmEmThpOiCUuL+dsiKlx4dBdmDe1vXRvdVBdNDHEkKFiS
6DuGkMtGIjxf55GuiVn1gah2IaF/cWUpX7v2y6Wi2wPFsBL1cUW8/qYso9U9N8Hv1Oceaj5hcNYp
iz3CG5hn4aF/cr6el9aoLproEfDYK16E06BIZ85Mff5hcmlCETKbUilYEDpSa8kJZanaqiol9IK4
xV5I1D+Rqey2az+CiSWfYydPQLTDWccwPgqP6ZnmR/hTPKPo8WXwvRAwfkF8axJQ/0QZspu13/wW
HNrhdhcx/4c+fI2SYAE9YlkEViJGFkIRvJNUWSQvLOqfz1cmY8uon8YwTwSSwwkZ8wTAP74c90Qg
yOwDZF6lqyLIO5iwMKh/LFMPtEWciZ4w5Vy7PPce0u8Clu2bTC6jULVMaa0p/Lmw+scy9UA1cizn
ttZabp+hk/ajsIS2dI+mEgOG/rF8Nagu/siw5fexTGSctx+EpbVFtCQw6B/LVEO8LEvvy5oiALsP /E319cjV4weyOAK5/SwIuHHVbArTpIL31wQFWP+AUf/itC
iOqdSMGasFALsA2FgetS7lQLTdQgeXZSE3n5NDsICgtFfLYfSqFgTXioGbnmgcF1CaqFJqqPr7Ip
qkd4fGj/gb0UZtk27fk8BWvCIzDkyU4ChutAy3OxAKqFJnqpcPrVXnqTs/flepCvHcFb+7Wzupzc
XArWhMdhBOVEkOuIVgDVQhMqUjSbMUm7RamlpQSaTHyGJq5DvLW/QyP5GSFIhf6teByGlHPgcB2B
k+0esVQRTdTyWJvNeJJTGk2EJ8Dbj6kmVAR3yt0jKcAj1Eg7pGwLBdclqCKadHqwo/zqqiUN5jbA
hNt2baNkmogMWfshid53QA+l5Q1048jQVEs8eRYWrktgVVDgejPjwU5yaxlXL7zKLi0IeprbDxi6
AGDttEQqqLBwXYJqqgl5Drb+TEBJNiREKKVHwMey/Wpyf7vAVFbgcF2CaqoJC1IGKspoOCMwepqg
xB5h7W+7rI11F1x7paG1DG267KDBdQmqqSYsyCFRsVGU3iSKNtepaD/vAtZmgamIwsJ1CaqpJizI
OZVTKlMWRsHQczqfY90FEMpaLpAyDwJcl6CaasKC/IJ9L4QiQmsOO8+iCyDI6v0awpM2CHBdgmqq
CQsKAMrIIyxU7oIK93puGYv7XGaktIWC6yGmfmb9Vz95lU3RJSiXVi5pVmLS/YnMX55QPpiNB7he
0uB6SYPrJQ2ueygTV2bAXQNiB8Xia/mvfPIK/Ip54eas1WMWnC64qq968jtp2aTk65PBAdH0GeQk
Vn6r/h49fhRCI2Mi4bd2u9r4ZcG6zeva3dQOHKdy1W8e6nSoA7+MPfv2NOzasOu4rnBMFZ6QyUff
fHR1P8NXk9VS1QnkLumM8yuoPP3O0yteUC9G9/6711A33WUCM5XbL4D2y982AStfXgntl33swM8V
oP3w239yf2j/jzvVKSxloP3X3nUt80TKJ5SX2w8cPnYYqjplxRRUoSvnrp4LDtF+nHAP+OL7L37/
+3d0EwbFiPf2w+85LXUf2G7e2z/3I3VawH7zDO0HoP1L1ixBd9n4sjGDYo5lHcPt/8POH9Bfpved
vcvEazcsPcx+cjZW9fXPXoff1iNbQybgEO0XM1dd2ftKP9rvHPnbm8Co3b523XTP+gommg8nx4TF
1JJu47uhwyHntz2/fKLV/TKulzS4XtLgekmD6yYOHTsEv/jRAu7nFZMqwlEEHLm5qmlEcM0HtG35
BfnjFo4Dh/hcFe3lws+UhCEJ6AO88rFqU3fs3oEqHHHRgcx9UrXh0QOi3/7ibdl/xjvkwNdn0TzL
7Du4D37F57PiG9lyieXg9/p7r0eVMChGus1QqrXV1RppNdABx2FsvwDa2WWM+sJzqdhS0ddGi/YL
Lu2ndJlu235c30Ruv/j08vE3Hof2j5ihf/kK7e87T3VAB016YFK5BLVVwKzHZtVqV6tUHH3/B+2/
c4nh+1e46Ph227d+tB/Bzz7kbz6//P5LbP9XW78Sngi0H35zcnOw/W1vbov+0H74harjd8vVU6vD
r/ftjxw/cRy3vziGs+3P2LxjM/yOXTBWbP96HWmyar+3f4mA6yUNrruUNLjuGLqTVZKE9cBZAtdd
ShpcdwabbhrOkc9pEezvM2zMjPp9EUbQlu1RMU4cSPGMIkdwMcB1Z9hNOI7C5hPyRoL6EoQdlJ1R
9BGQ4lmbU5o6jyJZiYjjE3l+c1lYtLMErjvD+whA2fXXLpaKkGYO8A5lZBR9BMSX1yMnqy/hUgx7
oYS+cEeAb5yMAJR/jhzUtxNOh47zwjuAsjAKfWUO+z1G81SJgn2JiO8FdwT4xvkIQHn9m8/VrRWv
3bnJMLxA6QVKbBQ+AgDHmx8Fm+AFdwT4xm4EfLvzJ3JZSZVBaeonN5BDOi0A6R1KZhT9KNCCPhuj
AKPgKs6kmIRysMEdAb6xGwG4SR72fBRmFprzUd6D7aE0RlFHAIR6zv7I1yTeMwHB5AY8SeSlHWTh
8c8OuO6MpjcbpjwQIjoROJ6tfiVpKbevXirHtINiG4VGgH0EEBHBSzTzwxTx0Ye3ESCy7dRY/9xX
pkNDipBCj1DCHa47w7sN0GPGlqIAK6HI9lA8o4gRUHDaMDODEJFcEGGTFeSgV1X6etV2BHQ3feHq
HcxZXPuIssIKrjuj6Zj+1CtGUUNjSyutL9B7oWf8+h1bKdgk7276So7JoEhGwRFw8PhR0o0iJ5ep
PLA1xTDKzn1/spiA7QjIuILF9lHoMVTb2L74UZxw3Sfa3ER266xQU62gGFbCYgoo2CgwAjbv+pkU
o5Tuw1c8k7ntsQUUzyj/HjvCYtqOAJ9rHTGkW1WqKtxhBded4eMoYMOnP35H8ayERQYoQJI9B/75
YIu+vIssjW7txZKb+euQusi7WR77+E05WtBGABKsxZ9CBNcZrDEeArABAopqJcvffcl7zMnPPkiu
YMuMFx8X5QZ5BACsV8MKrstg7aUZkwS2NiDdsNSaHWMfX0wJrKT/orsxGuma5OXnD102g5RAJaKn
OjURKSbpNX8Slhv8EQCY+jBc4DoiVx1HQGot9agGJ8waTcdeS71iFD2HFIvVaBk5eYbvoZn8ddBg
sasNbkuuQEUumrxMUuv6ThCaft8Y0o1SqBEAiM4JK7gOsHrjCPBMnIXYHgViSqnXwfKlcJz9d04a
lNKr1L+5O7n8lD0H9l0x2jCLo4BimAQGAblMUtgRAIhuCR+4zmoM+DUCWA7yybDlZEoeKL2VeAmV
c1DLEiPP8vO6VjXVGYw8qjxNTYEmpNjIr3/8GoQRAARlcosgorvEVHkCEWSaP8vpCJDBJwIqETzI
w4AlUykjj1iuW4miT9EqjzOg4/+UZPU9XB+0rXfpqN6UlwNRkxRyBHS3+Haq+KF/lou2YRDz1Ahk
BAgwW/vMAThlU3Oz3/uTJt+gdJHmZjAPXwSCxPiQ/TMp7aRlkyhHe1HvGgVxx4X6QAVS9TfPixmu
m5E7zjsYv7PXmQ5kYtTVk1Siba2CBS2kNcE6XsZDLcHINocheQYnWe5es0qPhiPA+brHjO4x1vcT
sWLFC/2Ltf803wo7GxCw5OXnlU2U3vkxA9cgotK4G/nCbtN6n6ju9OnT+fn59z58LxWUVEkFJycN

eATYoU2ZUczoLlY5rwR9BMiSk5tDBcGuA70vaiidxzkhsBFgKepHY7Flgj8CWlTVW1dc6C7xWNMB
IR0BQpr2aarElXO4x5sJ4ggQUm+E/mw6OIj+Ly4MCqucPUUzAlB6zJvISneI3Qgo06fFrn/2mjlx
Kpti+BJWUGER56rFgu5q34DXzB556XlZKCu4Ljcl8c4p43yJZmHxnWA3Alg0L1ACk/y+fy+LGSDh
8NCI6wxWYw+2I0Cseu51klUvUEY2wiJ7p/AjAKA0JmHRAiGzid7PxQjXzcBJuOmUVV5vXRY9jvTK
jQ+6NtNTeaDsrOSzbZt4DjbsNS51JYRFs0Wrye6/d1Myo/DI/tLaYmqc4oHrXki/VNxttbUBciMZ
xm+7DFi9OuzlbiBIZK9EFp+T2VSeqlEWHtNMxpVUMeMEsrLwJP6SZlhAuTjhuhekBjgdAZAqpRJN
COiTnsZzfq3Q4fcZFtmR5ciJ4xQTzqRkwEdbryTAEdCNbNKUNasogUm+/uVHnspfsEvDAa57x9MA
3yPgplp8AzunDz8uUO5WUq2VOlWYJc5HQFSvxIVvPguXAxTDl7Dk/tE5PA7/Aq47w/Y8AFp4Zzm+
RQMjxlCi3TspKHJMgZcRkLQopf2KdrxEZFgDpX19SH769GlKIMmHW77Rt2UAmCpZ/HDdGd5GQP8r
5QlRAyN6kfVJAxVjJbcvup1F9jICUpe1woLSH+zAR4BMQoWK16ZiquXvGd5gCwT8bDLc4LozfF8L
NFcazW0otqhDMld2Vu7Rc7CkfmZ9KsxK5JheRkCDu6JZ0Xzby7ATlMCQKhZecN0ZTkaATm+lxsxz
Oz6YzjodSVyaWOqeUkqqKZVXsnO83b/DON7PA1g1EL7tBTAu5c0ZAMb6hxFcd4Z/IyBkUKl+imer
cDMg4JtfIDanc8LtvM8M150RJiMAqN2+NpXtWOTkbNvL8M0PTPJ/EEhlhSlcd0b4jAAB1cCBsIRV
R1Zl216GDwJM1dX/e95SieEF150RhiMA2bRjE1XFXlgSJLJVJNv2MuWmey5x5VRsG/sk4wpD8jCB
684I2xEgiIyOtLygB2ExzdQZXQeuStggACreW5HFVLqoX1EabkfaAaHh+fkY110KD2zvthcp6Zep
7zilVFfa0KS+YQrXXUoaXHcpaXDdpaTBdcdc3e9qMXeoPCePWIVmzhNzhKdgzlplwEIl0vPUp8dM
9Te/gJY/QPLy1GnxJy2bFKG9mVI6tvQ1/a/BoOycbHQA761/T7jFAgqC3rPVUmpnkIqLPiCRMZHD
ZwxH9559e+AX1zeqmVaz/S3t0V9mxH0jjp88ju46HerUalfr4VcfRpUmxpJYvkH9XfTMotJxnq8h
mivPf/A8/FZOqVw/U33mhDz6+qPwW+BZfmL337vhF3q1WqtqYlUEuV3po9KzTmahu0rLKvLKSUjT
Pk3lZZPa39y+Zpua4ODL6TC47piARwA6bl+j/uIIYMtAjJg5IqJ5BIyA1W+tVt8cl4IcjoDqbZXI
WNWRMoZ82AhYv2X9V1u+6j6+O/rgCMB1RBiHjx9Gx4trX4RfHAHgwCbbjQA2pqE5w6YPsxsB0MxD
R6lo0as4MkS7cMkQ4O4Vd8Ov5QjYf3g/8/lr/1/wG6YjALj/fRoBkNWqV1ah58OvPHx5z8vBIWxA
2fiyMPwx1OEIuH6F7l74mfprZwP+OahuexwBAGxRMDnohtJxVRkEehy2nxgBwGXdLxOreAhGP0WO
E9kn0NG0b9P3N7yPbjEyxHIhwgZs+WUL/Mq92u6mdtguNIpI65Gto2KiLEcAAPnjMiUVkiocPHoQ
PUM1AlzOErjuUtLguktJg+vOuOZ6Je4mlf9dSz7VU6vPeXJO5phMEQeZsmLKkGlDhNpjQo8BUwb0
n9xf+DDa3ayuNorUbFtTLCMG4MqbcJYAOQC4WBejVifdjasz1kirgecTSL1O9ZKGJmEOCHii48o+
9IrwhekXRkZHQiVFHCz6mn50SQLcPOvmsQvGChUOz8INdBzVUVaxry7lJLVO+zoiZ/TpPLoznDbh
SpB9JvbBoORh6qKtCC7CimAotEL4AHCCMvfJuf0m9QM3nKnAuYIIatiloXBbwHVnzPpQd9duX7t+
F/0UF3j5o5fhd/Xbq2VPPKuXl6iD05nUEalCBaDqFZMqnspRF5sFWg1vVSq21L9H/kUVT6PYGnbr
Nq/T1Wh1SbcVX5OK54AJQxLkCzMYgujAdd4Qsdobnpd1GdtFLPsmn+Te/9j98Hv8BF0ZIidOqmd8
b3/xNgwacfLLltIWq8Nh3Trc2qGstEwcu3CQT1oRuBaF08MarWmGFHH6iZeyy55fhqoAhiMuKwfA
ZQhfXI7BdWfII+DZ954VbgRqVi6+HJzWyp54LcsWKZy6aqqsrv167cApAwHcPDgCwPHpxk/h13IE
7D8kXQJpIwAcbe6AM3m/R8CxE8dQ9TICoqKjbpl9i/ABPvrmI/gVC0Li1aPlCFj0OalsBCBjF44d
PW80ONgI+O6n77BPvv7xa/TBEbD3APUkG5FAUY8AAIwSXHtUSqkEV2ivffoaelZsUREursDijZoz
SlzFwQgACwHX4mzgA+J2B1C1VVW4iBIjAACzJkYA5ABA5mzZZTECEFzcGoDS4dK/5Q0tcSlrxNIG
fLnlS/j1bgMAKLpJ7ybpt6aL3VFeErRux7p2NgDvgsAIePWTV7EVoILhqdaq2sOvPtx3Ul9QYQRg
0FNvP5U6PPXc1uryKQhWRhQ6f/V82MDgWL9l/Zufvwn9D/YArnWLYgS4nD1w3aWkwXWXkgbXXUoa
XHcGvW9VwoR1wlkC111KGlx3KWlw/b9F4jlKIj1LdQkQrjuDDoya5OblittVQYRyN4n22rUWR7yI
LaU6arX+0LEsutnnYgHXnUFdaxIWzRGptSynnaIcTaJPLioie7KKiI6gSCYRcZxAaYxiu4zyfx2u
O4N6xUr8swfdovUNaYSyM4mFDfCsgnLo2CGKZBJcgtQhlMYo7ggwQL1iLyw+p/0l+vazgTIyiRqK
meD3OojmQzFshFI5gBIYxR0BBqhXvEokzsZsRmw2r1AuJrE4CgDNldc+tV3qFuXtdfrDG+9QAqO4
I8AA9YovKdNXWgAwSXuOF1dO9/EKZWESqoPIBy4HHFeJ0vqCYhvFHQEGqFccSLl+KWKjUnKheoXS
m0TNIakSRfNMYfrC2hco2Ks88uojVAevUGyjuCPAAPWKMyndJ4k2GCZHty8osUl4Dn7Wh+rgFYpq
FHcEGKBecSzy1tI3nlcopUnUHIQNALrHjpg5gsIcSOZY/iajGYpqFHcEGKBecSzqtzWwtTB5u/r6
9rOHUpqEMoHDv9eYL619KSc3hxSjUA72UDyjuCPAAPWKP5KTl6euWo05SFvaDkpmEnUGF8xEm8ol
ZcpICjAKRCgbX5YUo3S4tQPlYAPFM4o7AgxQr5jEy5YD+e6n7ygH0/Y2Q2lMooaKmrSpR75GyTqV
rUbr2ox0k+g5yHgWLKNIRnFHgAHqFZN46UGUFte3UJcY06J5hxKYhCIkq+9PXtHrCvI1Spm+yRht
5KrZ5GUU86u68nT4FMko7ggwQL1iEuzByF6JpFuJ6GjvUGyT6HFsqqF+bSnieMmHNSq5mvck7ggw
QL1iEtGJ3heKFtG8QFFNIiJUSK5MXka55KbuIg7w899/UIBRLCYl9yShGEZRR4DItnu09RIRLc9T
F8yACN2ieVDYwnVnUK+YRG2858nNzbNuJl8r0XvTBopnEhEh2+5UX8oEoQCTiOao+Lq4MIwAmbQL
lNjSSkJF7g/Ii2/KZYUVXHcG9YpJ1KZ2aiyieZmx/+G1r+m9YwXFMwmGluptfaAZ9cgCkYPg6Mks
CjaKqKeKFJ+CjWI7AuzAu+AiZ3EdFG5w3RnUKybR43ge3BXYr+ldVr5hbIIimQRDc/PzSDeKSC5T
oX8rCjZKVvZJFhOhYKP4PQI8Dyx0H9E5YQXXnRBbmnrFJKo9hJYb3/igMCuRozEohkm8hP627y+R
nEExTMKiIRRmFL9HQDvPHB/RnlWVRQeGFVx3gp8des34QRRsJSyygIJNAkE/7vmNFKPIyRlXjulH
kYyy7U+L7UphRvF7BACix+DcKGwnGee6T7S2Ua+YRG+8kd/3254QHD5xjEVGKNgk3oO8QJFMwqIB
FGCUQo0AIIjr1wcXrnshvZFoG/WKSUQEMxTDSgY/MJ1FBijMKJt3/bxjr/UCgOde147lwHj+yw8p
qlG++GkLi0kBRglkBIgX2sIZrjuDesUkvAuMUCQrqTa4rZPIdv4gclo7KKpJnEQLZAQAYhHWsIXr
zqBeMQlvv5Fzr2tP8awksleCHJl8JcnLz1/+3kukGCX2zqFyWjuO2VwWTnv+YTka+RolwBEAmHov
vOC6jOVdDg3qFZOwaGZe/fpTimolckzyksT7KqROxO4uAoj3okECHwFt/7tzi7OWSFCvmIRFs4Si
Wok6jY9NtJM5p0Y/tpCUQAWyzS/IJ8Uotz/5gF3RKIGPAIB1bFjBdYFYC5j5a1CvmERvs1coto1Y
xqnQvyW5CiGQ7QU3dCbFJFiuuWiUQo2AtAtYB4YRXEfk9/lZkAb1iknU0PT/6WntoQQ2Yo7Qdvqt
5ApU6o7o4r3oJmOv9RKhUCMAMHZgGMF1oPUFFlWHCxuVWIR6xSR6JnIOVsDFG6VxIBff2I1cgcr3
v/8sir7z6eXkaxKMQIpRPv72Y5FDIFgtsh8WcB1gVbfypF4xiZ5JcyUiQX/ibkncxKGUzJfUuSGD
XAHJlDWrWNEUYJJGt/ayC1UnzTNm4jfSLI9hBNejo3i90d/oSb1iEiWlhkqyZ7bPZt6+DATGPL6I
UtpL/MRh+faPl7zL7FeeZCUifx06QDFMcusj88lllNHzR7NMAgG7JazgOqsxYOVPvWISQzSRp/1V
JXDjqjmU2EZqDOlALpOoOXQ3vYthzN+OKoPawG/lQWlDl81Y+s4LYx9fBGrCxOspa5NclHGRSBs4
YbjcmEFJOZfXGMAgoyf1iklYNKXjZXrmsKlYqIeUKbYv/PdbNIVcVmLIR78FG6FegstBCARJKmWh
vckOV6EFNkvTCWHJA4cqGTYYFFZXQBy6jP7UKyZROl3OYqqI/GNK8SAP5w1NpyyMAkHkMkndEZly
DuqDaSzlamk/A38YGYZvWOlZbY0h3m5QmoVyKyRh+J6I7mJ1lZ9mZvDtSr1iEqVNXRaTgJEhcuvU
mId6oFw88vDa1w5lHSPFJHpCeUE/uPJufaH+fo4MezrXI44yciA9J/RUk4gSA0Oa4jyMoH8ta/Dq
tqii+sMv89egjjGJ4XsuMzH6DM88yEP6zDGU15kzEfa3gVvcNVyNL7+QCebKmJUeBIi7FHH6e+It
b3B6l4mSiJy90/YiNXKHhuoej4Cnp1DdVoUJ9E9uAIIjoFVN7q9BHWMS66xk5G0GZwks1EO3OXc8
u+4DL2+YqdHkXaq7/ra/gWTPC8GwVYSn9NCWsvMqahJP/MKCx0GpAsWP+tfe6kO+EI0ARN8PPG9Q
2VC6Tws4S//q5x+oAE1uWjDekxzM/oUsCQejwXGB+QPNI95e9zZlaiOemJ7iHCIf9QRsuiQWWlxw
nWEzAizoHkNJmL8dHfVXipXMpjzUDuhEkcp868ISMeeI9FWQDG1qo2zds7PywDQ9GuYgVH+xPPWB
Ky/MtnjR/kWovWlJ6vm83l7AHJmnd2JpGn/ub4l49xKwv7a0AE2OeNZlCTRWZG6e6AT9mWchEftM
8UL/WOV8QXtKkASuyBc9s0hpa3MdgYgaw6BhQTZQ7kYZvHQ6uWwETj527dU+EIsvp3S5Sj23BbBo
UxGFBbMtXjwuH8djBvVWsEVdOQWu2UzF6dXNuIIH2UOZGsXnCGDSZ2IfvXRTEYVF5FyM6C5WOa9Q
94RGrp1/JxXUvoFePQBOoaU6+ISyM4q/IwCl3+T+zm2PH8itKy7oX3Qkr5xXqGNCJmLRJ8J8re8A
yssogY0AkFN5uSz/ICC3sbjQXaxyXqFeCaWoE89AreRpI/2EMjJKwCMARH6JLTik0AJyxYnuMt36
9QJ1SYilkD1OuRilMCMAZOe+P1kphUX0f3Ghu+Bai1XOHuqPIhFWtHMovVFgBOz6Z68lFMOX6JPj
BQu46BBboejRXdrETA5JnjLSEsrKFN+OGx68n/rVXvKMc4I4h9IbBUYAi2bJ0RPWXxaAqMsemuIH

jmdhw2JDd7GaeYU6wyQBZAXUHZFJ6W2EJqPzE0psFIcjAFj6ju08pSxm4IjOL0boX3SEYTB2j+F1
NUI9YRJKbnP/1Tt7D9q+uQXyza/bWHyfUEqjOB8BAKUxSYspI1jMQBC9XbxwXcb++pt6wiTqnSVM
a0rihAmrl1JGVjJk2QwW3zuUzCh+jYBmNt+9f7jlGxYzEEQ/Fy9cZ7BKe6CeMIn+oaQpiUOa3z6Y
8rKS6r4+EJahNEZxOgI8D3ApmUl4fH+R32opXrjOaFHF8mE2dYNJ9DiswV4wLUPQ5sY2lJ2V8OT2
UAKjOB0BnspQMpPw+P4itbeY4bozqBtMooYmlPd2+zbD6sE5Iyaq17zJlKNJnJ4VJlaiBEZxNAI6
NMKanDfU+jXlg8eP8CT+Ire3eOG6HbDlwB547hpRT5hEbyGjazPbSTRs7vi+t/krytQkW/fsZJEt
sBmmjkaAp2I//mE9Xc1jH7/Jk/iLaH6xw3U7jA2gnjAJi0ZA8gRFGagoU01kejte5OVbf+cLkjFz
HIvMCXgESE2mNCa5ckx/Q5IAEKUUO1y3w2jYqSdMIsdRMq5UE95h2uqWDNGnqFHxGAzK10pK9fbc
m4O6CdDHPq3TEZDZlBJYCU/iL1BPLCUc4LoXRP86HAEjTZvZJwM8k3B6Co2MjqSsrUSOaYYiGcXJ
COg82vYLc5Ag3BOMNc1rXYxw3QvS9x7UGSYREfimdc7EMkrmVXK5GbfZfjZ66NghOSaDIhnFcgRk
zp7w3W87HD4aqH19J5bcP0z1LGa47p3MJupbOm0vos4widbIOL5RA8BY7q69u6gAkyx/YTmLLKAY
RqERMKm0XtY9ijK8ntKbboN+//svFNVKcgr5loD4pjZ84LozqD9MEpzNjzgrEeSCDtYzdFCwUXAE
dFmVyYsTQBOaK19s/oISGMWwOf0lrA7/Aq47g/rDJGXuqgidGxSUNEOJUbFRVIaVyDEFFGYUMQLU
Iti2F0yxzsGwOQOgeJ8C28F1Z1CXmATaWXVGVbEVA0YZyksEWg23niAahUUGKMAo8ggAyk0vxze/
oJd6QSgOCrQVA8byG5JwgOvOwE4xi3p7p7lSaWol0cUBoAzmxQk279hMJVkJi0y+RmEjAKhwb3m+
7QVwKdsz/oYVM/UNGTDGuoURXHcGdadJ9Di3KZkrO8sd7YQ2y9KUOL0US6gkKzl+4rjPmOYRAFS8
tyLf9jJsWwZAeJ4BIFx3BnWnSQzRYpVKM5wag4yVGRF3OP24mgqzkh92/uA9Go6AziszWAVq31+L
b3jBWOsPqP1AfBoVhnDdGdSdJmHRVKIVZbJy9cKrWI8L6s2uq4wwpfIKnPxTeVby/lfvYzTSjYIj
oO7d/2PVAOrOvpBve0EvH6/M+MBY//CC686g7jQJi8Zpq6ineKMU5WbtMUGMKYJjBt3jbc2CE9kn
IA4pRsERALDNjzSa25Bve4G8Rf0i/VK55mEH151B3WkSFi2krN+ynkr1R8QIaLe8Ldv8CJgrvu2R
wY5myuSYqh12cN0Z1J0mYdFCzcGjB6lgxzJ4+nBKHqewbS+IXtScb36EbV2fhMnXwd7hujOoO03C
ohUBx+wnGrKUwXcPFmmvvPdKtu0FSUsS+eYH/Py+Vp3ZRKpqmMJ1Z1B3moRFKxoOHztMxTsQeQQA
GQ92Ytte0PKBFD4CkrVUbDN7B8xAeN4KFHDdGdSdJmHRiozsnGyqgS9hIwBgG16m/Yp2hhEwwZOK
bWafpNYSxYUdXHcGdadJWLSiZOHTjlYfMI8AgG14mfQVHfQR4HleQEvL+kXYrjPBdWdQd5qERSti
KqdYr0Qsi+UIABLnJrBtL0h/0DMI7paSeJaq9wORNqzgujOoO03CohULn2z8hGpjJXYjQCVJyTTd
KxTwEQBIL005RU4eJnDdGdSdJmHRipFNOzZRnYzibQR46Pyg9TjQjwIC2KgwDhB5S5v5L60vcBYR
ER0Rf138zEdnbty+Ecm4LYPFsSVGqdShUuMJjVvOSQEaj21ctUNVHofBtrpATGwZhnDdpZC0vVj9
dK51HXXDt6mnfmQhpiILT7juUtLguktJg+suJQ2uu5Q0uO5S0uC6S0mD6w6IHRQL5Bfkw2+za5vV
SKvRsEtDEbpt1zb4/e2v3zDaNf31lXUiopUHvyE3MP8Tcjzw/AOvffJaw64N56+eL97x2vnHTkj+
0tqXbp51M6iY27RV0+C3XEK5Ne+twWjARRkXndPiHKEiE19SWtxG7ojoiMnLJmMOoO49sBccve/o
fTTrKKilYkv1uqMXxjyVewqCGnVttOGHDegDFJwuEO68/Dx10THNHRkdmTQ0SQQBFZKVWhmqo0xc
mazsrMu6X5Y6IjU7JxtDIXN0ADv27IDfBl0adLilA5QI2aL/mTNnKiRVQDd0bK129EipfEJ5dXZF
T/LcvFzhloE40OFX9buK5uNsrjz9ztPY8OgBpkXZEK47Rv2AUnPYjQDhI4ARkDhKmfYmqTgCqqVW
6zK2C/oAV/e/umnfpuD44Vd651M0Bhh8D93R8zkCrl+hLF5HbhgBfe7UJ4hW56/GOPdeHxkTKUaA
vIUE3/30Xf3M+uUS6QkvbKqffv8J3V5GAGx+2R/fX7UcATXb1kSf+U/Nh1/o1SPHj6CPPAIOHT2U
cF0ClIiq5QgQwwjJzVfjwAiQPS3gumMCHgE12it1OqsqjoCdf+4UEZB1m9bBL44A2Dxrv1krghyO
gPib1d9qbZRySarDbgTk56tNECNg7IKx6C+DpYutgr2M0x7bjYCLMy4+t7Vh9YjDxw/Dr5cRMHDK
wOqt1U8KsVd/26v2njwCnnzzSfjdvGMzquYRENE84q4Vd8k+L330EvyG4wgAx6SX1F8cAfhWp8wv
e36B30PHDj33/nNvf/G2HORwBCzfQI7JL6u/5hGw+q3VYo/BEQBHlpTrU0QcpNUNrcrEqy96r9+6
Hn0wVem40qPmjrIbAXGD4iA32X/Pvj3wazkCnv/w+X+P/Fs5mRZHw149v+35LYe3FCNg1JxRGPrr
H7+iwzwCoEoZow03vBc+vRB+w3QEAGCicQT0uL0H66/u47vDL9qA/3X/H5wfiCAnI6BUnNJqnHJx
D5U7nld97GzAn/v/hF9hAw4fU/dUGdjeMYNikKHThqIPBt33yH2lY0tbjgAobsmaJbI/fsoif9CC
pyDCBvx79F/0F7366ievihGQk5uDdUi5IQWO6OBjeRQQhgrB4sJ3BJSOV5Z8Qe6sk1kwhMFRPqk8
tBY9xXmA3FonI+COF8gBlElQLh9oOwIG3DUAEooR0PvO3oufXYxBcOwHu3rn0jtRBXDbixEAwD7N
RsBNj5Jj8TOLxSOo3X/vxta1Gdlm4N0DwVE+sfz2XdvBIZ8HgFmCX9GrwMlTJ2EEQDW6jesmPDGC
5QiAyoj6g/mE81lwhHAEBJdKyZWgu6u29PXwLfSAeR82fRjzdEL7SdwHWsSGCBw4wJOdJQSXW2bf
0m28PmJ8w3WXkgbXXUoaXHcpaXDdpaTBdZeSBtddShpcd0bcTYTwGTJ1yMxHZ0Zps8gI2t7Udu6T
c+t1oo8l4NJ2wJQBAN75tyTtxjThvvaua4W7RusakTHqXXHMIfn6ZBEkkOsTEa2c01J1yJn0n9wf
fjEH5LLulwGq+64BIlrvib2hIXI0uIpLH5UuIlzV9ypoF96cQXpO6Cnc8sMwoGY67yuRbcWkiqBG
REfMfnw21k0ORRVoPbK1cNdIq8FCkeunXz/nyTnQS+DuO7Gv8O9xew/htobrzhCP3YDa7Wt/vulz
dGeMzpj+0HR0nzx1Eh0VkiqgG7oV76wBG37YcElnaR1hjcFTB8s3tvLz80fcNwLd8YPj8dZh1kl6
6AIFrXp5FbqRB79Rxj5N7tLxSoPeqkN+pHYqR78v+/JHL6Nj1NxRsA3A8f5X75fWVigWdYALdxgf
6P76x6/RkV+Qb35CA7US9y5nPzEbHUjKGHU4guOWx5SoWNWBNwSRqNioqaumCpXdvEK2/LKlxbAW
6E4cmoj3lyYvm1w+QZ17Fwbc8ucNkyrKqzX++Y9639MbXHeGPALy8vTbZMDve3+HX3ZPsHGPxnU6
1JFHACDfX0Og6yunVK6eStMunsw+ufAZ9eY2YB4BwOufvC7cAIyAet3UW7PgDmAEwHaNG6xO+ONl
BIj6IFVbVU0dngqOTTs2/fjbj+hpNwKUaKqSPAKu7H1lzTZ0WxAwjwCoQ6XkSqKvxAgAg4p3rvYf
2o9BgqIYAbc8rnSboXS9V3WzhzeX97wctmJOHt3cFUx8YCIbAWKvQqBhzQeoi8uL0QMjAH4xK8sR
0KRPkyotqwgVXz6Y8a766+8IgF7Gx6mAlxFw8MhBVAV/HfgLfmEEwC/eb7YcAWUS9OdVUI1Zj80C
UF23ed0Tbz6BbqjJK5+8AkH3P3Y/+uTkqM1PG5lWKq4UOMQIwNv+FVtUhL0LHDJgpb7d9i0i7rLb
wnVnyDbgu+3fCTfQfXx3OGDL/Y50G9eNjYCDRw29+dPvPw2cMhAQz0BxBECqF9e+aDkCYHcpFav2
CyJeP1nwqd8jAA7qrUa0Qh8vI+C3P/nzjtc+fQ1+cQTUbFszc0ym5QgA49R4APnINkCA9TTbgM++
+wy7Bfc0HAHntz1/xqMzQC0TX6bDLR1EZKSojwL48FuALblt3m3y05pPNn4Cv/IIgOPfxu0b0Y18
8+M36IDBPnKmunQhjgAg/db06AHR5hHA3ukQI6BUvNJ8OI0A+QUT3J8Q81FAmHEvI6DZtc3AyKEP
MOzeYXhOgCMAWPPeGnHugoijwF2vko/lCGjQpUHZ+LJsBCx4aoFw//qn+mhY2ADxEEhuFFLUIwCA
oxTs+g26NpC7G2oMZ2qVUipln8qG4wL4wAj4dvu30PVnzpxZ877+cA/oPLozxkHwxSwxAoBDRw7h
CABbDTmAoTt0lE8sLkYAMOQBGgFwvg1jFKqx7+A+8QIWYB4BqufHqqeXEQA88+4z6zatgwz//vdv
MaDFCADkTgD084Dmys3aw0M4f4TSgcH3DE4aljR91XQ4h8dUUBM4R8ZQMG/yyxPQP80GNBMjAMAt
Db0KaeEMBo6hu//eLfyRUI0Al7MHrruUNLjuUtLguouLS4mC6y4uLiUKrru4uJQouO7i4lKi4LqL
i0uJgusuLi4lCq6HkkrJldrf0p5xRa8rWLTwhzWBc2t6+9sy2o/r0X5C3/Z3XluuTR11WRKWSXJ1
pUesPuGsOYKHMQvG/LHvDyeYXx12cfEN10NJ075NtYm9fUhuXu6cJ+ZUbVV8n5DHllYSKihJlZWW
NdUJgjMuV7o113fXnvFUUWdSb2QXdW+X82/fQM5NBfKXI3joO7Ev5eJMEockshyCRYMuDda8t8Yh
bOYMl7CG66HEoQlgwqbFCTYRbPd2AtXMmViYgI6XsQwtVx24vMfllIU/0rSP7XdYhSFucBwV4EB2 /bWLJXcJX7geSgIzAShZJ7Pkz/MKS3Sk0qkx3w8
jXs0pvR+yunTp2MGBn+BS9cEnLVwPZQUxgQI+XDDhyxbR7S7mO9yhYCq4kzIBMirTjezX6VOi9C4
Z4D7vxDxcUOwcE3AWQvXQ0lQTADKX4cOVB6YxvcfOLC3qKrE6J8PqhTiaG8HVcKZ1BvSxlAfoF19
lqHS+Up11UIt9KKMiyhl4QSnQA0Wrgk4a+F6KAmiCUA5knW84rWt+O4EsKXe5XvvwYCKdyZi2hSV
hAqGrHrEKfH654tARPMIShYMiTJO41IYXBNw1sL1UBJ0E4AChsCwXyHyuo6d/sdDCwcV7EzIBERH
WVz/d7lKr6RGQUEBJQuGnDx1EqeaKDyuCThr4XooCZEJQFm/Y2tkrwR970qU1hgIBxPQ5kKWCZFB
M1DAefuxrGOUJniSnZNdNp4uMQqDawLOWrgeSkJqAlDmvf407Vqx0pVwm7r6LhcMqDBnYrgQaB5h
eVUS1Tvx2MksSuBLcnJzFj27iBRnIlUgQFwTcNbC9VBSBCYA5erxA5XuxsXUoiPVC2/TvhcYVIwz
qdfrakNNgEJkePr0aZxf8dONn5KXAzFPeucvrgk4a+F6KPHXBMCx8aOt35Lipxw5kaW0rCFus6u0
qsl2vIChMpyJxatBSNuLMLfdB/6mqA6kbqa+gtPOP3eSrwMRkzL6TWotJbNp3O0DKSMH4pqA/xJc
DyX+mgCxyz356dvk5afMeoLmaVUJ3qsBlLszofcCANjnRWWQ6Mj1O7ZSPAfSa94kUQcgslfCX4cO

UJgDkRfO9UqE+f3FuInDKBcH4pqA/xJcDyUBmwDkzW/XUYCfUikzyK8GUL7ORDcBCFyPeN5c+Oib
jyiSA1n45rOGfDRK9U46nn2CYjiQb7bRPL3e6HINKwVwTcBZC9dDSdObu9AYcSZsFCInc05RsD/y
2Y+bWD6FgTJ1JtwEANqzwHWb/bBoG37+gWciQZGcybtfvStvFAuio1j+gN8mIK680uVqJbW2ei0W
E6Xei7H/GtIZkLyQObhYwfVQ0nR4OxojzoSNQnU8xZZWoiMCu61YUFBw8U3deJ4BQTk6EwsT0DP+
qY9eo2BnwpIzqgxqQ/GcyeJnaBJ6W0y3TgM5CzDmwOkerXRQF0G2JsX4MTUDgjpfobQ8T33VqkU1
pW1dpX19pfUF/MVQFydwPZQEfiHAbu9rPPX2UxTPH/n17z/0bAOF8nImZhNwz3MPUZgDOZWba3jf
wYaOM8dSAmcydsFY1p863Sy+X/DbBATv5qsFGVfqtU1vxEPTLtBDXXzC9VDitwkw5aAivWN77pD2
Rx0/Tpel/YzRIpMAoFycCTMBg5ZOowAHkpufV2lgazm5F+a8upqSOZMhc8epn1TEl1dpUUXp6O0F
Kr9NgCmHYBJn/PwBKs8iJOkL07j4gOuhpOmw1jRGnAlLrtLpcr6xe8bPf+MZSuCnsHycQ+mdiWwC
rl18D/k6kNOnT1cb3FakdcLXv2yjxM6kz4K7WA52+G0COjdhOQQTuARgAwN85AjdLE4bXazheujo
ck3TcQNojDgT9epO3q72lOnbIjsnh5L5IyNWzmJZOYESOxNhArrPvZO8nEnj0X1Eic75+/C/lN6Z
tJl2C8vBEr9NQFC/zuZ0Nb1tBbSpp0cI3vdRZz9cDwUZV+CG8dsEiC3qjPFPLqGU/khOXi7LxyeU
0pmgCYi9cyjpzqTnvIlyic6J6p146Lh/3xrUvr4Ty8RMeJkAoM2FfJgBWGhb+Y1sF19wPYgkVzNs
s9CbAORwQB/brP70HZaPFyiNM7lgeAacz5PiTODShpXoF+X6pZzK9e+c6LyhHVgmjLAzAUD7+nzI
AfK3IS5O4HpQSG+kPrYx0XRsfxojzoRvcseMfWIxZeGnmO/eW0KxHUjGzHFl+iaT4kzWbd/MiguA
8v1TTp8+TTk6E+9WIBxNAADjqrm6urdL4HA9lBTy7UC/iOiVQLn4Kf8cOciyMkNRfUmfBXdVH9wu
388pAFhZAVN5YBrl6EzyC/KrX9eOZSIIUxOAmKZdcPEDrvtF24uUdpc4p+nIdBojzoRvaf8Z/MB0
ystPee6LD1lWMhTJq3S6f2ylAa3z8vNJdyDZuTmsoELSe/5kytqxsBwEYW0CADYyXZzDdefAORjb
DL4omnsBZv45cohy9FNueXgeywqhYHsZ/ehCJ9FCLVCH+a/798Q0Jy9PNFMm3E0AjEb5q1AX53Dd
IfIEuN1jCM81vwl627S4TABwxZh+/l4bC4mfOIzlRgE2svy9lyBOVvZJ0otJ+i6cgrXd8vsv5OVM
Dhw7HGFsLxDuJgBxrUAAcN0n5nfIEgwTYHohkLcD4yqpRoSVGChvBfqtYcHp0zc9NFfkQ75W8t7m
ryCCX1MAhEK++Ol7UVvgmD9fE4LsP3pITg78N0wAHGyMQ87FN1z3gnkZLCSkJgBppijx51h+xOov
pfu2OHj8CBXgv3z8w0bIhBSTvPPdegjdtX8v6cUkM19+XLQX8febYpB9h/+Vc0i/bwwFOBD1k+Ri
MQEAWIEEadpIF59w3ZKYUryjZWQT0Lo2D5Xw+0JAZCsR0ay00ulKlrO//O+2Pv7eqPcpH2z5GnI+
cPQw6cUh67YbDv4yVQa1ycvPo3jO5Mc9v4nk055/hHwdyMfffIxsJgBpU5cNGxdbuG4J619G0ZoA
nWvgxMS0OJ8/dJ09gUoqtODesnX3r6QXrfx18ICX53mCate18/eGyFsb12Fa0p3Jw68+XMwmAOjc
hA8YF0u4bsa8BiYjdCYgvjzLQV0C1OL17wilzSU8pmP8+nTPTiCfZ9e9T4pjmfbCIxcOS78w/UJv
9Gl24YhMBuzw5fu3lFvhEDgX6DFv4stfZzj4PVBuHZoPmHwhcMzSXcsaTemFb8JANLqmIaKiwmu
MzKb8m41EzoTYDV9DdG1mXGhTg/ytyL+MHLVHCrVTzl6IiuiV0IAXysuenONoQ7dY9S1z9IbWbQr
rqwhZuHoPX8SlP7r3388/+XakStnJ0y6oYJpRaYGt/QY9ciC7/18lIByKueUWudwMAGA5UvELjJc
F8DBlvWmJT0M6+EG/0Kgq69bgN1jlRZWH4en2Szd4ZULbuicm+fHBTPs/2X6tFjwxrOkO5aHP3yN
FW0AehV2IdYimaRKFl/jQleYP56BIyH4G2Mue/dFqkcI5Kl3nlLLDRMTAMjj08UM1xG7pW8EXay+
1gTMa2ZJBGIC7B5DWGI5UUSr88zTYPnkjY2+Hx9m556CmJOfXUm6Y3n9m8/lsnSg9xIr8vp7J6mK
0sHxga7dJaIrNu78iWoTVMnLz/OUVdwmwLNMk4sPuA7YrXstSDmXJ2lbz8nT+0BMAJsKwglQE/OU
EgAYCD9twblD2m/7YxfVxiRw/t9nwV2kOJbd+/9mpSiZV1l/3w7n/92ieWRogvdL3MTKlApOoOxe
lYmOhF2UKhQ8OXHqRES0Z4bP4jUBlp8Su1jCddaVlrSoosf3Z4q4QExAYS6DYW+BCxNRVQHYgu6m
XcsrpXonTX/hkVO5uVSzM2dqDGmfNPkGUhzLCbhOFtm2tpniDoavE1MFPc8SIp2tnph2utxsDqJi
ok7lBjIds6U8/dl71ndnigwo3XxwAtprS7nDeas7uagluiu2tNODZFGaAMDrxYVTLG1BQgXfpzxW
RPVOhN/bn1z6xU9bcvJ0u+BdsrJPluoZpyRX5dUA4CwgvRAPOOWsPIsU2dKpsZh777w25+U6rr+d
vLdJfSFSpXhNgBnYvt2a6w1H3IeFDK77SygmimXffsJ5MotQGCynlIHjQ1AMjR1wTm45Bz4cmf08
H7EmWV1lUKdDQx7Bjo6XNeh6aQBfT+QXFHy5YyvPTTYBTp4lBRH5sRRsTZ+XpXL8Eg7X/SVEc0XL
80C0007kgkv3WPXemCiCiAiyIYDdQF1Cg5WirdLn4NaJf3RsbCgCDvUsgj1X+prKZf2W9Xc8sfii
G7tVHpjG0hooRhPgL+0b6FUt4egu2H6mp0fBpcbQDuOfXOKIJRPHLxpPPHAXDw0iTyy5YebIjqM6
1s/03FcP6GmiAdi9zc8mwBZ0MM14HygjV83mDQGW3KF32tJJ0DT0v2J0v6heiXo0X1z3wPTOkwZ1
HtM5dlBsjbQavCEJFdXralOVVP5DJgAQVS3hcD31fN5TwcPfewHFKD/9/lOXsV3Ud5PUSdAcP0eA
yKw/gTSn8yA7Z+8hP6YJHrx0elk/Jy/zKXv27Rkzf0ydTPvlgMLfBFieoJVAuA6wngoe/yETIMvG
7RsrtKzK2qIDp04w3M2zVjp8tyogit0EmGX0vNGlYqVb7uFvAmLdyQU0uA7Xw6yngsd/1AQIeeXr
T5XUeuoKPN4fL6U7vhsXKGFoAoR8/cuPrLZhivvuAMJ11wT4kqyTWVf0uoL3G1z8d7ws+Df5bAhn
E4CSk5cXe+dQVu2wg23EkgnXAbgAdn716w9nhwkQkjFzLGtgkRH+JgAl69TJC4Z3ZpUPI7rHuHcE
TDri15v5jjnLTADKoKXTWDOLgP+KCUCZ89pqVv/wonu09QvaJQSuI14XmQ2YMn1bXHJTdz/IvETn
ho48NCAa3dJr6PIZD77/SkFQZw3qcN8Y1tiQ4q8JYMkdEtEzodKA1nVuyOh439jfCzcb4pc7trDM
wwu7t61LAlwH4k0TdQSJtVu+oRHhTAy1alOX5RZEmk0YvH7HVio1UDlxKruWg8X5gkLRmABLSvVJ
emTt65S1P3LXsytZVsUPDCrxXVOJheuA6KAeseoXlx0aqC+cBuMtXb9NQFxpvVZJpjXkQwOMVL/W /2Cy/+hh/IIgpBSjCRBs3vUzFeBYfK5cWHS4kwgI
qz54leUWXMLBBABPf/4eleFMbn9yKcuheOjWzDCuSjhcd07HS3nP+sJvEwCpuhq3lvnDrxDTYcZo
qo3/cvHIbiy3YFH8JgA2RGyZKi2rUBnOBE6veD7FQlyYfdFYvHDdL+S3iWFfTdTmb4dTLLhwALVF
VfV7rOTq6gfb7S6B0LVfr6Wx4EwMZSFFYwK6a9P4pV2ofn/eoooSV+bqfldTnfyUnfv+LNM3medf
aIrTBKQ3lLfl7r93UzHOhOdWxMCWlSrvosL1wGhj9QWuicKagNRafIs6R55HKKGi+tF+QiUV+csW
X3Qd1zWwVclufsh6bcIA6Xzl3gN+rFYSTBPQI1bukIhu11AZjoVnWMT4s7lLClwPOrDvxZVVaXne
2k1f0kBwJnz7OadHnPqJvuUcMjLXaAg1OlJ9LQp+Y6LUCVTgpKZNXfMkPPe/8iTVzx85cSq70oDW
LKtA0HbCYjAB5uNnTOm0abdSGc5k064dPNsiBqw/a4UL1wtJurfvYQO5F+Acuxn4kGhFaWHyBOCy
xf8bnFG9E/8+7MepuJCnP3+PZeU3WhuL2gR0bmL4LCJRXejxnGtbUQGOpeucCTznIsZu2tuSDNcL
SStv3xqHygR0a64kn6P0V5SxijI1IKZEKqOrKwMv5zlbkn6ZklxNSarSZEAsVdQfycnLvfTW3jxP
h3S5Bvu5SE2AeSr+7tEr33+FcvdHqg5qwzMvYtj0Si4A1wuPOgmX9XE1aCYA94RkRRlj2pmDwt2K
MsxqqiK4KJBbqvHm529Sdf2R1+R5xOEYa/7WWACXM12aqmZOeomlqM8CRGWaK898+hbl66fc9thC
nm0Rk1pLbogLwfVgYfWVQXBMQP+mfI8NKbeep/T0fDQVb/s+SQCvG58+ffrqfgGelxaZCSjXL6V2
l8umrSrsmmvF/AVx9xh14hZTN7qocD2IsM1QeBMwoQLfP4uMeyKUVB+flD38ysNUb39k+67tEZYz
i3ol1CbgnAGpdUd0WfTWGsqicPLtr9tY/kWHeve0xL8C7B2uBxHDAxh1M/j9UFBsyEll+D5ZXLQU
LbKgemp1qrqfMuCuASwr7wRmAmJmpbRZnsZbZAl0+NhqSn99zbLz+idOWjbJ3+XJQXrMnSgyKWra
XsT6zcUCroeSAExAk3tSYhbHhBXR86LLtfD2hvnKl/xeYgxk/6H9lZIrsazsCMwEpC5N7bIqE2i7
vE3UtCi+23vnxspKLJXeqGujrb/6/qrq+99/oV2xWGjtLivsDK6HkkDOAnpFl59aAQduOBC/JE7p
w9tlpmxC2QAOmCAvrX2JZWVJYCag/Yp2clsyVnYq5a8hAKYoSgpVo8aQ9kdPZlExknyx/fvIXgm0
KxYLPeLUL0qMneZiDddDid8moJM2bUHL85QkpfKMyvLwLXqaL2qmDOEt8s7cJ+dSS/yRgoKC9FvT
WVaMAM8ClqSxRgFgCKKmRvL93AnjFDGb+IPvvYxlNR13LfoUG+6Tf3/heigp7AvCyUrk3ZEtliax
QRxSOj/Y6dyZ1ZUexpo45tzW5x7LOkbt8UdOZJ9gWckEZgJiZ7VkrROAIahyXxW+kzthcqTSp6i/
3fJGcjXWVy4+4HooKawJEHRVou6OSlyawMZxEElf0aHmzJrKCO21Qla6/0xYPIGa5Kf8vPvncgkW
9x0CMwGVbrmCNdNMtfuq8Z3cCRPL6DthMeI++QsAroeSoJkAQbyi3Ky+yZO0JAmOY2w0+0Xmys5w
qVwdDvh3KEp7U0GFJiomyt+P6oT8tOsnfdFujcBMAJC+vCNruCW17q/Fd3InDA3ackkB4s4FGgBc
DyXBNwEMsAhdFeUuJWpaVNnpZevMqhO3ODZ5aQvYvcXgbvVAS/C5dG6j8tPLl55WKmJqhDJcURKD
c7T3Sd2Odalt/suO33dEeoZ4wCZA6d1MdIVPGsxtwHdyn0wqrZdV9Bh728URXA8llTcB/xGWrllK
LfRf8vLzLutxWeAmoGd81VuuYru6dxrP+x/fz71TxBcFqeez7nXxD66HEtcEyMBRndoZYlFNQI84
9VZ5x8vUb35iS19404VsP/fJ1Quv4ru6F8aXC9FSFAagCHkaCJfA4HoocU0Ao2JSxUNHD1FrQyaD
7x7MygXK9yzPdnInqK9FsL3dDrgiA3PDdtrg0sm4nrpLYHA9lLgmwJLyieWpwaERSxOgEqt0etDR

3UFG8tJkvsNbAkXElFankGO7bhDpYJjFzCUQuB5KXBPghfPbnn/g8AFqeVDF1gRoVO1bRb5d6hzf
nxsMkApqexHfe4NOxuV6cS7O4XoocU2AE95d/y61P0ji3QQgl4y/hO3hDvH2ucFdxlLkyWZDR2pt
Q6EuPuF6KHFNgHP63NknNy+XOqJw4sQEIOV6lQvs9Qrtc4NS3ATczfNXSahYFNNAu9OEOofrocQ1
Af4SER0xZv4Y6o5AxbkJIKKVmjfUDODqAAxBpPy5gaUJQDKu4Dtt0GlRhRfqYgnXQ4lrAgrDNf2v
2b5rO3WNP+K3CZAok1amyfQr2a7unYwHPZ8beDEBQFIlvtMGl67XqN8Lu+8L+oTrocQ1AUGk2/hu
r37yapbVt7pMCmMCGKXalWp4a8OEWQmwn7M930z1aT6/2IlQOjTSn+3LL0HDJX1gbxaU5DWCA4Pr
Li5hRaY+c5E3wF64c4QEBtddXMIQdj7vnt4HEa67uLiUKLju4uJSouC6i4tLiYLrLi4uJQquu7i4
lCi4Hhpqta317bZvLVn79VqIUKVVlQ1bN1yYfqGcCpm3et4LH74g1Nc+fY3l8N7690SoTES0MuoJ
pd987o+MXq2kTeCeDbs0XPj0wp93/3zmzJlDxw69tPalZtc2Y3GGTBsil778heWNe+pfrX7x/Rdy
qOCbH7+5OONiiDDzsZlLn1sq4gtqtav19Q9fl0/0/WZrk+uUiS8qZRK4f0TziE83fsrKvf/R+9Wg
6Ih3v3xXeK7bvG78ovGl4/RptqNiot7/6v20G9OED3Ju63MnPjBx4/aN0CEFpwu+++m76Q9NZ7OY
AeAJyUvFSqsPa9RIq7Hhhw39JvZj/gDUFvrkqr5XMX+ZcknKnS8o57YzeEZGR3YZ2wU2+slTJ0+f
Pr311613r7j7nBbnyHEqJlVcv2X9BR0sphJ86eOX7n7wbnRfkH6B6BPglY9f6XF7DxETuLTbpeAf
O1Bd0J1RtWVVaNq5qRYL2K94cYXlZPBQya+2flWnvR8PL6/odQUMMByQe//d+8y7z4APi3Pvw/fK
rQA+3/R5uURvS10Y4Hroubrf1fkF+WzZDBgruXm5sAfKnsgrn7yybdc2of72129znpgjVC+ACZiz
Vhm8RFnxtVKlNQ+d/4nSY6auznx0ZlZ2Vp0OfPNUbVX1yLEjj7/xuPCZtGzSD7/+IO8GI2eOhLQw
JoQPkp2TPfge/lrOmvfWWNqsizIuys/PZ0PZTIVkZckXSruJyqLPeRBU6ejxo33u7MP8gciYyL0H
9g6fMVz23LV314dff4hu2Hv/OfRPrzt6idBBdw86deqU2QKa6Xhbx30H9y1+dvFrn7zGgqA/8/Lz
nnjjiX3/7pMtDgB7MuzASUOTZE8GNHb5BqVWBqll4socO3EM7JeIIIDawvi5vBd9LFg5pfKp3FP1
M01rIjdXduzZ8ejrj6K7QZcGBQUFNdvqbxPBsITB2XdiX1RxrK7btE5d981o+GDEwvYCwy17AjAY
vvz+S9jES9dwQ1+lZRWo5CWdL2H+ljz/wfPHTxw324vKyZWzTmaBzRU+T7/z9O9//y5Uv+F66Cli
E5A4SnVPf1vpeq8hVDYBU1dO/eWPX8wHNwHsP4ueWYRuswmokqJu2nqd6gkfJBQmAMxZ/V6q4+ZH
ldFPGYL8NQEwjDb/vBndzATA8AUV3d5p1LURtB137y2/bLlx5o1yKJoA2E9g+57IPiHv8P6aACgC
mnD9vdfLEWSu7q+OKzAT4A7YBAD/Hv533MJx6BZjFWLm5OU0yGwgolmagPjr4qGZ0JlwjnM062jG
bRlyqHMTsOyFZb/9+RvzFMAp2+97fx8zfwyqZ5UJUF9ntRJmAqBz9/y9RxA7yOI8DZBNAJA6Xt3t
wRNV2QTAKeUdS+5AtyXD7xu+88+dOHsnmIAjx4+seX8N7Mxw6gi7ygsfvGA+BwbsTAC1ykq8m4Ap
ryo979fV+Z8qrcbpKpqAA4cPiJ6BgfK/7v+DIDQBcOINpQMff/sx7CHyQoayCSiXUA4uglKuTxGh
dlRIqgDFpY5IRRW2KWxE+dxemABwQ/XeWvcWnAljkL8mIH5wPAwbyynVEdjr9uzbg2bOuQmAOsBG
hD557v3nftj5wz8H/6nXUTfl8liFLtq8Y/MTbz6BQWYTcF6b82D/F8mrp1aHOsgHBocmoEx8mQNH
DnS6rRPzl1nw9IK///0b3WAC8vLyxEYH4NJAxPQN10NPsZwFIOVbKA+sV6JHqG7ZBGzasen1z15H
tyUfbvgQTszQLZ8FlE0oC+Nm3up5GMQI7llAz1nq/jD5ZZ27X1Me/Eap1YkiOD8LgNN7qJs8FtlZ
AIz12Y/PFqF2rN+6HozFxu0bBXDVCufqsAdiBNkEIHGD42A/gaL9NQGQSU5uDuy0cgSZGq1rgCmv
3V6dLyCws4DZT8yG623csoh5rA6bPuzfI//CRR8zAXBk/nnPz9DJcm+ASfpz/5+wS2Mc52cBYCgf
euUh5ikDV/sPv/owut0LAVvMJgAZtES5fY0y8SXdBMAOAHZ34TMLRRyZRc8ugk0rRob5QuC5D577
6oevzGuEB9EENOqrLFqnlE3k/k2HKEvXk9u5CUCgenAJjW5mAmB3gtApK6agasmMR2bAFTLzBCAV
mFTsDbMJAKAssBQTH5gIe6x3EwA7/7INqiFAteeEnrDHXtxZvavKgPMRaODYBWOFz0+7fvrsu8+E
ioBpgLHXpE8TVM0XAk37Ns3KzqqWSh84WY5VUA8eOdh1XFfZBKx+a/Wbn78p4gieeuepd758B93O
TQBcWsKmnPnITOaPPPjig/LSEiXRBMCoggEqw241IXYmALggUz1+yrcDVc/0C46fOA6ZwwaGE0L4
hfMruCSD/UGOZjYBwIKnFuzetxsGt+wJFQuKCSgVp94CuKQn90eGrVBmfaA6/DUBcOCCA9qMR2eA
m5kABK7z4YgNx95DRw9Bh8A5f9bJLNhDIHLrka3hGG53Wv7tdvVBCTgsTQBy++Lb7c4Cut6rzPtY
WbxOtW7V2/JQaAUkhIpBlQA46QB18bOL8TJNBiwCBME2xcpDQ/7454+o2CgRwWwCgCt6XQEb4tLu
l4LbcqwicCUoTABcUsFoKR1rNQibR8AZ+/iF48GNJuBUzil56EI/yPFl6nasCx0OSWAzqQPy6EEo
cdfeXdVaGT7B/O+ZABcXlzCC6y4uLiUKrru4uJQouO7i4lKi4LqLi0uJgusuLi4lCq67uLiUKLge
SmZ9qKz81sDo1XroOcnn7Pxz5+nTp7Oys1795NUvvv/izJkzp3JOXXfPdSKOYPyi8Tm5ORDhyy1f
QuT8gvyC0wXbftNfHwCiYqL2/ssX4c7Pz4ecKyZVlGPaUbVV1ayTWcdOHmP+QKvhraCqlh+EsVdZ
xy0cR2V7BBIezToq3qu1Jlrtn3kfqy8FsKDS8crCz5QGvUlNGJJQUFBg+WYE9F6PCeqnb0++9SSV
bZJb5twCEUbNHUW6R46eOFqxhd5LXcZ2OXL8SJm4MuUTy2PPmwVajW/Cff3j1/c/pn6hKGjap+mx
LPUB/l/7/4LttXe/ul0OHjl4WffL5Ghvf/E2tKXPRItXG2Y/MXvj9o3MU5AyxjCugMXrDB9Tdri1
A1ZSlosyLsLQS7tdChsahtAbn72BqznNXz0fg/BtC4wv5Ln3n8NQQaXkSsdPHD9+8jjzBxKHJlIy
j2Sfyo4ZGMOind/2/N1/78axAV309rq3ISb4RMao7zu0Htn62Ilj5u//IppH/PnPn14+nfAN10MJ
mIAWt3FP5Pufv1/7zVrz2x1A2sg0GFtirCQPS841vogugOT7D+1/4/M3UEUTMHTaUBEBKRVb6uWP
Xz58/DDzNwMmqfOYzlNXTjV/nQYm4GT2yTY3tYH9oXpqdTnIbAJgeIlQQezA2Lz8vI63dWT+RLT6
8tJVQ1UrwDotABMg88rHr7z80cvME0zAjt075PedwCJDttf0vwZVYQJEBODc1ufCtmC7MSCbgGqt
qmXnZN+x1PoTjKXPLT1w+IBQwQRs2rFpwVMLfv79Z/bylU8TMOMd9WUw4VM2UX2f6qLupIIJgF2r
bEJZEUEQOzgWWlE2ziII8PLClczPu3/uN6nfhMUTNu+gL68EYAJgQ8sbCLoRWi2+R4SgE9knJj0w
SUQwc5abgJmPzvxlzy/mF2wFI+4bsWffHjCHEAf2rrY3tWURZHLycrqN6wYOOxN6wYOOxOA7D2wd8maJcxT
5p0v3nnq7afQDRbqnpX3iCAATQBYEygFTPWcJ/V3lh2aAKDjqI7quIy3GnyaCbi0n+ruNVuZ9qYS
GUNBRWMCoM/Bnop9PmATALsE7NIiyMyGHza89il9ZYwmABz1M+vn5eUJAwT4awKSRikLPlWiYkn1
YgIA2It+/eNXy+qnJgA6E84bqP7+ZNAHAVDgGgbnAcbJoKSRVQhdLFFAZ2nD0mYNYH6sctyJRX
lQu7qP5bd271/pUODDIwk5VTKtdsWxP28Bpphjd2Gbv37Z74wERweDcB32z75t0v32WeAtgBoMeF
Cme/UAH55E2YAFRvuv8msOu4UZ2bgKZ9m8LgEB/VGJBMAHBuO/UDp3rdVHeITADUGXZyAM5FV720
ih2EAzMB0AmHjx1OHJIohzIeff3Rvw78hW5hAhC4yntx7Yvo9mkC4Ji/6HMV6LdBiw3mAAATAA3c
+uvWLb9sQeCsU44AwKFl/8H90KKu47oKTzQBYOVFws0/b27UtZGIMPDugXCaI9TSsaXhShaGh/AB
EwBdKvr2s+8+k42+ly+aZMAEwNZc+PRCsC8MuML6z58FtLyhJTTDy0dy0Gti1B46dgj3cEuqpVaD
M3OcLsaLCajdrnZ+fr7d/C1N+jSBULxskwV2V3GpwkwAUCmlEliNdje1c24CPt74sfjei2M0Acgd
zytjn7Y2AZa9B13R/pb2zNPJWUD38d0hrQgFAj4LeP6D53/87UcRxMBTYnFbhJkAAOoPRh82pV9n
AU2GKMu+0kMB72cBjJEzR0K70O39LODSbpdaDhXwFPeb2FkAjLrcfMPHQnAC4uVohJz99wIybsuA
bhowRf+CHYGd+Y99f7y17i3hA1tx22/b4HRL+AimPzQd9j1xj8fSBNRqVwuO/9t/3y52UQYcyWGs
dx7dmfkDc5+YCwYI3WYTgDz77rPbd22H/ceLCQA7AlWF/TZzTKbsb8DKBAAN+6r7/5y1ugkA4DQK
9hxWma+2frV+63rZB3F4IQA7Nhx2xEgN2AQAT7/zNKQ1R0u7MQ2K6DuJLokBswkAoF2w967/fr1f
FwLnpatWoEZ7Ur2YAPNIGHzP4OxcOrB7MQFl4sscOnqo3ySLadHuefAeOP1Bt/lCAPoNjnlJw/RP
pGBM7t2/9/y25wsfxlliAjpPoxlv7KjYouK0h6Z9vunzn3f/vOmnTY+/8biXE6TOYzrDWSLsbxD5
zc/fhF6QRzAA6r0P37v42cXI1FVT029NlyNYctOsm0bMHME8BXOfnIvTyzXs2nDek/Ms71/CScTC
ZxaKHRIOcaIOAAyvC9It5rQz03u2cl4H7gmUSVAnDmEz6lVKrgR7HVx4Q2+s27zuruV3weCQIwiG
TR8GMM+UG1ImL5/MPOt0qLPomUX4oWST3k1mPT4LrKocAczlgqcX1Gxj+NIOAKuXMdowYQ5wea/L
H3rloR92/gA1/GTjJ1BbZlAA6PkJiycwT2TItCHjF6nf21kCBrGTaRXTSq3UPoRfcDfu2VjeCgjY
NQiCRt027zY4zIARhKPL6rdWN+qmn+cDsx+fzRJiV8DV4qg5o+SYMjMentF/cn9wgBmFE3i8sS+A
awHo2+YDmsue8dfFg7n8ceeP0EVgwVe9vOqafnQ3BKo054k55kMOMH3V9ITrEpinH3DdxcWlRMF1
FxeXkkNz5f8CmT+1knNxnAAAAABJRU5ErkJggg==
iVBORw0KGgoAAAANSUhEUgAAANUAAABNCAIAAAC+F7b6AAAAAXNSR0IArs4c6QAAAAlwSFlzAAAO
wwAADsQBiC4+owAAQz5JREFUeF7NnQecVNX1x2d2dne279KXpggWuiX2joq9JMYeDUaT/O2xRo0t
wQhomhq7icYWa2yIClbsLQooGgu9qLCwvc7szv977m/m/28tzGzLKYPPPYzvHlz333nnPu6fe+cFlF

+eeffz5nzpyGhoZQKBSNRpubm5uamjhvf4TD4fYXE4lERkaGv85Xf97S0sIt/Kob+YkrfPJVBxf5
1C18+nvbPIi71GeHAHQI6sa+6CEJghSJRPRcPxCdgNKNDU9a/WdlZXXYPhaLpdVPuo2rKyv79ek7
YsSILbbYYvPNN7fbjzzuqIyczFBGKDMvOwT2+IOXOvtTg/Z/maEQf1nhtn9d9EP77IxwNMKf3cVX
Ggd77gKM/82fPPD/m+D9D0CVmZ2FMGKWwn933XWXSSLYbtSoUTvssEO/fv2qqqoKCgpycnKC8i84
0b3QaiOK2gsDXWGeIbqY/RJgejafbeSrlxZezrWRH/56ULSkO/l6sH1Qxgfln+AM/qqHernYgzBs
SFedyeONCicMEW4J19fWrVixYtasWYMHD/7b3/4WHjhs4E033TRkyJCamhrYorCwsLKyMjMTcWTK
zqtI/9VfCf4kXLT/Sf14xeo7hE7+CKrjeDzu6RdUx56uXlP/dxnR2xseSAGm623wwBWN63/n6IzP
NqqdEE5kREKRcCKEjPvrX//6wAMP/OUvfwmP2mYU/8F5dXV1sEtubm55eTkiMMhwnm88fr0B5w27
INL9r/TJLXSrG2EjKMFnfn6+bEGZg559GX/QFhR1/eFZuQ3Vv3+6in5thLSudGgXBuX39w9t+yf+
l/gvVFLYu2zV6s022+yFF1743e9+d80110T6DR5w8CGH1NbXoSNr6mqb4rH8goLmREvCxGXY5jKs
kxG2P51z0X0NRzL4mvzV/WRXvvtXXFKSm58Xzc3JimZnR6M5cHd+Xl5BfkNjI+0jmZn8ZWRG6JMn
AgC3c86jO/6DwO7PuTChllCCP135nv+A1h4tFIGDzIj9RSJ2JcPgB0KNKN7SHMf54OL3DmQXTwTP
HWIYgDcenDYNWsJgDum2fPnyF198cZtttgnvNGGXP/7xj19++SVSEbHU2NiII0yLoITzDqzEWCQR
wV3g0/8LN4dbMlr0PTOUqevhjMSypSuaYg31dY2NTfWhREY0Jys3Jz87mtmv74DMrIyszCifLc0h
2jQ2xGLxxuzsbCAMt4TiCXq0T3nGQgvnrQ409O3AzNpYoiXBrIDf1n3GYy2MLiPM/IGUWXxyjnZh
RIlQcyKWiIfiLU0tfHLeDHYcftr/6wbA64ILsnm67CJDrdvBX1hQ3GZEalNdVbsOygTc0g0AO70F
YBrqGvuU9EEbvPLKKzfeeOOvL7woPG77cX/+85/Xrl0Lw6EoIbLnNifU7PC82By3AWVFsltCzS3x
RDQ3O5qV0xhryM6M5hXkAu/ylcv+8+nnn3z6MZ/Lli/5ZvnXSd1qci3ihIJdQBaWlvYfOXL01luP
Gzdu62HDNsnPL+TXmvrqZigHzUJx8TiUhi8jWVF+bYzFI5FwdnZOfX1tU1M8PzcPvmZU7e39nkJb
Q1OcgBRPbGysr69nemRy3tTUwNN79y4B5rq6mlWrylauXL5kybKvv14Rb4wjvnOycwcPHTR82Ahw
0qu499BNhyxZtLRXn5KKtZXNiXheTj4Yy2Bs4RYYN3VQ4Qabhd+9w+Sqm5oYNlnOfIK6SBB0Cue1
1XXgJxLJyslhatsoysrWlpWtmjv346qqisbGmK7n5+duuulmI0ZsNmjIJmAfyjY01Tc1NkIzqE/P
0fwo40+EE2CD/gnTwBJMO+OWNhOi8/EQioPLURwlhUWvvfbalN9N/t3kyUn+w+bjRrkLQSNPzOdZ
MCORhYMCKNiLCEsg49fS0tLVq1e//vrrTz311IcffthUX89w+QmUZGUm/V8PlXqTnYsVopMBAwbs
vffee+65+467bJ+RZQPGcOQTeNBfYBMT0obdHOdeEMb4aRCLNedn5/qeg9ZY0CdNncDtW+bkFa1Z
swZIevXqBTB4ZvTct29fIP/ss8/efvvtDz74YMGCBRDc8JYFf2aBGeijrgqKi7F1CC8ccsghAwcO
lJEtG5FRIPVR2SaHUjvgP/3pCBI+3hRDfTXU14MrTgCvsa4e1kQiM0uBfOnSpW+99RbQLly4sLq6
uqioqLa2FuQDBsCg9ET3/qUD9tt/f6CFItU1lfQGtYzJso1kjbHGvLw86A4emHglJSWJplSBp3/4
LxHKaG7lv2m/nXyV+A//w8u/rvkvL1pIS1iQQdqEy8patGjRs88+e/dddxlKjMGR2gGY3ORQ2EVz
VLhjGFBC54y/1XkMbb3t+MMOP3TfiROZu6DJJlk0m1/rGhu8v2wKLyuLi2CtpTHZYRuPpKf4r7Gh
ubi4GHYnMgXMvXv3JkqwcuXKhx56aNi68eeWrV9voHAmbxXNg12COWiDXx5xhspaW3fbY4yc/+Qm8
SPSBhv379//m25UQsxv8F+Q8yT+EhEL9Fu1qMkhAYG40p3dx3zdeex1L67333mMicV2RZ8WZoYt3
jCAQd9TU1jiDPmPnnXeedPJJhIira2q4ZeWqlYw9JycK1eobG7iC3Q7OIy3r8g7rnUQd8l9kwKAB
Bx54oHG6079e2nnNqxOJwFgjeqe3vFRmMy40Lsw777wDHmPMIWeUAX3YYRyAJFA964jbGCr38slM
MpI5Ojk3ObK6bNXLL782+7VX+/TpM3bsWMZZXlEBspAr4Fl+dNwM+mbBmYDeHSVFeor/YHWJKx6N
qIALn3nmmWnTpmE+11ZVmUmBPnKSPregYNNhw4YPHzGgtNRkW1NTzNwO5645tCxbsmTWiy9Cv+23
3x7z+ptvvundpxf2fkgclMLhPYagBtY5HTIxeC5w1tXWIq2REQsXLLzjtjuffOKJjz76iLkqjCkc
S4NNNtlk+PDh6C5ECXcBMGrNzMlEAmoySWbOep7GUAEM5OZEEa1ij8qqSh5UXFzEE7MyjL4pHuAR
WoGMnGh0yZIlb7w6e+8JE8LjdxiP/EP/KlAiKNVje/sv3pgoKihgbK+++uqf/vSnRQsXmnz2ybGM
DBABu8Td9EIdxRqTeTy4TTwhQYUZYaN1h6Sj8ML4M7NDcSdKJuy3189//vORI0euKV/LT6bQM8Jw
JP046prqjzhtRIeK43gp2FP8lxnJwbRAVjEfmGb/+te/oGVDTY0gzy0s3HHHHdFW++yzz1ZbbZWT
nWPur/uJSYKme/PNNx9//HHEj8RMzGU1t9hyy1//+tfbbrvtvPnzioqdH5Da0cb+C/It4sjmZIvp
BGY1FsKcDz+6++67scOJ96p7ro8fP/6YY46ZOHEinAcmPVGYV5gT//nPfx7912NIytWrVjny28e4
bcafceaZW28zbtmyZbUNdWgDMSuGLNjOsrRVqkfH+hf+u/7668V/oq6Ip5Og/cdcjmaaeYv2uf32
280+pVlGBnKbOWdy23mqDvQwoptBHnrwIUwvTUe6guec6VDHaN999992 5c+dyxYwV15XdF3ECFOnp
8qXFvQtPPvnkU089tbrWSI5Gbog1oQeBAS2Aw5mIJ/MNPpQoFvRTKFXcdNKusqKWyDxoeeONN+65
554Fn39Ow8JevVAXxx9//P/93//tsP0OxKW42GKhhRB+MJOPqcKgsrOyuV5bV4vtdcstt/z973/H
Pivp1auivDw3L+/0008/4YTjlixfZt5+akcX/MfsNM8gFmf+wx8Ypg/988EvPvsymhUFtyD/uOOO
O+2007bbbjseBacq/iekSUcJvTj58Bn8cN999zU3x0KRjOameFGv4osuvhCxDV+sWlMGC4LhyuqK
wvwCfJXUYLdWXfFfRUWF5z/Ta60lAm34L9SccfXvJjOh6Q628zKMwTNORsK0/vGPf3z44YcjtySo
pHA7ZAgskvfff//pp58mGokVb3I+LwunzBuQkczQkE032XTTTX/1q1+N2GJzJCtqC8LSJ+YzbCFL
SMIvyII9xX8tsfCgQYMY780337z6m294VnZuLomjf/zjH1tuuWW/vv2E/eYWM0gAICcrGyGnaezJ
rHgWGoOIK5+Y7WAb7F162SVjxo/rBv8FJV9SFzebTwqf8ejXZ78Gr3+70smwltAPf/hDOG/XXXfl
Vy5AJogl307Ay4n0EWmkAzP83fffO+OM0z7890c5BbkNtfUDh5SecdaZO+20I9Z/YzxGAwVhiUFt
IP9FSoeUtrf/6FTy7zsqOBQ64vAfLl60WNarN11pwxgQ7ER0rrzyyr322gsbUS6FJLxPe3BFnCFj
mWHAWzDrz372M/zEb7/9dsniZUiTbOoSLE5p8eXK8splK5bBbQNLBxLNhpbRLKxBM8tsxrfa+EHl
K+BTx0sXLXv36ouovvPOO5ctXmwxjGgUXD333HObj9g8P88ZrxZjbiEMaONKtDz68CNQCE2H1Ack
saB58fE42uDII4+EurNnz+ZGgCcHeuzxx6Zl/xmokreth84JEcFY6Bmm8a233Lpi6crs3KzmWMsF
F1xw4YUX7rLLLuI5H3YIzk9vF3GCSSejfMjgwTiCxILff/c9ZndNVc2iRQsHDhqIWGGCoXxyc3Og
BQNPHc8d2n/JfKVXu3Qn4ccJsxbCY2wiA1Ai++67L+jzfqukDvhleNg65JKJoSg+JJPOy04Z7zI4
BK4fv9wxpuYvfvELNPLdd/0Ntd3U6IK9poidamtKPPPUjGnTrlvw5cIhgzcJhyKNtY3EdQlxe98o
6CR1g/kkUJlXwK/pgTICbD5vv/XWr774wmzZhoZLL774n/ffX1xQCNYaG+rxLLIyIjhefF2xfNkR
RxxxyimnYF3tt99+X3zxBYNldJqr3qS54YYbyLZzhccxurPPPpuf0GhwraQmj15PEQBYd8Yyn2AH
AAjiV1VU9u3dBwNp2pSpSxYszcnJaqqLXXnVZWQWmOEKO0gKyDfiKxbXUUcdhfGKgSuicxQwqVrj
qYNKB1599dU4WxZ1zAgtXrDk7r/fhflED3nRHOYW5Eyd+Tpruc7V8CzICahXFQxxICbNV199hWAD
Ptl8EFt0Qonce++9hP0wz5nxeoY8CWnDdOHDqCJMde655+hes6jIyIVCRUWFcz+cgxW1bOlS2R8+
+tie27rBf4wXYUy3Fmt0TiI+B6N7/LHH5nz0EdeZ9Oeed96PfvSj3ByLOOJecIIkakm0WJi3rnbG
jBnPP/cct0OeTz75hPg+5+BBE0wsJQ2IQrz44otpxsVVq1bh08DlzHBkD4+WxdIh3jA2XMLPdKVP
qcNS3CKFg5EAf2A9N9THLr7kQpibfqAUjZGOPBFQxUBcJ4qEAMb+wflIYtulWzVbpL56FZec9JMT
z/nV2SHM8Ujoyy8WPPzgQ4yCX72kTJfEbdqvk38SV17nMnEVTOdh+GuLv1rcTLAxESKeycyDEXfe
cae33nhzwl579+3Tt6iwyNSCyx1akBG3xP2lC1w0J4fH4Y8TUOxVUsQkp1yBTlwsMIRZDQuuWL68
T+/e2PJIPyGrzZHuQzX7oQoYYNQW4onHwTIi//nnn7dfW1p23mUXmGbsmLF8RedK75A0xAIm/Ysu
Xsc0LnNeWV5BeoCUMAhpiTfz2VBHBtLOBw8afMF55+87YR+CWfHGGPxH/S8MBBt5EdjFECCShD2+
DhwpqQajw0/Tn3yqcg3MFNruB1tfcfnlSEQsbNl5sgE4YfbqhCfiJnOuNvC0XXdmrBExFK6sqEDX
MQ8Jse2z714hbmoJPfnkk19+/kUec0/j2uAjSUKvK3UirSE/7rrrps/d34yrhAK1dXXge4dd9gR
95788cBBg6qJhLUeQG+a18L6ycmUFoSMuV///tzy00mTHnnkkZFbbRGNZhXkw/E2j5E2z06fAcHA
F+JWsfsOj7QeSmPEg0xyxck5QP0zT09HPjElKJuA+Qb0H4BqamxKuur1DfW0BxVNMVNnGEYjho/A
JafBoIGDiN8io0ila4bwSSf1rhqIc8Z4/vnnMzSwi2BU4JYYkQwk+R61/AHjV06p0/yGQ8//DBR
ERi+qMisTwQbUhm9hKJnIklkqsSd4CUC5aKLLiJ3gBa+4oorMH5uu+02BpssMXGPp09YgROU8mWX
XcaMy8nNrK9pfPDBB5kn2JrAnC6e27ePlA4uPfjgg5l8wr7wJcOF0ANFqg/c80BeUV6sIZZbkEO8
m6qOXXfe5emnnhpYWmppsVgsB28IMYkrgEWiiKs/0pSAxAvAJyDUVFaNHD1mwt4TXnjxxZUrv3b5
ojqKcuh4wcLF/fr133bb7crL12Y47dzm8Oojdex424hbFJJAKtx8002MujkWP/qooy+68CKwU1Nd

Q6SNpKKzvcKcMD5kIOb/sE2H4fsTGt91p53POP30gw45xLoiRQhbO33HQVgBjDXU1nJl+IgRK1Ys
++DDD7n+7epvCfPigcENjBTV5p3TNkOwEDSasRm1nwy8w/EI46ryimlTrgOc5jhzKUbP99xz34wZ
z/Qq6UPeD4edfmT8/fOf/yQWM3PmzI8//ljVwdjuBDWJqxNzGTpkyJhRoyAixm6EYLYzHuCzUSO3
mv/ppwsXLWxqjC9bsRRDf9DggShuWqSO5K78jzbyD3kO8wEiLm1mTqbEYX1NA3N99912JxJmQXNn
Aho6LIiftBuSzAc7ojjhyFRj+8lRiF3rqqvJnHIyZuxYpCCQMFR1VQh5KistFLdgATDgi/SI/JNJ
JKMHkmALfvrpp7VVdRoOskpyC4NELWnjl1AAhvzKPfbY46Ybb8TD+PExxxisZFdzc02bYzSDInxh
d6/xlnvQOeecU1BUCHprKmqI+jL5kU+pGM3t5R8ueZLFyfhmhRHZPHD+/PmwGnE7ij0hJc/FjkeS
oallvnsuR5jxlaevXL4c7hcqSCJg9TI0VDZXLv71r4WE5liCaCg/6q4NPDq2/3gqwP32t79F5ceb
rGJUj4lmR5GIQ4cNIxjBFOGKcJqU262JE6uXYq53wz+yKEYiz9npVU68jxs77snHn2CoQpl0/eKF
C4mBK1LQI/afXC4ZuzpRlIQDrx8S+p/Eo0EXAdLiJJ5BuOy00zCVLr/88gvOPfeUSZPw2D6eM4dZ
yh8I8VrV5i3J67q6UaNHI0jEu1QGIGYYkQLynRHVilks5G8H9W1mhLme0aQIv3gsseMO2+OAU4fA
Txig9EMmDVWLbw7nERdcvHgxF7E38KXQuaQAXn75Zc6x83CMiIoXlpSw/IyZg/AzV8yBh7Gx3bbb
sUiDc0j03jvvEMLcQM7T7aZ/Dzn4MFjd6tgoSzTFkhhYOvifDz4w87lZhHpy8nJj9U1lY5yiV19+
degmmyAG8D+yXY105dq1pn991KY1yYaicXyZHpDMObiWTCShCwwvzEFyhfiGiD3C1PTGr6AfpMz/
+OPd9tgNbdUaOkgKBT0vFSkShEzzTVFJGB3j74a/3GANEqELzr+AogEkIm3kn8r3pA0iEHZBRcB2
2FtUJLz++htvvv0WMbM58+a98cbr6MaDDzwQyHBZDSGtigL+hbrkSWpqqp+ZPoOI+tryNfvvvz/R
Bsw1nxbzEBpNBI2bbgpvGZ1ciBH+++N1f8Y2yc+PMgduufmWww4/DLy960J3mIB4b7ALpUl45ea4
ZGbCbRid8BPjInN4wAEHHHTQQeSZMFKNaABsdpSlkWwykGezXE6irGzNu+++3VDXBLfsN3FirCmO
7k+dwB3rX0rcqEhuqMftp7dsKu8o76Nu7LFH/lVdXkXxW0NtAwNvboxPvWba9jvugMrgkdk50dqa
GjzBYjx/pxpVuiw8WUlzK/NZrjAQJe4CXJM92VkWf87NxYonkVVUUmzOWEYY6UKwSv4jzpc5OBmR
226+pW+fPkwGGaywAvQrKytTDkpUdP5c8pDo6vDwXqRulTuO4NcxZswY6SmJJZGcE57LOc/iiWJ3
VBLVOtj5IBpDDeZbuHiRW3nlngtmjKiuU/cJzNCd0TU3xCLhzEULFhMxNhK0sExHpVac2h+Fd+6k
pYkW4QTkjyPrwommuK3XQfiJOWtrGw88CLszY8stRl4zZdrCRUuuuuoq2QmYDT4KCJzE/G699VaY
UiEhphypYZkWBl1mJsqNR1EISKWjc+ht8dwOO+xUWVED8OXlVcuXf92rF0GfZODQmwQ66YLKbX4i
kpfrZjYTkto18wEL8otemDlzwRcL4KfGhiYSLYwN8Uv4XiASd+Azv9DqzOASe17YsM+5kOvPYT7F
NUQhLAyZF656r+1SU2hPe4uOhg0j8oH8SjmMMIo1uEgPAMyB4kNtqRxQBhkTHYQGe/aKMqgx22PH
R53oh0GZcnEs0n/AAOK3Wg0jLlbcToyou/iqYDuH/GhbvQDfW9wmwHytbBdkQSIgA/sP5Jd4Qwz3
U1q+DXgqOCVNZzxt5onV/nDQmCfSnlHrloJCFjegi6gIo6Q0H8mHBYUViMkEeynJDqgMB+yhlAlf
4PnieeAgK5Va31pagX1lSyPIYmdb/ZsjX8bgwUNLBw5UlG3Vt2VwS+p81lnLZDmnMAjuVMCC1Y+G
dYMxic9FSlEoKVBAVQMQc1gSVkX57hD761z3GnIpXXFoRWbI56JnTsRGQaRz0UrwKS9wpZRWm6uC
mnicLAsGStAxrK6qIeqrgYkzYE34TwlNHYKha+bzcDIQKWKLRBjNQ5Bw6NChIrZEowYb1O/+KfpJ
vQX9uS7suYL8AlSh7kKOSlZ1IT80k/VE2QO6UT0wP0kucyIsgW0+ifNNmjSJUDMBGjwk7rK8mWtA
IAZ3mPwnVTxk6jB5qSJTV5hA6HWde3uA/qna4gqFKkxR+SUbeCSxCUCQmScheHD9MGVAIVUtSEVG
y0QhvWsPdhNOMHGIh1SrLAFgks+FcMXNQr0yb7JUtL+CJJY64YQeNDt5lroCd3AemOKr9zRxGOVz
KD3DCWXc8IqSrVwUf3RGvy640PNrG/nHV5FKwka41gB9b34W6Veuy0D00rELCqFZbCCuZzAgW6IL
4zU4uqD8IyWOP4I0lT4FJCEB0Sho4RUoCLqeeOIJ4gly5riuemwy76RP8bTuueuur1yNDyYQ8g+C
ARW9AZWSk3CzYSMex4lOS892hgTjEmEKYaaEx0svvaQwMvfwK1dOPPFEJAHRKZrBE3owP4nDEGZg
nBAJjEsOl4MTFxyyakJacouY29NSUpPb6ZNICgkrDqID4i2u4wwycllyiochEVXI7h/NyZpVZXhw
eCESTmJZZRHaHxs4U9vcrqHxUNlVsgvFdppppohbF9737KPb9yYd4iU9XzXDYUdxM4CBQNgRBCJc
Jk+ebJUEjqUQmapOoM2pPz8Vk3H2yy8T5OIuSObtDRCLb+S9eFtmkH5+tT3kJs+9UpM1zUoOFD+u
KB4oeGVfhGOPPZY7GQwI1dI4n9wEDqJB1FzhTBGAZQ5xcMJXLiL2GSS3SIbBSRKB3E4agwZsBQIi
yBZQIISGZWqCGkIGzFdJSg5llqVN8O904gdPjaeEn1Sw/FM/zqDM60L+efNZKti0WOvKAWFcik/d
ei3pjQ3Pi2bwuUMcKe70NGuPffw1y0m49qrJ9Sq+Q5b1yteDxKONLjgJLaaIZQsCrbSBurVyXZdN
pSXX0SHnnXceO/7gEZNwhzpe1pBLfPiRh3GHDzvssPvuvVerMgQJ99KPFSvg2EUihLWlizbwMECl
RsVYuH5YowJdGofQkRKFomtQRSK9CH0R5KQEgYoP4JPm5YSvXMRpxc7FURDHqBOkPd4+oSZCKlrr
zki4BfTBecw/omJ33HGH5p9WLcilQKYSiiNV4FUhF7WyQWYyo5Ah64WfAPaCoTNkabxSvgCZtMnC
IXqmHtOr9aBylFHLsxD/MmeDndNS1z0fdPho1lskbc1QCCRrmF3ME69zhRwxOjeq86+//lroogeh
SN6bio/Uhp+Ut4TvERMkUVE7+Hb6FS4mxEu3r7/x+qSTJ1HX/Yc//AGWoOySX5keYMNyXfE4Ukmu
5AYeVvOskSigAHMgu9G/1LqRr+ST4CTDELohMM8Dp4yBqYZ7BbvANJ7wKE0OBi+DDxDJB1AFRBsu
IldQzfAQwSeV/ajKBsHOuQQb8BAjpWqNag56gBXUObRBzwIGxqiqvIwG2Zll35SBdOFXVR7dsEsk
q0TdoPxbRUnikiVKm/qp5Q0+MQpgw2ciqoghpkRgqOo7KI/bUIspB8INpdEoIw2alR3SVfJP0Eok
S/65nGWohjLx1uwFt9MGqLBkhCuQrIGImiojUrXimWeeicAzyKnfRnEnWjjJiebM+3gemeKtt96a
cnf8aDJ1a9eswepHKyuzvIHMZ0+kF/ga+iFdoCulyEo6qdSKiBpuL+BKOgZduWuvvZYyYLGjclD8
iou00047MTYZQ6CGi9RoTZ06lZZMo7POOktzlFtoAEZowAg5QBN5DmkKMTcS1JjMRfKAEHxxjjEA
wIoEUR3O0lQMGkkaTQzZy0Gx59VrZ/jidnGeVLm8PFfGk4E1rEpvOoRy0layZcVwDA0ZBgllgXGF
gSD4sdDJEwoYLmqFK4cPD9EeI8TmquNdTBHxrl+N0B5aASne4kT2BhFKi1QQBMsIkdj1BpWMZnmp
+BlSMvgZ1GVxr1YkyZ9gGqCjbAYmWrCFfvmLX3IXUbaS4hJ+hRZUbiM1WG+AriQ7wh+WUo/UfyTX
HIm3gNJCXwpBOSFOUhyWUiBGrKDxMxtw1y0t69DNtCOMTp0w1hj5HFwQsk9cB3T4ZtiwYeQwaInY
Yw4p1MQtNKBgk+WbMD2re7iXZ/GTAgRW4N4vWeCuSS9fmIv8qjChyAkYMp9FmM6YbL3XFaTl6Qja
nXffmaI3nos1zBSFBSVcGX77yOV6e1ZxMkPmRCFMMRl5W3NTmppgPiQK0ohRyLXv4ggqaI139OjR
7ASACfjoo48KD0KyZg4iEAryRArbkGeQCXKgYahsQjtdeuml2ELoHOmQ3/zmN7fcfjs2/fnnne+T
3TyFX7GpbGVZRsb4bbdlivZI/UtyLS1ASwRKHegAEURfXY5r3SFhjlQARHEkV1CsBEd++tOfUmXO
UNndjXgSVgVzjvFQUsonzVDEqDOkrEwWfBSmFNXCsBTPYicEpi/iEz+X9C7sSLwKsaEnesITkNOs
xcyj/IBtLhA/Mj25GLTQ18sWvoGSNBKxipmTRbXempuZGFrvIqor6pR6z2opF0SmNiegCCRoymm2
E4FD5EijBa3bNg/q0DQE5t12242EEY0/+nAO81lw8slUYSwqFOBxrJcFn1yB0MhmisrOPfdciOJJ
eeYZZ+II0nir0aP/+Kc/kVQku6jyfUSJbd2CjUQ15M47A0k35mF7vJmpLpopfyDlaIeTN4pnSvbo
sgYGZPoqjKAC8KQ4Z7YxuZGjcC0siIcF5+Er0QNpIoSfkKKQKX7WD37wA05gelEdG+ixxx4jpIJr
LGMF3IkenipckX/g7QHdDmDSs+0Hud4rgCTtCYtIDyBRSvqY5kJskD8AM7Kl1ttVhw1gONkwjALa
y3QjAyb/oHTwYKYi40Vcde0ve4S3kihpWTBRWYLCRVIgiDSF7hmUQlHCJOtyKP3H89NIGRFg+OId
JALhfYhV5Jh17erViDpy/eQdpk+fTj7CTCmKx+rre/frh4Pog9jdQ4i/y6K13qswR93BqkOWuAxz
CSGNn2ezKodz4QuCISY1yTQk6WuEPOJQ/AoVibbLBhKLQIw999xTv2Jlir2YZzCu4AF33OXzb0FD
XuLTcxs2g1wHXexQSHSNJrEdz+JeYIBFEMksNeIurmMeII85V/FwN+Y93TIWoVrqFdOWQzBDTowN
pDjYBoYuplAbu9YjgQo/GIuvkIZiPsxKzuXYSbOBeb5S4kCRH1bQJZdcQjgaSBAWu++++y9/+Uv2
AKKwdMCgQUT5uBcmM1PPWTUYBrLjRRf0lfaB6IYeaE8F4z/PW8mT1kA/z4bSEjNe/MjaMz+8NQjH
TyhcvjJavzqJr9BJrh9ig8Fr8xQrY25VZKqL1OzUgfhEZSs6D2CcMI+9Pe7Pxd/EAVQd5HMnnHeD
+bhLgW5JQQknHk1iivwvSAcq6v4l8runf+lEWx4CHqOARdB6cDkEprQHBcevKqjh0V3QtTP9SzAB
44ea0HjM0mu4bmgb+lSIDpiRDjLmYCZkLUFWigL5FYMbZsW9ZW8Qhs+mDgTDFI+sqa4GJPCASiRN
LMeA3R2Ylt4o6npWp/Lrd3YGT97QqsJEBl2UduNElr7UsQivnBu/Mp5gTSK/ygpGbCDVmN+04aJk
FSQXRnRo3iNQ9SAfbhTNgtKXxsnJADhUvmYl07ICTxIilZEH20gy0a0EFbyoNUFEJRQVIloLC/LZ
Pf0u+OmfgygdoSVsYq6w0wXuPBat6u+htzytzuD38k8NvAZAImDkoEC5COSE9PDKrYrnu9Nb8X/5
xZKLXCE05kNm+c7WZ1ZjRdk2F0VFrE0h5k9XEIugGggBWua/tsVJF8/t2xspHTmVwNHIceVdHME2
wm9wIm3dSjaaaadAkVkSjgEADSQUX4qcNBPxJOEkAxS2gB6gQL6O9JHkIrcrsaNuZQwppKfRSl97

dhQAoqvG5k/SQg0Q8lzoQW/iPyxUeOLEE08YM2aURoENNHXqNS6jqiUgwknws9NnypbQgeChDpSm
jJfIwNHHHW1ppzWrUGraLtabHOpONKEYz51YHVT7x/QfWLp42VLLWxx+KGGBPv163/m3O6+ZOkW0
EOroVlu9cM6IuIjahbdgXEkZqdeqqnIYk50Z6ae2rvraP1z32OOPERik9J0immNPOBbM1DfUypFP
C8nJ4YhMjEWlelh8cAt7QvLJ/pBW48mqhtYpuGbNauSUwzJEN+aQ3JJdyP0CggknNa2LACdG4Ss4
Vb0McWMlEL0cJbQhmOia9pqawRiHHEbljsXuoo20f2aWc/GabN1/cmxOenXJgq54qN0fgo8cAZYI
1h0nfM3LM9OWIV9w0fmjx46yBWGR0COPPnbgwQes/GYF2+OR76cckQV6nPB5ys9/NuvFmYyIJXP4
yxjy3mwQzNAYnch2Irai1h1DNhl69ZSrqynzb6jNL8zjhP0U2ZATWkAe98cml/ZHOaE7yWBvS7dd
B8iwdXD8aR/YmrpqYMgvyj/iyCNGjt1qzZq1rNG98847DjvicB4qHErbeKiwrKiIJr2B8W2kdbGt
xnhDfnGhbZaZnfnVkgVnnXf23XffxV2gZfT4Uaf84pQs+CTMRnhNnLCLoRsHdEnpz9aPur/gYYkK
Bmy4Tri9FnOzqDokkkk9N58wu9WcUX4WJvab1IMgFJNF45HFRmGtFApjUDSbc2KEGLxyHnkK2R7F
QsXBdEI8SdknVVvBbYBBUTjBW4rSxJcwK73BvpJ5EkVS69g6JguaTb/LehNlvjO+DfhCgSfbnSAe
jj/+2JGjtqitsY185s79iLG/+urLy1csB0DyBBKBbHez3777YFohhMiA408IVEWqOSEIj42FH6Ov
eGxnn31mErr1bQHTuuFap0PTrK6oqhw2fLNJPzt5sy03a2owIc1kABhizuAQDGO3qdRAlPLyQr4d
0ykzK3t1eVldU+3Ml2btO3Gff9x1TySHgv/QsC2G/fTkSaPGjCSozlYfpnzjXc/zzvDuQhmtLMjk
iQwYUnrEYYfLnYEtXpj1Att0OvjMKURin3TiSebksrLPlJ2pQg54CIT6KaVZhWWAzUQ/jAeL4fe/ /z3VPogEKs+YZHJa+arZxjmJZiwJpLpy2zyPyAuxUKp
NsCgEJ+DIUiz09AnCbyF1D0+ZC8hJPCWI7caMnTo0uVLVq9aTbS4vqn+vnsf+GrRgr79+yHDyF/U
syMq5RpZlC7bc2QQaxJivGM1oukIizCZGQs/UXJB4G3b7bZhI4vU99/oYghya2RCEHPAef/626/L
vi1zu4O0EBEksIquJ3VOJ7LChU8/XWnWFGtcvaZsydLFCO/LLr6MnU9sSXc80be0L/UKJKiAHLRj
4tMDztN64+TtATaZDvO4/ddenz17rwkTln1K+/7wiCMU34LbPnj//UULFrlNGJIVy1QvMmngPxb9
M08Ana+kX6htQQ96U0z1FMwPnDui0wTZicUzUegZvPNUlheAILIjvl4XMUbkEwWBCUwZAR1SrKAy
YDQ1li/4IkZDM54otxR82TYdd99t7kKmbcoMoAcfejDY0WsjlEOTitdJF+b8epmyuKgYmcGQyQMR
EWQx5vIVy5rqYwXF+Z/MnX//ffc/+dQTrErkoYairEwW58OOzC4ineSH7r//frawYB7aHqluWwiA
QSCRhCRiWramzCmk9UKx/gYy4Bi+MivkoohIoDTZrIcKduABwwRWqTbVPk8qmFAanRkCqoH2ueef /c1ll06ZMnX+vPkmgEwTtuy+9+6k+LGdmPYQD
1ttvuSO5btK2Aoq8+soru+y8CwCxJgMzyVudMBmyio3LUTQwh2L3CrTK4uGc6QKgRJjgGFx9WpL2
QRLQxm/jQEuVWimUyInpgkQCXiTt6DOYnghELghfWV7VbdYG/W685UYCsCAIjKg8UV6ki1raEWDB
9KLTyDWtSQM2FDGkpWYHQpZ92xqlRzS7XQAKSwoIbbBwQ/NE1XIqfLSJbKXzYZQAS62pJ8LVgOo0
iOZF2+znvH5e66gFokhrh3k6Xh1cAjCrvvn2vbffw56hLiE3L6e+zsy14pIirVKgMQQCMxCLAdo2
w7Hm7LyspoZYToGVUUILDAalFfiqXXs5F57RS1xM19ppCVmZXHL/58mTr5w8OTJ0+CaHHXIoaAJ0
oKmtqZ0184Xktka28CMxfPhmaDd5/uhfDZ9eSFlCG8QVqUNu14uTtDhDbRQ1RL0Sdkd40DlXsAgZ
LaahgoJws4LY4hIOyTCyeWSQQZBKSs3edh4u/YNQot9JuRsO9R7Q+4QTTqClosdiOOFlw+VfU2Ny
n1YgJDnLGBkOGSpbEBRqKa8sZ6N7O8LsCBMrZ6/WNRXla8sryitYqU7sHKtVZQGlpQOYhDibhx56
KMMXCVlhZCnEnpB/PuwAlpT5ABv5BfnbjN+GRCJWPTRiPrLADCuWSdvY0FhVWbXGKofWVlRQ6mvG
Nz4Hu45nRK14h2j2lClTqL+iBZwHzKrNVnBAglPzPK0J04H+3WTEpvtPnKi+LOFRXDzzhZlsVmKi
xeGuurqKSCwrFZytbfU5ShUABy4FjMU8xpOAS2QFMn7VUdMbKTgC7ion4Qo3wnaU4GKg0BilQD/g
zrMszVBMpMnRUIqdikfF/XzF0cZ/RP6bSHNe17htxhH3UvhQcs4jZcP5r0/fvmvZfZXCnN69iXav
LlsNrL379Nljzz1GjxkzYvMROfk5cGFjfaMJuXVBqiRRiooLd91tV3KJSBESWWCM8jOQg1licVA2
+eoh/gO3qmQztnNBLiYqFKmprAbVsD4pFpKWUIoVn7ZbodtJwmSErTFKbsqLJN5xp+2POfYYJj/6
hNuZcoq30zmPoE++IrxlIPnYcOos2IH+5f0f106ZKgFDv7yekMzMJ3PMAjBa2q52oXnzPqQmwGzn
Jisp008+RMw50wvFhPcgEYWcIEpOwhFFIM9Lw9At4EgpcCxFEvCQBP5DtvMTj2aPTh9P0bTzw6MZ
oQ2fFmNLAV4hctgRhyIpEcOK4EiKyx/ccP2LDFPRIUNQ9haQAAMJAcZUTmwyZC11cWuQajVVtWz/
TUv8MLI7kEpqDvBUhye1xUEAq6a+LpLVQTAvdXL6lkIyIPFoOBsScIIKBh7WzYFweIWv4IRMCfKM
XCgWFyqbK/ArUFmN0tAhBIDExHQiQ4g+fR5LHKI4g9znoOBIBez2+je81bajHrj3PmDikbZWubKK
RNPFF1xCd9EcdtCBoqGDDjrgmekWEMHGVTGStCFjFhypPDuVNhJgUqDBMJ6cHoBEI+AdJ0eO/sqO
PPLYwxCb7JC0PzyB0SntoKjNhth/9sqKjg6pCyAEknUHuZiI2TeyZXXI51DMpf2RfB1KKqhxbdKN
rne2t7lWbGmK+k87SXfDlJQhV8O6BpMLvYqK8Tun/f73V119tSl70JSMqMVZi56HBCrpVZiVnQHz
EQXEMIDkM55NrnRU5kNpNBVjpglDV82lZ731JkLyIIX3/v3vf2M4cr8EJLpDe8l725GL8CiS5jts
EfhCPz1yeCYDKlAB9piW1XW1ayvKeboMJn7yE8lL4jYn6aLOs/UGnthrFNwhYazEDGJPkaONd6D3
OJRnMuOXnEXp0IEH7L+/kt8mMJqbkYJs8/jJJ1bhQnAfB44S6YaGOhw3tCgYVLhSHgBddMMO7Rrv
ngt9jIoT6IrvjOfBALT5M8Ll/04/bYstt5COQEDKcZaakOzREaB68Lwzrlh3vbPWwGDRUZeVCU4Y
XvZmPhtOhUtPYO/rz19pTVsk8xfqZCMebnus9n/uPRn2JxvaQyWXceMd9lIKyrYzbYnFG7Nn77n3
3sZJiBCtYJB4h3LYy2wj51ShKUSYlbgd0SxwrWCEOE/bGKTrBHXBfNIFahA85yvVSqqsFJCIwL79
+tg2ey6iC0hahswBI0qP6/DgeV7Z8BMPoddi4llxpAdefmgXckW/pn54j2oDTyThNEW9iRK0mNc/
NbvVAuUJp2G/mRehV2t5UBAqQAAG8QzwNogU4HzwHgS3l2S4oqIGhxz1pxy2kg0yI9JVIqm0p1vB
Q2NwhLnAHj+6EX0Bh2HysypZBfpwJOKQxiKkhQYDh2Zzt2c2Vl77P9uD2Rxw99ZP1zt/XrPrWUG5
2JlESQUVG6ONYPNQCeCgON/wKdphD6rQU7WHNjRx653cxJViBg6mBRYMscdBg2w1BtEjVDDh/UWL
lhEKh/DiCU10L656BE1CiuSHarE4J0xDNRGBex/6xljBXyOu4aNTZkm4xnwCkrdgGAvnsiODbkEq
9lPTOi+iq+br9DvbR1MNEZArkr5dqLN0yewtig088eKzW1Ks+zd5vbFOO22z63Y3/uV65bgsbNHc
YoVo1TUE68lbEzqGy+A/wgjU1SMOSQ6y1kvriWT496wLIvvSw8dLeVip4GtGIJhsWGbC/gdOxOQn
C6JScsV3FIURB/tDU4VPJRVTPNy7lTr2IG36th5B/Y79pxo2/0Svjjt6KLGi9OK36Zo69k6c9mHJ
70oND6opkjThSRGTvlkibP4DGwST7oOC1MmGNx+z+WWXXr52bVlRUUlNDZtmZG87fhyfrPNih2oS
MHM/mpeVHWmot0AMUoaZxxaLpDXpVKE+BUe6AkXFXql8EnCOsxmZvceap1HQcfNfb7r8ist1L9lY
Xj7GrrcTD9j/umnX8l6uBlc89tVXC/E+BTPbeXEOnEIyv9qqVgqY3JW0rAXRwriw3ftzqY/z7891
OyYSnLZP9sbyU1zP0mdnWoKdBFx7FdGs/5OcbYot1Rt5mg7p0hk8vAw8LXhSgTnQhiyRxa3YGJ0k /q033XTZlVcma7eyXeUff7379jnqqCOpTHniiX9RGT
zYpjcTvRuU5av7Kfn11svd7IznbuRz6/Xb1q0qmnAFIkmm2lLjlR7Q44cvSoJ6Y/Pe+Tj1965eX/
fPH5kUf9iF33LMGayVuCrWrS/uwN7R1+tlZwqo5zvX++t3CIpxQWF/hSN6of/LP8c4nf+gY5efBo
yF6LLB8TTmstk7OwswHp/zqDdkOv5+bn6EECTM/VeVFJoeChTRA2f045RWa2ee7f+aMDNnoUbrvC
c4eQ27viW++yk8m/v9p8f8vGJOxd3pTr1NdRlmwLYSZO3J9MNrOXBCIFVFJwcBsBfQQe7jCLyamE
UyguGC7nq3xkmWtEgU3CS6U6iWTn2gnUiX7W0xL00Zb5fDY0Ubua+elnn1551VWsF9RWvrqLlqxO
uP2OOyieW01NTSj04sxZFIzpfXluFEl54/bet87bfep6qn+Gk9Yt/AAS604BWgv0tLiSMCpAaeFe
w8nB/uM6sVVUcYsB2SahZt7bX2FBIYlXC57HXYbaBWo6gbM95N25wtMdqGzmbICxt4bZwQLS9jI3
pUQbPpXWoiXqhVebUHhmtVvNZlzZVzapcqC6W9yGo8776gjDXcBpvNc6ajvZZ8I+6/SFooKoV7gH
qwu245wEGhqWJC/lpQg8+FJrEDmhPo+FYUSAsRTluHCjzEG+el/BdnL19pxT4fxBGVlkpnvkcyRZ
gq2GG5548glKc5+fMcO2mdeaWW5hNVM0Sr0u9W0EjMho4aBcO3UqoFonLu0mZZdukqBDDaWLPsap
mI5X31rOHdTm0EJVPIKEX41mrbEYeXU+P04zhuAbdAHAhv/kVa10l7JqcJuvJFCGhgMgFedXhg3g
lX+jpfeT2gy5e+B5K5ZsVjJeZXzpWEfBW0IwRAjJxpIlhO1gMohNFkSlezCltp9GQCKigE95CBUK
qDSBX1XSnJR5kmG2ZM3tJ+vC38gze8MEks/xH0lHNqy9/oYbWKPP++ypYmD3SdaD2gt22UqspASL
leQv8OD2ImAohJn9yitCgWjPSc86Q+ocnIhImniK5/GVwYIWxiiPRzjkIJ2qSjCuMHtpb0omkaDs
AMbVFi0gGXT1bPSgQ26AWMr/KjJFGwAWS4FDCMpXDdDkeGsDAnVc5Ba5gxpXG++n2/M8yH/JsIXs
NtFPkwAMsoEBmw/xE/gFVtYh/+ay37AkkV15DLOFhSzR05i3+8EP2AWLOiheveKxIGGbylG+di1V
CDDfmWefpR3u0bMsfPLLUHr17YsLTFEGswJIABUD4KrLnV/i+ENRaAYmIyGVh6bSRnNS+OIpVO+x
zFFWr2KfMBOSmEIKCrYxmuEwaj8pT6QNELJkTiqFlmw2gEohAMZ+F1QqaCl0uv5sKjAH27BWl1eH
cgVgWAiB1FCZNFvAHH300YTSWFiJrJFgpsCRoBvlsSRggRNxQ9U0VZ7aMl8Y8HOs28B7PuZEXqwd

7cUGM4aDNfoglw1+wC+5r5tvvcX2FjezmhfHY8/iMEXYCBolinMweuyYy664/KO5c+zdeIkExeWm
pNr4HDgbsTirE+SCrC1bM+v5meecdfamQ92WP22sXWfhFvYqufn2275avOj5F194+/33eD/61VOn
YKQYAK2rKzzS5YmnG1frrH0QMzyLCSlJoEMygxPmJ6vatFcEVCS4wEXwRpBSwFA/rA1DWZCg2mOu
S7tt1IMkAtzGc7FStIOtnov7yEVMKSwrKSsWVlJbxHTS0CwS5w6KbSl59OgFWoUzfdQmXfg9dTj5
Dv+poyAjMlcQNiwWJP0AcJTIL12+7Nbbbxs7fhxs5za8b8cxGOSZkeGbjzjn3F89N/N53Gy4lgAy
ZT8oTUQFhemUaWE7sncWmw+xTsePzVaVE3iJZtuLhWAvx+j7HrD/62+/9eWihQ899ijM99pbb97+
97+J+bLzkgt8fA+ciLTpIqUL/gt2Tg0fJIHnkHBoBuoO2Zif9dtcxCogHi4hQWLGdktJJIhv6XbC
qHzFmCGHvoH0S2tolFrKTuVgLZIW/GMpEc9n8oj/uMLMoTRfzXitPWseqLHFBJdBz8JTve3Mo6In
+Y++bNlba++aDXx6B4K6eXZmgI2Y1i++/NLH8z95+913fvTjI40D2CMuLxdGRPiZXHTeNV8JVfAT
F0EWZY+qGaYKEjMRkcBgglwOAMnUs+dm9ZOVedGll8yd/8nsN99A8s16+aV5n87/84038FJufs1x
AligSkppCOo5LSJ10djDKbHKe4pFJKq47e1LTi8zIkQdF3mRml+Sw1oWrlCWS/SKlmg6vmpbDPUp
aHsKzs76QcmK7wU2s4WWYGzy5Ml8RclSGgyh/bgQSH63WZiSLfZoxlzCxdR1HXpc9+AP3m7yr0PQ
Pd51wmojbH+slrfeefuV11978913vli44O777t1ytC2MjebnwSv8SWIl/4g3cKXzI2j6JPdCaL0X
3jrw0EMeePihjz/79N1/f/DcC7OQfG+99+6Fl1yML173CGTwRj48uwgPLKFS7okMEE4GTAn92MIL
IqHmJkyY4AfFTJMug+QiNg0wDTecfmmNmHki2Yx445OyUy2Bw5hGtmEO6ivxNZqxBbffjF9wInro
AbkOL3rFEpQdaQHThmvpv1P+C3K6ztkc7fQzz/hgzkcwH9LoxVdfgTPe/+jDaX/8AzyR4SLD+vsO
I7buhNshH8pvWMeItp9axt777XvTbbfO+eTjz778ggc9/eyMf8+d8+Qz04885mj1z7NM/7rG3Rh/
Wrd0xn8sH0SocMiqg9XgQo1R8hjxhnsOp5pftXAhbfBFfJZIQ9bYN+oB60iH4oWgcznBoEeSSbAh
lQlmAQnWIQaftgPw5PAncJ7WH3qYNVJp4XQPPUKdw39d1X/TyGth9sek/oqVGTV1tYOHDoH8nBAr
nrDvPrxx6oqrrtzvoAPziossQsk7GOmcl99iijFKl5lAF5s4VPjbOS582v5BhDhdRHLzLbfAWH7w
oYdY3sZyJ2YqbhfKC48SEmKLPP7oo0ZdVr4Q1NWWRT2x/3qHE2O9FxF+jAyDFQ4jzkK0AkEowaAQ
BtKOFaiYuVQSsXYTRQzqFPXwPN3t+MV6wfMNFGrhKytlAQANxhoo1kVoaxgVDXFCNl9xQc51hYPM
gowEflK5sX71Q+jG+t/2kHfFfwr8qNaSpxIZQVDjumPckIGAM5hbIBr3AosblwoP//Lf/na/Aw9k
2Q5Qt8RjxoKWFbAqFHufSevY9G4TNpfmDZe86vcv11+PhU6FFeoAa4NABn4PZEPA4P0gWubPmyfm
M+q6wie9dO6/daBVMfvwalknxthRZJRlUJ8GlsCYBAMLovV6HKQjxYssVFV5rCQHnz0YJ+oMD1q9
Co1sOeaqVfgWtASfOOlMG09ZprpMcDGcsgnEZbhROkrrXdyUT2Z6FITacPwnJWGbjoREGa36yTCb
zD1F2LWJOSQaMKUUL1RwFU4D3ThWeLt8fvDe+3yFPPIHtW8Sn2hzMIJ5oVem0AOYoiVRMXw0LjJB
Wb7++OOPr/r6a55u4UDtdq0FGYIK/dWa+NpwRHTYAzBbusxtbc0n9h9SjZZEAdEGuoXhUKHDniFw
GMvgtQAZHcdwKOOlGaTihECGdsOVmPE1vBsJcnXLZiBs8Yvlh2/EDn8gn+WIhFrgRXQLoOL/kkRg
5rPDAavQceq1s6PSEEwtFDcD5BaUtZIO+slzRbrwewnKSVf6l2ess8xaxbJtDscLj6qqnps+nUWZ
OCUwGaNCAUEegiywIyf4K3AYBw0YGyNnxzEOVABWCKvKsWrZZ5dZCGoQn6CDuxgn2gpribAF0ezb
br4Z5pME9cxHhghjJDnmjVP6mgpCgdkvZWCnAcbLXQgMv/eNtJ6msZQg2kqLbLhRzBeMaKTy0G60
kUkAYrWtLcRi6xKEhfwMBS/BPDzKJ+4RXKht0PkJQUCACUeKXVC0OkQAaERB3ugGYP6W9dh/UiWW
QXcvPm2oq7Xwh6s3Iaf9+KOPHHP8cT/7+alvvvP28q9X5hbk9x3Qn0KGtZUVtQ31DJvluljo2h9c
opGqBaQ93cJ5DIlZCP1Yp4jOJdSOaiAif/8999gmtY7zkPJRqVr3IlAT+iyFZBrw9b9n/1EZSUCe
jUSx2dlSiGUADAfLVZTjU1YgqFPaN8hq2mSNn76H5JvW9ACJ9gXloQCMOCDyAiKhqVYNk9xnC0rE
IchHTMCjuClIbtwXmnGOjAzuLArXwoLBpbHdZsGO9W8b5ZvUwrbfTzTOLhys3WdU/KmSxX1G8/N5
UwMKiGgfxrh2bC1k1TqFM2Q/YWKIQWMrqkjUVFVRgs1KtcVL17JtzHsffLBi2TLb7ZXqZW2foJ75
312xd5GRiIRmLolsqHTmQWfrC7uNjjY3dqZ/lZ9UuSsYJD+EncpW3ZwzXpUXQE4Sklo0Q9iZ9dEy
pDBF5Ah7d6SnoG3fD8/FhgEA9n3DSJB5ivBjL3LMayBk5mjVNuYQFvxJJ50UfKsROhe3HSWmqSIx
FBSE3jxLfQht9G9y2bkmh7qTrdNxj8766uAImmUYsNnZDIP5gWPFRMnJtr154BV8EDJvfK5Ytryu
ob6uppZiILMqSXuw2IQ34cac75xKpWpqmeXU8bLelgwHac2IkNYyzLmFE5QahgeHdK4/YFAozVTk
Uy8yaX90g37rhTPYgLgxWhXIibDI59VuJ3hOeHiINGxWt8WeHVyHHWnPAWAYgmwoxV006yk4ve3I
DARdvADC+E/7Q/Jdzg6TO93QQIeqxBeGSCoweF/lwOO17qQNNtN9blrE6EZj6QEPtnrwJQ5So1yR
o6aZ7W8JMmKwXj8IxsYeL5AHd4cKPlohPZmkHFp9IU9LvBh0PXvK2oMlhAq5YkTmLRvDwzxjBquJ
UieYJpAkqC9V4nZFHHTwVYFHWUXq3LOmyJz6E7+3ln5oqjbo7Lle83KiiiZGpDItbgnmDII9dKpn
emh4QVUmpyEYNAn+KgYIXvH1oJ1Nnu7B6B+BKUKIPoQdEOwIrdGNfWV8D2KvtCDrxi1p9d+DjQEV
9EFIfUIh7wVLbATHnnTa0sRGD0JLV2g2gQS0ivvoEGwaRWfOrBr0LDyIPe+1EAMh4mOvL7N3rbja
IQ+cF1QpnrSBUnpctrkEgz+65rYUH/d9NmtPgCCTeemoZkzdtKbfxh6IoAqCJHIEGas9wEEaSZz3
FJyCBwOa/c1wus1ikV8NV3oLBuc83dAUIKJKpHklBjikizVgDdLbUsnVBq0ldPwkQvaUndtTs1Zg
+ymkbhmUtJUOmX06hAeFTr1c6UJrezukpwBu0w+wAQYAyMQC7VzB7UX3eXqJLiKBz9Bo4LqRI11+
6Gw49EMMDoWuN6hx/D9Oey8knIH9kAAAAABJRU5ErkJggg==
iVBORw0KGgoAAAANSUhEUgAAAHUAAABuCAMAAAFZzJxAAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAEUUExURQAAAP///wkJCdra2j4+PouLi42NjVdXV8HBwVhYWCIiIsXFxTk5OUBAQOLi
4tPT00RERB8fHw0NDVRUVPz8/D09Pfb29h4eHt7e3pGRkeDg4HV1dREREUxMTLGxsTw8PP39/aam
pnNzc/X19aenp9zc3CQkJAgICHFxcVVVVampqQUFBZCQkGlpacPDw0tLS25ubufn58DAwAICAvLy
8iMjI/7+/u7u7klJSYCAgJycnIyMjHJycgQEBHh4eH19fVtbWyEhIZubmwEBAT8/P3R0dL+/v1ZW
Vqurq6ioqGFhYcTExLOzszg4OPPz86KiohwcHB0dHQoKCmNjY+Hh4evr6wMDA2pqajo6OhQUFGxs
bAAAAJ9+iigAAABcdFJOU// //8Ag20X4AAA
AAlwSFlzAAAh1QAAIdUBBJy0nQAACQ5JREFUWEe9mb124koQhKWAxE4cEvACcA4xmQIHznj/17ld
VV0zPYNg7b2+9/Nquru6RsOPkBC7gHW5H84Iybp+fEa1xj/Vt3W9HHu9LPftcozS3L7W5c0lXJGv
JKv7trxpPlzrDYHZshwOh+uyXc+fy7YcoEGMx3NUxp3EqPWhYR9fWwzsiDtLpgi3+2Hpj29dj8vh
HTtDgWnr8vmRXc4L5a4ShP9y7kpNxkbzleWCCl5+1yyG48v3U5bNftbV23LZ4i
tXg8jJwfxGON9ULI3UQa+0dTw3HZvujOfuwSfllTWU/HNd5EPFjNgow9YcN4/Lhsy/kr2jRky9Xt
bbnEs5Tk2Qwg5K91i9fZPcD9IkY4fizLdkGbpEovh3s8P95rxX/EuUu2drPN5
q2C3myKu8by39evELqQO2nreXJtTNFtNtL/wEN7xonpGb2PvsTZeVHZBy2A43uM1x1tiOXcT4PFj
D+x0GTo78SdRFVXYOUUV/jH0Tq/UgG/qSm1661jDPwhQUjXo17+EJsBcQyqezEAVMQbvgn8WZIEV
JicsUofKCUqYaZAIDww04Z82WBnkyY1VQi0tamKOBnUsxZgJGixhcBFpnNLikLoelsN1wxgqPvtx
DomDYXATC9Rcc4Umsd3GiEgwsGmLUF9WOiua0rb0YOMMl9YQkWkmq26kVrqZUYEHjtLFvEwTibLm
jpBToChK2VTuq8IdhXhc40wUL/lhOa/vvaWsQDvRzjSXH+dEJ8psGnYyTC1cMbAuz5KyyICsxVo6
P8bcC44NPmauC/4wF2NcmBuXWBenyGboOYOxdItT37J8hsLTPugGE+J5IF6h8hyYUud4fL9YxLwsfl
GuveIKpZ0V5JPowA6/KkmuvGiVlNrdy2nlYDXiuw8flmw8BZFReQT8P7y7loa+vknKxKU+9vAyYh
Ezc13HbEMan3F/BChJaAlFEB4x7T8+1WFiq1aXzy/o62iF2UAJDjPdqWuO4G7bgq83JK4gaL+f3V
jD5HeSZCVX9/r/35pjcoFSdlw9n4+Q1mS9bzPKB1dd7I59ubMubclnJEjWMD7+8WWX5+0RYth1xR
C49ZDJ9foHwHzcVXlyXW1ev85JzDDEE0KdD7C8pcZR4poaHolj+/4L1/foVNmXYJ2dtbfFk7ITsf
bzg/hxDP+XY83uKliA2cYIg9kz4X57rr/bRc36/L6X5+/7fr32MPMGHU5iUbnr/7GcyKjM+CQOrG
OkX6Czjz+1PpJt2sytSeaQ3htjQ2Se2ZbDDstDz2SlmLteQsYkWaK2Ut1vIxVybGfg9pmnNlYuz3
0EwazdzveQ/Z8mjmfs8ZjCWPNtozepsM+iTriIBt9k02Omo/3wbysp3wUh/3nbqyI2LKkyt9rl/Q
LucM44i6pBfd6lqEGWJyhXLaezoaeuxI0QrGxCU3puSwtSt9MQ9nZDDstDz2SlmLteQsYkWaK2Ut1/Q
EUkGhSzWrRlRCHm6jqWY9VyXk4aaG2z1qE3YIKRFVaKxRm7BDSGFUwLhHs5HuzPIvpyp4GzNF8OiK
+CgO7eTRFbGLEkBrpoLaSu/0JEVQDYpd6R2Kwg0WNPS813ZlL+6OcYO8HuJry7ZhPBy27Xp1rinX
IL4FXqGh4lTukKjS1vOqDH3OyYazroheK8saYWxUq+i1sqxHUSgrpuaywtqiTUCZLD0XULiXlCNq

K87UFSV3W7lqK87UFS2HXOlTRLe6bkjo/GDqiKcpn6M25c4aats6R23KmSGIbtvLELuHGhXSbXsZ
YvdQ6xZvHoUVUxTLkixjFFZMUSxL6rmiMvWqg3Sb81N8737DXUt844dyOt3i2398+ec9AHTcEcTw
OBX7f1RHqD3eOGDiPe7ucH8Q9wzP7xu4BKlTFT1q65m2gf3mWAHvvGDTaB4rsDN1BAaDGreZurHW
jxi4ZcSNbny968AMsvw5OZ+g/t1V0zdgvUbfUg8/BSTlx7Vx4gx0goIHVOIm4j1A/IiIVdHHz4+n
qHmXCyLHc2YTNXJHaMY6GYrANeLM/AoDPqwgb6nHHVBIhvpZE/H01v/8vn4ej8ctBDzXj7iJ/4qc
K4ceZdziB94BohnqZ81Z96r4yUPfB/rR1N5Xg6ajGepnTURQ85m4EeIrnKcsgUaNZqifNRFBzWf+
3aoz1mkIkPuYxSsMfDQ1UidzbWgEWQ9YpyFAzgtC8DurPsMmx/lowo93wysccZjwV8w7+b1VYfgT
aSU8vwT+5AB+VgGKTF/y41X9Q+Heqjw3Zf4SzprZa0DD0dR/nhyPpuHsD5w/iw/sNaD93qpDkdGg
Bs59NBn8WO+jCbSz/0z2SRPmaFAD57+36szcoDNAjlXBfFVvxzCAUOMe6A3MIl0B8t9blUNCpbCn
+RXGVX1m9xVG4yFi2K4bP37IgW7A46Y79Frjao1VP6IR9+ID+G8kropJ9Q87gA5TqzEANDJlDrJs
dT0j+ud5g0/O07MEHUGWqjMfVv4uL49hiI6GDZD1/7hq5q1ZI6jat6/qzmsEyMG3jI7fvqo7rxEg
B7tGQLGQ8nClw/XVPHxvAlk+LsIqaEJCsZDycKX7+1X3qI3Z9PKag4SdxDUioBhkOVIbs+nVqg+f
V9eIgGKQ5Wg22WoT52tO/d4E2qqIFWsPPQgz2fqPVkVhUiIpNe3ZNaeR/ac7yVT9zAmFJKX/cFUm
CTtBlo36CtdfCED75KDItEFH4LyJTBLUIMvG768KBjGomvGVDmcJXiuD4f4VE2Z2dboD5xSDqhmv
iuurz00/X5XOF9iD6KOp4k/O7hkRpDSS/8G4iychXoKUzz4/QcBz5+cVBpgBahgRUyLwgCz38SRE
8OxK93BVR1GjQQ2GovJgSl7d0w2rmlo7R/zRqvVKZ/5+VSaJ6xrBfHdl8HvaKfNhR8Y6DcEgGtc1
gmerfvuTQ0MwiMb1rNdzE6hnCYLCEVTtgbnhetb//1WRm3rNGX7Rk/Sa5psnuK46cvNs1XYMvwI7
aMnMYAgoBn6F519qeUaEwRHMWo3NVBkMAcXg91Z9xmz00eQrXaW9r457oAey3McGxz+t+vTbmkFv Xdf1H5PCnevFc14cAAAAAElFTkSuQmCC
iVBORw0KGgoAAAANSUhEUgAAACgAAAAoCAMAAAHMJ3jAAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAAzUExURQAAAPb6+wGPmT+qsanY3Nbs7uj09QCLlQCLmZPP0////wCMlwCNlwCNmjKk
rACMlQCMmXeyfD4AAAARdFJOUwD///////81Nf//WVFR/zo6ogT/GQAAAAlwSFlzAAAh1QAAIdUB
BJy0nQAAASZJREFUOE99kglyxCAMBAm5ybH5/2uDRg0rAd6uii1aYxSoLaXUH3t09Kjlu7ZWMf01
mqU2e9XanjzZG/6F59S2uv/1DVSq32w1w1aonsWwXvlXbKBxcd97Wdurrfwr Jqju5H0NXxmIqMRU
Y55A9iMkq2d2yEXfx9gWtNJw0jY+WENKIIIxvnallEAse57csCwm0+VT4vJ9SI7jwTH56OreTnKd
xNtmjc7HkNGGA70MF2VnumSF5GLdJYsRqOSAzgS9QHOB5gR9hIiBuYRYyMVbjiy5eZc7MWexR0n9
dg2CF8lb/AeNTxYb8cRKPrNYiUGms1hIwRH99coVbLft0QHScmswR1EK7smZZdWx3DmaINZBXEDI
wR0gEKCRoHXgj0R9Rzil/APTfA862cV6igAAAABJRU5ErkJggg==
iVBORw0KGgoAAAANSUhEUgAAACcAAAAvCAYAAAEX9+POAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAAJcEhZcwAAIdUAACHVAQSctJ0AABEQSURBVEhLXZeLT1PZFsb5H+cG6YOCyEsYHPWq
M+rM6Iwzzjive30gpe9SChSKSsXBB0oUDEzUaIzGYIwhhJA0TZOmyUmThmTd37cPnTszp9nt6Tl7
r/2t17fWbtsz/+M196Z9KzJp21vr2leo2o/3btrH3hgDR4a12A0a0PRlH0/v2DLmmlWtSPpvB25
ErVIPGOXHj1mOSuCySmbanh2Ip6zYGrS2rw9zwaiOevhQW9s0o5cTzFTe2s6Lxvmcb/nb2T1PesY
y9m2V3V/2yqNhnWmcnZilI2Q7R52AyeQmbaTsaQF41l7WNm1tq5k3r4qFi0SS9vBaNqWKlVrS6+s
WU+CnccZiay9rte0Ozs77c08j9353W2gLWh8ZHrCPk1B1OR63U6lpy2MDuFs0QLjWeyjS++FEi1O
J2fQfsLCyWk7fi1qn0/MWerjK+tMT1ooNW0bHlt7LAjzoD2et9+Wl8E2YV0sCCcKdnxmxgJYaNmr
a2Ldgky8VWlYF6sj8SnrQ7MAC3uvZ60PtX+vNqythtgmgJt7DdDoI/U09I2aOFi/zrz+Ld9NXrJD
E3PsgV0+cJf80ECSTLCvu1X26n8ubDTZheEc5ntQ66v2Edv1JDP23ULJyeKvNRt1X6Ls6LHqPepH
CIpArGABvDKCEmWP7YVRE7Xhs0bN/oWhI5k5u7S4ZCdHx6w7O2U9o2nbRmOv5llb2dlx2joSebtQ
+t3O35y3kQTmIURCqSk7nkwCAq3fs/WF5TWMPGUFfPxlrmCfYsdwqmADY2nrjmacNdoU78FYzj5L
5qwzXrBD3AeAcSI3Zd08C+OAOnHQtml13IUXYhk7dT2G5ElLVDwbffgQj4E7MenM5ST2sG0vwdih
6B/PuJcRlMlXK4Rzjq3B+JF8OTaWtEPjkyzIsmDCD1gWKdTzL14iD4wNptdJiCYe8bjXfw15xOO5 /46gkOouIBj+5btP3tCv71oWkfnG2HOR7564bwWPLnl
gcoE156LI1ZqrmKGwQM3iB0h4b6hB5KyZ1WebTK+Lc5bBEsGUjO4Ikv8F+w0fnsLUuWFtm0IuYsv
IUSgotbB1m7YYYfbI8ouEiaI77ozeSwONeC2gzCWfCuyGhqfsFfaHD1Mkd4SKFBVYnGxvGV94ykC
YIKgzVsH6Rohz4+RnV/P3rT8m037dumRJV5sWIBngbjCcMa62WBxZ1vsRp7JKYTZLrtcXlu1s9iq
A1RhskCsUqzVLP7inV0sLloJ5N/P37Bj+SnrTM45QjmAFscmZu3KymN7urMjFa2N/HU2CUPEwfik
nZxbsLP5ooXSaRuIz9hva3/Yf55u2PFiCSF5CzEimSk7nEjZhcW71kO8dWKCFcjW9zIm+IjajrJ4
EWZEyKY+smmhXMYZaWvHBAr/Tjb8770VO4o9e2JZtMnCan6e3K3WXDyistkmFgiTTOHEtB2EOK8+
eQh7ZWD1KRsm6q88fWaXbt+1wVje5dIh3s1jql4hjk+7zF3c2VXw4WXFFje9iaQVYb4hJoVZFMbg
IewUTBdQ31c1yAjEpnEGm7NZz1gGJ72z/vG43dupoKco3sk1Ew9uI3xnr2IV/lUJJ0WawgKCZVNt
XLeqYpC5qps1zOXh2TK2c3lD+LSJIXU53lVwowo3zsDiwVZ88eVi1VHA/nP33lGzP8ep3CJ2/69b
4S9gkk+sCGjWyAZqqfjczfc5Xd9+pmk4df3U8QXpYjGXhLWuGkHvLgn6GzH4qPx3+8hcHrr/vsgG
gkTnElcF0ZajJezlVJRpqBfcOzNpjdtYwgRVIvZ3aPGC1PMw/PO6Z58Ra8V3bxySGvMdQt5rXZPN
ZBb9d5XJSUaC627waoMJTVw2+/aFDcaTxGTW+gni9NqKy/NdUDsio8Y4h8lMUrMlyOnEL00ReOqW
I716iaVPIAZlinK5F4FXKYG+DetWc3VQNCWkZIQ85rMyVE45aVIS75TrpBBBqkBNzFhHbMbaFcAI
7o5NWPbNOytrLrs36Fd0uXxVTXWQ6rKHWeHVpkVIMXUUXUS8Ij9Cj9QznnZEqizoTs7af27doe5K
EHZDhkzkaoYHo+4g+b+379Bx5EGBEOzUE52zrFex4cujdvzKqN3aqzpk4rmDoPyCjV4R/c5ESnzZ
bJN/X2az1onXxLTaPQhDfHNjyUYowan3761U2bGjUP2AbKi8ZYjvRsbGSUcZHQfUGhW7lpumFubs
gGxE4Y8werHZd3dKjgh6YZLJ7U07BSPrebuIlb4xSO8kVvmpMO3iEWR1O0szeeHOHRoq6oBUhLMG
R2Ou4N6r7trF+SW7WipZbPc96ouWYBfQyyTf3rpvP6BVXcKk8PC1lBP0w5NV66ObCGQmCYuUnZ8s
2I+lZTs6FreLSw+p7nQdoG+nxTtE/bi49MRGUvTVIK+o5ZO2aklE1Qdh2sxuHZ5LWYi+5tzsov22
8cK+ub/qiDOcpS5kChSZtI1tvbcBUIZoG4aiMdsiUyBKhI0nHY13YGzZLknTMZSACDF2hKakO0az
pGqWnrXOsaylvI88S7kmVCVzOJokI2ANjzQYiINEXqSAdGl3JsaePrFPyYADaUW/P/qIv5u03n2E
TQTDd7CZwkRUXyUb2hT8QyAK0gqp+qi5GmZMUQIzlboNj4664jyEaun32zax69kRkKjRD1PEQ8wd
QXiFg0qb8A3xpx24XZS8o7RPya13rhzqxJHa/EBPkrPEB1SjloZw1M8rK3ZKdYPuQAVmaCyFkqjZ
oBU9jDCdN07imUt3H3KSIDz434mduqmX369tYCOcRKHpAH0XAs9NzdvZwhwpNoE5Ui4V3RHnyGjc
zs7N2sXFB+yOLZJFxxShNJ0+anTwrBPbqakPkfgBwqITLS5RV39avG9HYgmrqt1VaKTvLtuVhTsc
piaIsxyNDJ5EXXnzEN3iIZ714Tm/c+QXe/WwyQBl72LhphWerICMdBLPKjx28cY2Ba7MqDqugpJ4
J2ZV2dvdq1EKPauRyx4I1MdVYZoq8aXS6Mpdnch1vESIKCXEoaoJ/jNXMv72q8rgyhwC1CI092uD
S3RPFK2Xqp2OdcGpxXrmBs9VH7Ta/WrOX96zxq3lnatOEujKl0huf9L/hf1juMX+UBFRhRdiNYVu
yGiSA9s0dOhydUVyNdCa4TFPB17XjDq5+4Ad4v9ffh3WAoSIdAVQIPyJWuSD8u8Bgqk0fGE+z2rI
V9u4YFenKPdOFmNzgWNolgwgUA4YH1Van/V9gK2rtR/R5uC5b33+vJjcmu+24ku1Xht7VEV3cNx/
Tkdpj7a3bGbjpZVef7S3BE25RvvrlCZm+JUU/6PgQg6ANHyrsbMUBqi73LMWuJZl9NE9L/w5EoLb
5cJ9wQ4Q/yvE7Otm2TZ4f+3eA9IoSfKSSiT8eZL39s5H1/uq6uxQvbWH6mv9T+8gC2UdKIWVgO3v
7U43Dhxff42jFgJ/IdqxsMaQIwRPHvpAv3G/VrVz02LmBOSQo9jQgENfQYhBxwM12Kd4Xnj9yjap
w74b9VHCIsRpqb20J+8ALZC6fGs6cCwQqNZDB1IveaDHuEiCKmijQ27+5Ws7BfX10kHowBOCrVS8
AnCmqqLqlIg6QLnVaUB8K2K+RrF7gzh12DXAwiw0V1WsCf0ImItLWeUvlpMurSOc3x8KFZgwd41b
DQm9fOe2ncrnrZtCGQKMqkFnihJDtQjr9AVQNRvtANJpTSWok14gyG+A3wjjCJR7Lp21F+ylw+qO
SwyBIWlIptbVShB3SHDpLBsLPb1To7xLQ1G1NRZ/lc1xqOJIA+XKIp3UwUiSk0hi1vpT81TnjA1G
43b+5k3LEQZzuPzmbs2KlZqNv3rNOzokDvoHdC7lsCuQh6ijn/P7CAu9BuQHb8fFdQ0qlidlRYUU
B19cz414qMbEbb4f1SsWff7atRPduKpDHZEs4IoNQLk/AMj+6LT9vLHOb9yOjMfs2FjMzpAYX1yP
ub7kzFTe5tisHyAdWLhDyrE2jKIRznM9gP5m4XcrkdlbGMPFERzYrFNQqOVtqh21GgcqhNx8/tJ+
pHs6JFDElU7jkQQWozsIp+cAlrd/UdS6ATaCey6vrtmnV+P2LY3UbH3XjlGC/03pHVu9byMAGAFM /MU6BY/TZ4oKKpkkSVAhQEujg7qahi6seyabtxI9w(

tNOhyGK6d2WbDQcBXyAKdIL4imZ1vlrlWRILZu3XB+v2y60FG6EJ++HhPfuuNG+dVOsQoeDaTKwY
JF7VCEdStJQo2gsF/Xr7ti1sbto7Yk09qmKQzoY2AqBCPDKaYYO0XbhdsiRxdyI3Q7ZhKQCFKf9q
RASw71qUZtizvutJu1Qs2gPa9Ny793aFw/7Y8oolnz2nr1i0r0u3XeugWA3FC8QtSrM+ghV1VO8H
1JWnz+2XlVUUTTiFlqscf0UpGIuEUJbs2TvS+fBoCgFqv/Kc3fP2eXHOfnj02C4s3Hfx0ZXDgpkc
YJPuWfrttp3KFq1/FGtez1gf/cm5pRXrA4woRNbXUSqA1WV5HeVDKHmyMGu/PV63Lwsl+xQrihMV
KsM0WY9rZSuTA0oM3OrT2XuyVSwfkKYsOIDgA8SDwJ6mZfvp9wf26/NnCIq5Q04oVqR7nbQTkzN2
mopwplC044UF16AGCIt2wAWIqXaUEsguYvHc3Tt2+dWGnZktoIDOOtCNuNFx5CRJlLBlkmEHr/jn
P2JH7fRHrDdACx2hndaBRywfBqi0lfBuFh+Fz65u/EF5KtkgXd1BgCigg1gnDL+FAdtFHxp0dEM2
8nuIPn6EUIm+fW1fzEAlnD663aFK1uQsgIcCzAvzOwy4+5D+LqFWB6ADJzr5ALhBgaMMBSHRAIkQ
JGhdIBMbPQjsAkyEM0F0fR0ObNrlxyvQTZS4gpjJ6gjv1fP2ALgPwKdyBVtCbok9jrKxWOAgluxW
zJG1ncgMqKIAslPgoilbKldp89W0qqGWT4m/d/DbEIQaEcMzWaDCbnCSIXiPISixU7FfVtc5DqVQ
ZNKdZKJP162AhoNYWrE2DJ/9vLxsU5VtEixBqOgsBklPFyxLVn/Ge/XQEVUVqEUGUMmLaC0Wvlej
1yPE1BzQbMLKgFPMHYaPQoDrYBwE1AALTufnXTZdf/MGUOI9CBih7XBVGCrojgKSc8iPi/dsxtu1
a08e2ghHiT7cG0gXmUcSKFRY08+xLvb8jY0+fmlnircBiTzCoxNC1ql/mIPm3WqdFFXDATgaIipW
w7U3g2wSwkXduO7c/A1HsvH1l9YPhwVJgsD4jDtgdnA4crzn3M4ApGN+YvQAConHNHR8EXW4xJAy
WD+E+3qx5s9QTrZSsfM3FmyQdQqZfrJ1sUJbJZ8y2lRD1Z9VQXvi8qh9Tdbldrbs0o0lGxhNEk/7
yYFrPxmH0akQEVEEQ4fUIFqHFZ+u4MNl/D9IOES4dyM+x+AXkI7fpAQAwxDzYY5M30zesOmdul2C
W7+Mx2ydQ3LrwnLqR8zKuHcTflnlODm9smaJ1VWLrW9Y/AnWW1u3KKfC2NM/LEa2xkiI2NOnFife
Yhqr3LvBXP7HtU6/rIuvbljiyTPkMOC2+GPJe2ZjD1n3aN0Sy48t+2DZnmxt20dcuQ3fVmmjaE1V
+P0OVZYU0Dptte7rPKsSnHV4p+G1hlKcTow017FLnYSaBr/dhi/50n+989twv/OtkX2S6w5CujQP
OY06aQzR1ipNR7xluhFhEPOqxW8TMAlR0yRQupDLM7+Vcs53QzP2hXP581srNOOf//95teT4b5y0
v8qXdn+7zP4HOvaOC8A8WN4AAAAASUVORK5CYII=
SUm8AQgAAAAJAAG8AQAQAAAAegAAAAK8BAABAAAAAAAAAAS8BAABAAAAAAAAAIC8BAABAAAAJwAA
AIG8BAABAAAALwAAAIK8CwABAAAASf1bQ4O8CwABAAAASf1bQ8C8BAABAAAAigAAAMG8BAABAAAA
kgUAAAAAAAAAkw91vA07+S7GFPXd2jckMV01QSE9UTwAQRcBxACYALnAAwgNjbCBISMMFRUAAAQAA
ACMBRwS3/wAAAQHU8EhRFOWMyTS/SJVu85pimDppGjqlTWtclJ2rwI1kAAABArkSaxdvm1LaqtNB
tc1BWwSJCRAACGtQUWCZRK6BFEQ/0OJRN72hcNAHNNwTdOqpLC/aWFIlh/CjWzOYnSR9r8ktlyEE
ClICYhoSlkIBAxZygkKoAAAAAALmZMgDIAAAbkX/PBiE7HGsJXgvif089TCW6PJOPTkYumokTNod
6dHwkJD1BkYjfLS0Zv+HPhmvoaJCBV4aecQoTBurhlmZYMBm2QItAaRBMpAo6IFXyVdiM+zYYw4a
REaWW0DnVSwsHxsu6usnsMy5QCcQSihP/7wHRQFmRwji40SdNjibnsQzvwc8odCEIOMEEDlllihB
ZmoVAfraSQwhGP+fLafq2aR0t5MERH3mmflAh7GEVlE91IAXymHvItLS0SBl3XRXUwAAAQMX427P
9ghxCIAaFrhCheELXCFrgC9GyT2F4QoXhC+HC0Emx1EyWnw8Kk94URh+0adFFBwwhBvjMJFHugfx
4etGm79qIJ0L00ssRI8ytJb6+HL8ezn2kiGPEvcxGlYI3bAG40HM/38kg5p4VVrryyuEbXCNK/XW
5rKh1e67FeDtZou9usprA43wApGL+qBjUsO4v4xfHYnVtcQq5qu6MxzuuEp4V1jG1oXNso1LGiKV
L1LGRWcmT4fKpRY2iQlVTvVvpyB8JHJKmPH8KHbyYqWbcgLkAbgglCFRmgQU5jV8dKRvCAXOlKMq
CvVIaYmkg5VjVAnMsYye/ylL0aCK6gFeNmn2Nn6YtTuuaHrj1R5hGJZ0xD7+Z217QdtbfZE9I6md
uJNew7gh4CBQy7onqNB8rzW9PyksGQKAiqsv1mPn16ZIB6PgrNuZ9VHLR4wSCGS7IsYXJDGEwelG
cdZQyMaiFH1MmGqTXJNZVo+pLH6DdYlumaD2Cft1U6R7jUYXqSjpMTWX2MJ0cyV4T0PaCT0JJO8a
JlWhkEjxErVFDbV+JHxejssDsD8k4RPKM9/X6VJzSI+7X1pkza1vbXVQtdmrUI0jXFth6ZGQERel
4gRDMDiXbk7ykV3p/1L5OX/hKYyAZEdAPTfUT59rFEyoXVdBlJeSRhQIesqKoDUjBOnKi8HalRR/
Wrq1LyqQbEGdG5DQdanj/y1DTnKvr5NVwJ1USefeWQgeAqOg3FA+VRRSlIsIYaxBL7xtQ3+rZlBm
OgaQUYqWMBlAjYsy2nbgcIRGNEKcKSjGiFqh3zNQolFGfbixbxInx0JZaPrn7BWaA/GtgHnCUyip
o4Uja8ioUO5G9mSKcHviqXFmXy0lzLaL/+2q4sonuIFOzDkku9BxT6B4kDiENcRGvEAeIAHqJepC
VIAH637RhBaSQbkoaloMslDzCKO3iNpudq/f+/7jJHruS2qfl0KQNCECN6mLMze1aIW5ZsisozM9
+bilujcspLwhpZzVuVTY+S2QW0j3pf5m8qpgcQhrxAFARhmhROg2qAvoAUhiZsZlF9WbHOTq2Ps2
c1Y10vUX/MXcSoQgUYRi9tDPso7TYotqJdqWnXohlN5tAMyorCkQzohYp0huRCn5g7jb8LxAHiAH
5geIBxp6BKgip+i9XY1lRxIAAAEEsCjzN92SSUChFgvCf9QiiM5Fxf3I2ewKfuJiWiyHzAh9YykQ
egw8YjJ4AfgTV1ZKgAAIAAAAAAE6QhAAGMYCRQAAAADLoWK2ACIhqIhQ1e5Oa3K0GXRszoYKAhgA
5pX4cAIAAYABgAQACAACSbi1W3Oz5seeqprgDsUeAyUxYAEwAIAAAACAACngAAAAAQsgBEIX5NhA
AxB4/4AAABAAn7VAwAgAEAAAAAgAgAAAAA==
iVBORw0KGgoAAAANSUhEUgAAAgkAAAJlCAYAAABQVGHZAABez0lEQVR42u2dD2SW3///3yRJkpi8
JUnMTJKJEkSk+TtLSOTydtHJJPJRCYzmUiSmUQmySSSt0kyMpNJIjOTt4lJMpOYJJmcn+f5Ovfv
3GfXdZ3ruu97tT+PB7ftvq/rnOucc53Xqec17Xdf1hPP744w8+fFbsBwAAivGHLxAAVnRnp48D
ABQXCRhPQCgAAECCzcRoAkIBAAAQCQCIBAAARAIAIgEAAJEAgEgAAEAkACASAAAQCQCIBAAARAL8
TiYmJhAJAACQXyR8+/bNnDnt3zmzYsMGsW7fOtLS0mC9fvpS2f/361bS1tdltdXV1pqOjo2x7x7LH1R
nj59atauXWuamppWhUOKpaulo9P5Scs7hPdqj7sUHDQiAQCgSpFw4c0F0ISQu/fbn/Gk/ly5sdso7e
cfbsWXPt2rXS9lu3bpmTJ0vVwJfd+0RPwvTi/XmkMPvWmZ8O6N+HaWLx9SN9zL20a/xSNi8ebNi8o75+fnmyEaf+
97fr/40bN+ZOn4fe4Sh7Sq1ZtoP+WcY1NVmm3Yx+lwKB3U1zzZOTyxwsvm/m+fRRtg7FKJFVTsOz+tw
tsPnx48fdjZEx2toaDBjY2O5O5ydN2ZW1Qd87BaeOI7/xR4P+nVvqNFbMrqrH2tJiQNiMoy6oIH/5hXHj2DQ
KFHtxqGEKy4Dw+X1S1zdCnSuuUVMVoWVQZJx6VVOw5tChnlhF0d8Ozy25NoUxmLa9Y14iYpAUlQbl6GTxYUD
RhrzG4SfwVl0xXY9fcvnlgWfM0SNuvTzc2mo6vhdoJZ5wfKwy/gUeSlGMWcXuUcqsE9/P+xCJGEUX5/E9Q4nN
1s3Mm5uMF8bRGsCxWlfOBwNKXdUkL7IwfxNCmJnk5uWh8KqRK2jeW0aixtBhfa
1ssa5y8LnxW6s89xqaWT/6gIQEF7C88MpZbmMFeiR3JqKPbBB1tb41F9wCJIeHe4hUobRKK/fCpL6ypbvN
3A9wqX7bNp8RBZOn8p49DK3xpcBmfz2XbT9m0JC1hPTqZ4xSqEWGIiGaoMJvBdfTK3B9fBy2XncfR68UvBTFNrkBVw
hc5vqDzv/Dqv3FrKs12nEMgUrqiK0OpLhDuAkYumKNc4b6iI/jWahUeBFmfEoY1c+R98pQoKcIrvi4anMMb
RtJibR5sUwd8yurYu8uo27fB/PCdVFrLFOi8/cbunBHBo2HBZj2w1Ai9XYVpEprc5YX3M3bVqpKGL5s2Z0N/
KUx4I3ou2R0dxdfLOKkjeUXd8vyYlOafqiJDNfrkiSsf7yydMGrjOXN+8hfm+AFXWovrUNz1NyuSMvmFNGw1
2TPRc5nUbhU2AB4GnDd7sPJW6PyuqnK7Ya3ReMr4khchXfXDN8fVEkvDd7RHpV88mDJA0m4RoeYDr+ZQYjVcSzodmXvm4sE0m
9MmZJNL12fgngJxD5Ml0ti9sHg4xO0jy9GAo0/lN8dZWZ1nLffZa99wG6BhaFw+Ai36hVlT4RBdZxeYeD3Nz2
p/QyamkQibzU2Tl2u6X31qx28+jqT1aZ+AEL8B2ygZ8w2Jy2dmc1L3dhGwFRzMBo5Ncw1/Xf3d8ib7Nb1KEt0vjv13
XjMbZ7K2Z0UKYsmXBkjuJ5d39PSsBY6qZ8tIC7w0yRv/+ZtX8lS3d4WSrPr/PoKRbNyRfBZgV+8APDnn+
A+gqN3ADiTOfHvvT1wvpqe+cbUP/kIE47Hnrbw0kbz+4nKN7gSyYBNcZdt1zOHjJrw7GdJVOMtpmMM7cFLzsp
X2AZYeTV6RYgLGmzbrtYRcz/g7wpuXvWxrh4JkApnEodnH3Udpcu0mUpc6YL1W1Pc8Ko7dnrPHyMjqbNT9h8Y9
EvsYAxeCs0fmBsGOzkF/cOl8nQz3FWo2BfAMgmYC4ZjB3P/GeStvSyfsJXPMiRfh5XlKWxZUMz7FYmyAp8ZDZ6k5
NjmfE3ZOmGOcxP7cwHvmCyLPGzYC3Gxr06wUZBhANQmL5M6F6x4ZD1HyRd3rI2tqNI+SHNQBHbEqWqkL6cmd
bvJ+X+1hRVXqXDmj+DUSAGUM9Q1nqMuk/ZMTrqeUfFqEB0J/Wz8b+9NPA6FkCYBM7pGYwtwlvwlZKgcDkRhdWCuC
pOlyD3/Ra9hCqyijd66rQR3tp+ilWS0MY+5wWdwKSPjLY8/mSXwpGsAw8dwVUT6rp3/L8cpRMQwnDTgfNt8/L1+
fZIefIZNBmrv//LzXNPuPkzoEgvdVrOmHsMxh8sHcH2TkNdjGg3mXG8mNbEu0pcYHzZ7oZLRvrxeQ2WD1V2h
Jml3V7C/LXPTsj27Nx8X3Ojhy0D+kDsvsMOOmlLZuM8nhvOBLehBcq3jdTUNdXrdvA0lEB4zTv8i0KFhqDPk
dhhQQfn1Vqs8UNSpjR0FIbLpNmCcvnZQ1IHHx0p0nPtnqHNbcB8AEiRLNd62U+G8/+e97k4Tm+dvR8Zc0qC7jl
P1ngwTfA2BU5/YWRpZ9Km+JRbxYUEFgJbaeWQAdtEPiMzmnQ6aVLoN0Mq1M+z2pUXVhXl4sj5z1+iVpHQDDGgh+
U7p2BBOEF7mXn2XAYoo1CyaFIBIQ2rpiO4n5yGVEYFWK+i0FQhSxX8WTY0Z30/ry0u+WeDSgsVjv
dBCwBrBA7eyqeMRZYGcBfeFEwjiT3XOZF/5r2lRV0l9HUBQCQ4FmTB6yXPZpq+2OuvWNFfXgSTtXBvP6l
wi3TggoScc4bwpDFGaJO4nOmIB4VCOLYd+vPHpSxbpfOf4OOyhJ0aSu4WGN4jvNqyt7K/ow/qTcLHYEdgMN
bHzkzxUDpIM/WNNHOeMBIQ3u3RP3PhTYZUWdAjFpV5qGqzlyIX8bjhkd3v4Dms3sMPcP2ZXDyPh2JUTfHCq
aHd1t4u8VP3TrbF0awjLkkvHvhLaY7j4hTjJSbfqYYfQE/V3uehG3Nqk+qYgpRHlUZDm37LJJZNbwMrJp1u
4dcnjtL2Twj6dtqsgdlOTutnRkn+5kYBQEROa5dOEl+F2yFfs6PY+6y0SSyBPj2XhHsghT6W9fByWHYw
tsDdOgEMR/2fhE3HHYnXlnyCU2j8gV3wHhb5jJJuPD4d72n6TPjEoEnFZXK3b46CJdpC98FD9R
AYFc6zZhPu9WDb1O4Ll4UrKxADaOZuZuRqMSJO6MVJt3qoJ7tKJH4zwojhbU0VrqhAuKSiAA5TMoNpm
NkzSNbgzjAB1LG+ssZoyggWvT8o0BN5XvzSDpffsb7r07Wr9lJZeDJ2kUnLiG3Oi77/XPWKDPfq
U1fOiYF7J/M5+xxN+kzhRoIrDvP1nlU0Kl0VQG5XcDDJfxA1aKwaEzA5VlxKIDV2pZvFcBlEixwmMbbnNhSXn8
GBzNKxwh8uo6M/QPRYKa9p/+U62NQO
Hpd0TZ4bjeg7Dg7b1TfQJ8w0VGwfV4V9YtMRfDVF0IjzfZMvXIo6MbwH4Y1qk2YKnkt3KiFOt/P8VqUXwWZzM/K
Jl/sOzbXRZMAzfMNRiINKAoYiwbHqG+Q2PmDd6AgEjKu+U3QZt27c5r8uTlAXz+Zzb3A7HSZr0aRpUvVZQfXkeJ
SYb6EhYDN6AsTmzsGOuUb8btlXYVdH/oGmg5F3q2Jd2HHO2EqAL9MjJ0DrHI6E4TOk6/n+CFdkuHU8hXn

2zfWRxAJAAC/SCT4swBJxjzcrjceutcPu9Gl3giYVyQ4B+vQKDx2zCwHoFGuX54wvyQ0ei3iXML9 /ZkDObKmpqbc6eWIw7drOpSP8vPxHX9ILfNKqmd4
H9HmzTMMFJTTiR0zywGEswxhfkLT5hoFt7a2WpETO17R/cMyZKXXiF/f5cS7u7sX5BMugSS1d63y

qraelfalavsIIgEAYImKhCRHUcQBxJx6tSIh3P/evXt2BHz37l0zPDxsp86zjld0/9CpxdI756zp
+ubmZjutniXAYlSaVyX1/FUiIY/wQyQAACxBkaAAuXC5wXeSYZrp6emy3/bt22fXmR1v376tSiRo
atovz+TkZNn+Cn6bm5tLLU+Yd5793717V1b/bdu25U7vMz4+XrZNbeunLULRvIq2i6ivr89cbqiV
SIj1EUQCAMAiiARFpWst2DnVSkSCAhcVxe4C3vr7+63z8EeBLpjuw4cPNkAtK3BRd0dUIxIUfHf1
6tVSfkeOHCnbXxH0LmpfAkIOyN8etklsf/1/9OhR8/nzZ3tMBU36gYux9Bq9664EEQbsqW1dEKY+
+q72SaOavPLUM0RLE1riEC9evFgQuFgrkRDrI4gEAIBFEAmKbteo3438KxEJwt0CqY/ubJiamipt
c85K090SD3JiYT5y6ro1T7csKgo/ayYijwO4fv26DZ5UnsrP3390dNQG7KlMcmoK9PO3h20S21//
6xg6ltJIMPhBeLH0Wh7Q+r+79c85eUdXV5cd5StvCSx3Z0ES1eSVp54h379/Ny0tLTaNjusHcNZS
JMT6CCIBAGARRMJSRI7Hn64HqKSPIBIAAFaASNCIX4F27v59zUr4AXcAlfQRRAIAwAoQCYqk17MN
NH2sp+ldvHjROgKAavoIIgEAYAWIBIBF6vQ0AgAAIgEAkQAAgEgAQCQAACASABAJAACIBABEAgAA
IgEAkQAAgEgAQCQAACASABAJAACIBABEAgAAIgEAkQAAgEgAQCQAACASABAJAACASABEAgAAZNtL
jCYgEAAAIFUkYDwBgQAAAKkiwRlRPnxW6gcAAKoQCcDIFgAAAJGASAAAAAEAkIBIAAAAQCYgEAAAA
RAIiAQAAAJGASAAAAEAkIBIAAAAQCTQ+IgEAABAJgEgAAABEAiASAAAAkQCIBAAAQCQAIgEAABAJ
gEgAAABAJCASAAAAEAmIBAAAAEQCIgEAAACRgEgAAABAJCASAAAAEAmIBAAAAEQCIgEAAACRAIgE
AABAJAAiAQAAEAmASAAAAEQCIBIAAACRAIgEAABAJAAiAQAAAJGASAAAAAEAkIBIAAAAQCYgEAAAA
RAIiAQAAAJGASAAAAEAkIBIAAAAQCYBIAAAARAIgEgAAAJEAiAQAAEAkACIBAAAQCYBIAAAARAIg
EgAAABAJiAQAAABEAiIBAAAAkYBIAPj/fYsPHz588N4QCYgEoF8BABSyG1gTjDnQpwAAEu0HFgWD
DvQnAIBEO4JVwagD/QkAAJGAUQf6EwAAIgGjDvQnAABEAkYdgP4EAIgEjDoA/QkAEAkYdQD6EwAg
EjgZAL+gP33//t3U19cv+P3r16+mra3NrFu3ztTV1ZmOjg7z5cuX0vaZmRnz999Q2+3r1683LS0t
ZnZ2tuJyPn361Kxdu9Y0NTVxvf6msvz9/IBIAC40WEL9aX5+3pw8eTJxn7Nnz5pr166Znz9/2s+t
W7fsvo4jR46Yhw8flrbr/6NHj1ZcEgEZ8+ecb0iEgCRAFxosBT60HDh82HDx8S99EMgZy/Q/9v
3LixzKknOofosLl26ZDZs2GBnHnTsjsx8lsYe168fn/16pXZsmWL2bt3b+n3np4Znz9/2s+t
fvz4YWdDdLyGhgYzNjaWqzpx1MbnD9/3rbD1q1bzeGmYFl53WzImjVrzVrzO7du83IyEhme6SV/dSp
U+bFixdl+R47dixaJ78siJ/J836L1SXWtnnSAyIBEAmwjPvT8PBw4eFsBSJBzm/hTIL/0aNH5tCh
Q6nHunHjhunr6yvNPNY+fds6u7Z9x7tb29trf9PSysGDB8vK7C+GPH/+3GPH/+3OzcuTO1Plll1/H27dtnt2k5SPm8e/cuWqci
IiFWl1jbxtIDIgEQCbBC+lPSPnKYWmJwjurChQt2hOyQ09q8eXNp9K//nSNLYeuEncLEcsxq+KJDsQ5F
RIl/0heKX/CFjPAdsxxouL1IecLjaUbBT/PmzZuycmvWwTnwGLGyy0nLECsxq+3z1KmlSIjVJVa+
WHpAJAAiAVawSFCQoqa9NTpWYKNGxv5MwokJ+xo3I3Er1+/XhazEOILDH/kXUQkJKUPlyr842Qt
f1RSnjA/1dvfT22k73Kw3d3dmfWJld05agmXz58/56pTEZEQq0vRtg3TAyIBEAmwgkVCyOTkpF17
diTFLGidPMspFnVqsTImOfYNyDlgGam5tNZ2dnIZEScvz4cTtz8CtEQri9krbFdiES
AJEAq1QkPH782LS2tpa+h4JAIkEBbmkokC+c3vdnJioRCcpzbm4uNY1mQNKm5ispz/79+8vSSDil
lXt8fDyzTrGy9/f325iAu3fvli03ZNUpSyRMT0+X/RarS6x0gpUwEO/fv7cj
Y607OxTUJwemoDY5La2fK9o9DS1NuBgHfeQE/eczVCISlKcLntNH33WXgkNBfloCELpbIAxcLFqe
Bw8emKtXr5aC9RS86e+n/HUnglAAY9aoP6vsClw8cOBAmcP+77//onVKC6LUHSxaHvK3x+oSa9tY
ekAkACIBVrBIkCBQcJqLSQgD8hTMKKGg0bc+Egj6LQt3y6E+CoycmpqqSiSIrq4uexueyiBH6O5E
cGXUQ55UBwUq+iKn0vIo9kJxAro1UMGF/n5aatBxNFWvYzrBkEZa2VVm/xZI/a/tsTr5ZXEiRWXR
+VNZwjpl1SXWtnnSAyIBEAlAfwIARAJg1IH+BADYEUQCRh3oTwAAiASMOtCfAAAQCRh1oD8BACAS
MOoA9CcAQCRg1AHoTwCASMCoA9CfAACRwMkAoD8BACIBMOpAfwIARAJg1IH+BACIBMCoA/0JABAJ
gFEH+hMAIBIAow70JwBAJABGHehPAACIBIw60J8AABAJGHWgPwEAIBIw6gD0JwBAJGDUAehPy5SJ
iQkaARAJgFGHpdOfZmZmzN9//23WrVn9q9fb1paWszs7/Gk/+v/o0aOl0q9Tl8k
586dM1+/fuXayEDnALsEiATgYoQl05+OHDliHj58aH7+/Gk/+v/o0aOl7devXzyXjWH
Dx8udByJg87OTnP+/HlOxDK/5rFL9FFEAhcjrKL+pJF+1m87d+403759K/37+q/X4e+vX9+s1WW/B+3y
mE2bNtfOzo6SoJi23ZtZ5vv372X7X7fj/b6enp226fa05Xu/Bf8cM+jMpa/LJxmkX2Gnu9Fq8
ffrU1mnNmjX2GCMjI4Xa9e7du6aurs5aurs5s3rzZZiqwbN27Y2RPl+Zez2I/e+ezZs1xDWdgxPv7i7y
amhoME+ePMksTyyN8h4YYGDDbt2+39Q3LmCf91NSU2bNnz4Jjz8/Jjz8/P23Onxhr07R2qPZ8ACIBkQCw
CDMJjkePHhl7js3N2eNxVGVtdo1u09KEHKK3PzZs37bnde/69Vr94nVgqt7f35V2qAv6v6PK7RX13bHD
Y2Tlc/r0afP48WP7v+oq6Xzt7763tbWVRI9zlMPgh7mxJQtDB7Cd3bnBIMHgRi5HX4cN5HH++yD8n
VlmT2k6O+MGDB6VZHM3obNmyJBM8sTQ6hkTAa8f7fewWwjq3/Jn7PTZQjHTuY2DAm+Z3ZGFwIh
1LA/vXv3o8A3QhW/+u3bnDKnr8+yb7v/WtvP0e/mHxjyDmPTw/TlzXPc
d47NP0ZWPvfu3b0CQ/zvf+z4sYJHDl2OxhxYGVm7u92e6x8017TlzXPc
ML0YGhoyzc3NZfvt3bu31Dey2jWTDtD0AkIBIAatifNKrUqN2NHBWDcPLkydR8FMTopv3TjhN+
tm7datNp1OiPFsP9fGek2QyNNoVGtipnUl2y8pHYcNPiKvP4+LgVH0LT6FqcCcKNVPpZPZ6u7urs5o
ZnyP1TnpHL169cpcuXLFiptdu3blsgtZaZaZLSh7/lTa8lCyco37x5Y0WCI6tNY+1QzfkARAIiAaCG
/UlT8P6oTv9rOv9rPTo8TNOfq8MQla9zJh7e7Bz
jtGNjhVkuRgiIVbWMK1mQhobG23Mg+r/6dOn0j5GI1MzVaurlz506uNs0zG1Lp
+QBEAiIBoIb9KRQEYYChpn79WyIVQKggvbzHkajQLIDW633MMk44Ry0ezIv/8
809pmcEtOaTFVUjQFLn2ioiEWFnDtIpv8Pd3wZdZxNLEREKR7OoX6j8SgwpCDINN09o0z7mv9HwA
IgGRAFDD/qQ4AY0a5swlEOSU/VsVtUygKV+3HHH58mX7X/KXIcORGtObvpfaEljt7e3l3K++h7eWqlg
Ni1V+EFt4TFi+dy6dcuKmv105NreUITRyVkS9CAP5aikSYmVVuRQICHmRJK7s0CzHtObvpfaEljt7e3lK++h7eWqlg
7YvahViamEgoml4zCH/99VdZvEmsTWPtUM35AEQCIgGghv1Joz8ZeC076COBIp0gx0H6COBGtObvpfaElj
cpwXL14suGuiq6vLt2YbNLXto9sXtS18uFN4jKx8Xr58Xbro9bO9f2///4r7aOpba29u1sC
nYPKcy0WEQmxskoMufMgRkdHrbhSmeQ4FcwXswuxNDGRUDT92NiY/S18WmSsTbPaoej5iH0HRAIi
AYD+tGjozghIRs5sdsw+ASACMOtCfViWK6lAMwLcgYBIAwtR6yIAMhR7hnRawCIgEwKgD /QkAEAmAUQf6EwBgRxAJGHWgPwEAIBIw6w6k
DkB/AgBEAmDUgf4EAgEgEAEgCjDvQnAAO4JI
wKgD/QkAAJGAUQf6E8SYmJioanu1+S92+QEDCRh1oD+l8ujRowX7ffrX8+CNiwwZw4cKsX7/ebNiwwZw4cKsX7/ebNiwwZw4cKsX7/ebNiwwZw4cKsX7/ebNiwwZw6
dcrMzs7+0n67VK6FdevWV5bW9a/P61rne15cNGASIBkQCrtD+tCtD99+/+dPMO49+sz
7t+/b7q6/ulalSIiVo9pyLjDANa43NgUQCYgEgr6U3nz/nvv/8W7Hf06FEzOTlZ/6Q4+4j/J2+OHTuw
6zj6/9WrV2bLli1m7969qb85H7W7r3W9X9bHJUHuPMUzXdTlHYFOAy/M7t277f/v
378vzYqsXbvWNDQ0mCdtPmB1ZxLkR2yE+9dm+m1NvdwrmpFZmpzZzsNvbYzHJQ6xPkaXHZ+Phkpcz2Hsr6p3X+rdVenv
bmF6/b1161ZiefK0w7737t0t0dzXV1dp/29vay2ka2abkt5vyay9ZzCr1PHh/Ja
XjV9fX2J+23cuNHOIIS/5Pa9Qnu4jG4bpkRo3MfXyZq92nfV/FOmRs3bpSV
5+bNm9aRij179pgHDx6IMJMwGaT5kCbCp6fy7rH4bFeDRSs4Le7/1j+ZVb+0t7fNf+43
T/s3NTXZ42u72vHChQuQuJ+V25csUuV4mhoSHT2NjIYIEACQLPf9pr1/IaztbkLaf75SyfksTCeHI
Oek3OaJQiOzcuTMxz6bTd3b93719JjLdahTtjLlbxcnY0h3xTtUtGeSbWPKhwY0X2MoP0h/dP8/Fw4eyx
asun/f0ZgW/fvtn2TPoPiAsCyASAJEAy7g/ieHh4dLvOmVb1Dx06
ZEfXQrMGbwSmnZ2lF/Ll8Axq3LatFEZ1qs0gcdx0KkMvfRSrPfzW09tXIU8aDcMxVHWLDw29NMEVQgR9
8ePHmfslSzS0UwW7qsmamie6rqW6tiQvbFIg1wPD5e2aX1dI+6d/+a37XcsZgiQeIcvRVCTE
2qLa8qUJOkdCdgSRGRgEiAVCc2dDZNlvQcAbJMcI8n7H3F21fXvRrX5OA4BcAhzM2vNVnWz
n3Z6enpRRYLKDa0jnzcNh6PcEq5vCduB8I6UfX/TJ7nEeFd7KupOgt7e3
FNymUbhuiaylSFAMC8xwMEXMSFAAnQhNMBuYcXQtWqgjMzWB2jsfTAXvPrZW7U4MH9Ugv1P60a9x3z
090Jrqz9/f3WmaYRpo+VJ09bvFXM+HUv56bkY2n758mVz8uTJxL4Coo8Cef58+f2/2/xcvXhC4iEgARAKs
BpGgKfkjR47YeSaY+irbXiLKWIkHo2QsapeoYiiNwdz4kpcnaV3z+/NluCx/6NDo6agP7NDUuJxY+

PCpWXokO1w5JJG13txjqozsHpqamUtsuTJ+n/WJtUU35dCyJqj///NPeBXLx4sWyc++XRTNMLS0t
tm0V6/HmzRvsGSIBEAlAfwL6DCASgAsU6E9AnwH6BCKBCxToTwC1ftcDIBIAow70JwBAJABGHehP
AIBIAIw60J8AADuCSMCoA/0JAACRgFEH+hMAACIBow70J/oTACASMOoA9CcAQCRg1AHoTwCASOBk
ANCfAACRABh1oD8BACIBMOpAfwIARAJg1IH+BACIBMCoA/0JABAJgFEH+hMAIBIAow70JwDAjiAS
MOpAf4KlxsTEBI0AiATAqMOv60/fvn0z586dMxs2bDDr1q0zLS0t5suXL6XtX79XtX79+NW1tbXZbXV2d
6ejoKNuedJzBwcFf3p+Vf9pnMdowb761PL7Owe+oAwAiAZEAq7Q/XbhwwfT395ufP3/az6VLl6xQ
cJw9e9Zcu3attP3WrVvm5MmTmcfZu3ev+f79+y8XCUvxmlwskYJdAUQCJ4NGgEXvT5s3b7bO3zE/
P182YtX//nb9v3Hjxszj3Llzx3R3d2ceX2JEsxfr1683hw8fNh8/fizbd2BgwGzfvt2sWbPGrF27
1jx79qzq6yVPvj09PbZ+ape+vr7Ukbf/9OnT21eynP37t1mZGSkbD8Jq7x1ScsraXYkqc7+bzpX
58+ft/XZunWrneHJmklQ3Tdt2mTPi2aM8pQLEAmASIBV1J9+/PhhtmzZkioStD1r2tsdZ9++fQsc
v+PGjRvWAbvZidu3b9slDX/fEydOlNLLqcpB1UIkZOUrAdHZ2WnLNDs7aw4cOJBLJPiO//nz52bn
zp1l+x0/fjx3XWJ5xers/3bz5k3T29tbqs/BgwdT66BzoPprXwlFCQrNIOUpFyASJEAq6Q/3b9/
31y5cqX0Xc5bI2E5Dy0haHlCo8nYcUZHR82pU6cSj79r1y4rNnzhoXgHf19fYOQpf56YhFi++/fv
NzMzM6Xvb968Sy6SUSJKoePXqUWq4idYnlVUQkaNnHb+es+jQ1NZWJQeELgaxyASIBEAmwCvrT58+f
rWPXSNKhIEX9ppFkfX29HUXxmmUkQ5SiexEP6eJDL80XXM+VUzk5D1W1gvOc08IkFtou9ytLFlllhZ
i+QVyzucsciqj/YNxZV/nrLKBYgEQCTACu9PEganT5+209JZTE5O2vXtPMf58OGDXXaIOa8sBxz+
ljVLUK1IKOJUw7xevXplhoaGTHNzs12yqEbw7M2raH2y6pA1OxQrFyASAJEAK7g/aQZBt0OFOT09
83n8+LFpbW3NfRyNOhXI6P/+uwLdwucExIeP+uwLdwucEfxf+umQQJGl8kvX37NrdIcIyPj+cWPDFieYXfdf7C5RO/
nSXw0vLTOZmbm6uoXIBIAEQCrND+9PLlS3Po0KGytXifxsZGKwzE+/fv7ShSa9t5j6M4Bk1Rh4GL
Ls5BH92CqaWM3y0SwsBF3XWRRySojRT9L8LAxKJ1ycpLd4IovsE5fj+YULM2Csr0837w4IG5evVq
qT5HjhxJrYPOiQty1EffVf885QJEAiASYIX2p23btmUG+0kQKADOxSTEgteSjhPeeifcLZD6KDhy
amqqapGQJ3Axlq+cqm4D1JKKIv7TZjj8/zUNr2BMd4ujc6aV1CUrL91toPK4MjlnrX11brRvmPfl
69dtUKjqpPpktUdXV5e9XVL5S3B8+vQpV7mwV4gEQCQA/WnVoVkQiSgAQCRg1IH+tMrRiFuBee5Z
AZrtIEAPAJGAUQf6E5jh4WG7tKLpdj1x8eLFi2W3gwJgRxAJGHWgPwEAIBIw6kB/AgBAJGDUgf5E
IwAAIgGjDkB/AgBEAkYdgP4EAIgEgEgCjDvQnAEAkAEYd6E8AgEgAjDrQ
nwAAkQAYdaA/AQAiATDqQH8CAOwIIgGjDvQnAABEAkYd6E8AAgEgAjDrQnwAAEAkYdQD609JiYmKC
RgBEAmDUYfn0p2/fvplz586dZDRs2mHXr1pmWlhbz5cuX0nbf9f+LECbN+/Xq7z6lTp8zs7GzmsT5/ /mw6OjrMli1bzNq1a82uXbvM4ODgqj8Hal8ARAIgEml
093dXdp+//5909XVlXqcr1+/mr1795qBgQHz48cP+9vr16/Njh07zL179zgHAIgEwKDAculPmzdv
ts7fMT8/XzbiPXr0qJmcnCzbfuzYsdTjYXLlyxdy4cWPB7xIKEg+O9+/fl2YoNNvQ0NBgnjx5Utr+
9OlT+/uaNWvM7t27zcjISFl+Ei+bNm2ysxuatYjV/dWrV3Zmwy9DVh5KI1FTV1dnt7e3t5vv37+X
7SNBpW2qw+HDh83Hjx9Tj6nv/idPHQEQCYBIgCXVnzT6l2NzNy4sUxEuN/SaGxsNB8+fIgeZ8+e
PebBgwelGYq+vr6y48p5Pnv2zP7P//Plzs3PnztK227dv25kKpZNo0VLGtWvwXMusuJ6/9P336lCsP
pWlqarKOX/tIUGjwXSEhpDK78iu/tra2zGOG5yCjgClBIEAkwJLrT1pO0GyA78hCkn7Lsy2GRtQO
CYZHjx4l7ifnDn+48QkBTARAJjEiAJdOfOnz694694MbJ5Utr+/uaNWvM7t27zcjISFl+Ei+bNm2ysxuatYjV
h2WUiBgaGjLNzc2ms7zDhEsGHWQEUDR5REJWHQEcPyTpbyl7e+h6KCL/e
sXZJOmb4W1YdARAJgEiAJdOfJAxOnz694M6FpKWFrOUGLSMk3f2a2ni7t27Znh42E7J
h2WUiBgaGjLNzc2ms7Mz00EXrXssjzRhkSWU/DR5REJWHQEQCYBIgCXRnzSDoNsgp6enF2yT89
u0PBewrSS0MjYq31h2gZ48CBA2VCY25urvRdx04r4/j4eNk2Bfn5aSupeywPpdFxHboV1BdHSh8u
N/gBn3lFQlodARAJgEiA396fXr58QaQ4dOmRmZmYStygtr7e3txSgp5F/1tS4nKmWDnRbpcSF0jx+ /NjeRTE6Olrab/v27aWZBd09sW/fvrIyapZB0f9CwX3+yI
y+bkyZNl6W/dulVKr/rW19dnHlNLMYpTcOIiq44AiARAJMBv708KxgvX5v19tQxw5MgRO0rW5/jx
42UPW0pCdzdo6UK3bpaX7cAvnjxomwfCQYFCsoxylkqgM8/rqbhJTaUXvs4Z+rQsxo0sleZdCul
u4OgSN2z8lAaiZg///zTBhhevHhxQb3dLZD66M6GqampgzGPq7gnXjnqiA0ARAIgEoD+RHsBIBIA
IwX0J9oLAJEAGCmgPy1reM8CACIBow70JwAARAJGHehPAACIBIw6AP0JABAJGHUA+hMAIBIw6gD0
JwBAJABGHehPAIBIAIw60J8AAJEAGHWgPwEAIGEw6kB/AgBEAmDUGf4EAIgEwKgD/QkAEMAsCOIBIw6
0J8AABAJGHWgPwEAIBIw6kB/AgBAJGDUAehPAIBIAIw60J8AAJEAGHWgPwEAIBIw6kB/AgBEAmDUGf4EAIgEwKgD/QkAEMAsCOIBIw6
f/9u6uvrE7dduntJbNy40axfv960tLSYmZmZReu369aty/wO1fmMr2tvB/7/7/tTh2kT6GHUUkIBIA
quxP8/Pz5uTJk4n7XL9+3fTT19jxM5tSwYxgnfTN1lAaMfstHxVG3d3d
717729OnT22Z16xZY3bv3m1GRkZyt9uPHz9WW1ubnuUPaaGgwY2NjZds1y6Jy6aLva8ePHj2VluXv3
rqmrqzObN2bx8Dx8+NDdu3LCzMirPs2fPKto3Ty7du32zr76dePatNJzJiQez58b/b8u6detW
Mzg4mDiTkHbsWUNP+79e3AmbVvXUNP9BJgDWzP7WpUP5dsmGBe3lbo9tPvhkWtZndOUMF/cwNMCi5N
fv3aftesnLZXWz5EKrh3SjbrdSKM7/k5Dyk5Wr6E4hQSGHmcfhNHrjzfttl/329b3jP6eG2i6xB
rqmrqzObN282Dx8/DLdtSZsEBAEKkHKRGIzf6F2eKmXqCoBO/n+XVzAc6OJaSDSPGcDXdsJHvLRnv9tOe2W+Wi
Mzg4mDiTkHbsWUNP+79e3PixAmbVvXUNP9BJgDWzP7WpUP5dsmGBe3lbo9tPvhkWtZndOUMF/cwNMCi5N
fv3aftesnLZXWz5EKrh3SjbrdSKM7/k5Dyk5Wr6E4hQSGHmcfhNHrjzfttl/329b3jP6eG2i6xB
b2+32z99+lQSNc6gP3/+3AqfvFy5csU8/xcvTLJ80NGQaGxtL2+TE/VkWlU2Cwi/LmTNnbDn//fdf
60TPnj1rv6s8vtgqsm+eNpDjM426VhFiB3v5s2bpre3126fnZ01Bw8eTF1uCI+dpw3D8+nnsWfP
HvPgPwgYNSeuUlQZF0vGr6QaxNs9ro9OnT5vHjx/Z/Z/iTbtuWh/993Vt5ryIRIw6gCL3p+y9jlQd
Ienz9u3bio/T1NRkWDWk4W5FXJORJ749EhZyGc/RFkSgIj+fYtWuXnWnzPnzznnnn3
raQNshx1jNjxNML32+HNmze5RULRsxTfo3Ek/atph/EypHVRvfu3TPnzp2zV///vf/+zItJbQlD
CYpqy4dIwKgD/FaR4NDUsKCK81Do6Vw2jnUcr5x3ejcrj0uwx5d3d3oXbLWlrxj5u0f6wuWc4z
63slbVCNSIgdL2wjOcu8IqFoGyb8NtEuHDBgxGKi1bZjnsOP8eMqGjaCAhdO+Pj42bbtm32
u5ZHtARRbfkQCRh1gESjVWk1MQpJTyOscKOnvOxItFZQ3N5N5Vzs6aiISkbZU6/iL7VtIG1YiE
2PGKtEOS6CtaVv83jdI126N4Di2baUkiK32l/SBWjlgbKc5ESzFOHCi2YXJysvS92vfIhEjDqAL9F
JGgKVMbNEU4HFz2ORlL+X6LJRIqaYNqvbxNkYNQvrEHkEPENPpvoyr6Y9r
Bzm/vCKhaBuGvyl2wy+bCwyM1bVoP4iVl9ZGunvon3/+KS0zuCWHDJGDUAX6LSNBcDAqUymYEAAK
XWDY5cuX7afSJhQvAp2HOH3WPqk42ukqchxEAcxdA0tqBxYsXXLxYELt66
datUlv7+/rJnTSyWKikDfzfwjaNETueAgd1a6wLXDxyqxX5EhqZLOZ5E2DH/TiNzdzSBxsm/fvtRj
V9MPYuWItZHqKHGt+ok7d+7YtCwy3Kh0j1AqAP8FpGg5vQVFV12uZ5QVcsD1uuqnEEZvQxr/fn4o
YtxFrQtFhOt3N5oMv8fSJ9+VBU7haq3a3rjlDnKdtJ9jBGvkuIWlHkq
8H9LatNY/8g6ntDzNOQEdQugIvfT6pZ07CJtGhOrR1fuRkFfiXduxq+kGe2IisNnr58mXZ
rY8uuPO///6rSfkQCRh1gN8qEq5du2YdhZyIE/b5T2s2ECqQVyQoytkQjT7PIF
hJUjFAAQCQCASABEAiASACQSACAANAqeEISQCACRhBAQCRgACFcASQ9AAQCRhA9AqQEIAhkBIASQIIQZSAACAAAAA
hJUjFAAQCQCASABEAiASAACRAIgEACQCACQSACAANAqACRhBAQCRgACFcASQ9AAQCRhA9AqQEIAhkBIASQIIQZSAACAAAAA
P1zcAAC/WCRgfABHSd0BAJGA4QGcJfUGAOxnXCRgdACHSZ0BAJGA0QEcJnUGAGwnIgFwmNQZAACR
AHR06gwAgEgAQCQAACASAHCY1BkAEAkAOEzqDEuDiYkJGgGREDc63759M+fOnTMbNmww69atMy0t
LebLly+l7V+/fjVtbW12W11dneno6CjbHktflKdPn5q1a9eapqYmjDrOpDbtQvfvv3019fX3itkuX
LpmNGzea9evX2+txZmYmercwrL4YYw4PDy+Z8/Orz3vseHNc+Pp/+s+XF1Q7du3Wr/f/78uens
7Pwl9ZW9rmWbYQNXqEi4cOGC6e/vNz9/rZ/Q6fNtWvXSttv3bplp48stV3WVHuvuEEJ5GvGtWWsfm
xsgPkYBISGF+ft5eg0n7XL9+3fT19ZWuxEXwMWlPo/PLXXMhHQxqgafIGQOTUUUuR2FjLGvQ83fSy
du3aZcbGxrg2YemIhM2bN1tj4hsgCS2ZR0Rn0ylqIRt5t5K7oxLzyK/b+E+kwR8uOjYhBzdvPt27sSrk
LVu2mL1795Z7+npMZs2bbblarbD58kZ/P5nnbTtoBDA4OFhWXcBL9cjKF0RHHZVD2vaa0DMpDHJsmcOp
smbNGrN79257fNeOvHHTiotdCgOnCMl8v2CCW/KxHKTrf1mdJ29BQUIU1wPKiVp7WKJEzXHFXuFWjrL3cE
7cg0FN5ZfPr0yWbts3+v2PHjEm7ZHPfqR8IqITn9/mxtcQu2gFDU8k6khmIw3+fwm5Rn9r
m/r4kydPcrVBZZ6a6kr0pw6eO4cuWKvX71w3XRf379799PPTKvjaPbH8fbtW7VNmW/77NNSaU8Qtun
61/p1IZqy66uLvu77JNEouuWBnJ93HvuSZGuT6u//FmuzMH2WrShS3i4QQdUx1+DSROO1Z
IiBMHyKD4Y90bt++bR1h3nJ3qe7u00r4yaUhwyCfpNIUefV7Id/MT969Kg0Gm0hsbCxUnvB4N2/e

NL29vfa32dlZc/DgwbJy+wZJ04cy3HlmTsJ9s8pdSTvEtitPGV4nklQu38HE0sfaBZFQmzq7JYE8
0+My1K2trVHnd/nyZfu/HJHShGXJ6hehozhz5oztH//++691KHJi+h6m27Nnj3nw4EHp2tN16NuO
rPrlSZtV5kr6qhyzrkN/9kUjfx1b9dN1qPr69tJx/Phx6xj9GVpdS36+nz9/Lok1MT4+bkWO7JHy
d+dUx7xz5461tTqWbJhsQVH7ssCBRERCrM38/2O2ooiNhCUmEqSE5Zwc6qBaYtDJllrV8oLUX970
SdNp6ty+qNCoo4hI8Ef6QvEL4YXpdzo516QLN295wuNp5O6nefPmTVm5Zaycc4+RtW9WuStph9j2
pDz9esXSx9oFkVDbOmftc+rUKTuC00ej1izkiDQyF9PT03Y2IdbX0pxDuK++y7HlrZdvW4qe9zBt
Vpkr6auKR/DrotG9BIKPBlB+vr4ddaJAeei6d45f+Sr26/Hjx2WCTjMjOoY/SyDbqpkaH+Xjz+7m
tS9FRUKszYrYiiI2EpaQSJCSlXFxnVcoCFG/SfkpUEqqL20mISl91oWcNB2aRyQkpQ+nz/zjZE23
VlKeMD9dDP5+aiN914XS3d2dWZ+sfbPKXWk7ZG2PGYmi7Ry2CyLh14kEh5bSNJ2b1f/CmIUjR46U
BTDG+kXWlHPsu5bM5PjkHCXYiwTCFU0b9uUifVWO3R/ly9ZJgPmO0M0kJKGRv2ZYhOJGLl68WLKv
Ll+dK8V3Oe7du2dOnz69YOAQihCVIc1WZNmXoiIh1mZFbEURGwlLRCTIsatDahopi8nJyVIkbiXp
kzpzEcOQtD1rZiPmbCspTyyNM2CaQmxubo5GK6ftW1QkxNohtj1mJCppZ0TC7xUJui6z+pGm5ENj
7qbqF1skyAnK6WlkLFEiJ5vXFlSSNsvhxY4XBi1qlB8GMeo3P6jbR0sNToxpRD01NWX/15KMy+fY
sWPWFji0JCFxEbvGXr9+bWMyitqXakVC1rmP2YqiNhJ+s0iQKtZtjJpqjBFOiRVNr1FNOL3vz0xU
IhKUpz8NGKIZkLRp+0rKo4AjP42EU1q5ta6Y18mF+2aVu5J2iG2PGYlY+iLtstpFQlZwbjUiQdO4
vlAPl898NB2vpYawj+m7fncBjIslEjTq9vuT7EdekVBJWv+3on1VcRv+mrpGv/53oVkNrdsnobZU
mTWCPnr0aGK+CkT0z4XEgx8DIcLZC6H0LqixiH2JnauwTWNtVsRWVGoj4TeIhJcvX5pDhw6l3kst
tS5hILRuKdWntai86UMUZONiHPTR9Jp/v3clIkF5uoAaF8jjT6Hq4tXFKXQ/eBi4WLQ8CpjSxe0C
eDQ96++n/F2QUhgwldS+aftmlbuSdohtjxnWWPpYuyASFoqEtDt6KhUJmrKWA3PnSAGJLigxRPvp
HCahKXEXwLhYIkFCxN2RIIezb9++3G1QSVr/t6J9VTMEfuBh+F0okFGj+jQ0+NA+/l0YLh/Z1nCp
4sCBA7ZuPgpQdPZKs0SaSVEQpwZqRe2LRImEonP8fjCh7p5xs0x526yIrShiI+E3iwSth2UZKwkC
Bay4mIQw2CSWPgl3y6E+CuhxU2+VigQhJa2LTBeiOreL+BcK/JEqVx20dumLnErLIyOqEZpu8VEk
r7+fptF0HHfrVWhMwim3tH2zyl1JO8S2xwxrnvyz2qXajp7mWFfqpxKRIMchR6Lzo/6svp2GnEva
rXO6jdLFMiyWSBgdHbVT7+rfchqyLXlFQiVpw9+K9FUFF/ptpe/hraYSLllIyMhe+jMBLl+dN7W3
LxSSZg0U4Kjz625/lL3KGqBl2RfNQCgPN3PqnLX2la3XvkXarIitiNlIZhaW2HIDwHLq6MwkAAAg
EgBWvEjgegUARAIAIoE6AwAiAQCHSZ0BAJEAgMOkzgCASADAYVJnAEAkAOAwqTMAIBIAcJjUGQAQ
CRgdwGFSZwBAJGB0AIdJnQEA24lIABwmdQYAQCQAHZ06AwAgEgAQCZx4AEAkAOAwqTMAIBIAcJjU
GQAQCQA4TOoMAMtGJGB4AGdJ3QFg9dqPPypNCICTpA0AYGXbjT+KZMCHz1L/ANcrHz58amc7saqM
+AAAABAJiAQAAABEAiIBAAAAkYBIAAAAQCQgEgAAABAJiAQAAABEAiIBAAAAkQCIBAAAQCQAIgEA
ABAJgEgAAABEAiASAAAAkQCIBAAAQCQAIgEAAACRgEgAAABAJCASAAAAAEAmIBAAAAAEQCIgEAAACR
gEgAAABAJCASAAAAAEAmASAAAAAEQCIBIAAACRAIgEAABAJAAiAQAAEAmASAAAAAEQCIBIAAAAQCYgE
AAAARAIiAQAAAJGASAAAAAEAkIBIAAAAQCYgEAAAARAIiAQAAAJEAiAQAAEAkACIBAAAQCYBIAAAA
RAIgEgAAAJEAiAQAAEAkACIBAAAAkYBIAAAAQCQgEgAAABAJiAQAAABEAiIBIKN/8eHDh0+RDyIB
kQD0LQCAXLYDS4IhB/oVAECiDcGaYMyBPgUAkGhLsCgYdKBPAQAgEjDoQJ8CAEAkYNCBPgUAgEjA
oAPQpwAAkYBBB6BPAQAiAYMOQJ+qhImJiSWVz2LnCcuvbyESAIMOS65PDQ4Omh07dph169aZffv2
mfHx8bLtly5dMhs3bjTr1683LS0tZmZmpuJyPH361Kxdu9Y0NTVVtD2rXrHrRvWrBbXKJyvPvDZg
OdmKasv6u9Nn5Vfp+UMkACIBlnSfev36tdm/f7+Znp42P3/+NA8ePDCNjY2l7devXd9fX12mz5X
r141hw8frrgcEgDPnj2reHs1IqFW19ViXJ+V5olIWBptteBphIgEQCTASuhTra2tVgiksXPnTvPt
27cFjjwLzTxs2LDBzjxIUHz8+LFUhsnwSdsT9uvqEhIO3ZPT4/ZtGmTLW9HR0fp91OnTpkXL16U
zXAcO3YsWgfx/v17c+LECVt/tVVDQ4N58uRJWVlevXpltmZY
1jmtPv4szZo1a8zu3bvNyMhI5nks2jZFyho7rxKk58+ftzNYW7dutNdReqaJ30amlX7/Pmz/V/i
WekkpoVm0bS9zFmmnL9bt26Z7du32/YuUKn4RCYBIgCXRp2TE8q6nzs3NWcmYebt+++/Yebt++
bZ1GpaP9/WomEpO0q28DAgC3n/Py8dSTXrl2z2z59+mSXXrTt+/fViy9e/cu13H27NlljZ2RcG6g9
JAj8crS3t9ttOk6s3leuXDGPHj2y/w8NDZXN9PmalMalbZN3rLGZuvNmzdNb2+v/ob2av/NmzdNb2+v
Pcbs7Kw5ePBgobrG0ofwvVKCjue+u/6cVR99Pp378eXEkgq91j4hqRAIgEWHJ9
SoZLDkOjPhdz8OXLlwX7afSoEZs+b9++TT3Orl277GjSHwXX1dUtSZGguAc5kXDmxHdEcjZyPhcu
XKjq+tRo0k/vnEeeesvRhuVM2i9WHwkV58BjVNo2ecsaO6+SY6HwIiMv2FxvzVZ6wgySYSMSYucYkQCIBFjyfyUq/yyBq ///3v/9ZUeyE8ZkzZ6wgySMSYucYkQCIBFjyfUq/yyBq
cVh+OSOJHDf9nPf61HKCRtVqSwmnIg4y/J41Ag33y6qPxKB+U526u7szy19p2+Qta6wNwnzUN4vU
NZY+C82KaDZIqK8rkHfbtm32u8S0liDyiISVatcRCYgEWEV9Smu2/ohLxjQrel9Tu1mOIGlbNY68
EpGQFjcQ5pUkaEI0ZazRcRGRoJGo0ty9e9cMDw/b6flfIRLy1EfiRcsAzc3NprOzs5DYy9M2iyUS
itY1lj7G5s2b7TKFEwdalpucnCx9RyQgEhAJsCr6lAs480WClh3CmqKWsXSEywchGnFyw2+6KhW
JLhAsloIEJVVMyhp9Pf323VvOfsiyw0SXn6+WWXOU+/6+vpcU/ix+vhodJxVj0rbJm9ZY+dVd9z4 /UgOukhdY+ljnDx50vzzzz+lWTW35ODPsiESAJEAK7
hgIXlYfbX85EjqNSR+4H23348MHeNVCpSJD40Tqxcx4qqwtu00ff3e2dGv0fOHCgzCn9999/ifmE
aNTp7maQc1J7xsoZ5hkGLmqpQOiugrRgwKz6CKXTnQgiFkhXadvkLWvsvCrwU7fbusDDI0eOFKpr
LH0M9WGJYfVfcefOHXuOJIyS6pN1/hAJgEiAZd2nZBA1Y6ARv4y1M/hCywuKxNc2BS1KNMRwt0Dq
o0jwqampikWCc2aaXpbYkJOrVCQoyE718Gc2urq67Mjf1d3dbaATv82P/2v7Wn5+IyOjtogOpVb
TlIiLFbOME9/H91BoPIoP8U3KAgvLa+0+ggtNSi9uyXPCYY0KmmbvGWNnVehW3PlqHWbo2JlitQ1
T/qs/vLy5cuyWx9d4KN/bfjps84fIgEQCUCfAlhm6M4FQCRg0AHoUwAL0NIIIBIw6AD0KQBAJGDQ
AehTAIBIwKAD0KcAAJGAQQegTwEAIgEw6ECfAgBEAmDQgT4FAIgEwKADfQoAEAmAQQf6FAAgEgCD
DvQpAEAkAAYdVmqf0u96pr/e3bB3797S7z09Pfaz93r/QkdHR1ma9+/f22fl66U2ev5+Q0ND6YVG
Qs/hd8/l18t/RkZGytK7dzsovV7Koxfj+OXRS3T0kiT3jgH3IqA8eQMAIgGRAFBDkaAXOOltee4F
OXoZjhy1ftMLngYHB+0Lbx79uyb+Dr6+uzIsPhO3a9EVAvO3LobX3a36XVsfQSKL88EiBO
OIRvK8zKGwAQCYgEgBqLBH8kL5qamqwD94k5Y43sHRIMevNhEnozoP+KZf2vN/Vllccve1beAIBI
QCQA1FgkhGi0rt/9jy8ChJYo9IKc1tZW6/j9fDTC13eJje7u7lQx4R8R8vqzx58wYARAIiAWCRRUKS
I/e5d++eaWxsNHfv3jXDw8N2mSLMRyJiaGjGINDc3m87OzkbRkFSGmEjIyhsAEAmIBIBFFgkKCJyb
m0vNa+PGjWXbp6enU/MfHx8v26a8w8w+WGdevWFRIJaXkDACIBkQCwyCJBwYW9vb214EJ9110IDt15
4O5mmJycNPv27SvR7MMugtBhIGEhAJAIssEkRXV5edMdAo
X3cbuDsfxOjoqA1klIOW01YgoZ+PlgMUp+BuYXRO3eFugdRHdzZMTU3lFgmxvAEAkYBIAKBPAQAi
AYMOQJ8CAEQCYNCBPgUAiATAoAN9CgAQCYBBB/oUACASAIMO9CkAQCQABh3oUwCASAAMOtCnAAAQ
CRh0oE8BACASMOhAnwIAQCRg0IE+RZ8CAEQCBh2APgUAiAQMOgB9CgAQCRh0APoUACASAIMO9CkA
QCQABh3oUwCASAAMOtCnAACRABh0oE8BACIBMOhAn4ICTExM0AicD0QCYNBh+fSpS5cumY0bN5r1
69eblpYWMzMzU9r25csXc+LECbttw4YN5tSpU2Z2dpa+W2Gd161bt+ps0a/uEyv5fCASAJEAv7RP
Xb9+3fT19ZmfP3/az9WrV83hw4dL23t6ekx3d3dp+/37901XVxd9l2t7RbQx5wORgCEByOhTO3fu
NN++fSv7be3ataTX/jx49aiYnJ0vf5+fnzbFjx3IdR/8PDAyY7du3mzVr1th8nz17Vtr+/v370iyF
tjU0NJgnT56Upb93756pq6eyjuT7e3m+/fvhba/evXKbNmyxezdu7ds5kT767gSRB8/fqwqT7/O
WXXSfv7HF2KbNm2yx+vo6Iey1j5k+ocnqO7d+/aOm7evNk8mhefIL+fTp0/tdp3L
3bt3m5GRkVzbivQJ1x4v4qi8omAZtlDyVcz58/b/ffunWraXZHxliH30W16RIIPrnnJicgS9A9uzZY
raXfZHxliH30W16RIIPrnJicgS9A9uzZYx48eFCapZhwodB2OXlt
k/1NztCfObl9+7Zpa2urKk+/znnq5Pjy2lqXwkwOblr166ltm+e8oflSzpHZ86cscf7999k8
e/as/R6eI7+8vkN//vy5Zh5thXpE2qLzs5OW34taxW9j948GBV5yO2PyAS
EAmwKvuUYg00OtXn7du3ibMK/+fHjR+m+dR0kdm6g0LaqsddbtrKFxyC1rXTubLKfL9Up1yWrs6
V7MlfnvE9o+dj9j+gEhAJMCq7lOaytZtf8kbVIGFmVK1fs7IUcYJYg+dKDhtEb28Y14yHoR6PdIK
Ou1F8lhN9PqK//UF/sOU1d7+e3OPQ7P/9

onUK8w6nvbOcUp7yF+0LWd/9/zVD4GZaFKfik7WtSJ8IAwl1LrLqFPbFpP2LnI/Y/oBIQCTAqu5T
mnL2DW/S0kKR5Yas7Vr7b2xstOvjw8PDdno8lj7mEltsz1vmIiKhaJ2KjlIrKX+tRIJzoENDQ6a5
udkuC+TZVqRP5HH6Rdqj6PmI7Q+IBEQCrKo+pWli/5bGcPpaBt8PbFQQn3/3QzUiQWLDn+aenp5e
kH58fLz0Xbdj+gIlz/YQzZKE0/X+6LWSPIvWKSyPv3+MPOVfTJHgUBvl3VakT+zbt6+sP2rpK6tO
Wp7w20NBttWcj9j+gEhAJMCq6lNaXvBvcbx8+bL9OBS45wLD9NEIK5xOrlQkKMLdRY7LuMtBhOkl
SOQ0XNlOnjxZaHuIAv9u3bpVqk9/f7+pr6+vKs8idVLUvNbknWNTefz21fcsEZan/IslEjTC1l0M
Igw4zNpWpE+EgYtqi6w6KchQt+26/Y8cOVLV+YjtD4gERAKsqj6l5QVFw2s0qqBFiQYfTbfK8Gq7
PsePH7ej61qIhNHRURukJ4ciJ6PAtzC9DPaff/5pZzwuXrxYduw829OEkQvS1J0BU1NTVeVZpE66
c8G1pUPPndAIVr8p8j/troS85V8skaDlBK3Ru1sXnSiIbSsapyKnr1tCdUuj7t6IPfBIz/rQ7JfS
aP9qzkdsf+wzIgGRAPSpZVLmxagT197SQstb/t0lgEgADBXQpxAJqxTNCCj40T03QrMmYYAkIBI4
CRgqoE9Fp5kX47n7PMv/96I7CvTsA50HPXFRyz0SC4BIAEQC0KcAAJEAGHSgTwEAIgEw6ECfAgBE
AmDQgT4FAIgEwKADfQoAEAmAQQf6FAAAIgGDDvQpAABEAgYd6FMAAAIiEZdb44QcAkQAAiARAJAAi
AQAQCZBPKAAgEgAAkQCIBEAkAAAiARAJgEgAAEQCIBIAkQAAiATAoAN9CgAQCYBBB/oUVMTExMSq
Pj6sMpGQdMseHz5L9cOFvZBv376Zc+fOmQ0bNph169aZlpYW8+XLl7J9Ll26ZDZu3GjWr19vt8/M
zCBGKqyz2vh38ruPD6tIJDAyAUbTy7/uFy5cMP39/ebnz5/2I0EgIeC4fv266evrK22/evWqOXz4
MG28TPsg5wd+iUigowFGemXUe/Pmzdb5O+bn58tGmzt37rSzDT5r167NdRz9PzAwYLZv327WrFlj
0z179qy0/f379+bEiRN2hkLbGhoazJMnT8rS37t3z9TV1dmZjvb2dvP9+/dC21+9emW2bNli9u7d
WzYzov11XAmejx8/VpWnX+esOqXNbPX09JhNmzbZ43V0dETPZaz8qUY94fg/fvwwbW1tNi+VdWxs
rNCx7t69a9tK/ejhw4fmxo0bdtYpPNexej59+tSmUT/ZvXu3GRkZqaoNks57SFp5Tp06ZV68eFFW
tmPHjuXqH7GyZdUz69xl1auW7VoTkYBAAITCyq2znIaMUBJzc3PWILW2tuYWCXKYzkjKafgCY8+e
PebBgwelWQrNWPjHVvqmpiabXtt1bM18FNkuI65tnz59sr/JifkzI7dv37ZOspo8/TrnqZOPji8h
pX0l0AYHB821a9dS2zdP+WPnxOfKlSvm0aNH9v+hoSHT2NhY6Fhnzpyx5f7333+tODh79qz9Hp7r
WD19UfH8+XMrTqtpg/AchWSVR2n27dtnt0kAqCzv3r3L1T9iZcuqZ55zF9arlu2KSABAJES5f/++
dRwhGl1ppKLP27dvc4sEfxSVpxwa8fj7+iNbzWhs27at0Pbw+Lt27bJCyBdFGhVWk2fROvnI4fgz
OW72Jo085S8iEiQKwuMXOVY4gpeQTDpWrJ4SUk6sxChariRi5ZHzvXnzpnW4oUjM6h+xsmXVM8+5
C+tVy3ZFJAAgEjL5/PmzFQMakaShqVRNW+YVCbFyaPpUokSzEzKwYfrQAPqj0zzbsxx2rfIsWqcw
73AZIKmMRcpf5JxkLR0VPVbW91g9Ncp1o/Tu7u7coitvGyTtH2t3lUUOXtdF3v4RK1tWPYueu1q3
KyIBAJGQioTB6dOnzezsbHS/IjEJWdu1tquRrNa1h4eH7RRqHqNYq+1FDPFi1SlLEKQ5t2ravIhI
KHqsrO956ilxpSWP5uZm09nZWdM2yCM0Qo4fP27PZSgSssoTK1tWPSsRCbVsV0QCACIhdQZBt0FO
T08v2KbpSl84hNOn1TgsrWH709M6fph+fHy89F23ZipNke0hmgUJp4P9QM1K8ixap7A8/v4x8pTf
J3b8+vr61OWGosfK+l6knmr/rP5atFxpeWSVR3f8aK1fYi9cbsjqH7GyZdWz6LmrdbsiEgAQCQt4
+fKlOXToUOqzD7S8oGlKF4h1+fJl+6mFSNBdDy7yf3Jy0gaLhekVHS6R4o598uTJQttDFFh269at
Un3kDOQoq8mzSJ0U8a51ZedIVJ7e3t5SefQ96xbTWPn9QLUPHz7YwNGs42tZRFPSQhH9YeBirK3y
ioRYPXVcReKLMOixknMYI6s8mv05cOBAmSP+77//cvWPWNmy6hk7d2n9uVbtikioIbV6atliPP2M
J6ohEorUWUFXWQ+e0vKCIqo1GlLQokRD3uPEHOro6KgNspLhkjFTgFWYXg73zz//tDMaFy9eLHvQ
U57tacLHBWEq8nxqaqqqPIvUSYFwakt/dNnV1WVHo/pNjiEtJj9P+Z0j0DS0nJMcRNbxFb2v52Io
jeIn3rx5U6it8oqEWD01Ja7ju1tlnWOrpA3yXt9p5VF7+LdA6n9tz9M/YmXLqmfs3KXVq5p2rcQW
ViwSvn79ahtEBdV0pO7XDBvPEV44leDu/1RARiXbixo3n1o9tWwxnn4W5pm3nVeT40QkrIwyL0ad
GAQB/WORRILuj5VKddMemnLxp2EcmkbRdEi1jZ30sI4i26sRCbXqKEvJyCESqDMiAScA9I9FEwka
wfoBMPrfD+hwKMJS6zt5GjvtyVWxZ/InbS8SOZpVtqJPTUt7elee9wrkeSKd/wSuWL2znq4WluFX
P8WLC506J9mUarYvxjFhdUP/qKFISIrq1HPf9TSqPEarkieLZZWzViIhaXs1T+/KIs/T27Ke/hZ+
z3q6mr/f73iKFw6TOgPAChYJcuAuqlPOULeN+Pdwvn792hw9ejS30arkyWK/SyRU8/SuooRPb4s9 /c3/nvV0tcV6OhoOkzoDACLBBilqal2jTEVmaoTpZhIU
Fqt33ofg/I6neOEwqTMArGCREKJ7hLdu3Wr/10tAHj9+XCifap+qVQuRkBY3UMlT0/I+vcunkifS
1Ulk/I6neOEwqTMArCKRIFHg3haXdB92VsCeqPapWjGRkPU0q6J5V/P0riyKPr0tVu+sp6st1tPR
cJjUGQAQCXbE62YLFJWvEWb4YI4iRqvap2olLQnkfZpVLO8iT03LenpXmE9InifSxcoWBi6mPV1t
sZ6OhsOkzgCASLCCQHEHLiYhFthW5BbISp6qFW4v8jSrWN5FnpqW9fSupHx88jyRLlY2f5+sp6st
5tPRcJjUGQBWuUgAwGFSZwBAJNBKgMOkzgCASMDYAA6TOgMAIBIAh0mdAQAQCUAnp84AAIgEAPow
1y0AIBIAcJjUGQAQCQA4zKBOsVecAwAgEuCXMzExgUhYIiIh7/tGALBDgEj4hc5FTx3U0wf1ZsTf
UZ4i56XS91Sk/Z/2xMgl38kz3imyEj9Z6Gmc/mPPHXq7q564qcd968mnetPr7OxsZl56iVlHR4d9
pbh7uufg4OCKEpKVXm8r2Qb+bkI7hDBGJCypC8R/N8RyumBrYex4wdPynkmYn583J0+eTNynp6fH
vg7cvcfj/v379pHdabjXwuuFZu79Ia9fvzY7duywbzVdjX0EkUDZEAnm/17q5EYccpgNDQ2llxP5
I209718vORoZGcm1zRmqTZs22ZGMRihJI/ha5yuDeP78efv+Ar3yWiOhLCeZZJduyfUJnpBkl68
5KfROxA02pJRTSOrjFlOQOlU9s2bN5u+vr7MGQGVS+/GUDmPHTuW+k6HPK/T3rNnT6IT2rZtm3Ug
GJPFFQmV1Fl9Uy89S9rn6NGj9uVi/rlUH0lDLxHTC8FCJBT8fh6zFyqLhIZecubeEeKLcAkQ12eV
dmxsrNB1E7v2ilwXea71vPumXbt6b03Ra6vaNi5iA/PYnTznJas8WemTbLB/7Kz+EvMTUCORoA78
4MGD0ohDHUQXYdJIW28i1IuL8my7ffu27TjKUxeEOqpeYrTY+d68ebP0JkRNrx48eLCQEZahVBu4
9tDx1En9/dvb2+02/+VJPrEypjlwpens7CyVXW+hzHL2+/fvNzMzM3Z/vcnzzJkzuUVC+P+RI0cW
XGQqz9mzZxlxLNE6Dw8Pp+4jgx++Xly/paEXkUlwxIjZC5VFDs450PBtoxIj7iVyQ0NDZW80zXPd
xK69ItdFnms9775Z127Ra6vaNi5qA2N2J895ySpPEXsYfs/qL1l+AmooEpKQMnOoc6a9GTJrm9b4
QyPln8TFylcjDP8VzhpFFBEJWof10+v/urq6BSOVLGJlTHPUzrillT383x8h6Xh+XEVRkaALUK8J
91Fbvn37FpGwxOuctE/Sa8CzXg1ezWvDfXuRdH345ZORD6+NItdN7Norcl3kudbz7pt17dbi2irS
xkVtYMzuVHJeiqavpL9k+QmosUjQFJ4UW2trq70Y/H2l0PRdJ1prnD5Z22R0wqkkv6MvVr6hsVMH
KyIS/LyS8sxjtGNlzBtIGJY9tladVs68eWi68N27dyVDkbWcgkhY2iIh1o9DNJ2blyx7kVQW/7eY
UMl73VQqmPztRa712L6xa7fotVXLNo7ZwFjZKzkv1aTP21+y/ATUUCQoKElq7e7du3b6UtN44b7q
sE4Na1oqz7akiyrpQqh1vkmdqohIiKXPY6hiZUzLL3Zxx8rhX+yViISrV6+ac+fO2f8f81lXrnzh1E
wjIVCUlLC1nLDZriTrr7QdPD/np4zF5UIxKKXDdF9km7Lopc67F9Y9dukWtrMdo4FrydVfZKzks1
6fP2l5gPgRqJBBmOubm50vfp6enUfcfHx3NvUyCJn28WtcxXU2f+VJuCt4qIBOUfTiumGZk0YmVM
u+D37dtXZqg1HZnl4N3IxJVTgVDViAQdWyNKTT0qyEi31yESlqdIkNH89u1b6bvOpYLt0tBITOvG
IborQmvUee1FzGHods206eMi103WPnmviyLXemzf2LVb5Nqqto2L2sBY2Ss5L9Wkz9tf8voQqFIk
aBrMjRTUmdRhwjUhRZGKMCAla5sCfVzwjD767hupxcpXAT9S7S4IR0FDRQMXb926Vcq/v7+/7D70
PB0xVsa8gYtKk+XgFcGue9u1v45XNHBRRktrib5B0Sjnr7/+sgFiy9FhIhL+D0WT+31Qo9KsKVk9
V0HT2urvEhcu6E/R7qOjo7ntRcxhaApd08TixYsXZYFoRa6brLbIe10UudZj+8au3SLXVrVtXNQG
xspeyXkpkj60Q3n7S5afgBqKBBkABZGogdXoCgTx99V0joyHu7XFnZTYNqH7sqWKpbgV/epHJC9W
vuL69es2qEiKXZG1RW8xc7c66aMLW7cxFXVUWWWMTfmr3Lp1SWXPWkLQdu2rfWQY027fSvtfEcZK
6x9Dtxhpn6X4FDREQv591N/kHNz5PX78uBUCWejuhtOnT9t+r2tP6+YyzEXsRcxhaATd0tJSeliT
H2RY5LrJaou810XRaz1r39i1W+TaqraNi9rAPGUvel7C37LSh3Yob3+J+QlmFmokEmDpogvEnyr9
Feji1UhmuTrM1SgSYHlcu0v52vrddgcQCZADKX8F4bj7iTVy+ZXBODquFP9SjRRGJMByvXaX8rX1
u+0OIBIgJ4pk1hSvpt20Fnzx4kV70f4qtDao6dmlFrCISIDlfu0u5Wvrd9sdQCQA4DCpMwAgEgBw
mNQZABAJADhM6gwAiAQAHCZ1BgBEAgAOkzoDACIBAIdJnQEAkYCxARwmdQYARALGBnCY1BkAAJEA
OEzqDACASABAJAAAIBIA6MNctwCASADAYVJnAEAkAOAwqTMALE2RgMEBnCV1B4DVbUP+KLIzAE6S
NgCA1WM7/sibiA+f5flBrls+fPjUxn5iURntAQAAJPspmgCRAAAAgEhAJAAAACASEAkAAACIBEQC
AAAAIgGRAAAAgEhAJAAAACASEAkAAACIBEAkAAAAIgEQCQAAgEgARAIAACASAJEAAACIBEAkAAAA

IgEQCQAAAIgERAIAAAAiAZEAAACASEAkAAAAIBIQCQAAAIgERAIAAAAiAZEAAACASABEAgAAIBIA
kQAAAIgEQCQAAAAiARAJAACASABEAgAAIBIAkQAAAIBIQCQAAAAgEhAJAAAAiAREAgAAACIBkQAA
AIBIQCQAAAAgEhAJAAAAiIRVLQ7CDwAAACIBEAkAAIBIgHxCAQAAAJEAiAQAAEAkACIBAAAQCYBI
AAAARALUWigAAAAgEgCRAAAAK0skJN2ux4fPcvgAAMAiigQMLTBTAwCASMDAAkIBAADiIgHDCggF
AABAJAAiAQAAEAmASAAAAAEQCAP0ZAACRAIBIAABAJAAgEgAAEAnVMjExwdkFRAIAwK8UCZcuXTIb
N24069evNy0tLWZmZmbBPt+/fzf19fVFF+7p06dm7dq1pqmpqXDadevW1dS5LJajqVW+1eazmOl/
t5NGJAAA/AKRcP36ddPX12d+/vxpP1evXjWHDx8u22d+ft6cPHmyJoZZAuHZs2e/zTEsJ+eylEUC
MwkAAKtAJOzcudN8+/ZtgSP3kWj48OFDbsOsmYkNGzbYmQml/fjxY6kMsefwu5mGNWvWmN27d5uR
kZHUtEl5+L9J9Jw/f97OkmzdutUMDg5mziT09PSYTZs22bJ3dHTkKlee2YqBgQGzfft2mzYUST9+ /DBtbW22rRoaGszY2FjuWY8idY3VL0/6SuuISAAAWI
27dvWyeYtxy+g3n+/LkVMWlpY47z5s2bpre315ZjdnbWHDx4MNXxqpxydNpXMydykteuXctVrpgD
PXHiREkoKQ9fhF25csU8evTI/j80NGQaGxsrEgmxusbqF0tfTR0RCQAAy1wknDp1yo4w9Xn79m3F
hnnXrl12dOyPlOvq6nLnsWXLlpLTjB0/5jj37t1bVpY3b96kOl7FSMhBhrMsecoVc6DOeSZtlygI
j1uJSIjVNVa/WPpq6ohIAABYATMJQksFmk6vNA9NNyfNDuTNQ6N07SOn1t3dXZVICEezcpJpjlf7
hksafl2yylWNc88acVeTT1jXWP1i6aspGyIBAGCFiARNRac5rjx5JKUtekfBq1ev7NR7c3Oz6ezs
rJlIyCpLkrjJW66lKBKK1i+WHpEAALAKRYKm0bUG7QiXB4oaZs1ChMsN/q2LRYz7+Ph4pjMKv09P
T5f9tn///rKyTE5Opuancismo5JyVeNAdVtpJcsNResaq18sPSIBAGAVigQtL2j63AUaXr582X4q
NcwKXLx161Ypv/7+/rLnK8Ty0Bq97iQQYQCc7gDQ2rdzZn4woe6+UPCcn/+DBw/sLZ0uGO/IkSOp
zk3ldoF7+ui7fytoVrmqcaAKXNRShnjx4kVq4GK1dY3VL5YekQAAsApFgpYX2tvb7WhfQYsSDdUa
ZncLpD66s2Fqaip3HprSV/Cju5XOOWahaHyV081MOGetfSVEtG+Yv54DoZkR3fqnCP8s59bV1WVv
AVT+csKfPn3KVa5qHKgeUqUHWCl5a+AwaT9qq1rrH550iMSAABWmUgAWJadnP4MAIBIAKA/AwAg
EgAQCQAAiAQARAIAACIBAJEAAIBIAEAkAAAgEgAQCQAAiAQARAIAACLhNzAxMVHRtlrsv5zaAhAJ
AACrTiT473UIyxluqyav5cCvLP9yd7KIBACAVSAS8j76dzU6PhwhIgEA4LeLBL1rQc/01xsh7927
V+i5/O/fv7fvAdDLl/RugYaGBvPkyZOyfQcGBsz27dtL7z1wLyrSNv/j5520LetYaXl9/frVbNu2
zb4jwUcvidKbER09PT32nQV630ThrEvp9iz549C/bVuzF0fJWjkrbQy7KS
9s9T7qRyJp3DrP0QCQAAq1gk3Lx5s/T2P73wZ+/evYVEghyj3iDo3i7Y19dnxYa/rxy73t4owjco
Zo2ew215jpWU17lz5+xbD8N6y5Izt5+TtrvcFx586d9nn+9OTF0sMr37Nmz
FbfF8ePHU/ePlTutnOGxsvZDJAAArGKR0NTUVDbKHhsbq/oNfxqRR+vs6J5d9n+9OTF0sMr37Nmz
o3k5U6G/O3bsKJVLbeC2ObIcpYTJo0ePFvw+NDRkmpuby36T6Hr79m3FbZG1f6zcaeUM88naD5EA
ALCKRYI/MnUOtKhI0GuUr1y5YlpbW+3rjoukLyoSihzL/37o0CE76evWuGh3m+DcLrfFx8hGm1r
Hznp7u7usm1aGpAoEXrts0RCLdoibQYgq9xZ5fTzydoPkQAAgEgo5Kj93xTD0NjYaO7evWuGh4ft
ksViiYSix/K/a5SvGAahdelSEips56OzsLP2upRstb4i2tjZz586dRRMJecqdVs4koZe0
HyIBAGAVi4QDBw6YL1++lL5PTk5mOq7p6emy3xTwODc3l7q9liKh6LHC7xrlKxZBSw0+Eg1+vkUY
Hx8vO87s7KwNrJyZmbEBhf5STq1FQpFyh+VM6w/hfogEAIBVLBIeP35s727QMoMcnILv0oLaPnz4
YKfp/e1yvO4OAwmMffv2FRIJcqhad9fBrFtsWNl5SUU1Ld169YFQYkKauzt7S0FROr74cOHUxtY
sxm6I0CEwYRuBuGvv/4y7e3thZx+rPzhb7FyZ5XTzydWH0QCAMAqFQlCUfIKXh42L5W2e2T
U9v19fXWmfjbR0dHbbCc9pGzUQBcEZEgh62HCLkHCWVtix0rKy/x+fNnu01iKKSrq8vOVGi7hJCW
MtLQ1LziIdxtic7BOlzwZ/gExWraIi2PrHJndPPJ1YfRAIAwCoWCRg2iJHrVkPQCQAACASoIJSm /TW6Xy53CSASAAAQCYWMatF3JsD/R3EFR48eXfCl
ACASMKqASAAAAEQCIBIAAGBZioTwgUIAiAQAgGUkEvQWwOPHjy9KYZbD7ZS1cDh589BTEV+8eEEv
RSQAACwPkaBXBLvXG69GY/4ry6h29l8fDYgEAIAlKxJevnxpH/4T7qvXMdfV1ZnNmzebhw8f2pcH
6R0B/gufHD09PfaNhxs2bD3dHR1l+fgf8f79ezua1kOHlJde3+xe2pRGLI3yHhgYsI9Cdu8f8MuY
J/3U1JTZs2fPgmPPz8+bbdu2ma9fv9p3Grj3WOgNjCMjI4ntm7WfUHur3QGRAACCwpEXChQsXzL17
9xbse+bMGesg//33XysOzp49a49+HbwnUy6HkoPU4Ym0fHBwse8tieFw54xeTNjX12dfLpVF
LI2OIRGgNyiKsIx50gu9ATN06Kqb6i588aElGr1sKqmeWfsJCTC1OyASAACWtEjQ65b12uVwX+dw
3fe5ubnEvLRUIcfrk+Y809CIuyh+mrC8eY4bphdDQ0Omubm5bD8tDbx9+b+L2GhN0/G2jdrP+Fe
cw2IBACAJS0SNAUfOvlw36zvGjWHywpJDthHrya+cuWKaW1tta8ozmPws9LkeaVy3vRasnDxGW/e
vCmLH9CsgPaVMApf4OTnkbWfUHtraQYQCQAAS1okJI3ii4iE2CxAmFZLG42NjmtbDXbKfXh42L5W2e2T
FMMQS5NHJBRJf/XqVXPu3Dn7f1tbm7Z1zCseFmHDo7OzNFSdJ+vrgCRAIAwIqeSVBgnr8UETuu
4hv8/aenp6MGP5YmJhKKpJ+dnbVtMzY097mOD4+Hi1D0n5CsRvMJCASAACWvEjQ2rim1SsV
Cbrrobe3txQUqO+HDx8OuEyGKF/jx44f9rul8d2eBW5uPGfxYmphIKJpeMwh//fWXaW9vL/tdsxG6
c0GEwZF+Hln7CuU4EJOASAAAWPIiQVH2ukOhUpEgurq67GhdcD07SXQaaznfoTgf97h6qNDo6agMb
5TjlTBXgFzP4sTQxkVA0/djYmP0tfqklhAUz+Bus3RCIMwjaz+hJQzubkAkAAAseZEgh+iP/MFY
kaPZh8Xi4MGDVkgAIgEAYEmLBKEoFN6Y1VTlKRnOeTkCSlveQaWvMGCXRQ+eQRAACwLESC1s21Bg//F0Oh
JyKmBSxWi9qZdzcgEgAAlo1IAEAkAAAgEgAQCQAAiASMKiASAAAAkQCIBAAAQCQA0J8BABAJAIgE
AABEAgAiAQAAkQCASAAAQCQAIBIAABAJAIgEAABEAgAiAQAAkQCASAAAQCQAIBIAAFalSMCwAgIB
AAD+wMACgEAAAqLBGdo+fBZjh8AAKiO/wcCvkKcdmkYogAAAABJRU5ErkJggg==
iVBORw0KGgoAAAANSUhEUgAAA5QAAAOmCAYAAACUhNruAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAAJcEhZcwAADsQAAA7EAZUrDhsAAMMvSURBVHhe7P0LjG7Ffed7r35fokQDEhNlhGUm
EsZAcpJgk/d0KyCQvW1gsMzhYgvN4WJsRVy6wzgGDMw2bIHxthEQjrnZQkk3l3gsDOxxGHMbkLmZ
bQsE0e6JwSTOMZsBNBaRUTlZRmAdazjq9/IVP//e1bWral2etZ7r9yNVP89aVauqVq1rPevSc2s9
BQAAAAAANf1/+p8AAAAAAANRChxIAAAAA0AgdSgAAAABAIzDCWCThYUF97lr1y73K4f64HxM3XQ+
vxzZZ5993OeRRx5x7XXhhcUhhxzihl966966aXiuuuuuK1577TU3fMQR5xTbtn2iOOigg32zwFjdF5eX
i8X5efe9ant0ntVmXTbBX98ZHHAAQcUBx98cHHVVVttPHq6mrx53/+58XLL79c7Lvvvm4m4ZLS0t
jXwZYG+x5alwzTXXuG2q6sEpaN53Ee4ciuuuuuK1577TU3fMQR5xTbtn2iOOigg32zwqFjdF5eX
i8X5efe9ant0KVWHKsvgV7/6VXHAAQcUBx98cHHVVVttPHq6mrx53/+58XLL79c7Lvvvm4m4ZLS0t
jXwZYG+x5alwzTXXuG2q6sEpaN53Ee4ciuuuuuK1577TU3fMQR5xTbtn2iOOigg32zwqFjdF5eX
rxaLi4uug6P4P/uzP+udhK4UX/va11t+t8mQWwY/+clPzkP+/+58XLL79c7Lvvvm4m4ZLS0t
1t4JizqSWgZXXHFF8fjjjxdf+MIXXDGk788888/cGB8U+u+zakysvRjxLa3k3XdQO6pHXW
jl+9A1TxjW98Y2N8N8F+tzWJ4dL3POOecct12aruqG6UaHEkAt+vXS/zX0zDPPPBZ6G3
c+fO4qKLLiqOO+44970p/aoruImd4/44970p/aoruhImd955Z/Hee+8Vp512mhvesvmsmWLOwjjecccdbngcvPnmm65Dym65d
5RbXJkcddVRx++2398vzx2398fuad/zzjvan/FiTp5am/lq3DKKae4/DbMN+/SVe/H/Tx4YXGffvnppH/Gb34e5/fhkNRNSqHrSs+fRV
i8X5efe9ant0ntVmXTbBX98ZHHAAQcUBx98cHHVVVttPHq6mrx53/+58XLL79c7Lvvvm4m4ZLS0t
jXwZYG+x5alwzTXXuG2q6sEpaN53Ee4ciuuuuuK1577TU3fMQR5xTbtn2iOOigg32zwqFjdF5eX

itZ9rbex4+Ty4rzb1nR807a21OsQ2iMMPqV5+umn+0NxVp7S+uVp211aWnDHhXsvu8yNyx2Pjf9j
pG1vtv0BPjqUABoLO3VdWr9it+dgZrfyDPJc5jDo9tD1m3X3+PWjj+5/26OttrSXMFx77bUbz9G0
xZaB+ehHP+o+23pGE8OjW8V1tUO31137/e/3x+6h52F166mucOgWap182m3VRi/ZOfbYY12n025J
T4mVZ/npbch1bpvucvsB2qZtSeu+tpPtkRe1zS8uum1NP9jpCr62pPDFVV/+8pfdsUTbj565zFF5
ejTEL88/LuhOn6qOiPzAE9v+ADqUABo7/dBD3ad+/ez6Yf3wmRDdAqvD4n/6T//JDY/rM1R2ldJ3
9u/9nvvUsyl21ceeSxyUPZ+mZ26Uf5vCZ+CuPukk90u43W7IszWTReumbmF+8a679nrJh17Co1vn
9Bblq68+yY07NLiioU7ipz/9aXf1Rf/io0xYnp2satve++pn+na8LrcfoAta99WPe+yxx/ba1nRb
uba1Lfvtt/FvcrTd+fRj3vnn/+9uW6vy5lY77qg8dUBtn63v4XFBx9EUvXBLtJ3ZdLqCCoToUAJo
bH55ufjDP/xD16GwA1buNromdKDVm+j0L0L06609E6Jbebbu2OFuyVG8rnb48ePEXiRkLr744uLs
s8929dfJgTrHOgFog34J18n46aefXrTVndQy0Ns+v/rVr7rlvfHMXe8M6eabb95YBrr1UfHjuAwQ
p6uPus30puC2bC1DPYOl7e6ooz7vOoLb7r+/H7uHtkP9yKMrJ1WuVPvlaf+hdfWcc25zL/3x2Xps
bzr2dbn9AF058cSrotvaZffe645dx23d6vaj2ofqZVN7m3fbmraVsjsCRMcdladjo7YndTA/85nP
FD/65S/7Kdb92/4tuXoLbOj8889325q2M21v+q5xQGhuraf/HQBq0XNVOmjpZE6/uupfeOjAaL+y
AgAAYLrRoQTQmG6B1HMfukKloF9P9Uso/0YCAABgNtChBAAAAAA0wjOUAAAAAIBG6FACAAAAABrp
pEO5+9Zjirm5Y4pbd/dH5Oy+tThmbq44plJiAAAAAMC46OAZyseKpbkTi5XFR4u15U/2x+U9tjRX
nLiyWDy6tlxUmwIAAAAAMGqtdyh1dfKwi58rFh9dKyr2J9WjLOZOXCmOvuWV4tmL1v9Rehu2bdtW
vPDCC+7tk++9d0RxzDG/UXzu1lvdP3HV/8vS/9W5995715xPXoP/JJrt27XKfXdJ/Gnpk+/bi4Yff
LPbZ58Vi3333LQ4//PDikksucf//K2eY9cTksPUi1MV6ou1M/wPrjjvu6I8ZXNP66/926Z+vV/mX
Jk22nWG3a9P9VxNN563O8m/a5vfff//GvlD/xubtt992/1Pt+eefd+Ps39nofxo+9dRTblxM1fJz
6Zqu73772vxofdX/VzSx8mJ1qTIffnn2f2P1j9Qvu+xe98/X21KlLm3Rcv7Wt77l/pG7jvcnn3xg
cdLVV2/803Z/no3qdc8992z8nz77X5Y6dzj22GOL448/3g2HbPt766233PnFJz/5yeKP//iP3XIb
5jwjz1/mw96ufvWrX7n/zaxwzTXXtPrm82GuY9qulpeXi6efftqdf370ox8tru5tV6Lz0yVvno3q
dfvtt7v/S2z/Vky2985lP/axjxVbtmxxwyHbrl577TU3fMQ55xTbPvEJtqsJ0fItr7uL//wfn+t9
Hl38/mHrY5zHbu115uaKubl+OGZp8+2wh/1+b4qieO4//udeDu1Y6e0wHn/8cfdPt3ViceONZ7l/
vLz9lFNc/Dm9FfWVV15x38fZty+6qNeZfLjYtbzo5uPLX/6ym49reydIwCC0Y/ZDF7Sdhf+wfFBh
favWXycR2na6ZvWpWq8mhr3/Cuel6rx1sfxD3//Hf3SfOhlRZ1L0z7w1LBavE6GcqvOU08b8vv76
6+7z5z//ufvskuZXx5U/+7M/c+vT9u3rx8dJpM6kjpUrKyvF8uK8+/6jW25xcQ8++KD71P/IteVs
y1onvc/fdpv7FJ1Av/zyy8nOpOIXFxddB1w/UNzWm1Zlhf+sHuPF9pfD2q5+8pOfFDfccIMr98or
r+zHTJ7vfe977lxa67l+dNG6ro6h/POTT7rPxfn5vbYr2xb97Uqd+VRn8tVXX93YrmyftNqbnu1q
crTcoXyl+Dv1J4vDi9+xC427e53JEy8unnPj+55bKS4+bKl4rD9YHPo7vSl6nvu7Xg7t2LF7vWuq
A4NoJdaK/tBDDxUf+tCH3DixXz306f+65A9rQ7io17E7pdcZtQOTnHnmmS6NNgRROg0rXWipt2Ho
13OFW/oHObFy9Iuo8gvpCqs82N8J2nws9zdam96Ew6JfihZ6J9PKX3UU/bJ03nnnubrqF1p/Ovuu
eAWjeqv+Rx11lMvT+NOKP2zfV3o7Ek2r/KwOGB86+dZy0nru07DGax33I7/WZ2PL+MnewUXLV2m0
vJXOKF6Uj9ZDy0f52/bTFh3sLH/b1jRsrC62XSud4lUvHfDaZO2q7dunYY1XfKy+ongF7XNUT6XR //2M7b+sXZWHteswt7PY/k31MFZP1clf/vqu9WYQr9
XbH1Xd9j81vXgQceWHz/+99331V/DQ+DneTpipvY/GuetL7pu9Y9sbYIt3ejZarjjX+sNGpv5emv
J+LnaeuHjjFqe31XfmXria5Myoc//OFivndiKrqqIjZfuuoYcldDeifElkYdU11VSdEJrn6wOOOM
M9zwfP9kusqdDxiR3jKydcF9tnkZPkPrhti6ldv/2TYQ7u9FW5fS2v4oVHZ+6W9XilcZ+q78yrYr
6xBqXk499VT3/eE333SfdiXxfSee6D59mmddlbU06pjaNhNz5513btqu7FyX7WpytNuh3P2zwnXf
jv79YuMC5aEXFc+urRW6s9aFV24p1nf1Lxc/27gceVjx+7pEuWncYHSbgWjnrw3JP1HUL0fGfk3J
0QFGVzb064z/67MdnOzE5fv/uH4icPLJJ7tPowOjfmnR9Decfnpx9913b+qQySc+8Yno7Wv6tUa+
9rWv7TUfVemWnKt6G7x+Kfv+tde6cbqNVvNy9UknbXS6Q5/97GeLO+64wH1XfVVv1f+KK65wt0DE
dmwpv/zRj9x0KlPtifGik7DDDjvMrefWEdGnhjVevzba8tftO1qfw3VYB447LrjAXSXasXXrxi2H
YtuZptd6eNdddxXf+c53XP5t/nqrg6XqauupbWv+rY5WF21Tn/vcH7h6qj6ql+5saJO1q37h9dtV
wxqvkxvVV/sG/SIb2zfowKx4tes9l14a3X998YtfdPV//vnbNtpV8zcMqm9s/xZb/pdffnnxJ3/y
J2557Nixw9VZtxsOwk5YbD9m+18btnh1KG39yLW3VNk//qi3T7P1XZ3U2PzWddL7379pfjQ8DHZc
sePN13vHGu3/NU+PPPKIa4sbb7zRKG39yLW3VNk//qi3T7P1XZ3U2PzWddL7379pfjQ8DHZc
wxqvkxvVV/sG/SIb2zfowKx4tes9l14a3X998YtfdPV//vnbNtpV8zcMqm9s/xZb/pdftfnnxJ/y
XbH1Xd9j81vXgQceWHz/+99331V/DQ+DneTpipvY/GuetL7pu9Y9sbYIt3ejZarjjX+sNGpv5emv
J2557Nixw9VZtxsOwk5YbD9m+18btnh1KG39yLW3VNk//qi3T7P1XZ3U2PzWddL7379pfjQ8DHZc
sePN13vHGu3/NU+PPPKIa4sbb7zRKG39yLW3VNk//qi3T7P1XZ3U2PzWddL7379pfjQ8DHZc
0bqvbbNXwdL1RLfjhd7fP/G1Zajb6XQir46w0bmCtkn7VFvYiXOM5aVtG5PhhN/6rY31UZ8aHgbr
ENr5aJX9n9Z5bR+2v5f7t21zabU/ss6pSe1/ff52pXi1gbarN3vbR5Ptap8XX3Sfa/393KO9Y406
qOF2pe3W5l3HOrv1NcbOo9muJle7HcpX/q7wL0TusbvY/ditxa29g80xh11c7Lm2EXqu+LuWLlFq
47Ffd7Uh6nY3/epTvzu255dP3QKjZzLM7/zO77hP++Xrr//8r91n+Cuo/cLjDlL9X051UuNL3QZw
Wa+TOeh8XHzxxRsHyJX+hD/84Q/Xv/Tq4z9P4Fuv07z7vlHfXnrLS78oVaU62C1E1p4YLfv10oKd
iOuXRP9T420d1/K35WjrtTn//PM3fvnVjxgxq/31SQdWHUB0pb3N5wDvvvun7lNXKGw9Detp9Jzb
v/yX67/Yqj6ye//93ecgwna1X1xj7Wr1VV1tHxDuG9Su9vxNqn5vvrne8VhYWnEnD+rQtPncak6V /ZvRsv7N3/xN1+Zf+MIX3LjwBKkO7Ru1X1RHQOuonpC
aba+DzIPm/TKU311xVkne9aeZfz1rQ6bRvOoDreON6LltN9++7krH7ZthB1Ef3u3+bfji9rXtY/H
jheKsxPL5eXNHe+P9KbRcjL+cFh+SO8WEF1xsRN5f3vRunFbr4NsP2zqOCo6eT+9dyKu7VQ/xGi7
VOdXHc8VmyGPTsoxWY488siN/YS2Kw1XMeh2dWmvQ6jbrHU+KlX2f9qurFNl6+/jj/+T+9RxLdyu
qux/NY2/XfnDZfsuayttV/6dCPJ6r2Ou7Wrb/fe7Dq2/XWl7Om7rVrd9aXvSebG2J21XsYsRbFeT
r5N/G7LJbv1bkMOKw675u6L41L8v/sPao/0rlN5tsR3QxqLbW/XyGuuQ6WChX17r0mV4s374XKcT
Em1M7hfL3oamT5UVPnztn1zb9GUHR6P0mg8d8AedD9GLfcR2Isrf39GkWH39+W8q9osXhk+dDj/o
JE/rsw5GOvDqU8Mab8tfD+BXObj624zvqqtO3OgE6O6Brcftua2nDbZ++1KdW932oxNJbQv3XnaZ
G9fGQS1sVx3otd347aphtavV1z9pyR3gU/XTM2NaVtoP6cqkllPZrUxtqbN/04mEnjNUvJ5vl9S6
UoVdUdOdF7/+67++0anQp/LVL/uiF7JJ1fauu38cZB58x/3Lf+k+n7rhBvdpw2X89a0OpdeVQLtN
2JafrnjomPMbf/u37o4EUfum7Jn/vTtgOeH2auUbfzhXvujWOJ286ryrkX/zFX6xvD32K01Uh5edO
vHvsSqO2Q12J1adOznVCv7O3b9IVpB07tro0Pj9fTIZTf/u33ac9j2fDZQbdruyFV6bu/m/P/j69
XQ1yfill+y79QKdnJLVd/fWf//mm9V9x2q60j4xtV4rTp35MUidW25O2K21flbarydduh7L/ch3f
7v/8H9evWh7+qeKiT/Z6kI89kLlCGbzMpwVamdUhu+qqq9xwakPzV2ad9PnCnYJPv95og9QvNPoM
r07KEZEN9tePDlsqTwc56yCLnfDk6hZjnTk7EZNwfmP89MbyspORnHqnGRgV/aqog5gOvPq0q2u2 /P0DrA4Wdemgo/V4sXewPeGEE1wZX/rSl/qxg7Pba3y
Wyer0i/XWh66LVEn1drehvUiiDr7N7u9Sif4bbz10Pa39sy8/ZpuV9vtNipLV7W96+4f26l20bFI
86PPsI2sI2yd4Tbo2Sh1GnV1QVdOZGvvpE/qLqe6J4Wx7XUQ1nHUlSCdaNsPDFXoByZbT7T96CQ5
9mOU5WkvfcIE6K3jWje1P3DraLC/72q70lU7XQC4tv9cdNP9n11MiGnj/LKMjtfarnTXi7aJ3BXe
cJvRj1O2P9axT9tV7E4by5PtanK126HMvVxn5UT3htfDTrTupP+8ZORlPgPSw8baOdiv9L/d/0XK
Dgbh6ePGSefqqnu+yadXgovysgOuOe20D7hPm+bij3zEffr0QgHRAUsbl8RetRxj82FXcX73d3/X
fdp82M5EG2FYN6P76VW22EZrD4urPlWeadw40PbSW15hZ8Ne3BKjt+3ZsrCdC8aPOnk64OogqI1E
w+Ivfy1nrZN2a0tO+IOHngPWtEf92q+td+R6Yj9WNJVbT8OTXTuZ1fzYdtmVs8763Y121aeGxeqr
X67VcVHb+M+hpIT7L2vXLfvt505WpM12zcnt38Llb/srtbktn0HYlQadqIi1q+0fbby1RdX2rrt/
NHV/4IvRPlr1jp20+R3hKjR/CmX0Q4+e6dWVhE0d6N7xsM5ysjprmvA5LtsOFWe3vNnyqCM1T1qO
Wu9Uf5Xh/8BrLyTR/Nix1OpjdOeAHb+1jSqf2Mm6OglaznarofJTfarsDzE6Wje1Tgxzu9lFDW1X
L95116b1qe7+z98fhdvVIOeXvtx2pdtUVf/V1RXXhnYOZ9uVzj9tuwpfaPX1H/xgI73mYtP+xaPp
FM92NblavuV175frHHrRfygeXbRfS44uFm95pXjlFg17z0vGXuYzoG9+85sbt79oY1haWnEnxxf0
nyv6t9df7w4KtrLqXncdRBZ6G2S4w9H/l9LzJfrF/1+EHcb5xY2TCPcrUvDLl+jq4tlnn+3qol9+
9d09f1LB1Q895Op96aX3uLftbd261Q3blcr55WVXb9UtdXDWyZR+GVP9TuufxOv/CGlHt9Q7wOpT
cidDul1B9Vb9NR/6rp2lqO2Ut14M8pGPbL6/3+jkXXXUMvn0pz/dH4tRsgOIfyDRr4f27xWO+Y1j
aaPp

Nm730/LXQUHL/zOf+YxbjrYO5pxz221uvbKTdj2jpWn1enCtz/put9S1wdbTpZVVt57qtj3b1nQi
qG3F6qIDmNZbzc+PfvlLN64NsXbVodTadX3/sr6fsPredNNOd/uttm27myIn3H9Zu+qZFe3vtL/S
s2LDkNu/hcvf9lenn36DuyI2sN7+dtP+t9+u+vV/fXh9v2bPJFVt77r7RxPObxPWGbbPQVWpt+j4
odtKdRVd645aUutTndvndHxRe+l4E94ZoHVCV9K1nqj9tRy0PJqIzdMFF1xQrPbWBy1XdYy1f7Lb
8PQMm46Dmh/dEeGvo7JxVaR//Na+4aSTTurVd9kN+7Ru6V8o6NY+nUwrP+0bq+wPMTptb1dV7swS
rRvqhGm7arr/07s73P6od1wLr+rn9r91qW4hbVfadrQ9qHztL+09CjruKE7Hc20H2r7D7Ur1taux
2p60fYadTlGaz/c63trf6Bhm2ynb1eSYW9OrV1u0+9ZjisMufq5YfHStWF6/sFfusaVi7sSV4uhe
Z/PZizp8sLIjuoqoB7311qxJeUOVNlidYKtTqNt79IuWTkjt6kZb7IS66i9/ADBqw9o/dk0ndDrR
bPPFV6Omqzv68VK3zgMjsbpanPn1r7NdAZ7WX8pz6EVXupfurDxQ/U2ejz2gy/SLxZUT1pnUr5M6
8RD9AjpJrzu2f8as+n++F3SypBOotumX5Kq/kAPAOBjW/rFrulKnf1MwTdRBtheaAKOgd2Zc1n+R
27TQXQVt3i2E2dP6FUpZv0pZFLe88mxR2kfUW2DXE0/k1UkAAAAAmFWddCi7pBf7AAAAANDjv/PF
6irv08dwxLqOE9ehBAAAALBO76vgXRUYpdafoQQAAAAAzAY6lAAAAACARqa2Q6lXIOt/gdmbWPV9
439NJSjNnv8bl6b//ZZLp/vYlZf+z57K37Ztm3v1fBnlWaX8KjSv+qezAAAAANCVqe1Q6hXI+gep
er34jh073D+R1T/Wj3njjTdcB7DsH81aumeffbY/Zm/qyG3dutX9U+ef/OQnxZe//OXi8ccfL74+
5M7dOeecU7zyyiv9IQAAAABo39R2KPUPqJ966in3vyGtY6VOXsxpp53W/5ZXJd19991XvP3228Ul
l1zihrds2eIelPb/Ae727ds3rpzecsst/bF77Ny5010FVRp9N0pr091+++39sXuubGoaXZXUlVHT
1hVPAAAAAAhN/TOUS70O1eWXX14ceOCBmzp1vhNOOKG44447+kNp6+ku6A/F/dPjj7vPgw46yH2G
1CnUP8y+4fTTiyuuuKK4++67N3UO5ZlnnnH/RFsd03suvdSNUxqltemWl5eLe+65x8WZz33uc715
vMxdGTW89QsAAABAV6a+Q7nc61DpauGbb77pruDFXHvttf1veevp5tcHEsqelbz77p+6z/nFxeLU
U09133VV03f11VcXhxxyiPu+e//93ac6oY433Z133uk+jf4PUVn9AAAAAKAtU9+hlLPOOst9vvzy
y+6zS/v3O4Ap++zzYv/bHu+++27/2950lVL0PKjQXQQAAAAwLmaiQzlMRx55pPvUC3xiDjjggP63
PVLPdvoOPvjg/rc9qkwHAAAAAF2Z2g7lKaec4l5gU6yuFk8++aQbd8YZZ7jPqv+eo2o637Wwnneau
Ut50001ueHV1xeWht8PKscce6z5XV1aKBx980H23euXUnY4rmQAAAAC6NrUdSv27EF3VO27rVvfv
Qs4+++zi/PPP78d2aH6+uOGGG4q33nrLvW11aWm1OPnkkzde+nPxxRe7uiytrBbXXXddL36pUr1s
uq07drjp9N1u5Y35t9dfX+yzzz7J50YBAAAAYFBzaz397wAAAAAmiO6E463+GCWeoQQAAAAANEKH
EgAAAADQCB1KAAAAAEAjdCgBAAAAAI3QoQQAAAAAANEKHEgAAAADQCB1KAAAAAEAjdCgBAAAAAI1M
dYdybm6u/20zG5+Kr0v5WAjl4iQ3PjedL5em6fSp6VJpLYT8OD+YXFxOmC7Mww+p+BQ/LvUd5ayd
Y+2Wi2tDLv+mccOWqkOujrm4NpWVHcanxksuritVy8yli42PpZsUNj9l85BLl4szsfhcemPTpaaP
jc+pO00sXSyPcBgAZsHMXaHUjn5tbc19t89BWH4WwgNLKk7CYVM2nc/SxtLk4qqoMp2VkaurH2/B
F8aVlWtl+un86WPD4o9TKCsHzdkyirV1Lq4NTcvOxQ1bquxxqH8uX798Mw519lUtM5fOj7PxNm4S
5ebVl0tXNQ9RvMmlC/n5mzrlmrrTxOJTeeg7gG7Mze3cCBgvc72d39Tu/WyHb3LD9j08KITDZWJ5
mlhcmCYmlyaXT5UyUnGpaf3hsmnD7zGx+KrTpNJVzbPK9KnvqGeU7Zgrr2lcl6zcWPl16ttV/ZWv
NC3LTzusOvualpGqt30fRt2Hpeq8pNpEUnnEpkmlNWXxvjppTZXyxU8TTuMPN6kDMIiFhYVi165d /aHhUbnDtLp6Y/9bUczPX9r/NhyjaN9JMjMdytgOPo
+sO5fE1Zmlh81WlS6armWWX61HfUE2tHfUrXbZpbbk3jhiFWvo3Tp/jxYfou6u+XH5bly5XrTxvL
JzdtG6wMq3PV8lL1rpvPJPDnLyfVJpLKIza+rDzF+8rS5uJjctNYXJgmN5zLD+jCqDqUw+ZfmVxb
29L/hnEwE7e8Vt25h2nqHhC6OIjk8vTj9Klhk4urY5BpjaYPgy+Ms3rH+PF16+aX4eeDbsXa2sbV
XYZ1lC3nVFzZdKNmdeuy7ZqwOqXqNU7tWqcNY/W26cLxNm6ShfOUEqbz26RqHnUoPwvKP9Sk3K7q
CqAb6kRawHiZ+g6lHSz0OY3sgBibv1xcHYO2n6YPgy8Vl6p/anyZVDkYvmG0vy3nputJ3emGZRht
F6P2SJVdpU7j1K512jBVbxtvrH1iaWeBP/9tt4HyK9Ok3LJpbJ4AAHlT36G0g0HdA01dXRx4quSp
eAuhXFyX2mrnVP1T4zF+xvWEbFzrNe7UbrZ9t7WdT7ppWpeqzss0zXMZzaut6/YJANhspt7yqgNg
FweELg6uZXnG4m3+cnG+sjJ8sekHzbOuWN6xOmA8dLku5JStD6l6sR7lqc0s2LDJtd2ktuusrQ+p
7SJUNV2b2l6/qk5j67vN77DnGwAmxcz92xAdEJocgFIsL31aMFaWhaoHI8vDn3YcxOpfZR79eAuY
braMY8u86XZRVS5/DdunBdN1vdqQq+Mo69+0Xrm4ruTK1LCpUjd/vJ8+lnacqc72acHEvsfSVWmv
OqrmnYvTcEyTaUK5PABg1kz1W14BAMD4GGbna1QdPTqYGLZZecsrxtfMXaEEAACjow7XtJrmeQOA
FDqUAABgKHTlblhX70ZxlXCY8wcA44IOJQAAAACgETqUAAAAAIBG6FACAAAAABqhQwkAAAAAaGSq
O5Spt63Z+LbexqZ8LIRycZIbn5vOl0vrx/khJjXeF0tTJz+NsxDy4/xgcnE5YbowDz+k4lP8uNT3
aZeaV423EPLjYvFtKSs7lIvrQqocvx5hmtR4ycW1wc8/LCM1Xvy4MD41vg2pPKuU6aeJpU2Nm2R1
6p9LWxYXxlcp16aLpc3F5VRJn8s7FpdKCwDTbOauUGpHb29ga+NNbJafhfDAkoqTcNiUTeerktaP
T6WzfHJl5VSZzspI1UH8eAu+MK6sXCvTT+dPHxsWf5xCWTmzKtUu1u659vPjuxArM1evKnVuU1n+
fl3MONTfL8NUKduPN13WOZVX1TL9NAo+Pw+b3sZNqlQ7xOTSVsnHb6cq6a1twzaXXFxOV+XqOzBt
5uZ2bgpAaKY6lHYAMOHBwT7D8f5wqOnBQ3mmpq2aZywPDefqO4iyOufKHXZd0b3c+pDTdLquDbNO
uTZoq33anp9hLO+26tz2OtZ2fuNmVPNXtdy269Z0fv1pRtFeQJe0XaRCKJbGD5g9M9Oh1ApedgCw
NAq2UfjDbSqryyC6zLttk1RXbDbIsrPtq+3tyti2O67K6jZI+zSdroqm9SqbrkmeOW0ue9WryvIa
5/WtTJ265+a1bjuMqs3qlqv5UgCmmbaLVAjF0vgBs2cmOpRVD3JhmrobRd2DaRVt5GkHQz/4efrD
+tRwE4NMa6x+fvCFcbm28ePr1s0vw88H1Vh7p9pPwxYUPyxl9TK5uGGwtrH6GhtO1d/GhdO1xfLO
5R8bn5uu6zp3wepqdTc2Dt0J29xfFmFcGyxPKyfUVbkAMEmmvkNpO/rYgWBW2MHQDnixA58dFAdt
p0Hb2q+rBV8qLlX/1PgyqXJQjdrbbz+//btuTys7JlevcZFrn7L656YdVC5vq4vVz1dWpy7r3CXV
26+7v2zC5TItYsvX5OK65Ld7F21fNk9dlQuMk7W1LZsCEJr6DqUdDLre4XdxMG2aZ24+U+2g8RaG
qa1lkqp/ajymm9YrW7fqrmNKz/pS3zRuZ1XWhVlbXzS/tk3Zp8nFtUF5sm0CwPiZqZfy6EA0KQe5
KnnG5qduXWLpB803Nv2gedYVyztWBwxf18tAy9mCDVfV5TpZ1biuo7l6NY3DZMltW7m4NozDtulj
vQaAPWaqQyk6ILV5ILC89GnBWFkWqh4MLQ9/2pQmZbTdBjGxelSpqx9vAZMnt6yrrAddyZWtYfu0
MAq5OjaNa0PTspvGdSVXpobr8Kf38x3GfAxL3TZpi1+ufbf29ePaXJ5SNe9cHADMmrneTpC9IAAA
6NwwO1+j6ujRwcSwLSwsFLt27eoPAcM3c1coAQDA6KjDNa2med4AIIUOJQAAGApduRvW1btRXCUc
5vwBwLigQwkAAAAAaIQOJQAAAACgETqUAAAAAAIBG6FACAAAAABqZ6g5l7m1rTd/EpukshHJxkhpv
yuIlV4Yf54eY1HhfLE2d/DTOQsiP84PJxeWE6cI8/JCKT/HjUt9jLD6Vrix+EsTqrnEWQn5cLH5Q
ufxT4325uGGK1SNX/1xc1/yyw/JT4yUXN6hcnnXKi6WN1blOnuOoSv1tvmNpc3EmjK8yjeTS5eJy
qqTP5R2LS6UFgGk21f+HUjv1NmcvzM8fzsWJhiVVn7J4qVJGbPpUulR6E4vXOImNj5VhyoZDsfiq
06TSVc2zyvSp76Ewnfhpw3G5vMZVar7qDLctlX+VemicdFm/KmL1yNU/FzcMqfJGVWflJak6SZWy
Ymn9etp3f9wkqtIm4TzG2sGk2mPQaaRJHiGlk1zapuWGcUCX5uZ29r+tW1vb0v8GDM/M3vKqHb6x
7/r0x4eaHiDaOLjE8tBwrr6DyNW5rNxh1xXjz18fcutWG+rk32U9ujCu9c21+SjqnKtP1+vfJGqj
TcalTavUg3UA00DrsULIxsfigK7wDGWfNjwdYBTa3gjLDlxWdhOTdFCcpLq2IbZcNWzrV1n8JChb
dxUfmx8bH4trQ1n+qTiNy83PsIxLPeqwNo2167Dl2q5Ou1ZdDpO4vHyTXHdTZ92bhvkFtB7H1mUb
z3qOYaJD2Vd3wxvXEwg7qPrBr6c/rE8NNzHItMbq5wdfGJdrbz++bt38Mvx8MBhry9jysPGxuDbk
8s/Va5LYfMSMYr6sTVPtqnG5Ok8Sm8dwfmzcrOtyOcfa18qz5TIM/jpg5QPArKJDOWJtH4jsoGp5
xvL2D4KDUN6D5OHX1YIvFZeqf2p8mVQ5yFM759orFdd1G5fln4ovm59haVoPTWPr/7Dno0p5SmN1
nARl7WjzYyz9JM3jpLA2TS2T2Liu+cvb6geMgp6ZnJ+/1H3y/CRGhQ5lA6mDWlN2oLTvdeTSpw5y /kFwmOrOW0qq/qnx6I6WqS3XtpbvKI3L/JTVQ+Ni6z
HSQtz1TeGh+e0NStSyz9oPnGph80z7piecfqMC6sbl21x7Co/hZsuIqul0vT/JvOT9vK6pFad0a5
vufKHmW9BlG2HLC31Lo5qEldhwBgVkx9h1IHojA0ZdPG8tJB1B/fxUG1SRk2TZdi9ahSVz/ewjRp
0vZKH2urSZNb/rm4Noyy7K6pzvZpwYxy3nJlN40bBdWhDr/O/ryMej7a5LdJbnlZOj++TJX8JJeu
ah5V+dM0LRcAZs1U/x9KYNTqnmhwYgJgmg1zHzeq/Sn7cQzbwsJCsWvXrv4QMHzc8gp0SCcVOrmo
gpMQALOg6j5xEk3zvAFACh1KoGNVO4l0JgFMO+3nhrWvG8U+dZjzBwDjgg4lAAAAAKAROpQAAAAA
gEboUAIAAAAAGqFDCQAAAABoZKo7lLm3rTV9E5umsxDKxUlqvCmLl1wZfpwfYlLjfbE0dfLTOAsh

P84PJheXE6YL8/BDKj7Fj0t9j0nlmxpXlt84sfrm5qVuXJvqlp2LG6ZcPZrGdS1Vtj++LL5tuTyr
lJerW2x8LN0kqVJ/m+9YWj8uFi9hXFl6k0uXi8upmr4snR/fpB4AMOlm9gplk7ew6SBhb3BTCA8i
qTgpO8CUxUtZGeLHp9JZPlXKjKkynZWRqoP48RZ8YVxZuVamn86fPjYs/jiFsnLqsDqFYnU1bdeh
KzYPFvw6N41rUyzfcahXmaZ1zMV1LVe2P17B12Wdc3lVKSdXNz/Oxtu4SeXPX4o/3/68+/z4FIur
kp/k0lXNI9RWujBedQBGZW5u50YAhmlmO5T+QcC+6zN38Gh6oFCegx5kYnnUOXjWlatzWbnDruu0
yLX5OMrVtWncKI1LvZrWY5T1r1p2uI53VefctlR1O+uqbuOojX3PJO2/qtZ1kuYJs0nrqMLq6qr7
9FmcH4Cu8AxlnzY0HTgU2t7oyg5IVnYTk3Swm6S6tsFfrvqss17VTY/NBtmm0I1hLpNcOV3UYdLX
t7bqrnawMM6qzm9Zuklf7ph8Wv8U5ufn91oXLc4PQFfoUPbV3dDG9UDiH9At+PX0h/Wp4SYGmdZY /fzgC+Ny7e3H162bX4afT1f8MurWdRyVtVsqrmy6
q42bVWoLC121Q5ivvywU/OUBABgOOpQj1vYB0A7mlmcsb//gOwjlPUgefl0t+FJxqfqnxpdJlYNq
rN2atnvd6coov0GWY1f1aoPNW66Oo6z/KMseNptX4y+bWZj/kN8WbbM2tTb2+e1u6YYhVhdg1NbW
tmwEYJjoUDbQ9oFE+dlBsO7BMJc+dXC1A++wD4Z15y0lVf/UeIyOlvkolofKtfWtrfVu2EbVdl0o
m5dxntdJrvs0URuPWztr2SvYdwCYVXQoa2r75MEOkpZnKm+NDw9YdesSSz9ovrHpB82zrljesTqM
mtUpVddw/Lgra9/UPHW9XFSmBRuuout61dFkfRhl/Qcpu8m8Dss4123cdLn+jXLdTtF6YcGGAWBW
TX2HUgeiMDRl08by0sHEH9/FwaVJGTZNl2L1qFJXP97CNBmk7TVdrM3GSW4Z23z78SY3XddyZY+y
Xj6VbZ8WzLjWv2nZSmufFkbJL79K3TTO5tVvg2G2fdf8+c4t51xcSm4aDZtcuqp5VNVkGgCYdXO9
nW/5Xh9AI+EJTlVNpwOAcTbMfduo9qPsvzFsCwsLxa5du/pDwPBxyyvQIZ1U6OSiDk5GAEyzuvvE
STLN8wYAKXQogY7V7RzSmQQwrbR/G9Y+bhT70mHOHwCMCzqUAAAAAIBG6FACAAAAABqhQwkAAAAA
aIQOJQAAAACgkantUOpNa6lQxk+T+h6qmi5H01kI5eIkNz43nS+X1o/zQ0xqvC+XJpe/Py6XB8Zb
bhkPQ1m547Bupepg7RaLz8V1LVW2P74sfliqlplLFxsfSzdJqtTf5juWNhdnYvG59Mami6XNxaVU
nSaXLhaXSgsA02xqO5T2pjV721o4nJNKU2VaqZrOpwOQ1U8hPECl4iR18CqbzlclrR+fSmf55MrK
qVIPTLZRL+Oy8sZhnUvVIdd2ubiu5cr2xyv4RlHnqmXm0vlxNt7GTSp//lL8+fbnXXJxIcWbYZZr
qk6TS5eK03cA1c3N7dwImFwzfcurDgAWfOGwiaWLpU2li6U1TQ9CynPQA1gsD/8A2bZUncvqEX4a
DYfjxMbH0vufmB1a5rF1b5zk6pir+yjnq2rZ49j+41afURjVcqlabtt1Y5kDadouhxl8sfhhBAxu
ZjuUWoF0ULFQd4Xyp89NO2g5ZZRnV7rMuwmrj1+v1HIoa3eLx2wpW+bjsF5M63o5btuc6hPuF5qa
9P3JqOo+res6MMm0XQ4z+GLxwwgYHC/l6RtkhaozbZW043pyYidgfvDr6Q/rU8Nda9pO49i+s2gY
68i0Crc/o/GpuK7VLVvpbJph1tnKsvLr8uvt19nGzYJwPv02UfDbpS1t591lXQFUs7a2ZSNgcs1s
hzI8+HVlWOUMg+bFgg2Hxmlex6ku2MPfJmLr0KiMW32a0jxYGw9b3bKtzYddZ5U1KKuz8edlFG0/
DDZvNq8+f/67aoO28+6yrgAwS2b6CqUdTLo+oNQpR/FKNw5ydU3Niz+vo+bXZRzqgz3GdZlonbb1
Orf+j5rqNknr9KTVt45pnreYcd12AQCjM9PPULYll1edckZ1YqIyw3rWrUssfd1826hHSpgvRmdc
l4XWMws2PI5S28Qo25XtazaMajm3XS7rKwC0i1te+6HuyaM/fW7aquUozj4tmKp5hOpM16QMm6ZN
VepRpcwm84PhYNk0p/ayTwtmlO3atOxR1DlXpoZNlbr54/30sbSTSvNjcm2Si2tCeZim5Wo4puo0
uXS5OACYNTPRoUzt6DXegs8fTn0Xf9oq6cLxPj9NLG1qvMmNz03ny6VNTW/jy+JNKp1PaSyE/PFh
fGzYT2/CYQxfatkMS1m547COxOpgbeYHX2r8MOTKztUnN11XUmXGhmPpTCr9pIrVPTWPqbSpuJxU
Xr5c3rm4lNQ0seFYOsnFAcAsmelnKAEAwHDpit60muZ5A4AUOpQAAGAohnlFbxRXDrliiUm3urJS
nHLKKcVxxx1XPPjgg/2xQB4dSgAAAGCG3XPPPcWHPvShYsslxQPP/xw8fTTTxef+tSniqOOOqq4 /fbb+6mAODqUAAAAwAxSZ1Gdxs985jPFyy+/XLz
LtlrQ1lYWCouuuiiYrUfl7OwsOBCzEsvvVScd955/aG81dVVV2YVuTKffPLJ4swzz3TfVX/Nl+ZJ
YWllpXjjjTdcnD4tHz+IfnlS+pWVPS2wsrTk6piiuIVeGms/lWup/bx1a4TqCAyb1klbD8XWyzCI
tg9/2wn3B9pGbH3X9pbbNqad2sbaLRTG+e3sB6NbprSPcPuRYJ+z0vtucfrU/rVtWu46Dvh1krC+
YbzE0iiITqyUr9Ybs3379mLnzp39ocmRW96vvvqqi9cy0vzq+KdxoiUZtk0sn1xcrmyfyvXTabnq
+Kd6KfjHpyrC/EKp/UHuOBsOA2Ortzpr+3nf+97nOovqNJbRFqC0mkbbbZ3tDTNgbUotLy6uzc/P
r7344otu+JlnnnHDJ598shvOUTqFmFxcqK208715ufnmm933K664wqV74okn1h544AH33eJsHr/y
la+4Yd9ib/zrr7++duyxx66P2LVr7Ywzzlj/HtOLV1qVJypPeZ977rluWN8VZGVlxeUPDE1v/bzw
wgs3rYehXb00ilM60bqrYe0TbFuxbcC2Ja3n2k6OPPLIjXV9luzevTvZrmoXa8Mwzli7WtvZfkPt
a+1qy8PiNI3tb7poc+2fwjrb8ra6VBGuTzqWqL3smKL5q3J8GSeqvx1T/PbxKV7LTWkVlM7297YM
dbzNieVfZX2SVDod9zSsOuxaXnbfY8e+kPLTdh/m5/P3B7t6w/56a+u4HRtDuXyBrtRZ57QuH3DA
AXrQd23fffd1n6lQFu+2i96+EZjaK5Q7du92n7p8L1u2bCl6JwTFQw895IbDXxFjvyrqF0r9au5+
newN65dK46fVr9J2JfSWW25x4zRsLK1+2fR/6a1yFcQ9EN1L85GPfMQN6552Of7444tTTz3VfbdX
P/vZz9znYYcd5j59u/ffvzjooIMKu5Xh9v/yX4reyY/7HrP9kUeKt99+u+gdyN2wylP73XHHHW7Y
d/DBB7v28X+pB7qkKwdvvfVWfyhO2+U+++xT9A54btj2BR/+8Ifd/kBee+0196lfZ5VW67m2k+ef
fz66rk+7008/faNNQqeddlr/W9qNN95Y/OpXvyou6LednsNRu2pfZe166623urj77rvPxbllMT9f
PPXUU623ufa5qkPI1p1eJ9Z9VhGuT8rjkEMO2Wiv733ve0Wvo+K+Twotb9suUq699lq33DSvP//5
z9243zjmGPdp8/6+E090n3VUWZ8klc4/Fs4vLrrVe4qUH69k+T+UJy/P5jvDfvr7d/8zd+4z14n
030Ck8DurtNbiO+8886NfaDOCcPtwR8ui//GN75R7Nfbh+t8tos7TDA5prZDecABB7jPm266qfHt
a9rgrr76pOKVV14p7t+2zR1UjDpXotuedMJyQ+/AfMUVVxR33323G6eTI2Npv/a1rxWf+9wfuHzu
uusul69uO82xk6He+ZZzxHvvrX/xWCfRTgy0s1CnVZ3X9ZsU1unkyqZXvmeddZb7HvPDH/7Qfeok
oowOulLllgmgDYu9DeLee+/tD+1NP268+eab7gTf1uFPfvKT7lP7AtsfnHPEEe5TJ6c6SGpfsWfb
mT1qV/vRLXTCCSf0OnwX9If2Zm2uDld/d1X8P88+69pVJzL6Ec3f31lnRHFq86WVJbePatP3e50h
6wD6bF953XXXuXqVLe/Y+uSOMb31yI41Wody+9RxdEyvY5ha3iH9iHPppZe6Hyxvvfvzbtxa/9j2
aO/YpnbUsqyqbH0y6+n2/qEhfM5L3t9bRmWU31VXXdUfivunxx/ftN7664ettzqRXlpYcHFtr7dA
W3SsW1paKI4++mh3bijhttPGsH4gPKJ3POURqNk1tR3K66+/vjjwwAPdd3XclnoHQ+3463QrL774
4l5Pbv2Xz8cf/yf3GVpeXj+g6hdSu2KoDStm/aC46K5iXn755W6crhzm7Lla0D9F69dHz+nYRrt5
4553ndVrrrmmeLZ3Mrdt2/1urK406tfo+cVld3Kkq5OxZ4CMrk7WRYcSw7K4vNz/FqdtcP/etvUR
bcN9V199dW/zmHf7AgVdgZjv5/Pee++5df7jl122se3MYqcy1666UrWxH4rQyYr2ueeff35/zPrP
WWrXz372s+4HNz0zae2q8Wp3ddLU5qsrq70yvu/i2qBfy1d6n/aDV0jrx23PP+86nGXLW+uT5txf
n1Tv47ZudftW7UOPPfZY94y6Osexfeo4sqtuVezqrRtaP3Q8tePK67/1W64dt91/v2vHH//4x5W3
m7L1yayn21vsGFV2PBXlp6vlObbe/tEFF7j1Nlw/NM86zmr/obg211ugTf/8z/9c/MM/HLhXJ7Ar
wyoH42dqO5Q6YOiX10suuWSjYk6kd/9fPXH+5TVV2uPvVr57rf9tsn31e7H8rp9tX9UuRrnze2ztx
ldhB0RdunNu2fcL9wvqnf/qn7iqjDmx2+4FODnbtWnbbidRdluQfjnXldHFxXl3cqQ8NP3Kykq0
A6yT7br82yCAUdEvsrqapB9N/NNVvbRDV5R0IqhbM9WZ+XZw8qsrdLbtlN0KiD3045b2ZfN2K0VA
t7Wm2lXjLe7FF+9yn23Qfm25fytkSPtK3UWi2toPganlbevT75199qb1SftU5aFPdab1A+SOHVt7
YUex86ab+qmmi7YPseOKOmdqAx1zytqxbTr2hdo+mY3tD2zd0Txbezz33DfdJzButP7qXPjFF190
P4KF52ltDSvvZ555xm0bts1gtkz1W15FB3ttTHaLi13x8w9GVW5XsduaQqnxMbq9StwvrokTr1C4
8eogpul/8pOfuAObQqC5OoTT68Tv8MMPd/noJMl/BsinX9vF3uYHTIpvf/vb7lPruc9Ogv1nKO2q
+jBOTqeZfqyTj33sY+7T5Nq1yY9WdTz++OPuSnT4rHxd+iffEq5PRvH2PLo61dq3VrlSNslyx5xh
bTexOtQ5HufU3R+0VS7QFR339JjIc889956627lhuF5r2D9vLItXR3L37t0ubzuuYjZNbYdS93Hr
5MFuC/3t3/5t92knBRsbxOqqO/GI0a2pq6vrJxMf/ehH3WdqQdL51UuBfo9GgDk/CgZAcdddLs
JKXMnpOY9Zt19YyXblNVHpo3XWWxF+foeQ8906FbvWy+wxfv6Jd0nWSJu3Lbm//YwdDlOV8UT91w
gxtWfmrP2DMy1iHnJQUYB/aygfBXUtuW/Gco9UIpse1E26XF2XaMcm++uf6s9wc+8AH3aaxddQuo
tas9y2r7Le037V9t2P60DXp23YKx77Yf1f4v3FdqP+d3PH/wP/+n+0z96v71H/xgY9reLnMqnqfz
28CeK3bHrf7x0ObX2lHHHFuGtlybCts/xdYVrT927D3ppPe7z6p5+Pxp/P2BzZftD6w9enuRjXIt
PTDu1LHURYl33nnH3cERO//L/XhivvKVr7hnqPUoV5V3bWD6TW2H8pvf/KZ7/KZ74YCuCroXPiytuNs8
7e2DermAOnwLvQNGqiOkk83t2x9xLyE4Sc9f9Zxz222uU2kdK93mdPbZZxdLK6uuLHXW7BkiPVOi

MiythtWJ0z+P/dEvf+nGlfmDz62//GDnznfcp35Z0g5Aeag8PdNiJzqK09v39H+CLr/8u+4g554D
7dMJneZJv6CL4u0ZoJB2EDeedaN7Bkntp7L89vO9/vrr7jP1Cz4wTLEr7qK7FObnF4vPf/7zLmj/
cFn/xT62HW/dscPFadv49Kc/7eJQ7sUX139os32LsXa96aadrl31rPkf//EfuzjtJ7W/1L7lS1/6
ktu/nKa7N4ZAz2xqX6j935VXXunq6O8rfan1SdSR0v7YTqj0jLqeVR+0UzVO1FY6RuqYs3XrDtdW
dozT9qN21DFHy1DL13+GtktaX1Se1h87Pqn9jd423JS/P9B8+fsDa4/PH/V592Ke3LoDjDOdP/7i
F79wjz7FOpZ7my9uvvnm4m//9m833kkAmDn975D+d4wpXW3Vr7HjetDS1Qdd+dS98wAA+OzKn3+1
uFOrq8WZX/969k3QXRn6vAI9Wu8GXef0okady/kvWNTdfP/bu+8WS71O57B+LMJkmvpnKKeBrmyO
8wtC9PKL0/u3xgIA4NOdOrqzR3e7DIPeOntZ/8V3w6T505XR2DOYwLhTh1Evb3ziiSfcRQxdidfV
y11ra3QmUYorlAAAAMCEauMKJTAIrlACAAAAABqhQwkAAAAAaIQOJQAAAACgETqUAAAAAIBG6FAC
AAAAABqhQwkAAAAAaGRqO5Rzc3PJUKZKGqmariujLh+zI7WuabyFUNO4WZFrAz8ujE+NN6nxAAAA
XZjaDqX+vaaF2DCAanIdF3+78tM1jZsVVdrAjzdl081iWwIAgNGa6VtedfJlwdj3cFyYrkxsmnD6
MC5MLzYcxvnjjaXxxwGD0Lrkd2jQjlybNm1zlhUAABiFme1Q2smXBeuE2QmZfabS5dSdpiy9H29x
+u5/luUBNGHrF4ZL26+FqlhWAABgFHgpT4k2T9L8jp4+q+bdpA6cXGJc2XZgYdbX1VgbaNiC4o0N
03YAAGBc0KGswD+Bq6ruNHXTh8ITTWBcaf20zpKtt9gj10mk7QAAwLihQ1kiPIGryp+mynR108f4
03OiCYw/278AAABMKjqUNTTtpPnTWWcvdxLZpJymdQMwGqn9ANsyAACYJDPbobSOnYXwxM5O6vx0
uU6gryzvUN30PqWXQfIAmsitc03jZoXm2z4tGNoOAABMkpnoUKZOujTegi8c5w+H41Nsmlia1LhY
+txwmN6G/XFAG1LrVG6daxo3C/z5j7VDarzk4iQ1HgAAoAvc8goAAAAAaIQOJQAAAACgETqUAAAA
AIBG6FACAAAAABqhQwkAAAAAaIQOJQAAAACgkanuUOr/tMWkxoeqphtn/jw0mR9NkpSWv4eqPFRPVM2n
SrqyPEK5PKuU40Kq9wvB8XKkuTm7ZMOG2unDqq5GFprEw/tKFqfrl0XcRJOD6VLsbSWv4W
BpHLp0qcL5YOAAAMH1cop9yg/5Mu/J934XATbeQhOqH080qdYFZJV/fktGrZMUpvnxbaEMvPH+eP
D5XNT932yfHLGkSVOllZxsq1MOh8+fOSyy+Xros4CYcllq6MX8YgcvWtGmfjbRwAABg9OpQ9Ojmx
YPwTFxNLJ3XSij8+jLe42Hj7DOPExodxNux/lqWpy/JM5Wv8YUs/zieFYf1NrN7+ya7P5tPnD1v8
IO1Qdfo65fjpmtbP5s1nw+H4cTeJ9a26zKrMm9LUybOurvIFAADdm/kOpZ0kWbCTKzvBsc9UOuOf
bOXS+nGpPKrE+3Fl04nG+58xubiUKmWHwrr7NBwLXVL+sXmv2x5hess31S7+uDBew7GQUpZG46vM
TyyPuu0gVl4475ZXmKeVG4YUxZXVq0qaHL8eg+QzCrn6Kk7zZKq0o/G/i7VPGLqk/CdteQAAMM2m
vkMZnugodKHJCU7dado6iVI+1g76HCTfpvPtB18YZ2ESldU7N49hnIUUP03TddzWhUHyiFF+Zazc
MLRN8+WHVBkW11U9JonfDmFbhHEWyqh9Y2LLRd9j420cAAAYranvUNoJjh9CdmJSdnJSNd0gmpbR
dLo2jLLsQanOsXVikrRV/0lph0GWmabzQ4riJnm9Hkd+m6ba3pZL2OY23lgesbQAAGC4eIayx05M
LKRUTTeIpmU0nW5Q/oldG+Uqv1jokl/GIGW1WU+rUxia0HTDXCeaCOfTQoofn0s3CH+97qqMSWfL
IQwp1p5NKe9BpgcAAO2jQxnInQz5qqbLKcujaRlVprOT5DZPznLlVp0XO+EMQ1fCMqqUpTTh/LTd
llanMMRUbdtRqVK/2LwqxITxqXRtGkYZk8hfFn6Iya0H474OAwCAtJnvUOrkRyczFsKTIVvRKUvn
y6X148I8ctPl1JlO8Sm5uBS/7LDcXFwb/PzDMjRsculy/DxCTfPsQhvz10YePj+/qnm1zerQpVy7
+WXn0nURlxOm1fAwDDov/ng/fSwtAAAYnqnuUKZONMLxGrbgC8fl0oVSaSU1XlLTVRkumy4W78vF
SSrezzdMk4trg+Uf5h0bjqXz5eJicnmG4/zhWPpBWT1ieafKC8fn8pDU+BQ/L3/auvnk1MmrzXJ9
yteCLzYcSyddxElqfBWDTJuSq28suLxubQAAGB4uOV1yOxX9VH/us4v+5gFWse1rmMd2z0AAGgb
Hcoh08mcH0ApFk8y8ptFG5SWjluMesgbjQfFYnWAwCDoUAIAAAAAGqFDCQAAAAAAGqFDCQAAAABohA4lAAAAAKAROpQA
AAAAgEamtkNpb1GNhUm8y8Qo9FFtFxedP40FtpQNb9culyce
8eNy6QAAADCdprZDqTcXWogNt00mR0/n013mP878eR9GO1j+fjmDlOfXWSHVcMcqlq5gHWTFrjT1c2bRVV
65JLVyWPcFwqHQAAAKbXTN/yqpNfC6FYnH0P08fG67sFXyytLzZdmDaMC9OLDVdJW1Vsevvujw/j /ThfON6+h585SqOOzCAGnT6mizwBAACAcTO
Ta/v9ul/l1yZflwsL/+zCeUZC10rK0dxTebL8g3DqKjs2Hxo3CjrBQAAgOHipTwVDNKxiambn3+S
njqRj/HTtT0PbWpat1xbaHwslCnLU/EWwnQ2ztJV5edpeYQs3zAAAAAAo8Qtr/3g04l6Km7c1Kln
nbQxTaZvMk0Vym/YHSor00I4T03r4+fZNI9hGkXbAwAAYDzNdIcydyLvj2+7M9Qmv54KKWFnqAl/
+qp5NJmmDZrfWMhR/DDrWEc4HxZGxS9/lPUAAADAaHHLa59/UjyOJ8jq6KheuQ5P1Xq3MX9N8khN
UzcvpS/r+Ck+FlKq5DlK4XxYGIWw/FHVAwAAAKM3sx1KnQSrE2HBPynOxYnG5ZRNn1J3ujrp/bRl
+cbUKcvkpvHjwrw0zv/0+XFhaMqmjeXlf686P2Gcz9J1KVcXv+xculxcTp20AAAAmHwz0aFMneBq
vIVQKi6X3mfpYuNzUtNJalwsfS6tfTep7yGbPkyTmz41jcTG++Ny08RCU7m8/O8SS2NycSl10taR
qktsOJZOcnEmFwcAAIDpxy2vwcJpE6YredOGq5MAACzhw4lMALT2PGiMwkAADB76FACAAAAABqh
QwkAAAAAaIQOJQAAAACgETqUAAAAAIBG6FACAAAAABqhQwkAAAAAaIQOJQAAAACgETqUAAAAAIBG
6FACAAAAABqhQwkAAAAAaIQOJQAAAACgETqUAAAAAIBG6FACAAAAABqhQwkAAAAAaIQOJQAAAACg
ETqUAAAAAIBG6FACAAAAABqhQwkAAAAAaGRqO5Svvvpqcd555xxXHHXdccdRRR7nvL730Uj82TmkW
Fhb6Q5tpWj+/paWV4o033uH7qHpFZ588sn+mD3j2ra6ulosLC25+iwsLBXbtm0rVvtxOW3Wx9Wl
AAAAwOyZ2g7lN77xjeK1114rbr755mLHjh3Fj3/84/LKK6/sb/sux26s6YJBfwVzW57BHTzyeUQ9ommmV38rKistvdXWl
WF5e7sfuTeV3qteZ3Lp1a3HCb/1W8fzxewL/r7f7z/4
1luLp556qvjwz9vcPLKK27cvvvu6z6bDp75e6Gqe9DwDrtN4/PlzaEfPMDOjQO7/4zpUSDJqwXzZrm/
GhVbWzzIIoXD36RVsl7y7PDdWEYvRWYTYhtNGRjWbZlMrWRrzh8sMiNbdSBHgPN76Vzz8ZZ
PPjgg/2hzbZv375xpb+pfOVwfOW275pj5PpgTl2UlHVThzs4hp/hj6zXXHBCZd8sTXOzbxI5J34/PcEOb
7SruuOMONyNK28q5FvbsBQNvH8PR7ZKkgnwSVzO8Krt7/KXXnldPoRTXQT+tJKXJxJZxWOZHqqjuzMn6bl1ofi4zrLPEWnJ9Xdv+/3lDfQZs6
rOCyJoxdrsN52kH5/HUTVXoFgYc0RjO/K/b8t16T5fRT+j4Qtlh3GeUzc9yh9zh7yQhtnD+IKyMOcNg0FAgy+8rsOZr+eUuJYnU2o8YfirYvr
PlqkuQUq+KVZdqSq/fKkwGGDyiu2GlfCqnYJS8WXbxr9DNqqx6AEQv6rmvb3/uzH7Gn7SUueJzkB6C7j1/d47nc5ugmUvQ0Bn32UhlHdQrx
d9b1tAkFwSdUhfHJdJsHCvWE5m6m5A8dkmgc3N9+nh/xhiJyTXGXE1Wcu6Nly8QX/hLQPT+OM8Xk7tv
VkN9PWwP9W9fnTYhYKsCfrOjdW9JIdIHx7n2PXyvAVzpvM4S3k1QXnIh8ibNFBGJgm8pjRQY6vAqLKc
ySKlCMZqrl6Dk85YDlTQzTYTnnR16rzBr3C71VUFR42avN6n6dGCHmBzV1T2TYjibxnOX8vptpXMHFmk
5ra/2qCYFSCgBn+tnYe9GqXhmmRUTdrfpvUo/XTh4cyIxpl7nK3uk0C1bnyzS0ZSPQ0d1OQKuc6nIhZ
RWtBQMp30gY2RhF0KZaN2dxDDBeRl48HTJa9bH2XtgXEHR2eBb8XCPQnRb+8nbBbT8pUPs2BMWSzq
Dv/vx0O3Bc/5nJN9K7+1QvD8wkUmLhHyM2odmzi9gJ3Z8EqtTYHe7f3j/iX4JzOWJ9c7Dg6Ryn3pY09MLo
d9fhbRiVDZEGMFuEJDkqpi0DRNC2KlzgJZAU1e1bSi0/bKs00NVZaQB5xdJ1ec4jrgHOZ1/UJYnBHj
GX6eQVzbhL/0eDpmzrTcjO7nrfyBDUOGu1WhO0xmb1mfQtwKEdAMmb37kxA8dsbTLH2U6GZ0kfeQ8aQ
mX3hUvwhG9jjw6HQJSOUj6V6fl0R1LUpMkYybYHMUCSgc9DbBiOWtEhR9UEq5n1JLuPQO8WXBfTwN
+bR+4mj+x2ZkvNh4RmZ9TnGEh9R0lmsSCpOdpKSLjS2cPm1Z5YDGvPJ6CF2S7HmAAF8zIdQ2xgvc0T0
8cz6v1p9KMmR1bfZaNOVmfT6T9vqKqABDF8WRbdrgy4GJ+3uN4FcHUMyZZhS3HPfnOBdRrK9SVq36vAVu
9A2Tln09GHZVUP7hmOIvPNCzhEVhfC0Gh6kQt2xg0hMzRRUc0rPGxOKw1OZ4E/kWkVBWIg6ZhxUD2aZ9
7bJeubxH3R7AKKytbdkUAOEZyiGxk41xkDvZiR2sReMtjJpfl3GoD9LGab03uTopztb/2HYwLIOs
26Nq80HKHVWd2zDJdQcAoA10KFtQduLZ9glHWXlGZYZp69Yllr5uvm3UIyXMF8NT1vZtLeNhUV0t
2PAo5Np1lG1eVnbKKOuMdjVdBwY1qnIBANXMfIdSJzI6WFmoemLjT5ebRvH2acG0UXbZdE3KsGna

VKUeVcpsMj/oRm5ZaNg+LZiul2HX+XctV/9cnIbt00KbcmXnjLLOdfnlV5lff7yfPpZ2Uml+TK5N
cnFNKA/TtFwN1+VP07RcAJg1U92hTO3gw/EatuCrMhyOC1kaP/hS401ufG46Xy5tanobXxZvUul8
SmMh5I8P42PDfnoTDqN7uWURBl9qfFty+Vcps6t6VVVW/1icPz4W34Zc3rnyUtP542Pxg8rlF4sL
x1mdUvmk0k+qWN1T85hKm4rLSeXly+Wdi8tJ5eXL5Z2LA4BZwi2vDfm/TPLrJAAA1eiYOa2med4A
IIUOZUP+L5N0JgEAKDfMY+Yojs2cEwCYRXQoAQAAAACN0KEEAAAAADRChxIAAAAA0AgdSgAAAABA
I1PdoUy9ba3pW9g0nYVQLk5S4yUX58uV4cf5ISY13hdLUyc/jbMQ8uP8YHJxOWG6MA8/pOJT/LjU
91mVagONtxDKxbXBzz8sIzXel4sbhlwdm8a1IZe/H+fHh+P9OEmN71LVMv10YdrUuElWpf4237G0
uTgTi8+lD8XSWp5186kyTS5dLC6VFgCmGVcoK9IBwt7ephAeQFJxkju45OJ8ZWWIH59KZ/lULTdU
ZTorI1UH8eMt+MK4snKtTD+dP31sWPxxCmXlYLNUe9nyiLVrLq5NfhmmStld1aeqXB2bxrWhSv5+
vPHH+eOl6zrH1C3TT2v8PGx6GzepytpB/Pn2511ycSHFmyrlmljaOuWaqtPk0qXi9B3A3ubmdm4K
mC4z36EMDyThsGl6kLCDTkwuzhdLp+FUXQeVq1dZucOuK0Ynt56MUtn6O+7GtY65elVdF8J047w8
xnX97kIb89pk+lG1cdUyc+lGUW9gXGjbrRtCsTRlAeOLK5Qd6/KANEkHNA6+02ecl2nTA5DSs642
U9bmk9i2ZfNkJnHefKOqe51yJ72NgWmibbFuCMXSlAWMr6nvUPonBBYGpTzGccUO5zOspz+sTw03
Mci0xurnB18Yl2tvP75u3fwy/HwwHHWWVR1ajhZiZUzK8g7raPMTq38urm2x/DVsQfF1dV3nmLJ6
pubJhsM627hp5c93OO++XFyXmrR91bqm0mn8qOYXAMbF1HcotZMPw7QK5zE2r3bwUxiE8h4kD7+u
FnypuFT9U+PLpMpBd9TOtqy6aPMqedry9teXrurTJqtjrv6xuK6pvElhbWPtlVI2T4r30/jtP8y2
HyZ/Hoc5n7llZfXIpenSsNsCmFRra1s2BUwXbnmtaVQHrZjcASx1gLOD37Dnoa2Dbar+qfEYT+O6
rLSe2rra1jrblMof1zaqW6+yaYY9ryqrrfLGdTmNSlftoXwV7Luv6fKsWteu5gkApgUdSk94kAqN
6qCiMsO61a1LLP2g+camHzTPumJ5x+qA8dH1ssnln4vTemPBhkcltl6Pg1S9Blmmw57XqnUdZJ5m
VVfLUnlasGHTdDlVrWsqHesHAOwx8x1KHSh0YCg7uNjBw9LasPh5KFQ5SNXVpAybpkuxelSpqx9v
AdMjtw5UWT8GMcqy26B62acFM8p5U572acE0Ldvy8KftWq6ufvlV5skf76ePpZ1Umh+TaxNL58cP
our0VeoUsvH+dCb2PZYuVy4AzJq53k6QvSAAAOjcMDtfo+ro0cHEsC0sLBS7du3qDwHDxy2vAABg
aNThmlbTPG8AkEKHEgAADIWu3A3r6t0orhIOc/4AYFzQoQQAAAAANEKHEgAAAADQCB1KAAAAAEAj
dCgBAAAAAI1MdYcy9bY1G9/W29iUj4VQkzh/fCw+lEvnx/khJjXeF0tTJz+NsxDy4/xgcnE5Ybow
Dz+k4lP8uNT3aVe1fXwab6ELufxzcSYXNwxldcyNz003qFz+TeL88bH4QaXyq1NeWR6+KvmNs6rt
EZt3ycWZWHwuvbHpYmn9uFh8yqBp/TIt3v8OALNi5q5Qakdvb2Br401slp8F/0DSNM4fr5CTy8f4
8al0lk9s+iqqTGdlpOogfrwFXxhXVq6V6afzp48Niz9OoaycWZVrl1ScLZOu2jaXf5Wy265PXWV1
TNWvbLpB5fJvGuePV2iTX44vV59QlTwsjY2bVLl2MP58+/MuubiQ4s2g5Ro/vooq5ZqyefHLrVo+
MGpzczs3BWAQM9WhtIOS8Q8S9l2f4Xh/ONT1wUNlp8qIxWk4V99B5OpSVu6w64ru5daHsnWlS7n8
uy67C36dc+3ata7btc15ayOvUbb1sFWd11yaJm01quXE+oFppnWzSgjF0sQCEDMzHUptBGU7f0uj
YBuOPzxsVeoc02SaUZmkumKz3LKb1OXadJvrgu2DfNO6vbTd7m3kVSePcVpvmhhV3dsq17aVcHtJ
aWvZ1i0XGAatr1VCKJYmFoCYmehQ5g4IvjBN3Q2najnD5h/0LPj19If1qeEmBpnWWP384Avjcu3t
x9etm1+Gnw/a1WXbli27cV6uVjcFfa+ryTR1TGq7tsWWSzivNm4WpJZzrF26prIsDLP9R1UuAIyb
qe9Q2oFtlnf2/kHPhkNqHwuDGLSt/bpa8KXiUvVPjS+TKgeTw5Zd1WWvdOOyrJvUw+Z1nOZjmqmN /Xa2drflMKuG3Qb+Mmhbblvqslxg GNbWtmwKwC
6p8aj9Fre5upI1W2xts62da6OUzDWNdzyy0Xl9JkmnEy6fVvYpbmWfOqYN8BAHubqZfy6ADYxQFh
VAfX2PzUrUss/aD5xqYfNM+6YnnH6oDR6HrZ56TK1jgLNjxJhrFu55Zbl8sU4yO1nIex/sV0Wa7m
04INm1HNLwCMo5nqUIoOCG0eCCwvfVowVpYF/2CUi6ujST42TZdi9ahSVz/eAqaLLdOulnFuPbOy /PhxU2U7iWk6XVXK0z4tmFxc1/WqK1cfDdfhT+/n
BYBZM9fbCbIXBAAAnRtm52tUHT06mBi2hYWFYteuXf0hYPhm7golAAAYHXW4ptU0zxsApNChBAAA
Q6Erd8O6ejeKq4TDnD8AGBd0KAEAAAAAjdChBAAAAAA0QocSAAAAANAIHUoAAAAAQCNT3aFMvW2t
6VvY/OkGycNCqI24WLwvl86P80NMarwvlsYfZ/n7IVQlDUarbJnE4oe1PMvKDuNT44etrB658bnp
BpXLPxdnmk7XVCrPqmXm0sXGx9JNkir1t/nOpS2L8+NtODeN5NLl4nKqpC/LOxyfSwsA02rqr1DG
dvZNDfrmNpVtb4BT8OvSNM748Sl180mls3xi09dVVpaEaTA+ytaBWLytPxbaWI9icvn65Zth1atM
WT1S9eq6/rn8q5SdGlc2XVOpvKqWmUvnx9l4Gzep/PlL8efbn3dflXysnarkJ7l0VfMIVUlXlncs
D6UDRmFubudGAIaNW157dFCw4LPhsk/RdwspXRxoVF6VfGPpYgfItlStV6jLOqFdgyzjUWla51Hy
65urf9fzNUnt1sZynqT5HdQkbheDqDq/uTSz1mYYHa1rZWF1dbWfel0sTSwAbZn6DqV2+LbR6DM8
ANg4C+EGFpvGhu2zLI+uqTwLddk8AHWVrTu2XYxCruxBtpdhitVxUrdXzccw6z7sdhr2/LWtrbpP
Sju0UcdJXt6YLFrXysL8/Hw/9bpYmlgA2sIVyhJVNrgmG2WbB17bMSiEJ6B1afow+PX0h9sorwq/
Lpgetkz99WsYVJ6F1Do16nXN2iVXxxSlt+m70lb+Nn/DqHNTsbr59fbH2zi0q+p60mXb58oFgFlH
h7Il/sFumNo+wCk/CzYcGva8hnXC+NO6Uba8bJm2vR7lys7VyepSpe5dG6R8TWvzMg5y7Wlx41Zn
X6puNt748zKO89E1m/8u+G0btq8Nd1k+MAnW1rZsBGDY6FC2IDzYlRmnA59/YA6pjrH4OvOK2aV1
x9af3HrWhaZls16XU3vWbaOmy2MSNGmPaTWq5dz1dssyBoC8mehQ6kAwrANC2UG07XpUPWhbG/jq
1iWWvo18fYNMi/GhZWjBhk24vrStadld16trw6h/k+0ztzzG2aSvD8M2quXc9XJqss4DwKyZ+SuU
OlDogGGhzoHDDmR+HrnpLb2ltWHJ1aNpXKhOWmPTdMWvT9U6YbI1WQ/bkit7lPXyNa1H1/VXnvZp
wYxrnWNyZWrYVKmbP95PH0s7qTQ/pkqb1JHLT8Mml65qHlX509h3y7tJfgAwC6a6QxkedIz/XTRs
wZcbDtP7w/54n6Xxgy81XprGhXJpU9Pb+LJ4k0onfpy+hyEUG4fxUraMUsvVQpfqlp2LG6ayeuTG
56YbhJ93rIzUeF8srsp0TaXyTJUZG46lM6n0kypW99Q85uYzFxdK5RcbjqWTXFxOKi/j52shFBsH
ALOGZygBAMDQTPOVPq5iAphFdCgBAMBQpK70dWEUVw+HOX8AMC7oUAIAAAAAGqFDCQAAAABohA4l
AAAAAKAROpQAAAAAgEZmokOZ+x9Sdd7IVpZP23GhXFo/zg8xqfG+WBp/nOXvh1CVNJhusWUerhOx
NMMQK3fUdaoiV8dc3DCkyvXrFaZJje+SX2au3Fya2PhYuklSpf423xZ8qfG+ML7KNJJL14tLqTtN
Kl04vk6eADAtpr5DqR27vXVNoemOPpdPF3GhKmn9+FQ6yydXVlVlZUmYBrMjtY6NwzoRq5ttGxba
2EbalqvjqOtfVp5fNzPKOvvlxuTq5sfZeBs3qfz5K2Pz7s+v3yYKufxsuqrT5NJVzcNXd5pUfGy8
8gOm2dzczo0AmKnuUNpBw5c6eGhc6qAhozxI1JmPNsTKq6LLOmGyVF2Hmq5rs6pOWw2zXXPLMRc3
imVfdZ0bRd1GZZK31yb1aWMexrEtMP203sXC6upqdHwXwReLH0XA6PEMZY9WRh0YFCZpxeRghnFV
Zd207W7YRlXusGj+hr0fK2tPq9Ow65XSdn2UzySvU3Xq3nbbjbvUsp3mfQjGl9a7WJifn4+O7yL4
YvGjCBg9OpQ9dVfGtk4elId/cB40Tz+vWJ7+sJXdNb8uwDhre3vsUqqONm5Y23dVVqdcvWLz05Uq
9fGFdbPpwvE2bppZu1kbDFuqTGt7f3lU0WQaYJatrW3ZCIChQzlCdiBr6+Ds52XDITvoDlpWVWGd
gFGybS7G4iwMaxtpIlVHjRs341antupjy8D46884rzuDaKvt6rI2tTaO6aLtc+UBAPagQ1nTOB1g
cgfO1IHVDrocJDFKo9yOVLZtG7ltCMMzyvWhTFndxrnu00Rt3HY7V1l2SqNg3wEAe5vqDqUOFOEB
oMoBJGWQaQfRxnzE0reRr2+QaYFh0PppwYYnSbi9ToKyOg97v1GnDdmnbTaq9S9XbtM6VVm2irdg
wwCAvU39FUodAHTgsND0gGAHLT8vkyujaVyoTlpj03TFr0/VOgHjqsk2Nmy5Oo5r/XP10rB9Wuha
lfqIfffThjTOpvfz9fOcdP5859ouF5eSm0bDJpeuah4+G+9PZ1LTAADSZuKWVx1gLITCcbE04udh
wZcaL03jQrm0qeltfFm8SaUTP07fwxCKjcNsSa0D47BupNZZC+MqV8dc3DCkyk3Vyx8fi+9Kqjx/
2E9jIRSOS6WbFHXmMZU2FZeSmiY2HEsnubgYP304nf/dV3c8AMwSnqEEAABDM81XAbnCCWAW0aEE
AABDEV4R7NIorh4Oc/4AYFzQoQQAAAAANEKHEgAAAADQCB1KAAAAAEAjdCgBAAAAAI1MfYfS/seU
haqavqktV1YuTlLjJRfny5Xhx/khJjXeF0szSH6j0mbdxnk+RyW1nljoSirvXNm5uGEqq0dufG66
rvjlxspPjRc/LhbfhTrlpdLEpq+S37iy+Smbh1y6XJwJ4+tMk0qbGl+mSvoqeftxZWkBYBpNdYdS
O3V745qFLnf0YXl+Wbk4ydUrF+crK0P8+FQ6y6dquZNO84puxNYhW79S618bUnnmyh5Gvaooq0eq
XqOsv1+ugq9Kvfz4rtVpp1Scn4elsXGTyJ8ff55CuXRV8xDFS9Vp/DQKvjrl+qqkq5J3OE7pgC7M
ze3cCMC4mflbXnUwsGDsezguTBdqeiBRnqlpc3G+WDoN5+o7iKr1StH0Fnw2HPv004bDxsaHcTZc
Jc4PJjbOpMYjbpD1pgoti6pldF2XJnJ1qjNvo1KnjuM8P5PQ1uNkWG3VxnKpmgfLH4PSutZW8IVx
q6ure42rE4BBzVyH0j9AaCPSsAXbqCyNfabStcXKicnFVTHo9F0oa0+LN356fQ+HjT8+jJPUdMaf
1oYll29ZnrPM2mbYqpSpuk3i8hpFe9bRZJnbshi35VFnPprMN+prq53bWlYsd5TR+tFW8IVx8/Pz

e42rE4BBTXWHUhuJnahY8HW5EY3rgSZsj7Ce/rC1X11+3hZ8Ze0SxpcNV9V0uqq6zn/a2Lox7Haz
MhX8ddOGR1WvmDr1GMf6h1SvkOppIRbftjbayc/Dn97GzYLUfMbaZRpM4zxhsqytbdkIwLiZ+iuU
OgD4ITwI2sEvHD+t/Law4dCgbeKXYSE0aBldUp3COo9zfcdRrA1Dtm4Mu01T9bI6j6pegxrX+ltd
rH6+cHgY2monm974+TbNc9zZvNm8xkx7G5hcGwDArJn6l/Lk2AHBQlvG6UCTawPVMRbfRZv4umr3
NqSWnV/fcavzuFJb2voVW8+Ql1oXx1WuvtO83UzachrUqJblKNs5VbbGK9h3AJhVM/9SHtPWwSB1
4OmaygznoW5dYunbyDcnzHsSpOo8ifPSFa0fFmzY0E7l2tzGRi23vFkXJsssLsvUtmj7N4ublu0V
AJqYuWco/Z2+Hx87GGi8hPnE0oqI99OaqnkMokkZNs0w+fVssx2azL9P09inBcnl68fVLW9W5dqz
a7myR1kvn8q2TwtVjEv9Q7l6jaLOuTI1XIc/vZ/vMOajTVXbJJcuF5eSm0bDVbSRh8+fxr5b3k3y
A4BZMNfb+Zbv9QEAAAakTtmwTjuGWZZvVOVidi0sLBS7du3qDwHDxy2vAABgaKb5Sh9XMQHMIjqU
AABgKHTlblhX70ZxlXCY8we05dVXXy1OOeWUYmFpqXjyySf7Y4Hq6FACAAAAM0YdyW3bthWHHnpo
8fDDDxerKyvFpz71qeK4444rdu7c2U8FlKNDCQAAAMyQlaWl4ogjjiiuu+66/ph17777bvH0008X
H/vYx9xVSzqWqGKqO5T61UW/shx11FHFwsJScdFFFxWr/bgcPdysEPPSSy8V5513Xn8ob3V11ZVZ
Ra5M3X5w5plnuu+qv+ZL86SwtLJSvPHGGy5On5aPH+See+5x6VdW9rSAdiaqY4ridPuDtZ/KtdR+
3trhcIsEhkXboLYrrZfavlPb9fp6u2eb0vah7UXjFWLrcxhmldo0Nf9hXG6/o92L9pd+m9v+SlZ6
CbT/UJw+tWzbkquX0fLXOhSON8rDr7/mXb/oy+233+6m1b7VbN++fSJPvnLLW/OreM2/5lftYW2g
9tMy1fFB8f7xyJdqf8mVncvfz9MPVWk+cunDfC2tyvfbQ99j+xFgXN1yyy3F+973Prc9qfOYo6uW
6lhqXdf+Gkham1LLi4tr8/Pzay+++KIbfuaZZ9zwySef7IZzlE4hJhcXaivtfG9ebr75Zvf9iiuu
cOmeeOKJtQceeMB9tzibx6985Stu2LfYG///666+vHXvssesjdu1aO+OMM9a/x/TilVblicpT3uee
e64b1ncFWVlZcfkDw6D19vDDD1/bvXu327799dJom/DXUbFxWpd3LS+777FtxfK88MIL+2Nmh9pU
8x22nWj/oXYO42y/Y/sKn5aV2+f09ifKW+msXW2foultfxMux0Hk9odG+y6lUYjRPFn9Nf9KZ8cQ
fWqebFjxVY4v40T1t2NKrg2OPPJIl9aWoe3v1bYa1vZky9OOR75Y/qn1yVc1f1vWVbZZlav1Mleu
HVtj+dn2sau3Tijou38szeULdKXKOqf9nY6dOvW3sO+++24aDkMYr32ctkUgNLVXKHfs3u0+X375
Zfe5ZcsW90rlhx56yA2HvyLGflXUL8/61VxXB/W7jH6RNH5a/SqtX28Ur19+RMPG0oa/bLp8S37x
efDBB93P/B/5yEfcsG5DkOOPP7449dRT3Xcb97Of/cx9HnbYYe7Tt3v//YuDDjqosF+jbv8v/6Xo
7Rjc95jtjzxSvP3220XvgO+GVZ7a74477nDDvoMPPti1j/9LPdCVe++9t/jJT35SHHLIIcWHP/xh
N+61115zn05ve7n7pz/tD+zhbzvzi4vue2z7++IXv1js39teieO/TGz4/TTT9/clp7TTjut/22z
v/mbv3GfvU6H+/RpWT311FNFMT/vlpfYcrjvvvuKffbZx+2bFa90sf1LU7n9oWh/rF/fc6699tqN
+vc6Im5c7wTLfb711ltunqy9vve97xW9joX7Pim0vO0YmaI2eP755928/vznP3fjfuOYY9ynbT/a
nrRdSVmbmtT65Kua/6W9Y4/WpUsuuaQ/Jk3l2jJM0bKVY4891n36bP3tncC7IJYeGEe6svihD32o
WOxtR9re/fVf54Th9pCL1/Znz1iWnb9itkxth/KAAw5wnzfddFOljluMDhJXX31S8corrxT3b9vm
DqrG/t+PbnvSBnZD78B8xRVXFHfffbcb505C+izt1772teJzn/sDl89dd93l8tVtpzl28Owft4oj
3ntv/YvHOol2YnDnnXe6Tqs6r71DshsnOoGy6ZXvWWed5b7H/PCHP3SfdhKYYwf6F154wX0Cw6IX
CIh/wNOPIVedeGJ/aI/YrT3vf/PN/rd12nb1Q4p+bKmy7k+bxd6Oxn50C51wwgm9Dt8F/aE97GT6
G9/4RrG0sLDXfse4H8d69AOUWEfMbildWlnauJ2xDbH9oZ//t771Lbd/r0I/LF566aWFdsPqJIs7
xvSOK3asUUcjt08dR8f0Ooap5R3S4w9qA3XQb731c25cuP3UkVqffFXydz9k9paDfvzUj6ZlVO5V
V13VH4qzdUfPlunEeX2dXmc/xOr2bDuviP2YAoyabr/X+qv9sv/DUXgsbDKs/Z0ulmjfyDOWkKnt
UF5//fXFgQce6L6r47bUOxjqoFCnW3nxxRfrp1H3/fHH/8l9hpaX1zuL+gXVrhjql/eY9V/fF91V
zMsvv9yN05XDnD1XC/o9yn59tAHbc4ubN/Z511m95ppriemffbbYtu1+N1YHW/0aPb+47A7AOijG
ngEyOqmuiw4lhknbwNYdO9x3u5qo7fvv//7vN7ZFX2ydDrc/bc+6Oum2/Rm0uLzc/7Y3Xana2A95
tP9Rm630Ovfzvem131la2ryn1Ym3vfjBlpWWx3vvveeu6ml/tbqy2ivj+y6uPZv3h5a/ngFUneb7
+9My6nTp6pfmSs/0iep93Natbt+qfaiuZukZdXVeJ+VujVtvvbX/rdyu3rLV+qHjqR1XYsfT8OQz
JbU++arkrx8MtP6df/75/TF5KrdKx1N53vb882591bpjnUpNr3OLc845x51XKN36vADj5f/eb7/K
22NT+kHxf/yP/9Efwiyb2g6lDhh2EmAdSx0Uvt5/uU1Vdrj71a+e63/bbJ99Xux/K6df6JeWFtwG
eO9ll7lxZR23cGewbdsn3C+sf/qnf+quMupgZldndHKwa9eym3e7ami35+iXc10ZXVycdx1e5aHp
dRIY6wDr9qG6wtsmgM70OgNf/epX3fajqw22vn+7d9KnOwVitK2E/O1r/VfW1eyt4Nib9ju6I0NX
dHWFU1588S73Keq8ff7zn3edR+2PbVkZDds4f7pBxfaHlr86t+pk1mFXH+2HMw1rvvWpTo1+hNix
Y2sv7Ch23nSTSzNtbPnacSV2nGjzOFCWv35U1T7gox/9aH9MO2yd1tzaj1N2hUePuLz55pvuh4rl
Xgdb5ftXMIFxoe1V5306z7M7Q8Lts+mwfkD7zne+4/KP/YCL2TPVb3kVHezVsbRbXOyKn39yWeU2
K7utKZQaH2O/0LtfM+0e1hLhxqyTI02vZ8h00NMJca4O4fQ6AB9++OEuHx0U/WeAfNpZiL3NDxgX
2l5P6Z3UiU7o/IOZfjTSlQP/GWf77m8nduXDH/f9769fvdL2gcH4+x09t6N2vvHGGzc6ZdLkR6tB
Wb1+/OMfJ9eTunTbtf0Ioc6F9q1ld55MOttu7CTVFx5zBlGWv7Z3Oemkarcut+Gv/uqv3Kee37Zn
KP3bCYFxo6v3//W//tfi5ptvdsP+NhRetNBwLl7b5AMPPLDxYxpgprZDqfu6dYJgt4X+9m//tvu0
k8WNDWZ1tXj88cfXvwd0a+rq6vozWvYLaHgSZB0vnVTYM0L2YobwiogdhN3tVr30Vew5uV0/Bdbz
oLpNVXlo3vSrv704R88i6V55Pdth8x1ebdEv6bpNR9yV2978+yfVxuXZO1Y+dcMNblj5qT1VRsg6
5DxHgmHQy090kNMVAjuhM3pe2YKx77Z+ajv9eX9bPen973efYj+shFfQkKd9km7zXL+NdH2/Zvud
lZX1fY1OZNzLdzy239LysGdwbH/ahtz+MLeeaD9nnUvdUaL9rZ9H+OKdr//gBxv5am1s8znQUfHb
ILd8/W3K2mfQZeiXXZa/PcMY/j7r51GVP40dZ3V8DNcdq5PKtvU21vEFxo3uonjnnXfcbdy5H37C
TqRou9Nt77qYwRVJxExth/Kb3/yme+GArgq6Fz4srbjbPC/ov0VQLxdQh2+h17FLdYR0kNi+/RH3
EoKTrr7ajTvntttcp9I6VtpAzz777GJpZf0ZIXXW7FkObbQqw9JqWJ24z3zmM8WPfvlLN67MH3xu /eUHO3e+4z51O586gMpD5emZFjsBVpzevqcrApdf/l13/
pw9qP5Xlt5/P3n7llR0Mg27V1pUgva3RTgKrnDx++tOfds86a1229VnP/JnYlXqU062j2odqn7R1
6w63P7T9ziOP/INbVnp+O1xW2k9qf6ll8aUvfcktj9NafBZN+9vc/rCKxeVdbp+pPK688kq3/vjP
6qmjqf2xvcBJz6hrXmP71EkVW77WBh/ptaeWm5ahtY+2s7aU5b/nxDfoUfb86le/6n+rT/Os5a7j
o8r112nd7aQ66TZu3Xav84zYcREYV7rL7cUXX0w+HuLTtm9XJLX9ASlz+t8h/e8YU7raql+H6p4M
DYteQKErn9rhAADgsx8R/CvCnVpdLc78+tc33sg7TEOfV6BH612TdU53VHzhC1/Y+I8CRh1J/SjH
ba2oauqfoZwG2qjH+RkNvdTn9P6tsQAA+HSnju7s0d0uw7Dt/vuLy/ovvhsmzZ+ujIaPuwDjSnes
6T0jzzzzjLtwoTvNnnjiCfeyHTqTqIMrlAAAAMCEanqFEmgLVygBAAAAAI3QoQQAAAAANEKHEgAA
AADQCB1KAAAAAEAjdCgBAAAAAI3QoQQAAAANDK1Hcq5ublkKFMljVRN15VRl4/ZZtuTH3xV42ZV
qg388WXxoVwcAABAF6a2Q6l/r2khNgxgMP42ldquYvHq7PjjZ7Hzk2sDf7yCLzddLg4AAKArM33L
q064LBj7Ho4L05WJTRNOH8aF6cWGwzh/vLE0/jhgGLTOqRNjwmFsVrVtBmlH2h8AAAzDzHYo7UTN
gnXC7CTMPlPpcupOU5bej7c4ffc/y/IAumLrXkjjLaC+VLuWoc0BAMAw8VKeEk1O6FL8jl6dk8Um
dWiz3kATWgct0MFJq7MvKGN50eYAAGBY6FBWoBMzC1XVnaZu+pCdQA6SB9CWtjpIqId2BwAAw0aH
soQ6Z/aLf52TNX+aKtPVTR/jT0+nEsNg2weaSbUf7QoAACYFHcoamnbS/Omss5c7WWxSTtO6AV1g
fSxXth8AAACYBDPbobSOnYXwxM5OiP10VU/+yvIO1U3vU3oZJA+gbbn1kXV1z3brt0MVtCsAABg3
M9GhTJ1YabwFXzjOHw7Hp9g0sTSpcbH0ueEwvQ3744Au5da13PqYi5sF/vzH2iEc9qWmkVwcAABA
F7jlFQAAAADQCB1KAAAAAEAjdCgBAAAAAI3QoQQAAAANEKHEgAAAADQCB1KAAAAAEAjdCgBAAAAA
i0mND1VNN878eWgyP5omFZpqKx+pmk+VdGV5hHJ5VinHnz6XvopcPrm4UNn0FuoKp2maj7Hpq+Rj
8eE0Nn5QVfPLpesiTsLxqXQxltbytzCIKvnE4mLT5PIAAADDwxXKKTfo/6ML/69dONxEG3mITij9
vFInmFXS1T05rVp2jNLbp4VB5OpSp56pOH96hUH5dRpElTpZWcafRiHXHlX485LLL5euizgJhyWW
roxfxiDK6iupceE0Ng4AAIweHcoenZxYMP6Ji4mlkzppxR8fxltcbLx9hnFi48M4G/Y/y9LUZXmm
8jX+sKUf55PCsP4mVm//ZNdn8+nzhy1+kHbITVs136p1qFNXmzefDYfj66hTh7YMUt9RqNNGVeZN
aUbR7gAAYPzNfIfSTpIs2MmVnTjZZyqd8U+2cmn9uFQeVeL9uLLpROP9z5hcXEqVskNh3X0ajoUu
Kf/YvNdtjzC95ZtqF39cGK/hWOhKlXlV+VXbxNKG827Th/nY/IUhpWqaqvWN8csYJJ9RyNVXcX67

lc2bn9b/LtY+YWhC01Vp56rpAADAcEx9h9I/ybHQhSYnOHWnaeskSvlYO+hzkHybzrcffGGchUlU
Vu/cPIZxFnJs/U6lG3RZN1WlTJu/MKT4aWxdrsLayEKqDIuzMMv8dgjbIoyzEKPxVdo+5E/nT2Pj
AADAaE19h1InIGEI2YlJ2clJ1XSDaFpG0+naMMqyB6U6x9aJSWTr9yQuhzoGWV7WRhZSFDfJ6/U4
sm3Ngt+uFpdi0xg/L5YPAACjxTOUPXZiYiGlarpBNC2j6XSDCk8SB6X8YqFLfhmDlNVmPa1OYWhK
0w6yfAadvow/j34YJX+9HnVdxlW4vCw04U+bykPju1wPAQBAfXQoA1VPhqqmyynLo2kZVaazk+Q2
T85y5VadFzuBD0NXwjKqlKU04Fy03ZZWpzDElLVt23Wrq8qyD+fTQkyV/NqWqsusC5eXhbrCaZvk
AQAARmPmO5Q6cdEJqoXwRMZOXsvS+XJp/bgwj9x0OXWmU3xKLi7FLzssNxfXBj//sAwNm1y6HD+P
UNM8u5Cri4bt04LxvzeVysOvU9ttk5tfn6XrUq4uftm5dF3E5YRpNTwMTetr/Gn8vOrmAwAA2jXV
HcrUiUY4XsMWfOG4XLpQKq2kxktquirDZdPF4n25OEnF+/mGaXJxbbD8w7xjw7F0vlxcTC7PcJw/
HEs/KKtHrNwwGP+7iY2T1Pgcvzx/+iZ5hSzvOnm1UW5Mqi6x4Vg66SJOUuOrGGTalLL6SiouHF+W
DwAAGA5ueR0y+1V91L+u88s+ZoHWca3rWMd2DwAA2kaHcsh0MueHUeGkshxtVG4S2ojluEesLWgf
AAAwCDqUAAAAAIBG6FACAAAAABqhQwkAAAAAaIQOJQAAAACgkantUNpbVGNhELnp28h/FPw6N62/
P+/+97qqTGf5h2EQVfNJpfPHx+JDFh9OY+MHVTW/XLq6cbF0AAAAmG5T26HUmwstxIbbppPpLvMf
Z/68D6MdLH+/nEHK8+uskOoY5dL54xVyLB8TTpsqv6pcPX25dE3iwnQAAACYfjN9y6tOfi2EYnH2
PUwfG6/vFnyxtL7YdGHaMC5MLzZcJW1Vsentuz8+jPfjfOF4+x5+5iiNOjKDaDp9aro26gQAAABM
gpntUNpJvwW/85KK03f/04Tjc3mLxYfKpgvVKadu3qHU9Ppun/53yZXpx8Xy8j+bUJ6x0IZcXhqf
q3dZflqVGYZxo3kbx3oBAACgG7yUp4JBOjYxdfPzT9L1WXV6P13b89CmpnXLtYXGx0KZsva1eAVb
JoNSPn6IlW9lhmEUVG5ZfQEAADAbuOW1H3zhCfM4q1PPOmljmkzfZJoqlN8oOjJdlKk8/TDurO0t
tL1sAQAAMDlmukPpnxQr+Pzx43zC7NdTISXsBDThT181jybTtEHzGws5ih+kjoNOn+PPgx8AAACA
UeKW1z7/5HwcT9TVUVG9ch2WqvVuY/6a5JGapm5eSl/WcVN8LKRUyXOUwvmwAAAAAIzSzHYodTKu
ToQF/+Q8Fycal1M2fUrd6eqk99OW5RtTpyyTm8aPC/PSOP/T58eFoSmbNpaX/z03P1VZHl3K1dMv
O5euaVw4DAAAgOk2Ex3K1AmuxlsIpeJy6X2WLjY+JzWdpMbF0ufS2neT+h6y6cM0uelT00hsvD8u
N00sNJXLy/8usTQmNq5Mk2mqSNUzNhxLJ03jAAAAMDu45RUYMnXCdCVv2nB1EgAAYPbQoQRGYBo7
XnQmAQAAZg8dSgAAAABAI3QoAQAAAACN0KEEAAAAADRChxIAAAAA0AgdSgAAAABAI3QoAQAAAACN
0KEEAAAAADRChxIAAAAA0AgdSgAAAABAI3QoAQAAAACN0KEEAAAAADRChxIAAAAA0AgdSgAAAABA
I3QoAQAAAACN0KEEAAAAADRChxIAAABAceaZZ7rw6quv9scA5ehQAgAAADPsnnvuKfbbb7/i4Ycf
Lu67777i6KOPLm655ZZ+LJBHHhxIAAACYQboSecoppxSf+cxinfFcFeeutt4ovfvGLxdLCAlcr
UWpqO5QLvQ0gFsq89NJLxXnnndcfysvl+eSTT7oNVN54441i27ZtxVFHHVUcd9xxxxfbt2914We0F
v35+nrffrtLr1+NjKbduXnf2nvqr9uVVBZCksrK6588fNW3R588EH3HZhEWq8XFpY21umQtmM/
Tum1/Wi70HT6ru1PdLBUem1vitd3bUuzZHV1tbjooos29h36XqV99GnTKV7fbZ+j6W3fp+Dvj3Ll
NRFb3irP8lc9/Pw1bPOjdcHq5bP6a31ROr/+TfbP40ptn9qOtOzo95atNLtYWGrY2VLnbiqbwt
hHJl+8Lla1QH1atKHr5UfkZxYfCp3HD/k0oLjCtdgdSVSF2VTFnp7asPPfRQt/8Dktam3Pz8vAtV
1UmfS7vYG7+ysuK+33zzAH3/Stf+Yq7Le+KJ9(truncated)

okOZOunSeAu+cJw/HI5PsWliaVLjYulzw2F6G/bHAW1IrVO5dS23PubiZkWqDfzxZfGh2DgAAIAu
ccsrAAAAAKAROpQAAAAAgEboUAIAAAAAGqFDCQAAAABoZG6NtzgAAADMBN4Qvce0tMU0zAfr5R6T
2BZcoQQAAAAANDLVVyhTPfyqPf9p+8WnyfxompSmbRPmOUgb+3nl8smla1qfsjxT+Vhc03JTUmWW
1dPkym8jj5Sw3pZfk7xMmKepU1fLw5/GDFI3U7UuuXRdxIni/fHhcI6l9cuQqtPH5OpbJc4fb/UD
ZhXbwB7T0hbTMB+sl3tMYltwhXLKDbpCanoLseEm2shDbIOzoOGYKun8+Cqqlh1jZfjTD6rJvFed
hzbyqMrPr6lUHerU1dIaf7qyaauoWpdcui7iJByWWLoyfhmDyNW3apyNt3EAAKA9XKHssZMNsfFV
x4nl5+ebSisWF04jqeksnT+tr+p0JpUmzNeXivfzjuVr/GGbJldemVz+vrJ6pOpQNT8Ty1ef4qcP
00ksv6r8ssryyaVJxYXj/eFcXI7SidLaNDZOquQR4+cV5hGOi6UxflyVvFJS6cLxTdJ1GRemkdx0
vjA/iaWrqmq5EpYdfs9NC4yK1ksAGLVBjo8z36EM06TiytJJ1bRNp5NUPrnpwu+59DmxdLm8UnH6
9IVpYvw0JpV/KJcuLC82fShVjs/y9csJv+fKDuNMrly/jJRcmlRcON4fzsWlhNNLKj+xNKFcOal8 /HGxNFIlXWpaUZzJpSkrQ3LpuogzsXGSGu+zNPr0hWX(
6+Uek9gWU3/LqxZKGLrQZMHXnaatlUv5WDvoc5B8m863H3xhnIUu+eW0uX6U1dsvN0wbxlkYRGpZ
a3zV9SDXPk3arkqZNu9hGCZrIwup8i1uFHUcN347hG0Rxlkoo/ZNCZeLvseWl40DAADtmPoOpZ2o
+CFkJxhlJxlV0w2iaRlNp2vDKMseVGx9mDW2XaSWn8UphO2Vi5smmjc/pCjO2kMBg/PbNNf2MeHy
sjwsTwAAMDheytNjJxgWUqqmG0TTMppONyj/BK2Ncu3EMQyToM16hvNvoSlNO8jyyS3ftpZ9StgG
FsaVtYfCONdzlMJlaSGlbB3TtIPEAwCA5uhQBnInNb6q6XLK8mhaRpXp7GS3zZOsXLlV50X1iYWu
NGlj1Secru229OfdD02k6lZ13nPpquaRUmX6sA0sTIJJqeewhcvSQkzZOqL41LQA9sb2sse0tMU0
zAfr5R6T2Ba85bXHP2GJjbdxuXRhOam04ucbTlu1jCbTWRp/OJdnKBXv5xvLU2JxbbD8JSw3Vg8J
61A1j1BZnqm8yvJtKpavX0cT1suk6iupdFI1D59No3g/XW6aOlL5WLmSK6eLOoVSdQnLy9W5izgJ
6yDhuFgaSY0fRKq+/nhTpd7Sdh2BcZPabkJV002yJm0hk9IeqvckL7tZWAermth1sFfR2V5yIzbK
ncCk74C6RvsMZpLbj2W/t7BNaCNgfFXdXmdhu64zj5M4/6qzTOpyq7N8ZsGkzj+3vA6ZVhQ/jGql
mdQVFhgGbRvaRrCO/QUwndiu95jE/dw07JtZB/eY5OVJh3LItKL4YVQmdYUdJtpoMJPefiz/PWJt
QfsAmDY6obcwCdgPT59JWwcNHUoAAIAZpxPYWe+gaP4tTNoJ/TRgHZzcdZAOJQAAAGbarHdkMHqT
vA7SoQQAAJhhXBnCqLEOTjY6lAAAADOKE/l1k3R74bRhHVw3yevg1P7bkNxCGWSWcyu9lTlpTerP
U27+cvx5H6QdqpRv+YealGf8PFP5xMr104bxufrYfJbl2VSV+ZFcujbjNC5XDwBAu1L7aX9/7Kcx
07ivrtIWkko37sL5mCSzsg5WNbHrYK+yU7/U2tzQUnlN+sZsdW8yH4NO7xu0/CbC6avm18Z0sWmq
5pNStV65dMOIAwAAwOSb6VtedYJrIRSLs+9h+th4fbfgi6X1xaYL04ZxYXqx4Sppq4pNb9/98WG8
H+cLx9v38DNHaQbtpDSZPiy3jXpMA9oAAABgtsxsh9I6ABb8zksqTt/9TxOOz+UtFh8qmy5Up5y6
eYdS0+u7ffrfJVemHxfLy/9sQnnGQhuUT6xuVcpJTVvGz9sPk0TzPWl1BgAAQB4v5algkI5NTN38 /BNxfVad3k/X9jy0qWndcm2h8bGQo/zqtG/IL8eWVxV
Gzd16lknbUyT6ZtMU4Xya7uzYp20JnUdpC5WrgUAAABgUsx0hzJ3Iu+Pb7sz1Ca/ngop1gErS5fj
T181jybTtEHzGwuDUh7DnA8TzoeFcaW6jaKdAACDWVhY2BSOOuqo4sknn+zHTo9XX321OO+889z8
bd++vVjtjzdhOxx33HEu/RtvvNFPsU5to/iV1TCHNKWvomq6lEGnHzcvvfTSxjJbWlnZa1lofv2g
dEqvZVe178MEHXXyd9Vrpq6iabtpwy2uff3I+jifqOjkvO0mvWu825q9JHqlp6ual9GWdFcXHQsyo
2qOO2LwojKMqywcAML527dq1Ea655priuuuuK3bu3NmPnXzqYCwuLhYXXHBB8fzzzzxdXX3118e2L
LnIdDZ/fDk899VRx7LHHFl/4whf6sev+63e/W5x88snF33772/0x5ZQf6tEyu/LKK4szzjjDLbNt
n/hEcdNNNxWrvY6lz19mSnfkkUe69df3wgsvFCeccELx7LPP9seUY5nlzWyHUie8OvG14J8A5+JE
43LKpk+pO12d9H7asnxj6pRlctP4cWFeGud/+vy4MDSVq2fVfHHN5+Cxdl6rOTy5d0zgN26cFE6YF
AIy/448/vvjyl79cfOlLX+qPKdyVoYt6HbAPfehDxbZt2zZdKdJ1ujPPPNNd0fM7aLpyc/vttcL
S0v9MYW7eqR0ysu3urq8lD+p5xyyyqZ8FKcrTwqK01Uro3oPopTnuEVLHPnnXcWF154YTE/P98f
UxSXXHKJ62jknHXWXWcW7777bH1q3P2pnm/55573LzasMnNj0/T60pqU377qyyV
a9ROam+N96+0ahq1veolufZVvZVO86jgX/3TjxGaRstT5ftl65vyUrzWhz0xm2mZqTOp9VEOOugg
twx/9MtfuuGU888/f69l8/TTTxfXXXntt8dhjj/XH7C1cX/1lpnlLzY9P0yvMhN4JHoAhmtXNjt0N
AIy/Xier/20zf/zNN9/c+7vLfX/mmWf6/tj16Z944on+0Nra8vLi
2uuvv+6+K4+vfOUr7+rv0Og5unGiaY4891n2XI488ciOfXUEZysPy3LVreVO9fH5+KbF2eOCBB1zd
jOqo+ZXlxcVN8+dTXqqP8fP250f5hW0/P/l/lX5dfjr6vrKy472q3RS/uiiuWNu1vLy2e/fuvcjX
PJtc+2o65SuaW7Dz9/sHPNUEZ6suPy/w4BzNpWbB7szRPRmWgqA.
Kd7KmQXc8goMWW+723TlbhZwdRIApsfDDz/c+7t+dW/Lli394XXPPvv/uCt5xfx88dBDD/XHrrOr
S/LII//grjLJeh5vuu9y7733unGiad5++233XXQLo8rTlbTeyfumMn74wx9u5Dk/v7ipXr7wKmOK
rkpZ0FU3Xdm6/vrr+7FF8f3vf9/dBussLrr4FNUnRvOj22Y1P5rnsM1WVlaL++67r1hcXu6PaU5X
60Tt5l9TU717naLikEMO2av8U089tf8t376aTvmK5sPP//DDDy90Y6quVIbz6Oe5vh7El9nu/ffv
f8vzl5muIj766C+Kq666qh+7Pq+qj6jtc8vMX199mv6Rf/iHjfnpdR77Met0NXmptzx1FXRW0KEE
RmDWOld0JgFgeqiD55+4b+6gpW5a3OzNN9/clMc++7zYj1mnWwV1i6fdbml0a6rc9fnPr99C6t1u
mK/XHvvuu2//w56Met1O48cYb3TS33nrrRudHdIvs1772NVfWytJS6zMZqfv/2N34jOj7O6/ox/
6vbdNrz33nv9b3m59lX91JFSO+j2WZ/a7f/9678uvvrVr7pOv+SnDDPt956ux9TtdgutszU8T/4
4IOLbds+sWmZqZQqOpyp9vbvnbwMP5kVdeeaXYf/u/fu/tBsoEMJAACAJF2J2WF
ffpDRbH//vtvnLgr6OUnRFV5PJQh0Q0HHOwaouGvOOp6sIu6shaSPv/m6Bv+HJFHtu+T
0eBzHJ2rhzA/BzCK5fkrTfYyHJGqNvPR+PoGeLNvCbqBxEtdh+xAK2yvQCyhxaLLo1t4NuFHl6DYdh
1g4Fq/fu2PvamHTuPuPnFu/9aaU2ofTxa2DjHoqZQwNuxC1ahgzzFF/YXzvPEKWF1Nr5+JHsDVm4m
Xdq//YuR6hjUfK5mTrqVbq+Wx6AucuHxRq6Cmb/Ak1RZDr9hBo/QfRQTeLm/7lh47GPSmBP/+Sd
+8PNvzrWVwU3PNeshq7+l5qV3KAg+mjPKu1SzPpwzXgfTKO1JySSFKEbvFKi/wLjiKh/ziUVf
zOooptYD39UnnVToxTy2zLR+nfn1rxfL/dtsY9S51ZVEm0ZvdV1fd/fQLct13vYqYq/vz82q/9mvsM
aX157bXXXD1nwhoAAADQo5eK+KHX2djrxSV6iYpeKGL3MxitNLVxT0hKjvHx6fYteaKM8
lHb9dS7rVJ5edKI4vZDGn/bFF1906fViMX7Zahs5Xn44Ye76f3Ky3Fn44IT1FZs3
Uf4xFu8L86o6P2E6ewFQVf70uTqonTQ/qkNumeXaV+1p8xEus129OFueCuH61OuIu+nCdSmkuimN
K39+cf3lT56wvmLLTK/QiS0bUdmhXHvl5idMV3eZTao5/en3LQEAAAAqGxqO5S5t2gOMsu5t1Va
mcNu0kl9g6Zf73Ae/LYcVbsOg82bhPMXtonP4vzpZZZA2ytXFV1Zn06QuNl/G8ht0vqpMb+n8eTCD
lG/8fHP5laUL5ycczrG0fhlSdfqYXH0trml9AQDA+JuJK5RtnsCkCk8Bn8hrlSdKBVactKnqnqdr
Gy4zSFtVLTuXrmoeObn8nbmlAeUpZPWbmD1iWcPpVfWToNSzhtKr9QLF3VaWNi9bPh2PdBygIAAONp
pl/Ko5MbC6FYnH0P08fG67sFXyytr2w6E5s+Np344/341DgLvtywfY9NF0ql8fOwz3Cc2Hh/nDRN
G8ZJ2fg6cbG0ovHhibWdcIfK8rX4cTtRr1qf3PyF4+sYxzYZRNvzo/ymrY0AAMDwzWyH0k6LGj
pOL03f804fhc3mLxobLpcvxp/elS443F+99z6VPKypEqaRRnn/538adXCPOweP97WdowwsrsrOsnEa
riNM7+ft52vCevg0HAtdq1O0sXmz9rBPo3lHYaYcNoUTV81rS+sg4Wu5OqouDpl+2nD6Ww+wjAo
5dGknQEAwHjj34ZU0PZJUNUsvbVGRvzVjefjsrjmzStpqmdGxWxz3sryUrwffHGchS5S5Zp0Gh
biekSt0s7zC0zTpRFmJlhHWwMAhNX1ZuG/z6hmWEcRbq0jSx+bBxAABgOnDLa+Tkxj8RCuO6NKpy
J0md9qmTtopUfiy3PfyOwyTTfPhhWLT++OVO+voUtp8/f7O+rQAAMC1mukNpJzYWfP74YZ74jKrc
SeG3j0JOnbRV5PLzxw+y3Npc5sorFiZZbH4URiFWD4VJF5snhUFo+nCbAQAA04FbXvv8E6ZBT56
qlpuLF2Vaduar6bl+9qoS508mpSXm8aPa5J3rOOp4TZPuq2DG4ZxVaUdY/OjMAqxeihMutg8KQAA
AMTM9L8N8U9gw/hUnUNI2PpY+lk3B8OK0vNZ34Zfv52Hc/3lc2nc/SSt18/PiUsjxy38W3mlC3PyV
06bKqJqfVC0rVJZnKq+yfJtI1SVWDxPWoWoeiSd1ALWPoWoeP9VteGNQG8X663DR1VMmni3JDytf4+YflpdKZWP1ieVSd
dlB162vp264HAAAYjZnoUGUK/n/JUWeyq3zq2SVpOIERitzj3y0FgL7yKAAAAAAGqFDCQAAAABohA4lAAAAAAKARopQAAAAAAgEboUAIAAAAAGqFDCQAAAABohA4lAAAAAKAR

OpQAAAAAgEboUAIAAAAAGqFDCQAAAABohA4lAAAAAKAROpQAAAAAgEboUAIAAAAAGqFDCQAAAABo
hA4lAAAAAKAROpQAAAAAgEboUAIAAAAAGqFDCQAAAABohA4lAAAAAKAROpQAAAAAgEboUAIAAAAA
GqFDCQAAAABohA4lAAAAAKAROpQAAAAAgEboUAIAAAAAGqFDCQAAAABohA4lAAAAAKAROpQAAAAA
gEbm1nr634GZMTc31/+2zt8MwjgTbipKp3H2OQgr0/KLqVPHML9B6wcAAADE0KHEzIl1sPxxVTpg
ddOXqZLfIGlS6QEAAIBBcMsr0DJ13iyE/PGxeAAAAGCS0KEEeupcvVNHMJXe4iz4nUY/btidyVGU
CQAAgOlHhxIzxzpXfgiF8bE0g1AdcmLlh9NUSQMAAAB0iQ4lZpI6Xn5QZ8wXxisMU1hurPwqaQAA
AIAu0aHEzAk7j+NOHcWyOldJAwAAALSNDiUwAnT+AAAAMA3oUGJiqBNmYRB2Nc8P4e2iYbyCyV0N
DPP28/XjwvLK5Mo0uTRNygQAAADK8H8oMRHCDtGoO0htlO/n0cX8dJ0/AAAAwBVKoAF1ztRJq0Pp /RB28Orml+PnFSsLAAAAaANXKDERwk4RnS
lX5IjQMAAADQHjqUAAAAAIBG6FACAAAAABqhQ4mB7L71mGJu7pji1t0aeqxYcs8rLvW+Jey+tTim
l+aY9Qkq0y2r/vOQ3MIKAAAAjB4dSgzgseL/uvi5oli8srjo0P6oModeVFy5WBTPXfx/pTudCTwP
CQCbra1t6X8DAGA06FCisd23XlOs9D4XP/XJ9REVffJTvR5lb8pral6lBAAAADBe6FCiod3Ff/6P
z/U+jy5+/7D1Mb6fPbbkbm11t6ges1Q85vcdD/v93lRF8dx//M+9XAAAAABMKjqUaOiV4u/UnywO
L35nr9tdV4qLT1wpXLQ8t1KceJj3XOWhv9Obque5v+vlAgBoiv9DCQAYNTqUaGb3z4qX9Xn07xeR
C5TF0be8sv684yu3FLrBVZ3MBzZ6lIcVv69LlL0cfsYlSgAAAGBi0aFEM6/83Z4rkHtZLK60t/Qc
elHhHpnseXmv3uNzxd9xiRIAAACYWHQoAQAAAACN0KFEM/0X68TpDa6Prb9wZ/djxQN6FWzP4Xs9
bBl/oQ8AAACAyUCHEs2UvFjnuYtPLA7TG14PO9H9a5Hi6FuKf7/x30VyL/QBAFTF/6EEAIwaHUo0
lHuxzmJxy6OLe65gHr1YPPofLio2+o4lL/QBgHFz0UUXFXMLC+5fIX3wgx8sbrnlln4MAACzjQ4l
Gjq0+D/+T/ffJL0X63yyWNabXdeWi4s+uVw86773wrPLxSf9K5H9F/oc/X/+H3s6mQAwht54441i
odeJfOutt4pdy8tun/aXf/mXxcMPP1yceeaZ/VQAAMyuud7Bca3/HajpsWJp7sRiZfHRYm15437W
Uo8tzRUnriwWj/Y6ntWnqkdXEVi1AQzqfe97X7GyslKceuqp/THr1NH8wAdOK77znUuKs846qz92
+PR/KLntFQAwSlyhxAA+Wfz7W44uipVrilur/j/J3bcW16zokcp/31lnEgDasLK0VJx88sl7dSbl
oIMOKm6++ezivvvv648BAGA2cYUSKrlAAGpWcmn7nxxxmLLLlvgVQF2l/KM/+qPiF7/4RX/M8HGF
EgAwanQoMZXoUAIYYVJX9NQoAQCCzi2vABABEHHzwwcWTT7z7ZH9pjptRe2bdvdmnqbUVnBuT86/MWz8tbw
GgCA2cAzlJhKPEMJoCu2qyu+++W8Ht37ix/zd6zMcnFC2HFu7n3phgf4/129/8pH3roof4YAACm
Hx1KTAQ6kwAwZd56tX9tX7ix9DBDyx9YTZaPlqA6OJzw+x/X6Vm8sYwGOgAjVTDLLy8vFGYcdtldnUvSM5PevuKL4/33x
i3tevMOVSQBAQ1yhxFTiCiWAxcZVoAtSUHl/WcMPFdrNXT7G5UrXavozABYs9twjJhTe5rZGlbXeA5Vw3zYGdCGjQBBoXDDn9
7FUEAxVRTjD3JWxIc9jF78p24r5XVZsqlyvZA8bAnEjlbnEgtVK16pGexl4q8M9Vr4AD+VKT0v7bTtB0qoHEJ4VWcWnmI
pdArCyMSCpbmT+EpsN5HvaHA1LoRQSmOxyG4ShJZfAmqmqwv2RyAzDEbMf59gGH6Dw3vnTCOFJ7KN3i7B7V3onYEEHdqcb7
Y8Xf3HxzcfHFF/fHrl+ZfKfXmfxfTzxBZxIAUBlXKAEAmDLLy8vFGYcdtldnUvSM5PevuKL4/33x
i3tevMOVSQBAQ1yhxFTiCiWAWaD/Qxm77VXPTH73u991/wok5tVXXy1OP/TQYlkDi8vFOytL0X8l
AgBAGa5QAgAwZd56663iX/2rf9Uf2tshhxxSrPY+9X8nCzqTAIAB0KEEAGDK7LvvsvvPNNvz999/f/+O5fgvfFYPl2IRpZ4P
yWjwCfqY5SoIWfBPYnPN6W4Pk2x7vmcx3m27nUUp9+Lx0EHzCVmfbXPcAnaWNz8obLF61/xRh/fXujOJk3efgJUdyWlw5+ieRNu3/h
UA1EfXdd0pbzb+BmnUMXctMcTGI3aYT7xB4K31Frm+Ef1GgtWadwuq2F4ozmI4aSi1blUw4fxNGdKXFo6k8DSyKRBE71brbSQubjomqpo2t/Ha4
FQKf8k+66k8PgLTWuQgMbVR+7aPKO04kZQdI0GDQkU2Oh8y5GdE49c/QV7YvWCpzTp7vTDEPR/1u7xROsLwZdBudrh0NCGHDqKMGN1cLiK2u4z7ec5wGbNcmnY5Q
nMzU8dQtpKl9VQlEGF7BOJbvn47Aq9eQjQlBS92Z5Q9o5MMqGqTSaK6OHKpoQMaTlXc1CTW+qqKFQ9eQG0gdlqSn2fKhqO2UAqiYDiBALwJkzmBHe0xAoG5w7rrQiBEsu/MOwAVk5fZX6bE+95h/4iKhbQ9lXtW28kovUGEoYfqz2Mr02R2cSoQYbKJgxJ+a7jbbZHwF9Z9ynOxSjgvU+UuBFYiS6sOJXqXA5dVj6x+h7Mu4fZp3w3/iDfdEAnaW9RHDiyjGDfH5PQbeQXwBexAATuaFN6q/wiYWqIrqbs0T1e1LTWw9BgFdWqGOqFXHk6vzY3PLkbOP7yjDr7dRnxwFFy8tXBhyJQdY8eAA31NPfa5Zw5WPZ4OvzEO2i4+YYtD8Sd2Q0XtOUuD5xZBbU+2o7gEUJTg7lJ4qHqN4GTDvS0UNhfeDFWzhPzbMDtLA0j8SMMbHzf9cTFKb3VZbhDMlL5XSV5kLjpR95Ac+9zI4wZtS1C57GmYKPTCo6Te+KEsiotK9tFrDqMbHZmzfnjbJh0kCzJeVsSF8vD2dEIjSC79j5+Em3JfJXvpyhwrc1/g12y75HSsB+7kdp3r7pwbNkcSB3hp28RQZaWTDN+63Q8RTQXc0yn0M1DS7Fo1pxypZqPgBN9P96ZRUUhgXH2MEDZfhwYn6vmTeLPdnBEqjJvcxM6bbPwl1Thm6WHOuZ5m0CkUBU0vfUq7G+RavBvYTRvWfRV/PL1Y/1vPfpz2Sz+j3CMZYtgzpcCaLvmGvAt0E2bTypIxkaxQ/zEoRB+J1fgDaYjSGrBywm0MEpQFUXw2vlGo3Dwa0XXHrGh2c45kQ0+RjdFYW0Tcy/QoRdeDQk7dAVQfbHSxX7gr1I+NQ5CpyB+kz1LOzCaLsGYbLtbbRfyNlxDhZaPA8u3bF0E1DpWzJoR3g8afvyuX0zjdSdHC0FCL/xPBLcf0VsUQxb58h3O7v0kvmcnvM0FGshNvjZvLsDVEPnNyj82PJnOq5y2XqlgsmrUwP5LFKgJUFSBFmQsjH1kNLuuX1sC0A1eWqC0cQy5d9lHCjGz0NC9lpXHhPYoHJN3D8OGKPsZ3H+ezmYg4X4KNqtXCbi0AEUd5Tn4+sK1nxPB3hgtP9f1Nq/n8fAeDoI8rCZfw5Pse/9Pf6CKhDLGGR43lg6pmLVaODsTQFB/NLihaD7bOqbOdqcL0SCNuEz6FPTsMFMRRJnJ0y1YHY89MlsKxzHl54S2wZX4TsqOfYAPVkeoLmUOsKJyt6uOf8Ml6Tb8m11xz3nh2K2UW5Wz2gYjPDbQ9nHrvm5KQTy7ncJLHNyJuyKGxDMhDXLeYbaBgF6l/ww6h9lqTJNm5y8MXGm+YG6ACflfZ0pMjq0ueV3L2Y8olFEOMwFhd7shy23QZ5pq1DkYUkUQ9ufE2+jmLhgA0WuKa+Z4aZzdbvJ6j95ZMmn0OGEC2qNCNkxmDoVffTlDbhuQ1GRLgvE0nDp7mM9cb6UhPdZrE3qq8HRBw0MNNnxuSK0pfNJCwQVH3eZE/DPQXe7Ivo7BX2t4K0BNAOkcYvFxn0XhaHNsWkn9C5g0hufP5fDFvb6zGCvoVgjfVU0DMWRHMDqwdEJ8lF9cAp8L6ydAhYzB3q3fCnVyaNAIbsjNFfRoV1pljPmbiLSU/rAl9mNmNe2pTMSlV+rfoqnMvWzZOI/dV0GBuJ3iy7DJ5mb1pVtNKUMrtDlLBMGGr8u4gqwG6IpcqWpSInw8TyHeJFxCTQUAPnUtxRFyFyb0p7/bg2H1Lny9+P1qJB+cE2O6dUUwlIdYTm8uPjd48qEm6ck1sEiSr6iwZsfUzdiwTBC0iOlSaeZZv+cBw1IL4Ztsaw7MJazW6pK6EK7EvuQr1VbeMAWWE2A2jRIuwOFqf6tmTUzQVY9iL7LQJkzZmeGLXBWVdC39rIHqYf93wQSlhs9S8D7LGeUVbbUB9tWYoU99NkTTPr+jAubnyCb+zcMSwUyedO5gEvtuO4wmMdX2r+ANhgf5JiBIfhI0Y1oG5Z7QXvKhZv1zHBRzmzYmDWX9s3KGT/B+eF8UN8/hT9KRNGlfJJNV8aErgrFcrUupL/mmM7Mt1a+N+u1LKiFBp8zOj3oRtRDS+wPbEDkH8TGtEWbqIpAZvr8V6X5/u6eIh/4ALMqQcSjlhbzsTBCF4oY4RvK8wQVf8Y+bIlzoZVIgFUM61pI2vWZBXU+oWLU1yVEWmqEj+Ik/2q8fdL0kGdH+1YFoBR0LpNlwfrzPPwAO6bEGXBmTeEJMAoQX8LJsQuU4cUS3Mvo+wufjWeLM9wSUn4Ci6I6zA1+9jaqwP4rDDjBX2hGd7+BqQe6LrZT9jG/SOlyNNUTE7mXBgx5tiIgTxn0bTV5UIDhJpo4ws6Kzk42+9gP5wbXSmw1BK4RTOpFsZZqEpZ42pVnU/3OoqJZwMeBn7OF0fHNx+mvfZq82I3zXfdiEFk1ZECfu0WUZOyuKSCq56bjxI6YlBwbA1jX8UhfA9v6Jn9QRfXVntJgIRJfCLsgMmFmTjdmS9s3VkWhhKaMPxWnpnP7wUIR94jzdvEaWQ0fG+xhgeZrc9X6RVBtPRXE6xTzS0tt6snjiS6mPNn9Pf9FkgB5xDbp44VJqnZhoqcKP7YyUFZ3uE6ZIG92fqjmuWCNcHmK1RK7MJb6j6w0ocaT4Ja8Msi2cERE2gD6zNhjHTRZ9HkAv4ne0sO3Prp5BRbmjQkpDm+cN5I+CN5BpMUuy8xVfO8jNHhPDLhYLNvLfTOobOQZGjS8kG6PCgT2uyZAz0mCYyj5zNjyAqlPKzVC7wpZpwS7rNMnAfIGdXC8HG3RhSQT+Aatzv5B7IbAgf3sxq5zd8PLA5Xrou3h8QAG91EbPAL0BgMBhVfMcmCVddS9W3KlnehdgBClATLzVYd6w4EKWX1Xk8yxBxBexFtrApP1r7X1GdMeyR6TZ6wuxWtyd3JHxGKzGn4uFtVplJZuGwaw/EHGfDcU5Y8BRwf0QHMU0lUwwrMIvB6jZKxL0RHjUXKvVlqVmDvZzU2hUUUI0zpIZ0vFYr3UvV3Ss4DhWRWCXyAyqI9LuqBhBaMXNQjgIhmzZ6t4/c0p9EBzKzLi3Pa1n28hwrq9DNnsz7uRA3kbq87bsm27tfnPQwRNKKlN8I1dS+g3RgU8ZKROqfGdUnT0VvTjJEH2obwWYVCZFw0h3YLRLgT0mr5b3pJcb+zf/7CvXU9kUtGVJtsT6U4Iw/f52vfOPcYYNgPkc2LVgDLIbd+Rlp2vpgEgQyL8Qx8zHzLcWdY4xVQH7XZhR03NiQk5ckQXB0ExxwlZO6x1drwbxyjf8XCGYMaO1d5cNrQt9F56KFWGngf9Yl7b6djOCSbT0FXhTf9VwzjrVhE2I9K+LZVqzRzRcpRyz2iI2LVdOPT4hoz8dlBxkkpLQ6RVV8Tm6wKNb4t3+tB4F5QuvgPAGv9n6WIBgnYI8I2EYvWn+kjPnG8P1eAhoMSv1VLmL8l9dlCJsE8K0n0h9PUq46xTUBo5Vht6Op1q7I9dnZv0e9V1pYnp/8RmS3ReSAcPXPEBs0TbgWKN5hw28qr1SYXjljqV6ehxDSpFu8bjwrHyhe8EO7GK7uzbE7Y/wxuqe5M9QLbYqvRwVUIMNvyKL1kX4VmjX7+A/gfwrS3M0sIqM7pDyxvr01mhTdAewQEDdVOs1E9Tov6AJcMGRdbmAqe1MEvffE9n5jb2y8yROiyUcBnRamoyiNKwVvTcdkEYtjrXRCD4E8e6VyvtWfSjUX2/F0hzw9EDeoG7vpRMtq4FKM7LImPcXXJKPiD9bR/wy/8o2MH8V7Gpf9c9V7ZmHyEkI0ye2LMS6rrFnFK1MUrmk1I2mrwgkJYrz7vM1sbnzFpN+gGAPsnEGh5M9HXxRONbKBtiiP4ZWmQVZnwk4GaGXV/dKi1WU3Vn4K2jKSrN0IhnmRxXCfHyZjmT3bp1nc0XNTqKCfFZ7OgdxeC4xC7QVR2QcCuHAF/Fa9mdw/bh7p3uR0VdOVmf1s6AXbv2EzF5x1U6b97WDsOnR4jQS6yLJGXYs9rkpzN53v7tdBLRAeFmMWDDXgQmELQ8xW4cIMgcWCLQ6DjUsDw3MqF2F91nNzPqfPlQSmRL9cyyvOpwmS5D5JIdTaA2EkoV5+zrP7EpJ2FAzsbBW6ILZB5Hn5fv2Kf2TsLpK6ZBPJCxvDVC9pxyvpkQjamT4hGW7tVNDSBgvnbi9JCiBqbD1IFJ6mdPiiLKB6lpMtn6pBmjQmSXbsL/TVq3PsdWuZlOp0gn4HE0CsyB1f0fMeUBhNFqKQ2mjRCn+f3TJJmwHYnX1pcpcc2FqkMqwWLpnu/dGZ7lh6oGYBZbGOCr/ZY5rFwlmVOhY+iq9QX67gYr2kC7q0DBgCy5LMNr6YjXcKLr48RvAcyrvk1P6DJq0fcwshCglFJBAOGcCbOxDKuKeXuEHLVIGcv2ij2bSGS4NTh1aFTSlUNh+WIjvvEvPoFsMQwXMTD6qFkzAyOw0GwLQIeTT6tu8jyV7XbZ3vrxb38LPOGEbAXAGvCwiIHN6a6ZpNsS6VK+fAnqEcVvcuLkgwhR8jh9vdU4uqFOMOTdB7+RhbbfL+2PDHkdfm3JJNJaIo5oUSVy8C0mTz+C0ln6y1n5jV09S5BdzX9vV8mSdUvlHUnoOQLx8P56pbeBdY5BRyjHyeDw6ngy/KGX4wAyf7HPixeXW38N05j6WpG5y7OOGMdoc5a4Aye7hV8n6U6NxSqg4r4GFDk4fPp9LI2J2eGF1v9RGr8QeIUq2P4mlW5NIIF2gbJJYHv9Jw8nzc7y6yHdl0kh+2t1E5pIpp7T9aVqN6HrPxu68bWhzBTwW6B9Cd+ry3S5yuZgIhGeo26KgTZuQ5ycyN1MIP5AXSHXbdP5U2U23Xn7afd6eKeZP6HjNbqk3qdtljRLndGqVzzWeqe9Rfn1vRmfP6OyKQoFmqv2UPmhD97zOOmd2YRvpN2V2sjYkM6FDk7M9qKrIGoHGr9VcIxqDbK4H7qvHawSr8R0AYXe2mkflhZ4gSvQVoeG5Rl3P0eHoMtlQKAo2hHapKWVkNEqTehNm9Y6ZtxMIODeOIe5mwdH6NBeX3mdzgT6V4Bo+e8KHA4Q6HgU1AvCJ49sKHnGl8vZPMZ6QMO8y8DKvFDNc0+Zp9OdH+2WmaVGnM35uI0xfE9iXODbf0rtp8lsgrCsnCMxPaJAYdp7fLbWx3tgzbWpmFe2uHq9c38j1ZXx2V6DjR2L9NUbXnQfyfE3G7hzdO8d6pi8IF7IUE5VvHtTsPF6E4RmHyp27OGtEhw8xzWEeUaVi8xnnDRbBpKOjfSv5JhzkuW2lspK53T3UrCc7fdbfhGbTfRIF66tV1JWLaw==

2o95N+KW0qIUnF8AgIUjUFIZ27dvz71W8WiQ2cSELLWYRKaDeF7l//71r83atBiSd+2snNeGoq8X
L26uzW5xW7vLl+9vrlVUrZ7HUE6MRE9lh3GLje2xP0/c02g/l+hhnJqq5ZlYW7Ufu27ELaVFKTi/
AAALR6CkMuI2yqNHj+YxbREOYuKUnBQaokcqZvG8++67c09m+xi6VjE5zO9/+9urgSZeu3PnmrRx
48ZcD6tW/fLqxC8xKUs8iqQb6++55+oYwXhdfJxOIpzM1ZPWF+r1VB+PsZEj19/+GhP3NLbH/q7H
WjaMjf1Levfdd5u1aTE2sZgAJ85lnMcynF8AgAV0BfrQXN+a+/fvv7J8+fIrqVbLbZcsWZLr45OT
zRazm2y0awSY/JoojaDa3POTRqDJ+xpBpLllWq3xb7Zqrce/Hu0bASUvWz+b9tc1gk/++JUxPn7l /+K8NJbT9ckrk6nxNRX1WbR/7SGOeev277//Ph+TOHaxjI
RYviXbdZo2/EcylHRxs5vp4n7lkxlt3c5goAw861DYNKoKQvedPtY40gOdEIlfUYM2lWUwDoimsb
BpVASV/yptvfYmxgN88EBQCmubZhUAmU9CVvugDAIHFtw6AyyysAAAClCJQAAACUIlACAABQikAJ
AABAKSbloS/FwHUAgEHisptBJFACAABQilteAQAAKEWgBAAAoBSBEgAAgFIESgAAAEoRKAEAACh F
oAQAAKAUgRIAAIBSBEoAAABKESgBAAAoRaAEAACgFIESAACAUgRKAAAAShEoAQAAKEWgBAAAoBSB
EgAAgBJS+gfEXgy0o+Uf3gAAAABJRU5ErkJggg==
iVBORw0KGgoAAAANSUhEUgAAA5gAAAT4CAYAAAB9m21pAAAAAXNSR0IArs4c6QAAAARnQU1BAACx
jwv8YQUAAAAJcEhZcwAADsQAAA7EAZUrDhsAALWtSURBVHhe7P2/ViJd2zjq3q4z2AewMunA4XcC
GK5IO1gdmXYG0R6adLJHh509CYSadWrUSesRyAl8DoOGA/ll7ppAKSIiYAGz4Lret562+KPFvGfV
5K45a9bBUyEAAADgk/6v8b8AAADwKRJMAAAAKiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEE
AACgEhJMAAAAKiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEEAACgEpUmmIPuSRwcnER3MH5g
nkE3Tg4O4mShFwMAAJC7g6fC+OdPuov2wVlct27j6ep0/Nh8d+2DOLtuxe3TVSz2DgAAAHJVWQ/m
oPsrrot/W98WTxVPv7WK/17HL72YAAAAtVdRgjmIvze94t9mHDVGjwzddePk5CAODsbLSfv18NnG
UfGOiN7N3+I3AAAAUGcVJZj9eEz5ZRzHl8PhA6NrLM8uozd8fKx3HZeNdtyNV+PwS/GOQu+x+A0A
AADUWTUJ5uBfPKR/m0fx3IF5eBH3T0+RLvEcLv1OpAGxUbzy33N3ZSOOUhfmq8cAAACoo2oSzP5j
THZUvhjE4K4b3XY7ThqXw2s0Z+vFoy5MAACAWqtskp83hrchaUTj12PEtx/x++l23IM5MYwWAACA
nVFNgjmerGfS4O/NqFfz+FtcnBYZ5d2fOT2YU5MDAQAAUDvVJjzJuu5PhvOINs4K9PLyestZ0wO
BAAAQC1VNET27WQ9hxe/47ZV9ms2o9XpR78zvCnJy/WWsyYHAgAAoJYOntIUrxUYdE+icdmL1u1T
XJ2OH/zIXTsOzq6jWSSf9xe6MAEAAOqsskl+Di9+Difxuf7zfJfLD939ScNmW/GzhsllGvYLAADA
i8p6MJNRL2ZEp38fH+aMaZbZ0Ytr2XuZEswKiw4AAKD2Kk0w94kEEwAA4LX13QcTAACAvSLBBAAA
oBISTAAAACohwQQAAKASEkwAAAAqIcEEAACgEpUmmIPuSRwcnER3MH5gAKzA0FcAeEuCCQBLWLUnUkIKwD6QYALAghYdFjuPobIA7DIJJgAsqIpeyPQ7JJkA7CoJJgB8
ICWEVSaFhssCsKskmADwgZQQriMp1JMJwK6RYALAO9adABouC8CukWACwBYZLgvALpFgAsCUsldx
U8lf+nt6MgHYBRJMANiydV3jCQCbJsEEgLFN91zOoicTgDqTYAIAAFAJCSYAey+HnstSuQ16MgGo
IwkmAAAAlZBgArC3cuq5nKYnE4A6kmACAABQCQkmAHsn557LaXoyAagTCSYAAACVkGACsDfq1HM5
TU8mAHUgwQQAAKASEkyALUk9UeXCetW553KankwAcibBBNiC6eRAsgAA7AIJJsCGvZdMSjKrV5bp
LvRcTtOTCUCOJJgAAABUQoIJwM7Z5Z7LaXoyAciJBBNgw95LevYhGQIAdpsEE2ALppNJyWU19qnn
clr5mfVkArBNEkyALUkJQbkAAOwCCSYAtbfPPZfT9GQCsE0STAAAACohwQSosdRLVS77TM/lW3oy
AdgGCSZATU0nDvuYSEieACAvEkyAGnovsdqnhCt9Vj2XH9OTCcAmSTABqJUyUZJcAkB+JJgAsAf0
ZAKwCRJMgBp6r/duH3r19FwCQL4kmAA1NZ1o7XripeetGmU9UZ4ArIMEE6DGUrJQLrssJUO7/hkB
YBdIMAHInuSyemWZ6skEoEoSTACyJfkBgHqpWYJ5F+3iy0b6wrHY0i7eAUAdpeO4nsv105MJQJVq
lmCextVTPzrN9HMrbotGMTWM7y9XxTsAqKN0HAcA6uWgaMBr2IIPonvSiMvj23i62k4K6cw6wHqU
PWl1PcZqHwDYZzVNMAt37Tg4u47W7VNsI8f0BQKAWerePmjfAPiM+iaYW6YBBqjWrhxXd+FzaOMA
WJVZZAGAV3JJLlOiWy4A1IMEE4CtKpMHPWb52WZiN/23JZkA9VDLBPOuPXULkkE3ToqGJzU+o+Uk
uoPxcwDASlLSv43E7r2/KckEyF/tEsyUXJ5dp1uUjG9BkpLLxk2c9ydvT/IzHhsH0XYTTIBslcmC
nsu8iQ8Ay6jZJD930T44i4dOP+4vDkePpIQz3t6uZNA9icbNefTvL2L0ymqlL0YaXYDV7epxdBc/
16ZPBpR/bxZtL0DeajlE9vhLmTIO4t9DRPOoMV5/cfjlOKL3GP3xOgB52HSywuelWG0yXu/9LXUG
IH81SzBP41sr4vpPOfb1ML6eN4s88m0aORhlnvE29QQAVjWvd7FK08mk5BKgHmp4H8zRMNnrKK/D
HET3pBE35y/DZuOuHQdnD9Hp30f5UNV2cQgUwDrty3Fz1z+n9g+AeWqYYI4Nk8jr8cqU1ttrMqum
gQVYjgRzt2gHAZilvgnmlmlYARazb8fLfU0w03pJ+wiwv2o5yQ8AsF1lEpkSy8nkMpleB2B/1DTB
TNddjhq02Us73AITYLvS8TjRm7WfyvgDsF9ql2Cm+1seHIwm9UlfWmYutxFnRcN20h2M37Wc18nq
7AUAAIDXapZgDuLvTS+anYkZY2c5vYp+pxm9m7/FO5Y3M2mdWgCYrTwJ51gJAPunZglmPx57Ecdf
Pr73yOGX44jeY/EOAGBd3juR4AQDwH6qWYLZiKNmxMO/j/slB/8eIppHxTsA2AQ9l/tLzAEo1SzB
PIyv583oXTaiPW8Wn7t2NC570Tz/WrwDAFi3lGROLgDsp5reB/Mu2gdncT1ee6PZif79xVqTy3Sm
XgMK4Hg4TXmM6NEG2E81TTC3zxcIgBHHw9eUBwD7rHa3KQEgD3qoWESqJ2VdAWD37WyCObpfZjvm
XaoJAKxXOgHhJATA/jBEdkWGQAH7yvFvPuUzW9mLqWwAdpshsgDA2qXEUnIJsPsWSDAH0T05iJPu
x/eeBGB36YGiCqkelXUJgN2zQILZj8dexPGXnO4oOUp6y0bq7eLaSwDIkZ5MgN22QIJ5Gle3rbg+
yyNpG03e04ib8/5zI/VmuY04KxJNva4An5dO3CXp+ApVKU8KA7BbFkgw76J9dl38ez1M2l56CSeX
TSWfg/h704tmpx/3F3N6VE+vot9pRu/mb/EOgPqbPObCLihPCgOwWxbrwSx7Bt9dropXbcLiw3UP
vxxH9B6LdwDU23RSuakks/w76TgP6+LECcBuWSDBzEkjjpoRD/8+7pcc/HuIaB4V7wCor/e+ePtC
zq4oT1YDsBsWTzAH3TgZn2V8WU5is5c5HsbX82b0LhvRnjcm964djcteNM+/Fu8AYBll8upLP5tU
frcAoN4WSzCLhO2gcRnReT2xTr8Tcdk4mJ/sVezw4r7428NZfJ4bozfLr6PoF9s39zpNACAb5XcL
AOrtoDiYf3A0T7cEGc3aOithS7O6Nm7Oo39/sVe9hSmR1RACm5CON9Mcf/Klfficsr4rQ4B6WqAH
c/7EOibTAViv6S/a6/riPSuR3Qfpc5cL25fqt+QSoL4WSDDnT6xjMh2A9Su/dK8zudzHL/XTSaUk
Mx+SfoB6WmCIbCFdg3l2/eb+k8PhsZe9aN0+xdVm7lOSjX39MgawK+YlL585vmsfANhniyWYSZpF
tnEZvfHqSDM6/fvYx7l0flEAdsE+H8skmPVQxkmZAtTD4gkmr/gCAdTdvh/HJJgAUL0FrsFMs8ge
xMlmb3gJwJrtexL03ueXHOZp3gkBAPLx6VlkAaiX9EXdl/WR6WRScpmvFBv1FiB/S0zyE3H7dBV7
NpfPuwyBAmAW7cP6KWOAfC3Qg3kX7bPr4t/rOCsO6Omg/nZpF68CIGfpeA0AsE4m+VlR+qKm6IA6
cdzaDOUMwD4zyQ/Ajit7LiU97Bq98gD5MckPAFBL6aSJJBMgLyb5WZEhUEDuHKe2Q7kDsM9M8gOw
g9KxWZLDPkl1HoDtM8nPinx5A2AW7cP2KHuA7VugBxOAukhfsPXksK8klwDb906CeRft4gtKe5Fx
r+n6TENkAbKQvmD7ks0+c5IFYLuW6MF0uxKAXPlSDSNOsgBslyGyADvAl2p4y0kXgM2TYALUmJ5L
YFPK441jDjCPBBOgxvRcwvvKfUNC9HnTZahMgfdIMAFqSC8CsCnvHWscg4BZJJgANaTnEhanJxNg
cySYADWi5xIAyNncBPP67OVi7oODRlz2InqXjYnHiuXsevzqzRl0T15tw6z7dY5e4/6cwG7Rcwmr
05O5mveOOY5FwCzvJJincTX+ErPYclW8YzNS4ti4jOj0y799G5ES4VlZJsCOKE+oAWxD+s41aXod
oFSzIbKD+HvTi2bnd1wcjh8aJsP96DycxcFJt3gFwO4pT+gBn1fuS07aLKc8DjkWAfPULMHsx2Mv
4vjLc3Y5dhgX909xe3wZDUkmsEP0XAIAdVKzBLMRR82Ih3+zU8jTq3GSabgssCP0FsD6lPuWkzgA
1alZgnkYX8+b0bv8793Je06vbqN1fRaNNCMRQE3puQQA6qhmCWaRYl7cR7/zEGfFF6/ZHZXjazKb
41WAGtJzCZujJxOgOgfFQXXGN5i7aB+cxeI3IGnF7QZnks1BaoR8+QOqVn7BdXypL+1DfYkdwOe9
04M5dZuS29bw0Wan//LY8+PN6PT3K7kEWJfy+ApsXrnv6ckEWN0CQ2QH0f11HdG6jfuXe4OMnF5F
vxNx+X2zM7eme2Gmg3+5zBoqO3pN+91rNQFyUh7PAADqbIEEc3RrkNa32X2Uh1+OI3qPxas2IyWO
jcuITr/sSb2NOCu+mJk5FqgxPZeQDz2ZAKtbIMGcf2uQuz/XEc2j4lWbMIi/N71odn7HS2fqeFKf
h7M4cA9MoGb0XAIAu2SBBPMwLn62onfZeDMUNfUmnl03o/P7onjVJox6U4+/TP+1Yhvvx/fAlGQC
NaLnEvKlJxNgeQskmIXTq+IgOx6KOj7bnpbGzXn0n+4nehPXbX5v6unVOMk0XBbIXHkcBQDYJe/c

piRfo2swj+fcFmXyFivru31K+mKo1wGAadqH3SW2AB9bbBbZk4M46eYx8PTw4j76nYc4Kw7yszsq
x9dkNserAJnRcwkA7KoFejBHPYJx+xRXbnb5zFlMYBWOHbtPjHefGAO8b7EhsnftGOWY6xluWkca
F2AZjhn7Q6x3nxgDvG+BIbJ30T5LVzReD4elpoPq26VdvAoAYPeVyWX6DgTAa7Wb5GcTFm0wFB0A
01Ibon3YD2IN8NZitynJRroedFYP6nvLaj2rqbH4aAFYRDoWAbup/D5gPwd4sWCC+VFit6khspMz
xKZbkMxO/l4W14wC25OOj+lYBACwLxZKMO/aZ3Hd7ES/+KLUT9ld63aUwPU7kXK91u0mE7nDuLhP
SeZ1nM2+TwlAFiSXsB/KfT2dVALYdwtN8vPnOqJ5/rVI7Yr07stxxMO/GN4V8/AifhcJ5/Wv7mh9
Y4ok82cr4vrsnXthAmyPL5kAwL5a+BrM4y8pvSw0jqLZe4z+aC0Ov56/Wt+Y06vhGUP35gRyYlgs
7C89mQALJZiNOGqmTstxH+XhlziOhyhXAXghuQQA9tkCCeZhfD1vRu/yv/FEPqfxrdWLm7+jDHPw
9yZ6zaMiDQXYX6nHQq8FkDjRBOyzhe+Dedc+iLO4jafhmNQ0q+xZXA+fSbO55jdb66B7Eo3L47Vt
m2FwAMyifaCkLgD7aOEEk9c0GkDiWMA0dYJJ6gOwbxae5AcAgOWUyWVKNAH2wTsJZhoCO7qeaLGl
Pb4+E2A/pGNfomcCAODFOwnmaVwVX5rSF6fhctsaPtrs9F8ee368GZ3+pq/BHET3ZFaiWy4SXgAg
H+l7E8A+WGCIbJHM/bqOaN3G/cX4Xpil06vodyIuv3eLV21Gmrzn4KARN+dTye7kchtxViSaJ133
UgGqlU5iJelYA7Cs8hgCsKsWSDD78dgr8stvs/soD78cR/Qei1dtwiD+3vSGPalvkt1Jw8S3Gb2b
vxtLfAEAPpJOTkkygV22QILZiKNmxMO/2ana3Z/riI3dB3OU7B5/mZNcjm028QV2nZ5LoCqOI8Au
WyDBPIyLn63oXTaiPXVhYxquenbdjM7vi+JVmzA/2Z00+PewwcQXAGA5ejKBXbRAglk4vYqn0YWN
w4NhuTRuzqP/dB/zRqtW6zC+njdnJruv3LWjcdmL5vnXDSW+wK7ScwkAsLiD4ktTDb81pduonMX1
eO2NZif69+vtVU1fOn3hhN1nX2dZ6gzLUmeAXVLTBHP7NAaw2+zjrErdYVnqDLBLFhsi676TQMYm
j0cAdVMml45hwC5YqAfzrn0QZ9etuH26itk3K9k/qRFwthG2b9YXss/sm/ZtPksd4jPUH6DuFujB
vIvhnUg6PySXQFZmJZfJe48D5E5yCdTdgkNkF7v3JEBdlUmpL3fAtqXjkRNlQF0tkGCO7j15/cdV
lgAA65ZOdDnZBdTVYrPI3rXj4Ow6WrdPcWWc7FA6s+jgD9s36yz/MvumfZmqqVNUpTy+qU9AnSyQ
YH5wz8mh/ZsAyBcIyMdkkrnsfmlfpmrqFAD7zH0wV+QLBNSbfZh1UbeoWqpTiXoF1MHCk/wAALB5
KbGUXAJ1sWCCmYbJvtzI/O3SLl4BkL90zEp8WQPqpvzeBZCzhRLMu/ZZXDc70S++kPU7zYjW7ehs
Wr8TxVqxul/XXwIAbJqeTKAOFkgw7+LPdUTz/GukO2EefjmOePgXg/TU4UX8LhLO61/d0TpApvRc
ArtCTyaQs4WvwTz+ktLLQuMomr3H6l/W4vDr+at1AADWR08mkLMFEsxGHDVTp+W4j/LwSxzHQ5Sr
ADnTcwnsKj2ZQI4WSDAP4+t5M3qX/40n8jmNb61e3PwdZZiDvzfRax4VaSgAAJuiJxPI0cL3wbxr
H8RZ3MbTVZrOJ80qexbXw2dacfu0f5P8pDOGDuqQL/so26LusWllL6Z6B+Rg4QST13yBgLzZR9kW
dQ+AfbbQLLLtg5PovnfN5V27aEzdBxPIgzP5wL5Kx7/yGAiwLQvPIvuewb+H8U8AAGxLOrHm5Bqw
be8OkR1eczm6yPJDzU4/7i/GtzHZE4ZAQV7sk+RCXWTbyl5M9RDYhgWuwUxDZH/FUf8+9iyHnMsX
CMiLfZJcqIsA7DOT/KzIFwgAZtE+kItUFxP1Edik+ddgDrpxUhycTiZn+BlO6jO6iPxg3uQ/ABtQ
foEC4LWUWEougU17P8FMyWXjMo5vn16ur0zJ5dl1tIrHhget/nncNA6ibQpZYAv0FAF8rOwYANiE
dxPMu/8uo9e6javT8QOFuz9p1p9WfCsfO7yIn62I6z+bzTAH3ZPng2VaZiW4o9e4fQrsMsklwMf0
ZAKb9E6CeRcpl2weNcbrySCGdyRpfYuJnDNOvw0zzI0lcilxbFxGdPrjXtSn24izItHUjQp7w5l4
gOWVJ+YB1mnuNZjHXyanje3HY2866dy0Qfy96UWz83tiRtvTuHrqR+fhLA5OusUrgF2Wvhw5Ew+w
PD2ZwCbMn+Rn0uBfpA7M10lnerh4tHkUm0k7R0nu9DZEHMbF/VPcHl9GQ5IJO82XI4DP0YsJrNM7
CeZpjEa+vgw7Hfy9iV4043UH5qhHscj4ihRvExpx1Ix4+Dc7hTy9GieZhsvCzjG0C6Aa6USd4ymw
Lu/2YI6urfw1vg3JXfx3mcbHnsfXiUzyrt2Iy14rbidnAlqrw/h63oze5X/vXvN5enUbreuzaKTt
BXaGoV0A1SmPpxJNoGrvD5E9vYqn2+O4bKReg7O4bnaif38x6qkc3x/z7KF47Onq1aQ/63Z4cR/9
zkOcFX9/dkfl+JrM5ngVqDVffgAA6uPgSZfASt KXXkUH62dfo27UWepIvQWqsvgkPwAbVPZc+sID
AFAftUww79qjyT6Gy3Cc7CC6JxOPFYt5fgAAFuNkHlCV2iWYg+7J+NrP0YQft3FWJJSNuDy+Ha6P
ltuIs4M4Gc1QBNRIOkGU+LIDsHnliXqAVdUswRzdFqV5/vX5tijD2W6jGZ0fk1MNncaPTjN6N3/d
ExNqJH2pkVgCbE95sh5gVTVLMPvxOLzt5vRdN49j+qHDL8cRvcfiHUBd+FIDkAe9mMCqapZgNuKo
GfHwb7pf8iGmHxr8e4hoHhXvAHJnSBZAXtIJP8dlYBU1SzAP4+v566Gvd3+ui//24vK/yVl93g6l
BfJlSBZAfhyXgVXUbpKfw4v7uD2+jMa4x+Ms0uQ+/eg8pMl+yllkG/H48ynuL6SXkLNynwUgX47T
wDIOnpyeWkk62Co6AKZpH9g16jSwjNr1YAL1l76sOCMOUA9lcum4DSxCgglsXPqy4mw4QL2k47Yk
E/iIlbIzLHrwVHSwnHLfsu+wy1I9V8cB2Fc168G8i3bRcKfGe7GlXbxjeemLwUcLsDz7D0D9ld+z
AGapWYJ5Gldpxthm+rkVtxMJ3+zlqngHsG2+jADsjvJ7FsAsNR0iO4juSSMuj2/j6Wo7KWT6suzg
CsA07QP7ojxxqL4Dk+p7DeZdOw7OrqN1+xTbyDF9gYCP+fLBPtI+ALDPTPKzIl8gAJhF+8C+cTIR
mOQ2JUDl0peN8gsHALstJZaSS6AkwQQq58sGwP5xchFIdjbBHHRPioPcarcpAVbjywXA/nJyEUhc
g7mi9CVa0QEwTfvAvitPNNoPYD8ZIgt8mp5LAEopsZRcwv6SYAKf5ssEANOcfIT9VNMEcxDdk9FB
a/bi2kvYhHKfA4BpTj7CfqpdgjmavKcRN+f95wPXm+U24qz40nvSHYzfBaxDuc8BwHucjIT9UrME
cxB/b3rR7PTj/uJw/NgMp1fR7zSjd/O3eAdQNV8WAFiUk5GwX2qWYPbjsRdx/GVOcjl2+OU4ovdY
vAOomi8LACzLyUnYDzVLMBtx1Ix4+Pdxv+Tg30NE86h4B1AVXw4AWJWTk7AfapZgHsbX82b0LhvR
njeLz107Gpe9aJ5/Ld4BVMWXAwA+y8lK2G0HxZfFGn5bvIv2wVlcj9feaHaif3+x1uQyHRh90Waf
qPOwGPsKAPuspgnm9vkCsV6TZzaV8/ap77A4+wsspmzr7S/b4bsW61K725Sw+8ovZ+UyeQBkszT+
AKxL2c6zedPfrXzXokoSTLJSJpeTJJkAsLtSG6+d35z3yloMqIoEE3iXM8sArJueTNgtEkzgDWcx
Adg0PZmwGySYZGXWcNi07szm5ihvALZBT+ZmvFfGyp6qSDDJTjrAlWcxJTubp7wB2KbU9rNe0229
tp8quU3JiiQ+7JqyQVev4XO0D/B59iOoLz2YwFBqyDXmAOSgbI/0ZkL9SDBhz2m8AdglqV0rF2Dz
JJgAAGRp2ZE100mlJBM2T4IJe6psdA2LBSB3iySK771GkgmbJcEEACBr6WSoRBHqQYIJe0bPJQB1
ZOIfqAcJJuyR1ChLLAHYRe+1b9o92CwJJuwRjSwAdTevLZt+TrsHmyfBhD2Qei4NKQJgl7zXrqWk
slyAzZNgwh7Q0AKwa1K75uQp5EeCCTtMzyUAu8zJU8iPBBN2mJ5LAPaBk6mQDwkm7CA9lwDsE8Nl
IR8STNhBei4B2DfaPciDBBN2iJ5LAPaZdhC2T4IJO0TPJQD7TDsI2yfBhB3gjC0AvNAuwvbsToJ5
134+mBwcnER3MH4c9oAztgDwQrsI21PLBPOuXSaSB3GSMslBN05+HUV/fDB5evoZj42DaN+N3wA7
qtwPAIC3tJOwebVLMFNyefbQeU4mfz424qBxE+e/L+Jw/JqI0/jRacb1r27oyGSXOUMLAO/TTsLm
1SzBvIs/1xGtny/J5OmPTjTHP086/HIc0XuM/ngddokzsgCwOO0mbE4th8g+/Jvolzy8iPun3/F1
vFoa/HuIaB5FY7wOu8QZWQBYnHYTNueg2NlqtbcNuifRuDyO26erOB0/9tZdtA/O4qHTj/uLl4Gz
VUpnwRyo2LTy7Ku6B/nSPkC+tKOwfrXrwTy8uI9+5yHO3pspdjib7FkUGejakkvYltQgahQBYDXa
UVi/2vVg5sIZajbJGVeoD+0D5E+7CutTy2swYd+kBlAjCADV0K7C+uxWgpnuh3ng/pfsjnSGtTzL
CgBUSzsL1avZENnR5D3X47WPtT6YDGh16WDkzBcA07QPAOyzmvVgnsbVbWv4U7PTfx7e8Lz0R/fE
bN2Wj60nuYR1c0YVADZHuwvVqd8Q2dOrInG8jePLRhycdGPWRLJQd+VJEwBg/bS7UJ2aXoN5GlfF
QeD2+DIa792uBGrIGVQA2B7tMHxerSf5Ob16in4n4rJxECeyTHaAM6gAsD3aYfi82s8ie3hxP7z2
ssgy4+D7zfhRqB9nTAEgD3oyYXW1TzCHDi/i/qkfnegV/4P6SY2YM6YAI+WXe1/w2RY9mbC6mt2m
JB8SAqqgHsHusV9/zqykUnmyLWV9VAdhcbXswRx0T4Y7fLm078ZPTBi9ph0zngIAMjQruUzeexzW
LSWWkktYTu0SzJQ4Ni4jOv3RDp9uWRJnRaI5K8tc0WTy+t4CVdBoAUD+fP+DxdUswRzE35teNDu/
4+Jw/NDwliX96DycVXZfzPJs1bwFPkMjBQD14fsfLK5mCWY/HnsRx1+es8uxw7i4H98Xs6IkE9Yl
JZcaKYC33js2OmaSCz2Z8LGaJZiNOGpGPPybnUKm+2IOk8wKh8tC1XxRAnjf9DHSMZOcpPqoTsJ8
NUswD+PreTN6l/+9O3nP6dVttK7PonHphiXkxRlPgMWUX+J9kSdXejLhfbWb5Ofw4j76nYc4K3bq
2R2V42sym+NVyEBqhHxRAoDd4AQIvM99MFckYQBgFu0D7A/7O7xVux5MqJPU8KQFANg9KbnUzsNr
O5tgpvtlHhy0371WEzYhNTzObALA7irbeYkmjBgiuyJDIphH/YD9Zf+H/WTfhxFDZAEA4JPK5FJP
JvtOD+aKHDwAAICP7Fu6VdMEcxDdk0a8f6vLVtw+XcXpeI3VGe6RL7HJm/jkTXzyJTZ5E5+8iQ85
qN0Q2dHkPY24Oe8Pd6CZy20M75N50h2M3wUAAMC61SzBHMTfm140O/24vzgcPzbD6VX0O83o3fwt
3gEAAMAm1CzB7MdjL+L4y5zkcuzwy3FE77F4BwAAAJtQswSzEUfNiId/H/dLDv49RDSPincAAACw
CTVLMA/j63kzepeNaN+NH5rlrh2Ny140z78W7wAAAGATajfJz+HFfTyNZvEZzpQ1c/l1FP2np/nX

aQIAAFAp98FkrpSwqyJ5Epu8iU/exCdfYpM38cmb+JCD2vVgAgAAkCc9mAAAAFRCDyYAAACVkGAC
AABQCQkmAAAAlZBgAgAAUAkJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJ
JgAAAJWQYAIAAFAJCea+uGvHwcHBeDmJ7mD8+DyDbpw8v6dY2nfjJwqvft/bZfKlfGCF2Ay6JxPv
mVXeg+ievDyflpOFgk4lhvtOO+wGG7RwmS+yb9h/KrXi/nDXLsr+pFtE47XXx78F2zPet0R8tD2b
sko5LvYe+w8b8cTuu209RTSfOv131mdJr2l2nl5ecvvUKqpLtG7H67Ms8hpeWSE2/U5zxnvi6aXY
+0+dZhGHideM3iM2mzHeD6JV/MRmLFrmi+wb9p9qrbg/jI9rr9uh9PDr2BTBeWoWrxOaVS0eH23P
pqxSjou9Z/TYRKwX+M4Bq5Bg7rzRQac5dfQYNtIfHKim3/PmwDTlo+eZtnpspp9/9Z53vnCJzwaU
X4qHi7LeiGXKfJF9w/5TnZX3hzLpKZYZJzpntk1TiSgLWCo+2p6NWaUcF3rPrP1ndlzhswyR3XWD
v3HTizj+cjh+YKRxVByKrv/MHhIzfE8zzr++fs/hxX08PV3F6Xj9lUE3vl/2ijb+x+zneWuV2Czi
8CLun57iaioQh1+Oi/8+xD/DYdYjDXU+uy72gX6kb11swLJlvsi+Yf+pxif2h0H3V1w3O9GZftvd
nyh+49u2KcWmdxN/xWZx6zhe2XeqsUo5LvSe07gqXnN/8Xr/gXWQYO6FZhw1xj+OjQ467+g/Ri+O
48vhXbQ/GMtfuvvvsnhPK346cC1pydjEYXw9Twnor5frJoovCsX3hGh9m2pZptz9KV40jOtonYqd
XqURIRrvTaqozBfZN+w/S1o1NsOTlRGd3xfxZfzQYnrx2B//yMeWjo+2Z9tWKceP3jPofo/LXjM6
P+bHEJYlwdx1w2TxPbPPhA3+PRT/vY6zgz/xrWiAUiP09NSP85vG64l+nt1FOobpvVzSCrFJhj3J
t8dx2Rgn/2cP0em/PXP5yviLgBjBlEX2DfvPhgyiO8ouY2be0ziK5oxEctRmsW7ani1apRznvad4
LsWwMRx59s7+Bp8gweQdzaLhmBwOexgXP1uzh26+M2yJ9RjOrHgWcVsm//3zuCka/Hd7mFNDklqZ
1q3eNZi0yL5h/9mYYW9KdOL3e+V8eBHDZuhsYubL8eUZrJ+2Z0tWKceP3jPuwX7uPJgxWzN8hgRz
1w3P+L5n3lCLGc8Nf9d1/JnKMIdDMJrnIb9c0iqxKb5M/Rq2GRPJf/Gl63enGb3L/2Yk/6NGZnid
zdzTzLBnFtk37D+bMzE0dl5Tcnr1FLet3ksvWuMxfj7dRqs4mk5fbkCFtD3bsUo5LvWeceeBa5ip
mARzLyw3pGj+NYDTjfh4eOz517lfCnjPksO9hsNq37tu8/Ww2uG9rsaNjLPH8GKRfcP+s1mDvzfF
sW0icSyWoviLQ+RlNIqfJ6/OSEnmqPclLUXCM/hXHP2WuzaNJWl7Nm6Vclyp7N8Zeg6fIcHcdYdf
I12X/zB1QV//sRfR+jZ7LP/pt2jN6KkcNTBTjfiwYY83M6GygFViM7cheIlNamTStRWtW5POwKRF
9g37z+aNZimfTBxTT2XxRLMT/eLneR0xw+S0eRQ6MNdI27NRq5Tjh+8ZdONk6mTN0PC7XSs+mKsJ
llMcxNl10zfSnV6f4e19xWbfs3GR38UcK8Sm+NJVvGbiXljj+189x2Z6nc0bxtF93zZqkTJfZN+w /1Rvxf1heKybcR/M9A362QLHTD6wYHy0PRuySjku+J63+
w0anfM/sA5AbKH/eKrEZNfQvy2RsXv++6cUXsY1Y8Qs1nzCzzF/vP4vsG/afNVggNrO8/TKcjJNM
ManOEvHR9qzfYuW4/LGtNB3DObsgrOwg/aeoYAAAAPAprsEEAACgEhJMAAAAKiHBBAAAoBISTAAA
ACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAAKiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEE
AACgEhJMAAAAKiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAAKiHBBAAAoBIS
TAAAACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAAKiHBBGABg+ieHMTBwezlpDsYvy65i3bxWPtu
vPqh0etf/455ltmWBd21J7Z32e2fZ7Sto99V5e/dplXiexKrhAWA+pFgArC41m08PT29Xm5b0bts
TCQcp3FVPH51Ol5dl4W2ZRFFAnR2Pf45qW77B93vcXl8u/6yyFpRnrfHcfm9W6TbAOw6CSYAn3P6
IzrNiOs/GXTN5bQtReL632UvWt/2OrscSXGJy/gvh7AAsFYSTAA+6TC+HBf/PPwb91DNGEI56MZJ
8djkUNZ5vYyD7smKw12nt2Xkrv3O3x5u11mk/svrs+K5k9TL9s4Q0Lv2q9/x4bbd/Sl+byvm5pcL /M7X234S3W56z5whpwuUdVm+z8vUC94tr3dM/763n+M
RsyQEp7GZRzfvh7KmhK6WYlLSlYaqeeveP39xczfOMfbbUnJ0lm8DKftd4pE52ycoB1exP3TbZEG
phG3xfP3F7M/Q0oEz4p08fkz3MbxZeNNYjbp7k+Rtra+xbv55QK/c7jt1624HW/7Uxpqejk5nHfK
AmU9Kt+ITr98TfH5r8+ek8K55TXDm9/X70QUn2M6yTxMmX/vJv7KMAF2mgQTgE8ZXmfYS7nUO6lU /zGKdPF1T97p1TAZeXNtYpF0lcnlKtctvt2Wu/h
tildV1ikpde/3km80t+NaB41xuvTFvidRbJYvKQoi6uXJLUot/SSd31Y1qNhu83O73jJ3UfXnI6S
+WXLa8bvS0l7sZG9y/+KZyc0jpYsdwDqSIIJwOKuz14NhUzLhwnh6bci5bmOs4P264Rj2s33YY/e
66RrjoW2JSVP9y/JT+o1bFwWac4SBn/jpnjD8Zepvs0FEqY37ykt8jtnJYuF029zMsyPynrwL0Yd
vO9s17LlNRwG3Izzr7M+x3W8uhT28EuMRi/rwgTYZRJMABY3OXNrv1MkEaPH5ieEKWnpR6eZEp+X
ZHB6dGmvyGI6t2l45ff3ry+ctOC2vLo+8CzitnztZ40TppnGidzSJn7nYDjWd1mLlHUz3u1YLSxf
Xr24bLz8reGybBIPwM6QYAKwmvFQyNST+OGEN3EYF/fjZLBYRm97fV3fcJjl6UX8bBUJy7K3tHhv
Wwbd+D7u1Rz97Ynhpp81L4mcl3zOM/E7h9csruSjsp7T67pSeTUnrud8vSzUEw3ATpFgArC68TWB
vUV7HcdOr9LEOrMTndMfnWj2VrilxaxtmTXMdPjYEg6/xnlzxtDO4e+Z3xv47nDQRX7nrGGmhWV7
Nl+V9UfDVJctr+GQ3PnDhJ99ODwXgF0gwQTgU8oE5t1ex3Qd3/RtNcbX7s1Mzg5TL2bqdfvgms0Z
3mzLmyTtLtpno1lYp5Osd5Ou1CNYbFDvsjEx1HT8e1o/JybLmXQa6VLJ3ruZ1wK/c1Y5jCdBeteH
ZX0aPzrNqRMCg+ieHIxmr12ivEZGv2+6N3p0m5Op7VggIQdgBzwBwIf6T0Ue8ZTGTs7S7zSfUpPS
7PSLtdunIi96evXS29bw+Zel+TR86dDo9aP3lkaPzf57y2zLy/rk371tvd6G0XqxNDvFb5+x/cnU
Z3i9vTMMX98qflvp43KZ9Tuft224FL/vze+dMresR16XSbFMbNTH5fX2c7z5fTO2b/iaYfkCsMsO
0n+KxgAAqNRdtIez5FR8LWLqpRz+2gqvJ127NZUFANkxRBYA1mI8fHT6IspFDbpxcjA9A+xoyGqz
86NGyWUhDdNtdmLi9poA7Cg9mACwNun6xkY8/lyx527YWzm6BrLUql0vYOq9/BVH/Yn7awKwsySY
AAAAVMIQWQAAACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAAKiHBBAAAoBISTAAACohwQQAAKAS
EkwAAAAqIcEEAACgEhJMAAAAKiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAA
KiHBBAAAoBISTAAAACohwQQAAKASEkwAAAAqIcEEAACgEhJMAAAAKiHBBAAAoBISTAAAACohwQQA
AKASEkwAAAAqIcEEAACgEp9K
MAfdkzg4OInuIK3dRfvgoFhvFz+9Y9CNk+I1J6M3AAAAsEM+kWDexX+XvYjWz7g4HD/0kcOL+NmK
6F3+934SCgAAQC2tnGAOur/iuvi39e109MCCTr8VGWbxzl96MQEAAHbKignmIP7e9lp/m3HUGD0y
6d9dezgU9iAtJ+24m8wlG0fFuyJ6N3+L3wIAAMCuWDHB7Mdjyi/jOL68GR57HZdn1zF8Ouldx1lj
4rrMwy/Fuwq9x+K3AAAAsCtWSzAH/+Ih/ds8ihkdmNHs9OPp6Sme+p1IA2JT0vnnOcNsxFHqwix+
wz9dmAAAADtjtQSz//jSQ/lGK36Ws/4cXsTwksvCw5tsshePujABAAB2xsqT/DAyvM7UYrFYLBaL
xWKxWOYs+2K1BHM8Uc9saYbYu9EEPoO7+JOmmi0cv7lYc/YEQXU0HA78zvK///u/Mx+35LGIT96L
+OS9iE++i9jkvYhP3ov45L3UNT77ZLUE84OJenqXZ9FImXrjbHgrk2h24sfz3UzmTRAEAABAXa04
RHbeRD2t6Ny2Xno4m624/X0Rz7nkBxME7Zrj42EqTqbEJ2/ikzfxyZfY5E188iY+eROf/B08rdhn
O+ieROOyF63bp7h67p1cwF07Ds6uhzPN3peTAdVYGk+9b93eAADA4vYpZ1h5kp/Di5/DW5Bcv9x/
ZCF3w4syJ2aa3XEPD8P+WjIlPnkTn7yJT77EJm/ikzfxyZv45O8Ts8iexo9Os8gwf0V30ftZDrrx
q8gvm50fxbsBAADYJSsPkWXEEFkA8jCl7kkjLsc3qt6VS1EAdoEhsgBArdy1i+QyOtEvvsA89TsR
l98XH2EEABWRYK6ZceJ5E5+8iU/exCcn6b7TzeiMZ21/+D//T9w/3YcOzDzZd/ImPnkTn/zVPMFM
w4EOhl3Os5d20eQCwI4b3gLM/aUB2L7aJpjpNikHB424Oe8PxzPPXG4jzopE82SLY4Tcqydv4pM3
8cmb+GSk/xi95lHEsG08iP/5n/+JtjOs2bLv5E188iY++atpgjmIvze9jycwOL2KfqcZvZu/xTsA
YIf1LuNX/B6fYG3F9dmJazAB2LiaJpj9eOxFHC8wFujwy3HR6D4W79gO48TzJj55E5+8iU9mmp34
PT7p+vB//7/RafbicVuNH3PZd/ImPnkTn/zVNMFsxFGzqGD/Pj41O/hXVMLmUfEOANhRjaNobvFk
KgCUansfzHQNZuOyF63bp7g6HT847a4dB2fXa70XWLrWpaZFCMAOuWsfxK+jcXs3bP8ibp+u4r0m
EoDN2aecobYJ5shdtIsW9Hq89kazE/370ZTt6yLBBCAPaWb1Rlz2RmtzT8ACsFH7lDPU/DYlp3FV
BCoFa+ay5uRyEcaJ50188iY+eROf3BzGxf2o/fvf//1fyWXG7Dt5E5+8iU/+ap5gAgAAkIuaD5Gd
YXzd5UgzOv37WNPll0OGyAIAAPMYIlsTaUKDFKy0nKSbfQ26cfLrKPppeOxw+RmPjQM3mwYAANiA
2iaYKbk8e+g8J5M/Hxtx0LiJ89+T112exo9OM65/dWNb95o2Tjxv4pM38cmb+ORLbPImPnkTn7yJ
T/5qmmDexZ/riNbPl2Ty9EcnmuOfJx1+OY5wbzAAAIC1q+k1mKPbkzy8ub/lIAaDwziceGh4v8yb
87XdrsQ1mAAAwDyuwczeaOhr7/K/ItWc9Dq5TInof5e9aJ5/XSm5LK/vnLckk1316Wfr1kvWrVu3
XrJu3br1kvX9W98ntZ5Fdtg7eRmzZ4odzya77htNpyRzXhGmCnV8fDxeIzfikzfxyZv45Ets8iY+
eROfvNU1Ph/lDLuk1rPIHl7cF4F65zYkp1fDILrRNAAAwGbs3n0wN2yfzkYAAADL04O5Q9Iw2oOD
9tS1mgAAAFRt5xPM0TDaq9jWSNk0Tpx8iU/exCdv4pMvscmb+ORNfPImvnb+QQTAACAzXAN5ie5
BhMAAJjHNZi1MYjuyez7U44W114CAABsSm0TzNHkPY24Oe8PzwbMXG4jzopE86Q7GL9r84wTz5v4

file:///G:/1st%20Partition/My%20Activities/Editing/The%20NAJFNR/Submitted%20Man... 8/31/2019

5E188iY++RKbvIlP3sQnb+KTv5ommIP4e9OLZqcf9zNvgjl2ehX9TjN6N3+LdwAAALBONb0G8y7a
B2cRt09x9dH0sHftGL10PTPJpqG4tSxCAABgI/YpZ6hpD2YjjpoRD/8+7pcc/HuIaB4V7wAAAGCd
appgHsbX82b0LhvRnjeLz107Gpe9aJ5/Ld6xHcaJ50188iY+eROffIlN3sQnb+KTN/HJX20n+Tm8
uI+n0Sw+4xljZyy/jqL/9DT/Ok0AAAAq4T6Yn5QSWUUIAAC8Z59yhtr2YAIAAJCXJRLMNHPrSbx7
S8k0W+tBu3gVk4wTz5v45E188iY++RKbvIlP3sQnb+KTv8p6MIeztQIAALC3PrwG8659EGfX45UP
NDv9vZtQxzWYAADAPPuUMywxyU8aIvsrjvr3YVLWFxJMAABgHpP8zHQaV0+Sy2UZJ5438cmb+ORN
fPllNnkTn7yJT97EJ39mkQUAAPbDoBsnJiZdqw+GyKZhsWex4CWYhVbcPl3F6XhtHxgiCwAAdVDm
NpvPWQyRfZaGxT4NC2OxZb+SSwAAIH+D7kmR5J3FQ6sVzfFjrIchsmtmnHjexCdv4pM38cmX2ORN
fPImPnlbOT5ffkb/6SnufxyNH2BdlkgwU5fywbB79/3FeGYAACAvh6enYa7SzVjiNiVz3LXj4Cz2
7vrLJCXWVRQhAACwZmmSn8Zj/HQN5tpUM0T29CpuW9dx1tZ/CQAAsK8quwbz9Fsr4vqPIbJTjOPP
m/jkTXzyJj75Epu8iU/exCdv4pO/yhLMwT/BBgAA2GfVXINZ3lOmdRtPV/t1FaZrMAEAoCZcg7l2
SySY5Y1J39HsRP/+Yu9mZ5JgAgAA85jkZ6bTuCoKJRXMzGUPk8tFGCeeN/HJm/jkTXzyJTZ5E5+8
iU/exCd/lV2DCQAAwH5b8hrM0TDZh04/7i8OY9A9icZlb/SUIbIAAABvGCL7jrv2WVwXieTvIrlM
F8h+T8llmtinKKzb48touA8mAADA3loiwbyLP9dFPvlz3EvZf4zUd9n6Npp/yX0wZzNOPG/ikzfx
yZv45Ets8iY+eROfvIlP/la+BvMuZZvRinF+6T6YAAAAe26pazDv2gdxFulelzG6ZcnzdZfugwkA
ADDLPuUMK03yM7oXZjM6/fu4OBxE96QRl8f7l1wmEkwAAGAeCSZDqSIs4n//93/j+Ph4+HM5Lty6
9cS69cS69WST6+XPSRW/L7Fe3Xr5c1LF70usV7de/pxU8fsS69Wtlz8nVfy+ZBPr//M//yPBZDEf
nY1IFaqsXORHfPImPnkTn3yJTd7EJ2/ik7e6xkcP5lwTw2TH12D22wfx62h0b8x9Y4gsAAAwzz7l
DMvNInvXLgrnVxz1n6LfaY4fjDi9uo3jy0acdAfjRwAAANg3SySYg+j+uo5m53e87ag8jR9Fwtm7 /M99MKekbnzyJT55E5+8iU++xCZv4pM38cmb+ORviQ9
GfHwb/Yw2Ls/1xHNo+JVTHKReN7EJ2/ikzfxyZfY5E188iY+eROf/C2RYB7Gxc9W9C6/x/SlloPu
SZwV+WXr50XxKgAAAPbRcpP8nF7F09PPeGwcROOyF0W2GY2D9HNEp/8UV6fj1/HMOPG8iU/exCdv
4pMvscmb+ORNfPImPvlbLsEcOo2rp6fhNLsvy/2MiX8AAADYJyvcB/N9g243+hcXRQq6P9wHEwAA
mMd9MKekayxToYyW9oxbkQyie5KGyj6O1wEAANg3HyeYd+3nayxT1n3buo6zk26RUo4Vzx8cNCJd
ktns/Nir3stFGCeeN/HJm/jkTXzyJTZ5E5+8iU/exCd/HySYg+j+Gk4P+3yN5enVbbR6l/Hf3bhn
M00fG81hAnrvQkwAAIC99cE1mHfRPjiLh05/InlMw2EbcVMklb1er0g+b+Npj6ePdQ0mAAAwj2sw
pxx/meyZPIwvxzFMLptF4rnPySUAAAAvVrhNyVizE78Nif2QceJ5E5+8iU/exCdfYpM38cmb+ORN
fPK3eoJ5/CWklwAAAJQWugYzbp9iciTsXfsgzmK/r70suQYTAACYxzWYAAAAsKSFEszrs4Nh1l0u
wzuTXJ+9emy0tONu9BbGjBPPm/jkTXzyVkl8hvdSLtuQk+g+32SZz7Dv5E188iY+eROf/H2QYJ7G
1dPTsDt3seWqeAcALGDQjZOzh+F9lIdtyO1xXDacqASAOvvgGkw+ks66K0KAKqTr/n/FUf8+TFIO
wC7Zp5zBNZgAZGHQ/RXXzfP4KrkEgNqSYK6ZceJ5E5+8iU/eKotPGip7cBCNy4jO7wu3wKqAfSdv
4pM38cmb+ORPggnAdh1exL1rMAFgJ7gG85NcgwlQFddgArCbXINZG4PonkzeJmV6cSYcAABgUz5I
MNPZ5FmJ23vL5hK6Qfek+HuNuDnvj6a3n7XcRpwV23WyxRurGSeeN/HJm/jk7dPxGd4Dc6LdGPyL
B5P8VMK+kzfxyZv45E188vdBgpnrfTAH8femF81OP+7njaM6vYp+pxm9m7/FOwDIyvAY/TA8ETg8
Sdl4jJ/3JvkBgDqr6TWYqWf1LOL2Ka4+ymjTGfLhS9eT/KYvRbUsQgAAYCP2KWeo6TWYjThqRjz8
+7hfcvDvIaJ5VLwDAACAdarpNZiH8fW8Gb3LRrTn/cG7djQue9E8/7q1IVfGiedNfPImPnkTn3yJ
Td7EJ2/ikzfxyV9Nr8FMt027L/7ecBafGYnuePl1FP1iu+ZepwkAAEAl3Afzk1IiqwgBAID37FPO
sOQ1mB8NmXXfSQAAgH21VIJ51z6L62ZnOOw03f4jWrejobH9ThRrxermhsgmo3thviS4s67HHL1m
e4mvceJ5E5+8iU/exCdfYpM38cmb+ORNfPK3RIJ5F3+u43nCnMMvx0WE/43uL3l4Eb+LhPP6V3dj
95tMiWPjMqLTL6//HF+POXfWHwAAANZlySGyEcdfxhPmNI6i2XuM/mgtDr+ev1pfr0H8velFs/M7
XubvSRMS9aPzcBYHJ5tLdD9yfFwk4mRLfPImPnkTn3yJTd7EJ2/ikzfxyd8SCebUvScPv8RxPMQC
t6Jcg3489ooKVia7zw7j4v4pbo8vo5FRkgkAALAPlkgwy3tP/je+nvE0vrV6cfN3lMYN/t5Er3lU
pKGbMJXsTjm9GieZGQyXNU48b+KTN/HJm/jkS2zyJj55E5+8iU/+lhoim+49edu6jrNx4nZ6dRvH
l43hBDuNy+O4vb8YXp+5ftPJ7ltp21rXZ8V29caPLG9yAqH3lmSyoqefpyv+vOetb3c9Web11je7
nizzeuubXU+Web1169atl6xb37f1fVLr+2COJvrpRev2Ka5mTl87iO5JIy57rbh9Ws8MtynJ3Jd7
2gAAAMvbp5xhiQRzlKzdnPfj/mVmnb0nwQQAAObZp5xhiSGy702swzz71iVeN+KTN/HJm/jkS2zy
Jj55E5+8iU/+lkgwT+PqthXXZ+13r3vMURpGe3BQr20GAACooyWGyN5F++Asrsdrs63vWsdcGSIL
AADM4xpMFibBBAAA5nENJpUxTjxv4pM38cmb+ORLbPImPnkTn7yJT/5WSDDTUNnxfSBPujFIj7QP
4qSbftq0NLPt6/tSvl5cewkAALApyyWYd+0iafsVR/2n6Hea4wcjTq9u4/iysdEkczR5z+i2Kam7
eeZyG3FWJJrbSX5Hjo+Pxz+RI/HJm/jkTXzyJTZ5E5+8iU/exCd/SySYg+j+uo5m53e8vQ3mafwo
Es7e5X8b6jEcxN+bXrEtH9yT8/RqmAj3bv4Oe1oBAABYnyUSzPn3wTz8ssmzCYvfk3O4Xb3H4h3b
YZx43sQnb1nHZ9CNkz0fhm//yZfY5E188iY+eROf/C2RYDbiqFkE9d/svsC7P9cRzaPiVZswf1sm
Df4VlXBj2wXsi7v/LqM3/hkAgJHlblOSrsE8e4hO/z6+/j2Jxs159O8vIrrFz5e9aN0+xdWGboKZ
rsH88G8OtzcN6/1gKO0npMmElilCYAekY8uvh2j2juPnnt37FwBY3j7lDCvcBzPNInsW1+O1keYw
6VxTDjfHrG2Z0OwME+B1bpYEE/ZNmr36v/jy+yh+NR4lmADAh/YpZ1jhNiWncVUUTiqgl2UbyWUy
a1smljUnl4swTjxv4pO3HOMz6H6Pm/MfksqC/SdfYpM38cmb+ORNfPK3QoIJsK/u4r+b8/i9nTNq
AADZW2KI7Hg4aus2njZ1oWUNGCIL++OufRB/vo2v+06zyBoiCwAswDWY70hfrs5eXfC4rWsv8yHB
hH3x/jXfm5zgDACoH9dgvuP0auL6xttW8UgvLhsHwwIbLu19viPcbMaJ50188pZXfKau+e53ohmt
uC1+3tfk0v6TL7HJm/jkTXzyJj75W/0azNOrly9aT/3oNIvHrv+EFBMAKpCGYR+0p9rVNItxeWJ3
+jkA2L4VblMyNr7H5Ct7eH2mIbIAVK8ckp16yV+u8x1eqhKjtnbyZwDyZojsTJNnTYtlmFymazAn
hoxp5ADgUwbdk6KdPYuHVqtoZSfdxZ/rot39MWprT390omnkEACZWSLB7Mdjr/gn9VKWCeXW7n9Z
H8aJ50188iY+eROfNfnyM/pFG3v/42j8wNjgXzzEcXwp293DL8XaQ/wbjNcniE3exCdv4pM38cnf
EgnmeIILvZQAsDaHp6fh3C0AdbX6ENlyOekWz/Ce4+Pj8U/kSHzyJj55E598iU3exCdv4pM38cnf
Qgnm6HqQRtyc9yeGx46W/vlNNIpE86QrzQQAANhnHyeYd+1oXMZwMp/7GRdcHl7cD+8HF5eNcBvM
t4wTz5v45E188iY+GzZ9zeX0NZkTxCZv4pM38cmb+OTvgwRzEN1f1xGtn/Mn8zm8iJ+tiOtfhssC
wHqcxrdWLy7/G53NvfvvMnqtb8+3MAGAHHxwH8zRfbji9ik+nNtneF/M9NKX+3Xtg3Qd6twiBIBV
DLpx0niMn6/a1fL+mMnre2QCkK99yhmWmOQHANiYw4u4f5NAjmd0Hy6SSwDy80GC2YijZsT1n48v
rrz7cx3RPCrewSTjxPMmPnkTn7yJT77EJm/ikzfxyZv45O+DBPMwLkYXV8bcSWIH3Rhdqnnh3l0A
AAB76oNrMEfSbUoal71odvpvZpKd99w+cA0mAAAwzz7lDAslmCOD6J40osglX2t2on+/vz2XEkwA
AGAek/zMdBgX9+XEAhPLHieXizBOPG/ikzfxyZv45Ets8iY+eROfvIlP/swiCwAAQCWWGCLLLIbI
wh4a3p/wMkZXDDSj07+PPbwEHQBYkCGyALzjLtpFcnl8O7pMoN+JuGy0i0cBAJBgrplx4nkTn7xl
GZ/Bv3iIVnwb3+H+8OJnsfYQ/+bdymlH2X/yJTZ5E5+8iU/exCd/EkyAZRx+jfPmdfwpuyzv/sR1
8zy+GiILALBsgpluVXIwHEM8e9mtYWKzP+PrJZk8k5J+nj6zMu9569tdT5Z5vfXNrifLvH4z6/8n
Lu77cfRrfBz4//1/nm/VtNj7d2c9Web11je3fnx8PPf5xPr21sUn73XxyXu9rvHZJ0tN8nPXPoiz
61bcPl3FeHTY3ktfME3yA/vkLtoHZ/HQ6cf9xWEMuifRuDx2XAQA3rVPOcMSPZh38ec6otn54UvU
EvbtjEXdiE/esozP+BrMn+NpY12DSY7EJm/ikzfxyZv45G/pazCPv7jQCAAAgLeWGCKbrr9sxOXx
bTxd6cMsGSIL+2Z0LLw5N0QWAFjMPuUMS12DGXftODi7jtbtU8gxRySYsIcG3ThpXEZvuNKMTv8+
xiNmAQDecA3mTHfRLpLL5Prs9UyqL4ubjU8zTjxv4pO3bONzeBH3RSORGoqnp/1NLu0/+RKbvIlP
3sQnb+KTvyUsZNO4ev5C9d5iiBgAAMC+Wm6ILG+knltFCAAAvGefcoalZ5EdXnv0alhsWk6iu4dT
9AMAAPBiuQQzTfLTuIzo9CeGxT5FvxNx2TiItgsw3zBOPG/ikzfxyZv45Ets8iY+eROfvIlP/pZI
MAfR/XUdzSK5TFPzTzq8uC+SzGZc/+oWrwIAAGAfLXEN5l20D84i3rtFyfAWJunp/ZroxzWYAADA
PK7BnKkRR82Ih3+z+ygH/x4imkfFqwAAANhHSySYh3HxsxW9y0acTM3oM+ieROOyF62fF8WrmGSc
eN7EJ2/ikzfxyZfY5E188iY+eROf/C03yc/pVTyNZvSZmEH2oEgu07w/7wydBQAAYC+4D+YnuQYT

gJnSbb0aj/Fz1twE854DYOe4BhMA+IS7aDcuozdee23ecwBQbxLMNTNOPG/ikzfxyZv4zJbmJTg4
OIuHViua48dK856rktjkTXzyJj55E5/8STABoEpffkb/6SnufxyNH5gw7zkA2AGuwfwk12ACMJNr
MAEYcw0mAAAALGmFBPMu2kUGnrLwg5NupDti3rUP3twbkxHjxPMmPnkTn7yJT77EJm/ikzfxyZv4
5G+5BPOuXSSWv+Ko/xT9zsv0BKdXt3F82ZBkAgAA7LElEsxBdH9dR7PzOy4Oxw89O40fRcLZu/wv
7saPMHJ8fDz+iRyJT97EJ2/iky+xyZv45E188iY++VsiwezHY68I6pc32eXQ4RfBBgAA2GdLJJiN
OGpGPPybPQz27s91RPOoeBWTjBPPm/jkTXzyJj4fOLyI+/dmiZ33XAXEJm/ikzfxyZv45G+JBPMw
Ln62onf5PaYvtUw3jj4r8svWz4viVZs0iO7JeMKhmUvbkF0AAIANWeE+mGkW2bMo8skJzej072dc
m7k+KaltXPai2enH/Xt/OE1KVGS+c1/zSSmRdR9MAADgPfuUM6yQYOYg9Vw24ub848RxmIjenEf/
fj29qxJMAABgnn3KGZa7TUk25k84NGk4+VDvsXjHdhgnnjfxyZv45E188iU2eROfvIlP3sQnf0sn
mHftgzg46cbzZZjDe2MebPgemPMnHJo0+FdUQpMPAQAArN1SQ2RTcnn20Jkx3HR8XWbrNp6u1jUn
3mvlNZit26d490+6BhMAANgy12DONEoi472EbpjMpafXN+36W7MmHJrQnJUMV0uCCQAAzOMazJnm
D0sdDkXduNO4KgKVgjVzWXNyuQjjxPMmPnkTn7yJT77EJm/ikzfxyZv45G+p+2B+PW9G77IR7emb
Sw668X14y5AfG+y9BAAAICfL36akSCZPGpfRG6+ObP4+mLkwRBYAAJjHNZgsTIIJAADM4xrM7KXJ
fQ6GgVpsaRfv2A7jxPMmPnkTn7yJT77EJm/ikzfxyZv45G/JBHMQ3ZNZCVy5bCqRS5P79KPTTD+3
4vZpxgQ/r5ZNzmwLAACwn5a/D+Z1SuhySdhSwtuIy+PN3X9zWkqslyhCAABgz+xTzrBED+Zd/LlO
t5bMaabYw7j42Yq4Pns7s20FXvfOzl6Sya769LN16yXr1q1bL1m3bt16yfr+re+TJXow03WPZxG3
T7GlzsIspSRzXhGmCnV8fDxeIzfikzfxyZv45Ets8iY+eROfvNU1Ph/lDLtkiR7MRhw1I67/bGu6
HAAAAHK23G1K7tpxcHYdLb2Yz/bpbAQAALA8PZgz3UW7SC6T67PZ1yNu83Yg7xl0T7LcLgAAgF2z
RIKZbg0y6xYgk0t+twM5vLjf6nalceLkS3zyJj55E598iU3exCdv4pM38cnfkvfBBAAAgNmWuwZz
aDSb7HCwbLMT/fuL6LcP4tdRP+4vDoev2CdpaPDSRQgAAOyNfcoZluvBTJP8HPyKo/5T9DvN8YMR
p1e3cXzZiJPuYPzIpgyiezLrWtByce0lAADApiyRYBbJ3K/raHZ+x9uOytP4USScvcv/NpbQjSbv
acTNeX98/eeM5TbirEg0N5/4vjBOfEGDbpxMnhw46RY1bv3EJ2/ikzfxyZfY5E188iY+eROf/C2R
YPbjsRdx/GX2MNjDL5u84ekg/t70imT3g2G5p1fDntbezd+NJCt8Qv8xeq3bl5MD9xexfwOuAQCg
3pZIMBtx1Ix4+Dc7Vbv7cx3RPCpetQnzk91Jw8S391i8YzuOjzeZeNdXqj/No83UnknkzfxyZv4
5Ets8iY+eROfvIlP/pZIMA/j4mcrepffY3rEaRqumm6R2fq5qV6n+cnupMG/hw0mvqxmEP8emnH+
VZ8lAADU2XKT/JxexdPTz3hsHETjshdFthmNg/RzRKf/FFcbu9nkYXw9T9d8NqI976LPu/ZwO5vn
X7c23NI48UWMeqRvvpfXYJ68OYmxLuKTN/HJm/jkS2zyJj55E5+8iU/+lkswh07janIineFyP2Pi
n/U6vLgv/u5wFp+XiWGml19H0S+2bx9vn1Irg3+RDhXnv8v6lE5imAEYAADqZoX7YDIpJbKKsGrp
XqvpdjibP3EBAABV26ecYYkezPSlf0Yv4atFrxMAAMC+WiLBnDU0drzctornW3H7dFW8iknGiS/g
rv365EQaMts8j03M+SM+eROfvIlPvsQmb+KTN/HJm/jkb4VrMGc4vYrb1nWczZ1xB94xvF/pQ5yV
PeGNx/jpPpgAAFA71V2DmXqhzmLvejFTQlRVEQIAALtnn3KGanowCL8P7QIAALC3Kkow7+K/dF/M
1jfXYE4xTjxv4pM38cmb+ORLbPImPnkTn7yJT/4qmkX2LK6bnehfSS8BAAD2lftgflJKsBUhAADw
nn3KGSq7BhMAAID9JsFcM+PE8yY+eROfvIlPvsQmb+KTN/HJm/jk74MEc951l7OWiZvlAwAAsFdc
g/lJKbFWhAAAwHv2KWdYqAezPeyWTD+fRHcwfAIAAABeWegazId/sspVGSeeN/HJm/jkTXzyJTZ5
E5+8iU/exCd/HySYp/Gj04zeZSOG97qMXlw2Zl17WS6uwQQAANhXS1yDmYbI/oqj/n1cHI4fYphY
uwYTAAB4zz7lDCb5+SQJJgAAMM8+5QxL3gdzEN2TWUNjy8UQ2WnGiedNfPImPnkTn3yJTd7EJ2/i
kzfxyd9SCeZduxGXvVbcFtl3ysDfLldxOn4tAAAA+2XJazDP4qHTj3sXYT5LPbcLFyEAALB39iln
WHKIbMTxF8klAAAAby2RYDbiqBlx/cdVlsswTjxv4pM38cmb+ORLbPImPnkTn7yJT/6WSDAP4+Jn
q8gwz6ItxwQAAGDK0tdgXo/XZksTAO3XRD+uwQQAAObZp5zBfTA/SYIJAADMI8FkKFWERfzv//5v
HB8fD38ux4Vbt55Yt55Yt55scr38Oani9yXWq1svf06q+H2J9erWy5+TKn5fYr269fLnpIrfl2xi /X/+538kmCzmo7MRqUKVlYv8iE/exCdv4pMvscmb+ORNfP.
mAAAwDz7lDMscZsSVpG68cmX+ORNfPImPvkSm7yJT97EJ2/ikz8JJgAAAJUwRPaTDJEFAADmMUQW
AAAAliTBXDPjxPMmPnkTn7yJT77EJm/ikzfxyZv45E+CCQAAQCVcg/lJrsEEAADmcQ0mAAAALEmC
uWbGiedNfPImPnkTn3yJTd7EJ2/ikzfxyZ8EEwAAgEq4BvOTXIMJAADM4xpMAAAAWJIEc82ME8+b
+ORNfPImPvkSm7yJT97EJ2/ikz8JJgAAAJVwDeYnuQYTAACYxzWYAAAAsCQJ5pptfZz4oBsnBwfD
syZpad+NH2flOP68iU/exCdfYpM38cmb+ORNfPInwdxpd9FuXMbx7dOwS/7pthXXZyfRHYyfBgAA
qJBrMD8p6/HUd+04+HUU/fuLOBw+MIjuSSMefz7F1enwAQAAYM1cg0leUqI4Mcy1XE4+6oo8vYqn
5+Qy6cdjb/wjAABAxSSYa1bJOPGUKKYhruVy2yoebMXPi5fUcRGD7q+4bnbih97LZ8bx50188iY+
+RKbvIlP3sQnb+KTPwlm7dxF++w6WrdXsUyeOOieROPyOG5f9WgCAABUxzWYn5SGqm6yCIeJ4s35
xHWVHxsllxGd/n0s2ekJAAB80qZzhm2qeQ9mmrTm7bWJL0s7duuuHIP4e9OL1s9lk8vjuH2SXAIA
AOtV2wQzJU4HB424Oe+/vj5xcrmNOCsSzQ8nw1mjSseJD/7GTa8V3xYdGzvoxvdhz+Vyw2n3iXH8
eRQfvIlPvsQmb+KTN/HJm/jkr6YJ5qgnr9npx/28brnTq+h3mtG7+Vu8o/4Gf2+i1/q2cLJ4999l
9Ir/XTZe9+y2d6tbFwAAyERNr8G8i/bBWcTtAvdzTLf4GL50Pb14KWHbVBHetQ/i19EHSTUAAJCV
TeYM21bTHsxGHDUjHv593C85+PcQ0Twq3lF3g0gf5fjLAsnloBsnZY/lSXcnem8BAID81TTBPIyv
583oXTbmD/e8a0fjshfN869buzVHdePE+/HYa8bRh5nyXbRHU8YOz5L0z2+iYUzsu4zjz5v45E18
8iU2eROfvIlP3sQnf7Wd5Ofw4r5IoIaz+DxfW/hm+XUU/SLJ2o0hpadxtchMsIN/8RCt+Dl+4eHF
z2hd/4otznMEAADsCffB/KSUyGZVhGl4bOMxfj5fc5quV/0VR+6BCQAAW5FdzrBGte3B5B2HX+I4
ruPPeFTsoPurWOvFY3+0DgAAsC41TzAH0T2ZMTT2eWnHtq8+3Pw48dO46nfiYTx0+Hv8jE5z/BRv
GMefN/HJm/jkS2zyJj55E5+8iU/+aptgDronRQLViJvz0WQ2M5fhJZoHcbJvFyAeXsT9uAzuL2LB
yYEAAAA+p6bXYKaey1Fy+dEEPikRbdycR7/ItNZxCWLqJcy6CN9ckwkAAGxS9jlDhWrag5lu2bHY
PSEPvxxH9B6Ld+yLNKnPyfOssXf/XUav9U1yCQAArF1NE8xGHDUjHv59PPR18O8honlUvGM7Nj9O /DSubo/jsjG6BvPsoRP9K+nle4zjz5v45E188iU2eR
HY3LXjTPv640PHY0UdD8JZms6Onn6Yo/7/m1rP/f/9/n61D/9+r/if/z0ev3eD1Z5vXWN7ueLPN6
65tdT5Z5vXXr1q2XrFvft/V9UvP7YKbhoGdxPV57o9lZ27WXpZRk7st4agAAYHn7lDPUPMHcPgkm
AAAwzz7lDDW/D2b+9q1LvG7EJ2/ikzfxyZfY5E188iY+eROf/O18D+bwNiWXx3G7ptt0lNdhAgAA
vGdfejANkV0zQ2jzJj55E5+8iU++xCZv4pM38cmb+OTPEFkAAAAqIcEEAACgEjVPMAfRPZl9f8rR
0o55t8kEAACgOrVNMNPkPQcHjbg57w/HYc9cbiPOikTzpDsYvwsAAIB1qWmCOYi/N71odvpxf3E4
fmyG06vod5rRu/lbvAMAAIB1qmmC2Y/HXsTxlznJ5djhl+OI3mPxDgAAANappglmI46aEQ//Pu6X
Xnuj2Yn+/YXkEgAAYANqnmACAACQi9repgQAAIC8SDABAACohAQTAACASkgwAQAAqIQEEwAAgEpI
MAEAAKiEBBMAAIBKSDABAACohAQTAACASkgwAQAAqIMED/jrh0HBwfj5SS6g/Hj86zy
HlazdFnfRfv59RNL+278PGsx6MbJQbso/QXYfzZv4fjYfzZjEN2T12V8ssiOYN/ZkFXiY9/ZpEH3
ZKKcfXfLzfLxsf/kSIK5qnSwOXuITv8pnp6K5fY4Lhsf7AirvIfVrFLWg3/xEM2X95TL1en4BVSv
aBgal9Ebr81l/9mCJeJj/9mAlLw04rL3Us79TjN6l435X6bsOxuyYnzsOxuTkpfG5XHclmXsu1tW
VoqP/SdPRRBYWv+paDOemkVtnnTbiqdoFbvFTKu8h9WsWNa3raeI1pNobMiwvIuYDJePyt3+s3FL
xadg/1m/fuepWcRjusoXScycsrfvbMxK8SnYdzbk9qlVxOf1vjDaP3x3y8Eq8SnYf7KkB3MVg79x
04s4/nI4fmCkcVQ0Ldd/YuZ5ylXew2pWLOvBv4fiGPUtnPPagOEZ4esoGpJILfWH7D+btWx8Cvaf
DTi8iPunp5g+MX/45bj470P8m3WW376zOavEp2Df2ZTTuCric3/xel+Yy/6zQSvEp2D/yZMEc2XN
OGqMfxwbNSLzrPIeVrN8Wfcfe9F8+PVqDP9C1zaxvNOr4RCW5RoS+8/GrBAf+8/23P25Lv57HFPf
gSfYd7bpo/jYd7Zn0P0+GtL8Y156Yv/ZlkXiY//JkwRzFf3HOdckvXOWcpX3sJqVyvou0neAXpxH
v/hinb5cp+XnY8OBKgf2n8zZf7bmrh1nRdk3Oz9mn8G372zXR/Gx72xHGqVRJCKNyyI56fyOd8+l
2X+2Y9H42H+yJcGEodHQjKf7i5g8jp1+a0Xv8j/DYGAu+89WjIcyR+t26WFlbMBC8bHvbMV4lMbT
Uz/ObxpxcNIN6UhGFo6P/SdXEsxVNI6iOf7xrXeGwazyHlZTZVkPf9d1/HGU2i77Tz3Zf9ZnnLwM
r5OdN1uifWc7Fo3Pe+w7G3IYFz9bEb2b+Dsrg7H/bNkH8XmP/WfrJJgr68Vjf/zj2PBC47lWeQ+r

qbKs315/wTbYf+rJ/lO14X3ixsnLYj2X9p1NWj4+77HvbMQwGXm7j7yw/2zVh/F5j/1nmySYqzj8
GufNiIepwffpQuN3Z7Ja5T2sZpWyHt5M/iDe3KpseP2Fs5RbZ//Jm/1nY0b3ieulWfsXS17sOxu1
dHzsO5szt6xb8W3WzmD/2ZxV4mP/ydcTqxned6f59Hy7nun1WVZ5D6tZoaxn3dcqPdYUoPUaxmaB
e1jZf7ZjwfjYfzZgfJ/FpcvUvrMZK8bHvrM5w7Judp5eSnb2fS5fsf9szCrxsf/kSYL5CaObJxcV
e7hMH2xm3xx2/nuo0irxGR6ont/z9obZrMHMBMb+k40l4mP/Wa/X9X96KfcH+862fCY+9p3NmV/W
9p9tWyU+9p/8HKT/FMEAAACAT3ENJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAA
UAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYA
AACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBg
AgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJ
CSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAA
lZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIA
AFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkm
AAAAlZBgAgAAUImZCeagexIHByfRHYwfmGfQjZODgzhZ6MUAAADsqoOnwvjnsbtoH5zFdes2nq5O
x4/Nd9c+iLPrVtw+XcVi7wAAAGDXvOnBHHR/xXXxb+vb4qni6bdW8d/r+KUXEwAAYG9NJZiD+HvT
K/5txlFj9MjIILrtNGz2YLSctF8Pn20cFe+I6N38LV4JAADAPppKMPvxmPLLOI4vh8MHCkVyedKI
y+vhEyO967hstONuvBqHX4p3FHqPxW8AAABgH71OMAf/4iH92zyK5w7Mwd8YdmpGK277T/H01I/b
NCL21ZDYRhylLszi3f90YQIAAOyl1wlm/zEm+imHBn9vRo+1vsXpsFfzME6vUqL5FPcXz92cY714
1IUJGUgjD9KQ9omRBgBQW2/btUG3PbyTQbp8K93N4PX6nXYQtuTNJD9AHgZ33WgXDWQuctseAPbZ
Xfx3eR29Zif6w06P/tT6q8lEhrRjsBmvE8zxZD2TDr+ejx67/vM8sc/d8D6ZB3HQnt5JpycHAlYy
6Mb3s8u4fhyvb1tu2wMAcx3GxXOacTe+hZ52DDbmdYI5a7Kew69xPsow47IxGnZwdpkGzTaj86O8
lcmsyYGA19I9Zot96OQkTp6H7byeoflkeNKmeOz75Who+vXZ+HXle7vFs8mMIbBF4/k8NKj9N960
oYM0XGjyb5W/Kyl/f3tie05idA5p1vYAwJq9266lNvBseFu96F1GY/iayfWT6A4m28lZ7Vjx2Jv2
F6jC1BDZWZP1pDNA/ei0Jvo2m63o9O/j+RLMWZMDAbMVLdz579FZ1Ub3+3CG5tbtU/Q7zegVDV/7
rtjnfndGIwdaty9nX+cqEsRG0XiWQ4O+PcbDsCUtpefP4jLOR5N19W/j+LpohJ8T1rFesSf/uC/+
5m20ig29/pWeX2V7AOAz5rVr6btpaqcK4+dH7Va5PvEddehtOza7/R2+GPikqQTzML4OuyunJ+sp
dsyr9KVzNLnP0/3V6x13PDlQ8/xr8UpgruZ5fJ3aUa5/ncR/X34PG8mrVbK3uz/DM7fP++Dpj/HI
g7GJ54eTdR2exo+iQY3eTfydzDCft218ssmthwDYho/atYp8uv0F3ngzyc/hxc/hGaDrP4ufxrn7
kw4Brfj5ZlZZYJ7h/jZM5HpxfdaIRhqi+qpLcTGDf8MxBHH8zhj18vneZeN5OFBjONTdzM8A5Oej
du2zqmp/gbfeJJgR456N61+L7WiDbvwq8stm54dhc7C007i6f4p+/3Y0DL13HZf/LT9G5/DL8Orp
eHjnRrTl881O/2UkwnhxxhaA3HzUrn1eNe0v8NaMBDOd1UnDYafHr7/j8CLuiy+pb++JCXxkMJyR
+ST+Fg3dxY/RjM3NNBVzOeHWs6khq4O/cTN5jeXpt+HIg97N39E1lXf/xbCDsjTx/N3wBZOTHyzg
zfYAwBp91K4ta6ode7f9BT5tZoIJbMbhxe/oFC3ocIbmxmVEqxO/hydrTuNbOqNaznY3OIyLn62i
AbyOszTb3X8Rx6k1fHYaV/1ONMez6Z38ORoN/XmWnk8TlFzG2XA26EbxUytu+4tO2DO9PeOHAWAt
PmrXlvW6Het/fa/9BT7r4CmNkQMAAIBP0oMJAABAJSSYAAAAVEKCCQAAQCUkmAAAAFRCggkAAEAl
JJgAAABUorrblAy6cdK4jOE9cFu38XRV3l3vLtoHf+Lb06L323vt4OBg/BMArEfOd+zSDgKwblW2
gxUlmIPonjTi8edTDPPKu3YcnEXcDpPKzyeYy27irMY45y8PAGzPKu3MOsxLJLVh8DHf/2A1VbeD
FQ2R7cdjrxXfygzy9KrYyG/x56BdpJeLSR9s1lI+V5p8PJm1Ps8i77duvWTduvX9Wd+21LjPWlZV
fr6cPiMAu6+iBLMRR82H+DcYrw6dxlVKMk9+xcP4kXlmNappKZ8rTT6ezFqfpWxgF3m/desl69at
78969dLonpPovmobN2M6qZRksqvKkyjqOOSjogTzMC5+n8dN4yDar7osiyTz5/HouswNmv7CUH6J
cABi12loYVvS5SAv+99oacRlrxeXRdt4sMSIHmC+yf2s/I5XLtPSa4DNqm6SnzUpDx5VKg82mX90
WMqsRlQdh49V1s6MJ7uLTj/uLw7TA9E9+R7x+z6GqytaZftmHQ8SxwTqaLo+r7I/qPvwvqr3kb28
TUkqwLSkwiwXAOonq+P44UXcF23L7/hebM92hsaWpr8oaPeom8m6WtbfcllWWfeBzdjr+2BOHqzK
gxjUSVlv1V320XS9z2U/OLy4L9qV3xHf0xDZ8YNbMNnGlSYfc+wgJ2V9LJfJuloFdR42Zy+HyM5T
HngyLxb21HTDOF1PJ59Pz6nP7LLp/SFZpa6n35PzPrLu7Zs+bsCmbKvu5b7Pw6ZVvU/sdQ/mLKlw
05IKevLAB9tQ1sNyKetnuUybfq78uXw/sA1pAqCPJ/mZ3Ncnl3WbPG5s6m+yvybr9mTd26SyrsMu
mNyncqEH8wNlsDIvJnbE9MGh6nqnPrMrZjWkq9brbbczH9nG9k2Wr+MFnzG9r+ZUn8ptU8epq+n9
K1mlPlfdzkgwFzQZwMyLjJrZRt3KZb+CVVTeEGa+P2x7+8pjlGMGk8p6kUzXjXnP5Sj3YwC8Z3Jf
K61Sl6veBwyRXVAq9HJJQZgVUFhEWX/KZbJubYp6TF2V+0yW7trP+9XrZbszyn5WeXya/Ezst+k6
MFk30lLWmWz31Sll/QaqkU2COX1wKpcclQfNnLeRfEzW57SU9adctqX8++V2Qe7K/SdPg+j+uo7W
7ev9e7j0z+Pme7d4Rb1NfqbyuOHYQWmyftTRZL2GOphVV3PZ/7JJMCcPTJNLzsptdEDaP2XMZ8V9
8rm0TNbntOSm3K5yeyFH5b6Ur3489lrx7XS8OunwSxz3HotX7I7yuOHYwS6ZrNOQs7JNnF5yYYhs
Bcqglo2sA9Num47vZNzTMrmjp6Uuyu0tPwfkYHK/ylsjjprX8WfWVLGDf/Ew/nEXTR87HD9226z4
5r9/Lqesz5CjVDdz3+dM8rMm5YGpjtvOfPvQuCZ13ffYHZuqg5X9nUE3ThqX0RuvvmhGp38fF4fj
1SXVcV8sj5OOIbtl39qFffu85G9ddbLq3yvBXLO0/Un5Gcr1pM6fa19Nxm/SrsZyuv6yGY4TozLY
1Gff5N+a573jS1LXejCrLqvf9ZTLfrJpZX1VV9m2de6DVf9uCeaGlAeoabvw2fbBdAMzGc99iOH0
52d9Zh0r9q3cUxls8jNv+u8tK/ftW9Ssup04ruRvV+rgZygDtqU8dq6z/lVdv12DuSEOSvWUdrhy
p5uMYbm+L3EtP2tZHrAOk/sbu0dc68c++aJsA2GTyv2vbvugBHPLHKzyNNmoalhflOVRlg/V2ucy

tb9BXuyTb2n/Nqcs530u6/TZ67r/VZdg7ugNpqs0XUnKA3dZVmxfGYsyNsym7lZrXr3bh3IuPzu7
7736TV7sk+9L5aLertd02e5jWdd9H6wowdz9G0xXZbJsSuV6qkwOWNtRlv10bJhvsu6yvPfqXble
Plb+XL5+l5Sfn/1R1ucy7rtat+uojIN98mNlvYUq7co+WNEkP3fRPvgT356u4u09puc992KZnXRy
k2e9r+7Pl9Lrctw+z3u+5Pnln//IIr9/3u9d9/ZX9fys55Jtbd/k47lJ25nz9lVpnz5rbpT9asrj
iLKrzuSxubQP5bvNfbDqv11RgjmI7kkjHn8+xdV0Fjm8L9hj/PwgwXzPPh/wHLTWR9muj7KdbR3l
UteyTtud0zbntj3Tct++qtW1XtfZvtWxdVCGnze575c/J5Pru1rG264/Vf/96m5T4gbTa7PrO9Um
KcvNmSzr8udk38p+E3WuTvU6bWtu25nLNk3uJx+Z3N5Z79uF59Pj5b/TNvH3S573/DTPb/f5pHxN
jttX1+cnH/8s98GskbISKI/lKbvt+ejgtqu2UedyP17mun3KLV/7/NnXLZVtonyrpVwX95my2oVy
zukzpG2pcjskmDW0CzvVpiir7StjMGlX4zH5Wbf1GXOt82m7co17ztuW5L5965Zrna6zfa9Tm6CM
31flPl3X40Nu9aPq7ZFg1li5UyXK6LW6HnB20WQ9fU/d45Rjfctlm+qwL6ZttH35Uw7VUI6bo6xf
S+WRrKNM1vm7q5Zjvah6mySYO6JOO9Y6KYc8lXFJZsVm8vmkLvGrQ33b5jamv12HWOa+nXUpx02o
wz6XM3Vp88o6O2nfYrDJ/Tb3Op7r9lW9XRLMHbPJnTgn+/q5d1UZz1Juca1jfdv0Nqe/V5fyyX1b
61SWm6JMlrPp/Z/XyvKftA+x2Fa9y7W+53zcqnrbJJg7Ktedq2r78jn3XRnn0rbivQv1bROfIf2N
OpVR7ttbt/LclF3YHzdB/dm+sq5O2uWY5LJv2o7FVX2ckGDuuDpU6lXs6udiMWX8J62rLkz+rV2q
b+s4ttZ1v1xHWVQp9+3bNuXzPmWTh/LY+J5dilGOda4s/21sV132waq38/8a/8uOSpUlLanilDtY
nZTbXW57+XP5udhPZfwnl8m6kpbPKn/P5N/YJZNlVoXJsqI0iO7JSXQH49UPlPGYXpiv6rq8K1J5
2B/zMB2H8lhZLmX9rXMdLrd/+rPmYLqcNyXX8tiEbHow5wV8X4OzDmU516FMZ9UJdYFFTdefWXVn
8jXl83XaR6ry2c+c3l/n8qpm+++ifXAW1+O1t1px+3QVp+O1ZdS9fDdJWX1+f2a7yviVco9jHevb
Jra5bseiqrc3mx7M9KFmLVSrLNdUkcodLCnXJx/bhMm/O73AZ0weRybr/Ht1rHysfP0+mS6jZZRl
xmlc9TvRLH5qdvrjMu1Hp9mMTj/9vFpyyXJWrce7otwf7ZP1VcavXMr6nFudLrep3M46mSzbqk2W
yz4zRHZPTe5c0zvYRztc+Z4qlnI7Zi1QpUXq177Xu7Jsyv3zI+U+zNjhRdwX5fE7vhdls/jQWKo1
WY/3if1xN5X1uazT5bIt5d8vt6nOJsu0CrtSLlWQYO6593aCcoebtZQ7TxXLPNPPf/R6oBrl/lnu
88nkMaBc7JOzHV7cF2XzO+J7Iy574wfZuOk6vKvsj/ujPDZP1u1yWbfy75R/f1dMl+eqyrJhxCyy
zNyhlDn7YLLuq/Pv2/VjRO7tjHbw83a1DNUNSpPH6SrrRPl796WerfJ5d2E/rPoz6MHkTYXal4MI
pLpeLrA+aQKgdvFftiXt45NfwHfBLnyppTqT7VmqG5PLKsr3lr9zX0yX4UfKMuI1PZgAzDWrkd2l
43Lu7Yx2sDplXa57eaoTLGPyGD5db6af25V9pCqT5TFZVqVdKaf02ar8LNX1YA66cVJsXNrAg/bk
eVpnbgHqbLrR8cVjPYbt54yF6qS6m5Y6let0fUiLfZBllPW+rPuTy6SybqlfLybLbZpyel9FCeYg
ut8v4/h2XIG//SkCIakE2BVlf6tBneOu/fyl7fWy2Iyyk2U8uVC9VK5lfHI2a/vUCT7DsYVNqCjB
7MdjrxXfypt8nV4VFfdb/JFkArAXBtH9dR2t8kTr5NI/j5vv3eIV5KSMT5nElQnnppPOyb87vQDU
UUUJZiOOmg/x71XreRpXKck8+RUP40cAYDdNnWiddPgljnuPxSvI0WSSWfoouZtMAj+7PJ+ImLHA
Ok3XMXXufcpqORUlmIdx8fs8bhoH8eryy5Rk/jyORW4DNuugm5byudLk44l169atl6xb/8z656QT
rdfxZ9awncE/J1prqKwfs5b05bKqZZ7p5z96PSxr0bqIslqGWWQB2GuVtTNpsrvG5YyTqs3o9O/j
4nC8uiTt4PqlMp6mzIF9UXU7s74EM0128OdbPF3NGi+0uFkHfQCoUs7JhHYQgHXbqwTzM3I962u7
lmO7lmO7lmO7FqeslqQdfJftWo7tWo7tWo7tWpyyWkx198EEAABgr60vwUy3KtniWVsAAAA2K/tJ
fj5DN/ZybNdybNdybNdyctwuZVU/YrYc27Uc27Uc27WcHLdLWS3GEFkAAAAqIcEEAACgEjs9RBYA
AIDN0YMJAABAJSSYAAAAVEKCCQAAQCUkmAAAAFRCggkAAEAlJJgAAABUQoIJAABAJSSYAAAAVGKH
E8y7aB+0i//mYhDdk4M4OBgv7Xy27K79sl0ZbdazQfckTrqD8dr2TZbXQUZ1LJXT83ZlEshX2zRe
colljuWV5LU/zjiO3rUz2L73ju+5Hfe3TTu4KO3gcrSDi9MOLk87uIi828EdTTBT4Z7F9XgtB4Pu
97g8vo2np6di6Ufn4SyPRqzYSc6i3K7biLOcvowUBt34ftkbr+RgEP8emtHpp/JKy1Wcjp/ZqlRO
N+fRz6x+HV7cj8upWPqdaEYrfl4cjp/dokzLa7g/PnSet+vo10ls73vIrONo8djZw6j+F/F82Mrx
4r3je37H/e3SDi5MO7gk7eAytINL0g4uIP92cAcTzHSG9E98KxqJ1viRHAwPMFflIfgwvp434+Ff
BmewTq8mtis3RSy/38Rxqzlez8Dgb9z0juNLBm3DpMHfm4jzr0XNSg7j4v4pcgvr3X+XcXybyReR
N5px1Bj/uEWDfw/RnIjj1/OIm7/bOE68cxwd/IuH5nl8TRt4+DXOmw+x2cPYe8f3PI/726MdXIp2
cDnawZVpBz+mHfxIPdrBHUww00El1523dBf/XR7ncQZrbDRM4iwiowNfOtt9c/47fhyNH8hB/zF6
xcHk13hoRC5DSvqPvTiOv3GS2XY9G3Tj10MnfuRSuQ4v4v53xPdheX2P+H0fOeyOh1+Oo3fzt2gm
kkH8vdlWr8U7x9FU/4+/PDf8X4578dgfrmzIe8f3Ohz3N0k7uArt4IK0g6vRDi5EO/iRerSDJvnZ
uNR9/SuO+nk1/uUQjm9/Mrn+ZDx043dGXz6G0pnu37/j93i4S//oVx7lVbi+KdqH8XbdRiZDXcbS
WduXM8sZSNdPpPZ0WF7DFjaP8irq1+3xZTTGDf7jcUa9FlAZ7eBCtINL0w4uQTvIGkkwN6loLE6G
jWoeZ4lmaRzlMWQpDXXp9UYHmMZlL3qXjXwmODg8fNVAZDHEq9D6efG8XbnEceQu/lxncs3J2PQQ
nIufrbj+k8c3kdOr0Zejp6f7+Ba9OM5pHFrjKJoP/57PLKfrsHIYUkWNaAcXph1cnnZwcdrBFWkH
FyLB3JTUqDYe42exs2TVqKYzWBOnrIZDTDLYkScviu93mtHs9OM+h4KbKq8kh/I6/fa6YcgljkPD
6xWOIqfj7+shOEVY/1xHM4cWYrJ+FceMX8UXkm9ZdfF8iePeTQwvh8n0Oiwyph1cinZwOdrB5WgH
V6QdXIgEc0PS0IheXMfZsMt/tGRxJjINRYiz5236ddTP7qL4rEyV1/f4nUd5FduVhillGcdX1ytk
4tUQnIPhDJJZfHGbrF+NHCeDOI2r2+O4bOS6feRMO7gjtIPL0w4uTju4Ew6e0qkxAAAA+CQ9mAAA
AFRCggkAAEAlJJgAAABUQoIJAABAJSSYAAAAVEKCCQAAQCUkmAAAAFRCggkAAEAlJJgAAABUQoIJ
AABAJSSYAAAAVEKCCQAAQCUkmAAAAFRCggkAAEAlJJgAAABUQoIJAABAJSSYAAAAVEKCCQAAQCUk
mAAAAFRCggkAAEAlJJgAAABUQoIJAABAJSSYAAAAVEKCCQAAQCUkmLCz7qJ9cBAHJ90YjB9Z3CC6
J8V7D9rFbwEAgMVIMAEAAKiEBBMAAIBKSDBh2wbdaA+Ho46Wk/bEoNTBXXTbJy/PnXTjbnK860fP
T7hrj14z+etfKbbjpPw97b/xOH4YADZupbZxxuUd47btpDurcSwvJTkpfsfU+4CVSTBhq4rGrXEZ
18e30X96iv5tK3rXZ+OGMD13FpfXx3Hbf4qn/m2cx2WcNcoG8KPnX/S7J3F2HdHs9OPqdPzgK6Pt
6DU7w+24//YYD73xUwCwUau2jYdx8bNVvOY6/owbwsHfm+hFM86/Ho4emKVo785/F7/r6SpmNpHA
cp6A7bltPaXdsHU7Xp80fq5ICscPFCYf++j5p9unopkdrg+XmX9k7M3v6j91mul9reK3AMAGjduk
ldrGsu0bvnncljU7xU+zjF/77vPAKvRgwhYN/j2Mf3qrfO74y+yzrh89/8b1nzc9m6WlfxcArMln
2saI0/g27MQs2rzB37jpRTTPv4bWDTZHgglbdPjlePzTW+VzD/9mX1T50fMvWnF7Oxoy9GvmNSjL /C4AWK/PtI3J6SjDjF/fFxgeC1ROggnbdPqtSP+KZvD
8UMrfl4UjeVHz5eaR9E4vYqUY/Yuv8cox5yaCKH8XTd/x9vxX1y6BhOAbfhM25ic/ohOs3hNb9h9
GS/5pXs8wyZIMGGrTuOq3ymaxctopJnszq6j2bqN38NGMj13G53WQ5w1iucaZ3ETnbjtl5MQfPT8
a6c/OtGMXlz+N6tZHW1HszfajpM/R9EqGmcA2LzPtI3JYXw9HzVirZ8XhsfChh2kCzHHPwMAAMDK
9GACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAAFAJCSYAAACVyP42JenGugCwTjk3hdpBANat
ynawFglm5psIWZj1JdS+Ax/LvZ3RDu4vx3VgE6puZ7IZIps+2KwFAGDf+A4E1FU2CWbKmmctAAD7
ojzB7nsQUFeGyDI0eaZUeddLGbtZcbP/wMdy2U8mj8PT7Me7bZk22HEdqFrVx5WdnUU2FVS5MN90
GSmz+kixSgeE9w4K6XHxhA25aw/3t4ODk+jedeNk+HNa2nE3fsk85b48vbC7RvXj5Ti+SLzTaxzX
gZztZII5feB1IF5e2ejNWjZpW3+3DlKZ+DICuRhE99dDdPpFktA/j5uzyzi+HScN/aP4ddItXgGv
27Vh/VjgOD7NcR3IWXUJ5vOZ2+nlJLpa1dopG71Zy+w4r7bMM/38R6/fJ6ksUiyAXPTjsXccXw6L
Hw+/xnmzFd9OR8/E4Zc47j0Wr2Cfle3eZHv6GWV7DJCbihLMdOb2Olrl2drJJZ3J/e7MbZ2kuM3z
JsafWMoGd9bCbKlsUtktoyxrYF0acdS8jj/DsbCHcXF/FWV+OdQ8Kl7BPirbtLLdq5JjO5CjihLM
dOZ24mztpAXP3JYH4OllFVUfwHdZKuOy0SuXTZr+25MLr5X7xKplk9636j4FfKRIKn934uFsatTO
cHTPrzj6fVG8gn1RHq/LY/Y62zTHdiA3Fc0iO4juSSMefz7F1XSSOejGSeMxfj5Nnc1dUHlw/qyq
fs8uqUOZTDaaaVv3NY5Vfm77AryW+z5hn62PFKtkG/FST4BVVX38qKgHszxz+3LG7nlp3MR5f7Xk
skqp0NL2MJLKog4NUdrGcinXy7q1L6qOVVmGwKbcRXuBmWTLY9v0Qv7KWE22V5vm2A7kYu/ug1n1
76ujXSmDfYjlOj+jfQFGct8X7Kt5SnEp5RQf9QVYVtXHjepmkU1DYYuNSxt40J48T7vYmdtNSYU3
3MZi2Ue71PDseizXHauy/ABYXNnupGNoueTEsR3Ytupmkf0+cc+vb3+Kg1s+SeW0skHYtwNw2SDu
kl2MZfosm4rVPu4HAMsqj8vlsXkTx+fPcGwHtmk9s8ieXhUHt2/xJ+MkM9mXA/Bko7iryljWPZ5l

nDYZq33ZDwDmKduQyeNhuV4elzd5bP4sx3ZgWypKMNP9vx7i36ubXZ7GVUoyT37Fw/iRecqD+PSy
brt+AE6frW6N4qrKz1nXeJax2oY6lxubkepHuTBLuhzkdfv1esn7hOu+SzGaVMatbFfqyrEd2Ibq
JvkZ3o5kNEz21a1K0j3AziJut3ybko9s6u9s0i5+pkWVDWpdPn8OsdrH+lLWk2Rf95VFTJZTaZfK
q7q6n5LMX3HUv4+LCm96uY/75qap48A+q/oYsXezyM6zSwdgjcIIHcohp23cp3qTPus0+8xsu15W
ldb7dFL111H07y+iqhxzn/bLTZpVryftWpmrR8B7qj4+bCDBTGd0/8S3zHswS7twANaIvJbKI8mx
THKM1b7Un7JeTLLfzDarrKbVuexyr/P7sk9uwmRdni7Tec/tCnVpe3KtX/tQ7/lY1ccGPZgz1PkA
XOdtX7ecyiZtS5JrrPahHpUxmGTfeausC5PlNaucpsuzTmWZS32fVSdL6uZq6lwv1yWX+r5PZu3b
uR5z1I39VPVxQYL5jjoegOu4zZtWHky3WU51idMu16fys5X1ISnXd/Uzr+Iz5TFZtknO5Zp73NXL
5UzWPeU2mzq1WdPHw5ypF/up6mNCRbPIFtJ1J8XGvV1Oovtqdtl6SIWctr8u0rY6KHwslVEZ223E
t05xqts+sIgy7mUMyvowuV6+Zp9Nl9MqJst2slzLBaoyXbcm6x2zlfsk2zNZT7e1zFLuR/AZFSWY
g+j+uo7W7YwK3D+Pm+/d4hX1k7a/DjtZ2aCyuLJ+bjK+dYxTXfaBj6TPUJb/RzEoX7MLn3sVi5bT
ssrfWS5lTCYXWNRkvZmuWyym3A9Zn8k6OimXejpru8ql3HZ1hFVUlGD247HXim+zZvE5/BLHvcfi
FfNNVuTJZdvKnSxXadumDxAsbvIguk51jlPu+8BHyrJftvw3VTdyUX7WTdXTMiaTS7kN5QKTJuvG
ZL1hdeV+R/Um62lS/lyu5+K97Zp8fHLfg0VUlGA24qh5HX9m3UV68C8exj/OM1mRJ5ccpO3IccdK
25NLGdVZWdfWEd+y3tQ9Tusqn3WqouzXWTdyUpbTZ8qqCuU2lEsZw3KZ5aPnqa/J2KZlsm5QnXJf
oxqT9XVXTO575edTZ5inukl+Bt04aVxGb7z6ohmdT9x0OredNJftya1cdkV5wKyibHcxRnX5TOvY
zirrRi7q9pnK7Z1nlc+Se73OffuWNRnH6c817znWa9fq2aaVdXefytD+ujuq3v/NIruCbW9TjmWy
az5bxrsco5w/W9q2ZJ3btyux3YXPUcZ70iqfKfey2JU6l8yK2aRd+Zx1tUt1bZOU28u+rf7UU9V1
uLpZZPdICsBHjeS6OIhtRhnjVeIsRptXxiqV+7rL/jN1IxfqKDkp91t1cvvK4xuLKdsCdfdlPy7L
ZBfr0S5/tqrpwfyETW9bzmWxy5Yp932JUU6fc5vbUrd4p+1NdqmOlp8pWfVz5RLHyc8yre4x2+XP
toty2SdyVdZnZTTf5H6/i8ewXYp/1fu8BPOTNrV9uZfDrisPLO/F4KPnd9G262QuZV6X2G87XjnL
vWzqHLtZ+0f5WKJO5ssxYzblspq67veT2z1tl+pB1fU6mwSzzgFc98Fm3b+fxZWxmK6v+xqfbdXN
HPeJXPfTsq7uax1dRK6xK+W+fdPKOpeod/VWt7q3To6l1cnlGDG5He8pt2+R1yZ1rR9V7+t6MCuy
ru2sy+ffJ7MOMvsco03W0bLscy3v3LbP8WMxuZdTHeJY1v1Endst+34cKeu2er0e7x07PnNMmXzv
PJ/5ve+9d/pv16XepO2uclslmBWqclvLClqXz75Ppg8eyb7HaRP7ad2OBcm2ttfxYzm5162ct09d
2w+57yPrsq+fe1vK48ksZRzmvaaUU8xmbW+Odarqum4W2QqlwCxS8T9SBjnHCgizVFX3Z0m/t+oD
37qV+++6ymQex48tums/19fXy0l0B+PX7IDJz6au7YdtHc+2ZbJ+sznzjifTx5x5S05mbV/5WSaX
XSPBrFhZcVaV3pt+B/majo94jXy27k8rD7rp99a1jMsyqbJc5inLi20YRPfXdbRu336ZeOqfx833
bvGK+irrcVnHyoX9keK9qWPZNk3WcfKxSzEpP8vkMnmMLZc6k2CuwWRFWUZ6fXov+Zs8KPCirPuf
Ve4Lu1C+5eeoolzek36348e29eOx14pvp+PVSYdf4rj3WLyiXsp6VdatcmF/rftYtk2TdZ3tmo7B
PsQkfcbppayT5fKeRV6zadUlmHsyNGhRk5VjEel16fVQd8vU+2nlcWMX94WyXFYtm/eU5eX4sW2N
OGpex5+78eqkwb94GP9YB5P7obrFtFQfyjpSLnVWfgZ1PS9lPPY5JpNlkJbJfW5ymTS9vi0VJZif
Hxo0XVjlUndlhZgnPZ9eB/us3A92eV8oP18Vx7b0Oxw7cnIYF7878XD2th07aNzEef8qZnVu5mJy
e3d9P6R6qd7UkfpOnZR1dXLJVUWzyN5F++BPfHua1YDOe+5j5c5fd+99jl35fDBt0bqdXpfs237w
mc/tuFGt3MtzXdtX1sFEfWIZk3VnUl3qUbn96j11N2tfXKVeV93OVNSDuTtDg9YlBS0Fb3pxcGNX
lXX+PZP7wD7uB+XnnldG0ybLjDpJJ1rbxX/nK+M7vcx6btL0c+Xzsx6fXCb3vennJk0/53nPv2fW
a2ctk7bx/Ly6n5ZJnvd8zs9/5KP3z3qsCtXdB3PQjZPGZfTGqy+a0enfx8XheHVJ6UNXtYnbNiuA
u/LZ4D3T9T7V+V3ar6tQltG8MlFm65N72a6yfWWdmkU9ogqTdWzROrXNepn7fg7bVPX+UV2CuSa7
dECYdWB1sGPXqfeLK493k2VWriuz9cm9fFfZvsk6VFKHyNmsOjtp0fo7+XvSe8p19R/et0o7M49Z
ZAEyMfllqJTWfTECdl06zs1bXn+3fLsk5b+ltF6+H9icbGaR3QfTB7jpdQCogvaGXTP8TjlnmU4u
ge2pKMHcvRtMr8vkwRD2wXRdV/fZTWkin9k9K6Pl40l+qqa9YZ+o55CPiq7BHET3pBGPP5/iajrJ
HE7+8xg/P7hNSWqAAWAbqvlympLMX3H0iYntZtE+ArBuVZ6kyX4W2c9IjXKVhVUV27Uc27Uc27Uc
27U4ZbWANB/Br6Po31/EFpq9N8RsObZrObZrOtlul7JaTPazyH6GSrAc27Uc27Uc27WcHLdL
WdWPmC3Hdi3Hdi3Hdi0nx+1SVoupbhbZdy12g2kAAADqTQ/mFtiu5diu5diu5diuxSmr+hGz5diu
5diu5diu5eS4XcpqMRvowQQAAGAfVJdgpokNiuz57XISXTfBBAAA2HkVJZiD6P66jtbtyz23npf+
edx87xavAAAAYJdVlGD247HXim+zbnR5+CWOe4/FKzYvp7Hlk2zXcmzXcmzXcmzX4pRV/YjZcmzX
cmzXcmzXcnLcLmW1mIoSzEYcNa/jz6ypYgf/4mH8IwAAALurullkB904aVxGb7z6ohmd/n1c5HDH
aQAAANZmp29TAgAAwOa4TQkAAACVkGACAABQCQkmAAAAlZBgAgAAUIkdTjDvon3QLv6bi0F0Tw7i
4GC8tPPZsrv2y3ZltFnPBt2TOOkOxmvbN1leBxnVsVROz9uVSSBfbdN4ySWWOZZXktf+OOM4etfO
YPveO77ndtzfNu3gorSDy9EOLk47uDzt4CLybgd3NMFMhXsW1+O1HAy63+Py+HZ4I9Snp350Hs7y
aMSKneQsyu26jTjL6ctIYdCN75dvb36zPYP495BuvZPKKy1XcTp+ZqtSOd2cRz+z+nV4cT8up2Lp
d6IZrfiZwz2LMi2v4f740HnerqNfJ7G97yGzjqPFY2cPo/pfxPNhK8eL947v+R33t0s7uDDt4JK0
g8vQDi5JO7iA/NvBHUww0xnSP/GtaCRa40dyMDzAXJWH4MP4et6Mh38ZnME6vZrYrtwUsfx+E8et
5ng9A4O/cdM7ji+Z3dd18Pcm4vxrUbOSw7i4f4rcwnr332Uc32byReSNZhw1xj9u0eDfQzQn4vj1
POLm7zaOE+8cRwf/4qF5Hl/TBh5+jfPmQ2z2MPbe8T3P4/72aAeXoh1cjnZwZdrBj2kHP1KPdnAH
E8x0UMl15y3dxX+Xx3mcwRobDZM4i8jowJfOdt+c/44fR+MHctB/jF5xMPk1HhqRy5CS/mMvjuNv
nGS2Xc8G3fj10IkfuVSuw4u4/x3xfVhe3yN+30cOu+Phl+Po3fwtmolkEH9vttVr8c5xNNX/4y/P
Df+X41489ocrG/Le8b0Ox/1N0g6uQju4IO3garSDC9EOfqQe7aBJfjYudV//iqN+Xo1/OYTj259M
rj8ZD934ndGXj6F0pvv37/g9Hu7SP/qVR3kVrm+K9mG8XbeRyVCXsXTW9uXMcgbS9ROpPR2W17CF
zaO8ivp1e3wZjXGD/3icUa8FVEY7uBDt4NK0g0vQDrJGEsxNKhqLk2GjmsdZolkaR3kMWUpDXXq9
0QGmcdmL3mUjnwkODg9fNRBZDPEqtH5ePG9XLnEcuYs/15lcczI2PQTn4mcrrv/k8U3k9Gr05ejp
6T6+RS+OcxqH1jiK5sO/5zPL6TqsHIZUUSPawYVpB5enHVycdnBF2sGFSDA3JTWqjcf4WewsWTWq
6QzWxCmr4RCTDHbkyYvi+51mNDv9uM+h4KbKK8mhvE6/vW4Yconj0PB6haPI6fj7eghOEdY/19HM
oYWYrF/FMeNX8YXkW1ZdPF/iuHcTw8thMr0Oi4xpB5eiHVyOdnA52sEVaQcXIsHckDQ0ohfXcTbs
8h8tWZyJTEMR4ux5m34d9bO7KD4rU+X1PX7nUV7FdqVhSlnG8dX1Cpl4NQTnYDiDZBZf3CbrVyPH
ySBO4+r2OC4buW4fOdMO7gjt4PK0g4vTDu6Eg6d0agwAAAA+SQ8mAAAAlZBgAgAAUAkJJgAAAJWQ
YAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQ
CQkmAAAAlZBgAgAAUAkJJgAAAJWQYAIAAFAJCSYAAACVkGACAABQCQkmAAAAlZBgAgAAUAkJJgAA
AJWQYAIAAFAJCSYAAACVkGACAABQCQkm1NYg7toncXJwEAdpOWlHdzB+6kOD6J6k97XjbvzIfMu+
HgAWN7jrRnvYzky0aXcTjdqg+9LevVpOFmz7tHuwKRJM2KBhA9qtpqka3P0XZ9e9OO704+npKW6P
r+OysWhDCwCZuGtH4+wyHs5vo1+0Z09P/bg9f4jLs0a0p5vM1u2wzXtZ7uPicPwckAUJmzKoBvf
iwb0+nG8/kmHp1fDxvVq3LKefmsV/+3FY3+4CgA1cBfts+uIZid+X5zGqEU7jNOL39FpRlyf6UGE
upFgwkYMovv9skj/CtdnL0NuiqTzzZCg5x7IotEdPtYt3p3MH65z96dooOeZGF500v4bb/LcwV3x
+0+et+WkXf5dAFiTuz+RWq/m+ddxclk6jK/nRYZZPPtn1QxTuwdbIcGEjTiMi9+dSE3laHjPVZym
BLJxGdfH5ZCg22j1ruPy+woN3F070gngoomOo8bwkSmjv9VrdoZ/6/7bYzwMs91Sev4sLuM8bvvF
tvRv4/j6MhrPyS0AVG/w72H47/GXt+NcD78cD/99+DfREg1P0o4SwuHybjul3YNtkWDC1pzGVdHo
9b9F/G234+TkbHgWN3qPsdQo13SGdpRdFsnrz9nXokyfIT79EcMTw6WJ50/TCw5P40cam9S7ib9a
WgByMX0N5v3FVM/nmHYPtkaCCVtzNxwe2zj7FY9H3+L379tIV1EuJSWX6QztcKUVt1enw5+mzTtD
nJTP9y4bz2eFG5fpt7qmE4D1mdlLOfZR2zWPdg+2R4IJ25LOnhZtWev2Pq7SxAZlG9g8ipmjXN+Y
uK4zmtHpp2G3s81rwJPy+eZ4RtrJ5Z2cFQA+7/Tb8ORq7+bvaGhqOnE6nI9gEH9vUgv33qUf82n3
YHsqSjDvoj0x8cig+3LB9Ptj42HPHH6JUXP22vV49oJB99fUENlGHKXhPOX64G8M29rS3X8xPNla
SEnq66GxUxMCTTfgE+8dmnh+dNsx9/8CYBNO4+q2aIF6l/G9exeDw6/xc3jbrcaonWqex9eFOjC1

e5CL6nsw072MHn++nAn6HfFdkgmF0/jWKjLGchbZxlXcPq8fROPmODppPR5idML1MC5+tqJZpJ1n
xfMn/0Ucp6fHJmeNvT5LjeJoOZl5I8yiAe93olk04I30mj9HMfxTz9LzaYjuZZw10u8pGvZi7XZO
rygAVOL0Kvq3nTi+OSvaqMZo0rpmM/1/qD/ZrE1P8lMsb+6VOaTdg205KJLAp/HPn5B6MP/Et6er
aHRP4nv8jvvn7pSX5+ywAAAsZhB37e/x62jyeyWQuwp7MK/j7KQb8fX87TDAha8pAwCA5DBOr+4l
l1AzFfVgjj3PaJkmHLmPi0jrN3GefnZsAAAA2GnVJpgAAADsLbPIAgAAUAmzyAIAAFCJyhPMwb+H
aE7eETfd++/5vn4AAADsqgpvU3IW181O9H9H/Pf3a1xN3qbk5F/8uL+IVeb5ScNsAWCdcp6OQDsI
wLpV2Q5mP4tsalhzbvhZn1lfqtQFoGq5tzMfHQs97/lpns/7+aR8TY7bl8Pzsx4v5bB9pV16fvLx
z8p+Ftn0wTPfRNbko50CoAq5tzPaQai3Wd9n5tnk/j65bbkcZ3L9/pdjWVWl6namumsw79rDjXu7
nER3gRl+Zr93uR2S3SH2wL6Zbv/KBdg96cv8e8us48CqyzzTz3/0+kVM/u1Vl1lmvW6Z5bOmf0cV
v3OXVdSDOYjuSSMefz7F1en4oVIaNvs94vcnrsGsZBOphXKHLWM+vQOrC0DVcm9ntINQX+X+O/l9
ZpP78/T3qHWr4rPN2ubP/t51lcOuHJvLelqVinow+/HYa8W36eQyMYssC0gVu6zckxW8XC+XdR0g
AACqNPmlftK7zCZN/t3pZZZZr1tmqcL076ni905u4yrLLOnx8vvr9LLvKkowG3HUvI4/d+PVSYN/
8TD+EaaVO+K8HXhSuTMDAORo8rtNzqa3L6ftTdtSLjl4r6wmt3NyKevA9LIvqpvk53kG2WnjGWXN
IsuEcidbNbbqBVCV3I8njndQH/ZX5im//86yzXpTdb01iywbVe5YVcRU3QCqkPuxxLEO6sG+ymeU
35GnfVSnJt+3av2ruu5WN4vsu+6ifdAu/ss+SxW3rLwOvgCwmLL9TAt5mvyOA6sqvyNPL5PHgMkl
Kf8tTa9vix5M1qqs6OuKofoBfFYux5F5Xwwc5/bTrDqhLuTF9xC25b02Y5X6WHU93kAPJvsoVdSy
sq7zwJt+93s7GECdlMfL6QXIU9VfymEZOde96hLMu/ZzUvF6OYnuYPwadl4Z901+MUp/J/1NAIB1
m/yuA9s0XQdzqZMVJZiD6P66jtbt2zOvT/3zuPneLV4xX7mzTi/UQxmvMu6blv6m+gLArtPWbdc2
v+vALGV9zKlOVpRg9uOx14pvp+PVSYdf4rj3WLxivsnCmVzI27YTy0np72t4AdgFk23r9KKt244y
JsB8FSWYjThqXsefWVPFDv7Fw/hHdkc6yE42frnQ8AKMlMdpx8R6KWM2r23V1m3WIjEBXlQ3i+yg
GyeNy+iNV180o9O/j4vD8eqS7NB5KRu03GOi3gCLyv14scr2lcfqSY6J+Vs21tq69VPG7IOq67nb
lLCQFIekTrFQd4BF5HKsKI+zsyy7fVX+LjZj1XpYxlpcq6Vc2SerHn/eI8FkrrofYNUf4CO5HydW
2b7y2D2p/B2znpvFsXNzqqiDudfjOlGW7Juq67z7YDKUKla5TK6nylbng2za9vIzAaxVRrfrmj5u
T66Xx/WPltmf5fWyis++f9ekckjl/VllzPicquIB+0yCyZsGqTy47soBVqMLrN/nb9dVtcltWMXk
+99b0rF1kaU0+XMyvb5v0udP5ViVyZiwnLLcqowH7CsJJnuhbHQB1uPzt+uqo3Rs/f+3d/daqTtd
AMa39wIWLK4ArkBsrGztoJTm31navQ2U0tlS2QhXIFfAshDuxTc7ZDhjDJrgEHaS57fWnMNHzmEy
mezNhpDkaRQ9352qmPHHHPm4bXGK7QE0EQVmQ7lk36QERMI9H6vzzWq/UEVcrusnvHn/SmPOqceD
nJdPGdsCaBpO8tMQ6SSTHlP/+TqPN/OpfOm5pyxsA6v9QvmCxQUu15WLv+/petVt/X5T9vo2bXzz
cvOQsQHCxwkzBabb0bOw8xeXHk/G8B+Sbbl+2rctYm40j5WY0OQ86Na9zut5znVswvgWYWWfB6wI
vU+YOURWVyqrIR+dGH5jHA/T8dAxwvmk5+c5WhZ9PL0vuQb8bivT/ve50895Ctn0HHWtCdy6ujGr
G12nc25Pf3ybzm0LAKfDbzArzCViP3G5hp/pGJFoT8ufmz4r8/NQv/TvrObWJ90AZzm6E3lO5sxm
Ir3hIr79LHdyMcr6cSbS/P2tLnRddJ0sqNvYFuFitpVtAdQZBWaFuODoB0nXUFyTE+0ppeencrfd
fSuK9Mtf1m9ufbMammQpL7OuXLrfWbau5Xb9GF//snX/IMPZS7QE8vL3rSrT/uu6WOLGtkncdrC2
LYC6osA0zCVX11xwJEiGo+OoY4u/S8/TpnDrm9XcmKTbb4osWxaLfbJFzyK7lo8vR8MmBaeeRbbX
iZZAEf5+VEXab+2/RX58qhu3Xm7d9G+r2wGoK84iWzIX8FR6vfznFAGxPCSgv2H8iknv646OYdZz
5x5bi30KKdz8XcroYiCz5N5w8SlPbT2z7FxuOYvsn7g5WJVxqNI2q9P8cvPE1/R9B8gjdBygwCxR
VuDzEQTPq05zrSxuTjNuYfwWI6ypU2y2vC7Epn+qEHOquL3qMsfc/PCx7wC/Cx0DKlFgpvldruLz
v7Hef57n+azHHQv9c6r4/G+s9E+Xq2L/Dz3vP34uWf11LPTPEh0ri2NitV95VLXvP+03in0H+F3o /T9QgamHBb3IzeeTXEX3ttO+tMfJpaZ7E9m83cuRRwbV
pzhoaQ5Z3+et9+9c3PyyMDaW+vIXVVkP10+V7utPzwHIpvtNyP0l/El+liNpvz/EnYzbs8hdfyr5
rgJWXbph/LZf/1Tzpe/DBt0uug3xT3pe47TcOFsa62P65P+bdHNz6lDL65h/g3rw59I56eu7vlSd
lTFNc/u4a66fWWP+03MAyhG8wNx+rKXX8c6V17qU7updNsndQ9LBwzWLsvrpB7SfglqeZXB+un10
uzZden4Dobg5dai5uXeoKfe3k76PZvDnS9n0NfX168aN6Tm5berG2G8AbAtYYM5k0J+KXN9KN3lk
L8fp2dPBw7Vz8wPcoUBnoZ8IT7erbu+m8uc6UDY39w61Ju+b+O4c88LFyLpy41nWmLrXcs1t0zqP
MVBXYU/ys9XTsY9lJT2Z6CnZpVqnZ9fXSiOwocw5aIHbD5j7sC5UzLa+jzctBv1VGTGsadvkVOvr
tpVijgPnE3ofr+1lSvIELX8ZZXwocCahdzqr3P7AfoAqyRPrf2N9H29KDArtVDGtqdsj1Hq77aKY
14ANoeNauENkl6O4cxcXfZkup9KPb2sbyTJZpCx+8FK7fnxvOpB+A7Lo3ND5Ulfp/QGoEjdv6zB3
3b6YbjiOmxchx1D/rzrMtWMcO5ZuHrvmtktTxxFogkAF5lamj2uZbKKAsbmV+WAs3UUSQDYdeTRw
Flk/oLkG5KXz5ZjEalk62QM4L7cvphv+RsfQxbu/cPGyyfyx9Fua/5ybx64BqL9ABeZG3lddudTf
Wbau5bY3lBu9IKbKeRZZwDqXWOvAT/oAQtDrQf87YkevB71/k92AS3VZ5+LdsTHcxUzsxjJtP9eT
5sabMQOaKVCB2ZZObyYvcWZtyf3bk7j6MpbjLLIhpQMaAQ6h6FxKJ9IqcX1mnwBOqKHXg64CP4bn
QczMbz/fGSug8QIVmFFR+TyR9aAvUz+Dxr/LfJTO8320RLkIdChL3jcq5+S/SWKfAE7r2OtBoxwu
Drq4eAgxEwCOE+4kP617eftMXY7k6ikKzMdfogSoCvdGJauVKf267jZvkoAy/O160CiXi4vpeOnH
TWRLjw1jBcAXrsDcn0U23VLfah6Q/W/tfzMEKPdGJatlzetj20/Sz+t91wcAp3YlT7q/6eGw7bHM
xne73KfXhz7TkTzIx8VpFOPyCzkGQFqg62BuZdpvy/vDpzx9+fFlRJPrncjz23HJ1b1JBizx34yU
OT+Lvgli3wF+ZyXP/LR/sy+fVtbYM+YAmiJ0Hgx4FlnvzLE+fnuCGtKd0LUy+a+bbgDOSc8ieyH9
PIfsHJC1X2sDAKBKyvkGs/0uD5+pM8vmVPQbGwAAivp7KtQC80U6k7WMx11ZHJnzspAHAQCnFvID
zUAFZiQuJMeySu7+05PJ5jwn+gn9dW8o9KsY+lUM/SqGfuXHWP1kV2DexIWl3h7ILHp0uMj44LVE
bLNi6Fcx9KsY+lWMxX4xVvkEPots1uE9nEUWANAkyQl/onbz4k7SNYrKTgAA6i9cgXmQfpJLYgUA
NM/Vk/uwNdwhswAAWBbuEFmD+Bq7GPpVDP0qhn4VY7FfjFX1sM2KoV/F0K9i6FcxFvvFWOVTwjeY
AAAAAIAmCFdgLkdx9fy99XcXmwYAAAAA1FqgAnMr08dZfLY8/Xr2S9vcyvxuGi1RPktfFfvoVzH0
qxj6VQz9yo+xqh62WTH0qxj6VQz9KsZivxirfAIVmBt5Xw3lJusMBq1L6a7eoyUAAAAAAHUWqMBs
S6c3k5esU8VuP2Sd3AQAAAAA1Fe4s8hup9Jvj2WV3P2nJ5MN18IEAAAAgLqr9WVKAAAAAADl4TIl
AAAAAIAgKDABAAAAAAEFQYAIAAAAAgqDABAAAAAAAEUeMCcymji1H0pxVbmfYv5OIiaSM7PVuO/vXL
ULf2ttO+9Kfb5N75+eN1YWiO6Tjt+2VkQ37pU9KsbEuL46Vs7Y8ZcXQ5MtC/Q/HdWtw/N/JgXuTB
YsiD+ZEHiyMP5mE7D9a0wNTBHcgsuWfBdnon4+5C9KS9n58bmawHNpJYtJMMxPVrITKw9GYksp3K
3fj7xW/OZysfa730jo6Xtie5Sp45Kx2n+a1sjM2v1v1bMk5R20ykJ0N5sHDNIqPjFe+P68m+X53H
vpzvfUhWHI0eG6x38z/anuuzxItD8d1e3D8v8mBu5MGCyINFkAcLIg/mYD8P1rDA1E9IX+QmShLD
5BEL4gDz5EJwS65ve7L+MPAJ1tWT1y9rom15N5fusJfcN2D7KvNVVy6NXdd1+zoXub2OZpZqyf3b
p1jbrMv/jaW7MPJG5JuedNrJzTPafqyl523H61uR+es54sSBOLr9kHXvVq61g61rue2tpdwwdii+
24z750MeLIQ8WAx58Gjkwd+RB39TjTxYwwJTg4rVnddZyv/GXRufYCV2h0kMRAwFPv20e377LP91
kgcs2LzLKgomj8mhEVYOKdm8r6Qrr9l31q+97VQe1xP5z8rkat3L27PIXTxedyLPb2Jhd2xddmU1
f43ShNrK6/xc31ociKM6/7uX+8R/2V3J+ya+U5JD8b0Kcb9M5MFjkAdzIg8ehzyYC3nwN9XIg5zk
p3T69fWjdDa2kr87hOPmxcjvT5JDN54NvfmI6Sfdz8/ynBzusuk82hivyGwe5YekXwsxcqhLQj+1 /ffJsgH6+wnNp/F4xRnWxnhF82vRHUs7SfjvXUPfWgDBk
KVGWdsfGIUt6qMtqtQsw7fFKVuO2nRMctFpfEoSJQ7wiw4f7fb+sbMedpbzMjPzmJJE+BOf+YSiz
FxvvRK6edm+OPj/f5EZW0rV0HFq7I731x/6TZf0dloVDqlAh5MHcyIPFkQfzIw8eiTyYCwVmWTSp
tt/lIdpZTCVV/QTL+8gqPsTEwI7s/yh+M+lJb7KRNwsDlxovZWG8rm6+JgYr2zEW/16hI5bi79dD
cKLN+jKTnoUM4c+vKGY8Rm9Ibkx9xXMp3dVc4p/DGP0dFgwjDxZCHiyGPFgMefBI5MFcKDBLoodG
rGQmg/gr/10z8UmkHoogg32fHjsbcz+KNyU1XnfybGO8on7pYUomt+OX3ysY8eUQnIv4DJIm3rj5
86tt8WQQV/K06Mq4bbV/sIw8WBPkweLIg/mRB2vh4lM/GgMAAAAA4I/4BhMAAAAAEAQFJgAAAAAg
CApMAAAAAEAQFJgAAAAgCAoMAEAAAAAAQVBgAgAAAACCoMAEAAAAAARBgQkAAAAACIICEwAAAAAQ
BAUmAAAAACAICkwAAAAAQBAUmAAAAACAICgwAQAAAABBUGACAAAAAIKgwAQAAAAABEGBCQAAAAAI
ggITAAAAABAEBSYAAAAAIAgKTAAAAABAEBSYAAAAAIAgKDABAAAAAEFQYAIAAAAAgqDABAAAAAAE

QYEJAAAAAAiCAhOojKWMLi7koj+VbfIIAABQW5n2oxx5MYqyZR7kVOBUKDCBBtkupzKa5ku9AAA0
GTkTOA4FJtAU26ncDcYye0/uAwBQGy25f/uUz88nuUoe+RNyJnA0Ckygcubyv/gwIG19GfkfrkYJ
cbR/Tg/9Gck0PvZnK9O7saz05mxQ4BAiAABOYzna5bFdntIU1k9ylzts1R32miyzXUb3k2Wi1h/5
h7dmHCIb5cT+ftlRkh/T+S8rp5Izgb+gwASqJsp4nWf9lHYhw+jO7NEl2KWM2mOZdRey+UyeX81k
fKfPt+T+eSI9XWy4CPcJLwAAR7q6GUZ/ruR9o/e28jqPS7rooXfZPfQq8UO9W7luaY4byFhuZbGJ
ctxmId3ZWNoHf0O5y4mr3iTOiW83Ua2Y/PdfZOZUcibwFxSYQNXEiVZvtKWj2c8l4ij9PUVJdBMl
0dfRSPr9gcz04f3zAAAYcnUTFXVR4fey/FdMxmaye2iu9V+U9q6ltXyJc5revtIc2LqS/yZRElzN
5TWrwvSWj1Pm1X+ii39zMKcCOBYFJlAby/jwn/bgUd47N/L8rJ/GAgBg1ZXEX2LOXmS5ed8Vk5Nd
7tKic/eN5lAe7luy/VhHt6P6b9xODmeN8t1Yn3ffgH7llu9extUjgBJRYAJ1oZ/WRrl2uHiTp/sr
abmc2utIO7kJAIAlu8Nk1/L4GH/fKLfXSdG5ftx9ozm8iQ9PbV12oz+1AN3IZ/wzkH/tKeP4Vbf8
+iP7AFoAp0OBCdRMfKhRZDt9/HqIbOtSdukWAAAj2p2orFzJKv76cne4alx0Rg/s6sukekwOp13N
X2UZ14wZJ/Xxecvr4tvl/yT+wjMvciZwNApMoC6unmQx7EUVpp7x7kLa865M9L6sZfcBrn4q7J6P
EjIf6gIAzq11LbfJbyP3v5eMi041FFdfag572ujhs2MZtLWwbEe3hrLYHDoBT7T8Yii91VjaUU68
e+lInBJzI2cCx7r41GMLAAAAgNrSbzyjonQVFaWcFRY4Kb7BBAAAQL3sr4GZHEK73ci795tOAKfD
N5gAAACone10JHfjWfxbTtXrTeTh7Z4CEzgxCkwAAAAAQBAcIgsAAAAACIICEwAAAAAQBAUmxl
ACAIM7/B1Ov2AQBwDhZSIXkQAHAuIfOg+ZP8aMI13sXKKeNNTIhtltVPK3PB7xvzE6g263mGPBge
efDvyINAfYTOMxSYJQsdkLOSz2/Sr5v1f/y1b8f0qwynGvM6zVGgaXSftrwPW+9fUX4MPVVM/k36
dU8R14/pVxlONeZ1mqNA0+g+HXIfpsAsUZ6AXDQhhRob/3WtjHee8Sqq6PgWUZd5CjSNxgXL+6/1 /hWRJ64XjdOhxsZ/XSvjnWe8iio6vkXUZZ4CTaNxl
XRbnF8qn88Dy9rfevyIOxUkf++JXFuNU1nbUvh3avmxTuyzOL5RP50HI7U+BWRKCbr0UCchs+2Lj
VZas7cL+2Ew6Fyxve+v9y4tYWC9F4jrbvth4lSVru7A/NpPOhZDbPtxlSrZT6Uedu7joy3S7lFF8
W9tIlskiTbQbg91GS284duLqctszzzb0l/WbmxtZrU7S6xNi/fyxOrYBKIfb51zs86Xvozrc9syz
Df1l/ebH5HSrk/T6hFg/f6yObcCpBCowtzK9e5eHOGA8yHv7UTobF0Bu5KU/jZZoFrfzuiDquPv+
Y2gmfy6km58A/PabIsuG5L9uumXJWq5Iyxqzog3AaaX3V4f9EI4/F9LNj/l++02RZUPyXzfdsmQt
V6RljVnRBpxKoAJzI++r5GasK5et5KZavUdL/Cxr59FWNa7f7Lz4Cz8B+M3fN/ym3N9O+n6a/+//
2rL66lqWrOWKtBDS/4/ed+sDnIO/T/mtaly/Q+6vaB43f9LN3zf8ptzfTvp+mv/v/9qy+upalqzl
irQQ0v+P3nfrA/xFoAKzLZ1ecjO2lg/3leX2Q9a9TrTEz/ydxm9VkQ4wwCn4+4bfDiUDNy+zWtb/
c2z7Sfr535YvU3od3G03RkCZ/Pnot6pIxxbgFPx9w2+HYrabl1kt6/85tv0k/fxvy5cpvQ7uthsj
4BiBCsyW3D+IDOLJqIfH6mGyyQ7cfpeHt/toiXpKByngHA7NPTcvs1qZzvW6x3J9JcECvyMPwoJD
c8/Ny6xWpnO97rFcX8mDOEYlziKb5nf5XM9nPe5Y6J/D88173tHlLPaP53nesfS8/7g1lsbJ0eez
Hncs9M/h+eY97+hyFvvH8zzvWHref/yvwhWYy5FcDGbJHV9PJps3uT/yK0xd8ZAr/FduQ1jqE4By
sP/Xk7U8k0YeBGAF+389hc4z4c4i+ziT4eLf1//7trmV+V21zyKrg+6aWy8AzeP2fxcPmsSPgzig
xpfr8rc/eRBoLvJg89b7GAHPIjuUm6vkrq91Kd0cZ5G1yE0itzORUAGopiXY9Do2YZ2Lq+flutwc
d3NeGwC4eOBiRN2l17EJ6/wXAc8iO5OXrI9o9Syyyc2fuAmabufgXptkCuAnTUuw+Em9LtflXps8
COAn5EFkCXcW2eeJrAdfk2Lc2nO53TxJ1pebPjdB061Mrs/neG0A1eVihsaPutjH8APr5D//03LN
UY/LdbIteY7XBlBdLmbUKRe4eHhonfznf1quiSpxFtlTd9FNCONDAaACqhxP/OSY7v9Pzzn+Mqoq
Y6D9DtLX/cnu9OR2epjsQHanvhvK4vP3D1oPCda/H7htV5VtBsCuKscTP4+l+//Tc46/jKrKGGi/
Q/a1hAJTT3TwIjdHJtfQK+xzk6AqGx9AdVQlvvjJMHRf/f/bsTgep8wzIZyyf1WZpwCqpyrxxc9V
ofvq/9+OxfEInWca+Q1mVSY8gOqzFm/Sya7sfqVfX517bE6RZ0I6Rf+szUsA9WUt3qTzUNn9Sr++
OvfYhM4ztS0w/Y3n/r17zPgqA6ihc8afrHhoid8/p8x+6utbzgvH9i9ru7vHLK8vgHo6Z/zJioeW
+P1zyuynvn7I1wt0kp+I/vYk6tz3ptcDS5Ypib6uz/VFB87ipAJQfy7+uHh0au51/NhnNf75/XPN
77+2Q/Is00Tp8XBj5MYXAMqWju+n5l7Hj31W45/fP9f8/ms7JM8yZQtUYG5l+jiT4eL74HxubmV+
9/v1v/zB8Vso2hcAODcXG0PHOD9uatvH4IrGPr//2tLr55ovfb9q0uvmWihVnQsA6iUd10Px46Y2
9zpVjX1+/7Wl1881X/r+uQQqMPX6X0O5yTqLT+tSujmu/5UeRNcAoI5cjMtKEHm5f6vNj5va6ia9
fk1ZR20AUEcuxpEH80mvn+V1DFRg6vW/ZvKyTO769Ppfyc2ypAfc8gYA0GwuSfgJ1k+Yaf5z7t8S
45CWnhPMEQBWuTzm5z0/16X5z7l/S4yzJdxJfrZT6bfHskru/qPXA3uT+1ZytyA3eQCgCbKSqY94
+JU/XseOjfU8Qx4E0CTkwWIs5sFGXqYEAKzKSqzEwNOynmfIgwCahDxYvtB5JtxZZAEAAAAAjUaB
CQCGpD9B5FPbKtvKtF/+pboAoMrIg9XHIbIAgEYLk2eWMroYyCy5991QFp9PknWy9d+QBwEAp1Tb
Q2R1xbIaAAD2XcnTZiK96FZvsokT9efnRiY9PdGd3v69uMzKgdoAAKgSMwXmLhl/bwAAVELrXt6i
vPUsd1FhWPzQ2KwcqA0AgCrhN5gAAATUun+LCsNnkbu2jL9fuwsAgFrjN5gAgEaznmfIgwCAUwqd
Z/gGEwAAAAAQRLgCczmKq9/vjVO0AwAAAEATBCowtzJ9nMlwkXGCgs2tzO+m0RIAAAAAgDoLVGBu
5H01lJusc7C3LqW7eo+W+Fn2t5+cnh0A0AxZOVAbAABVEqjAbEunN5OXZXLXt/2QdXLzJ9+++Uwa
AABNkJUDtQEAUCXhziK7nUq/PZbvZ2TXi0y/yX0ruVuQfnpLggUAnIr1PEMeBACcUug8w2VKAACN
RoEJAGiy0HmGs8gCAAAAAILgLLIAAITAB60AANg5iywAANXFB60AACgzZ5HN/tSX07MDAKqAy3UB
AKACFZgtuX+eyHqQkRzbc7ndPElWzvV9+8Q3aQAA2MflugAAUJU4iywAAKcUJBWe8HJdAACcUsiS
sIQCcymjixe5+fz9W8zQNClbrJ/pVzH0qxj6VQz9yo+xqh62WTH0qxj6VQz9KsZivxirfMx/g/kX
TIJi6Fcx9KsY+lWMxX4xVtXDNiuGfhVDv4qhX8VY7BdjlU+462ACAAAAABotXIHJ9b8AAAAAoNEC
FZhc/wsAAAAAmi5Qgfn3638BAAAAAKotUIH59+t/AQAAAACqLdxZZE90/S8AAAAAQDXU+jlIAAAA
AIDycJkSAAAAAEAQFJgAAAAAgCAoMAEAAAAAQVBgAgAAAACCoMAEAAAAAARBgQkAAAAACKLGBeZS
Rhej6E8rtjLtX8jFRdJGdnq2HP3rl6Fu7W2nfelPt8m98/PH68LQHNNx2vfLyIb80qekWdmWFsdL
2dofM+LocmSgf4fiu7W4f27kwbzIg8WQB/MjDxZHHszDdh6saYGpgzuQWXLPgu30TsbdhehlRz8/
NzJZD2wksWgnGYjr10JkYOnNSGQ7lbvxKrljwVY+1j2ZbHS8tD3JVfLMWek4zW9lY2x+te7fknGK
2mYiPRnKw30refaMjI5XvD+uJ/t+dR77cr73IVlxNHpssN7N/2h7rs8SLw7Fd3tx/7zIg7mRBwsi
DxZBHiyIPJiD/TxYwwJTPyF9kZsoSQyTRyyIA8yTC8Etub7tyfrDwCdYV09ev6yJtuXdXLrDXnLf
gO2rzFdduTSQG3zb17nI7XU0s1RL7t8+xdpmXf5vLN2FkTci3/Sk005untH2Yy09bzte34rMX88R
Jw7E0e2HrHu3cq0dbF3LbW8t5YaxQ/HdZtw/H/JgIeTBYsiDRyMP/o48+Jtq5MEaFpgaVKzuvM5S /jfu2vgEK7E7TGIgYijw6afd89tn+a+TPGDB5l1WUTB5
ViZX617enkXu4vG6E3l+Ewu7Y+uyK6v5a5Qm1FZe5+f61uJAHNX5373cJ/7L7kreN/GdkhyK71WI
+2UiDx6DPJgTefA45MFcyIO/qUYe5CQ/pdOvrx+ls7GV/N0hHDcvRn5/khy68WzozUdMP+l+fpbn
5HCXTefRxnhFZvMoPyT9WoiRQ10S+qntv0+WDdDfT2g+jccrzrA2xiuaX4vuWNpJwn/vGvrWAgiG
PJgLebAw8mAB5EGcEAVmmaJk0Y+Tqo1PibK0OzYOWdJDXVarXYBpj1eyGrftnOCg1fqSIEwc4hUZ
Ptzv+2VlO+4s5WVm5DcnifQhOPcPQ5m92HgncvW0e3P0+fkmN7KSrqXj0Nod6a0/9p8s6++wLBxS
hQohD+ZGHiyOPJgfefBI5MFcKDDLokm1/S4P0c5iKqnqJ1jeR1bxISYGdmT/R/GbSU96k428WRi4
1HgpC+N1dfM1MVjZjrH49wodsRR/vx6CE23Wl5n0LGQIf35FMeMxekNyY+ornkvpruYS/xzG6O+w
YBh5sBDyYDHkwWLIg0ciD+ZCgVkSPTRiJTMZxF/575qJTyL1UAQZ7Pv02NmY+1G8KanxupNnG+MV
9UsPUzK5Hb/8XsGIL4fgXMRnkDTxxs2fX22LJ4O4kqdFV8Ztq/2DZeTBmiAPFkcezI88WAsXn/rR
GAAAAAAAf8Q3mAAAAACAICgwAQAAAABBUGACAAAAAIKgwAQAAAAABEGBCQAAAAAIggITAAAAABAE
BSYAAAAAIAgKTAAAAABAEBSYAAAAAIAgKDABAAAAAAEFQYAIAAAAAgqDABAAAAAAEQYEJAAAAAAiC
AhMAAAAAEAQFJgAAAAAgCApMAAAAAEAQFJgAAAAAgCAoMAEAAAAAQVBgAgAAAACCoMAEAAAAAARB
gQkAAAAACIICEwAAAAAQBAUmAAAAACAICkwAAAAAQBAUmAAAAACAICgwAQAAAABBUGACAAAAAIKg
wAQAAAABEGBCQAAAAAIggITAAAAABCAyP8BiEK6RZXN8ncAAAAASUVORK5CYII=

Salah Eddine Elherrag
Meghit Boumediene Khaled
2

2018-11-06T20:14:00Z
2019-08-30T23:42:00Z
2019-08-30T23:42:00Z
Normal.dotm
1
18
158027
900758
Microsoft Office Word
0
7506
2113
false
Title
1
false
1056672
false
false
16.0000
iVBORw0KGgoAAAANSUhEUgAAANUAAABNCAIAAAC+F7b6AAAAAXNSR0IArs4c6QAAAAlwSFlzAAAO
wwAADsQBiC4+owAAQz5JREFUeF7NnQecVNX1x2d2dne279KXpggWuiX2joq9JMYeDUaT/O2xRo0t
wQhomhq7icYWa2yIClbsLQooGgu9qLCwvvc7szv977m/28m0Pu6fe+cFlF
+eeffz5nzpyGhoZQKBSNRpubm5uamjhvf4TD4fYXE4lERkaGv85Xf97S0sIt/Kob+YkrfPJVBxf5
1C18+nvbPIi71GeHAHQI6sa+6CEJghSJRPRcPxCdgNKNDU9a/WdlZXXYPhaLpdVVPuo2rKyv79ek7
YsSILbbYYvPNN7fbjzzuqIyczFBGKDMvOwT2+IOXOvTg1/nhtnmMvNMKf3cvNz0fSM1KlUrcvT8a0Q2l
Ggd77gKM/82fPPD/m+D9D0CVmZ2FMGKWwn933XWSSLYbtSoUTvssEO/fv2qqqoKCgpycnKC8i84
0b3QaiOK2gsDXWGeIbqY/WdbYHtwCeGuTCkOicMEw4J19fWrVixYtasWYMHD/7b3/4gWHjs4E033TRkyJCamhrYorCwsLKyMjMjJmMCPMjOz
zqtI/9VfCf4kXLT/Sf14xeo7hE7+CKrjeDzu6NdVU9a/WdlXvMH2/U/dxnR2xxseAMtubums0MVSTrZ0a0
NqqdEE5kREKRcCKEjPvrX//6vEKiC
0b3QaiOK2gsDXWGeIbqY/RJgejafbeSrlxZezrWRH/56ULSkO/l6sH1QxgfIn+AM/qqHernYgzBs
SFedyeONCicMEW4J19fWrVixYtasWYMHD/7b3/4WHjhs4E033TRkyJCamhrYorCwsLKyMjMjMTcWTK
zqtI/9VfCf4kXLT/Sf14xeo7hE7+CKrjeDzu6RdUx56uXlP/dxnR2xxseSAGm623wwBWN63/n6IzP
NqqdEE5kREKRcCKEjPvrX//6wAMP/OUvfwmP2mYU/8F5dXV1sEtubm55eTkiMMhwwnm88fr0B5w27
lNL9r/TJLXSrG2EjKMFnfn6+bEGZG559GX/QFhR1/eFZuQ3Vv3+6in5thLSudGgXBuX39w9t+yf+
l/gvVFLYu2zV6s022+yFF1743e9+d80110T6lfGh1NbXoSNSNr6mqb4r8GHH8GBRpPc6mqb4rH8goLmMEvCxGXY5jKs
kxG2P51z0X0NRzL4mvzV/WRXvvvtXXFKSm58Xc3Xzc3JimZnR6M6cHd+Xl5BfkNjI+0jmZn8ZWG6ndZr
AgC3c86jO/6DwO7PuTChllCCP135nv+A1h4tFIGDzIj9RSJ2JcPgBQSJqd2nlmqqCb9KYFE&sfGP7h5EDUKiPvVWS30jYxAbhH9VNvK1ZVWr
7y0UqrQqRgvvvkZBCVHHTLDOPgZNkKKKPYDGvKHaDBEYENjB6bY8nq0YrF18qPuXAqE
PIjCyKWiIfiLU0tfHLeDHYcftr/6wbA64ILsnm67CJDrdvBX1hQ3GZEalNdVbsOygTc0g0AO70F
YBrqGvuU9EEbvPLKKzfeeOOvL7woPG77cX/+85/Xrl0Lw6wAWNbRVFsltCzS3Sd1qci3ihIJdQBaWlvYfOXL01luP
RDQ3O5qV0xhryM6M5hXkAu/ylcv+8+nnn3ZvnQEE3Z6SS4ZZ69/zrr0gBVgjmEOqgrh8JhuNzvEgtORBD8P6gsf3AOhY3JBHOMYgtRWzq5JvfsOmjXH
Gzdu62HDNsnsPL+TXmvrqZigHzUJx8TiUhi8jWVF+bYzFI5wdnZOf31hMU8m+Xt29Sp1M5Hpan0c2/DKrSIR
Q1OcgBRPbGysr69nemRy3tTUWNN79y4B5rq6mlWraylauXKL5Lb8Rb4RrqvnOycw
0qu499BNhyxZtLRXn5KKtZXNiXheTj4RyvTuHB4Kdu4tQkHyy7Bs6N3RYNKYO2cLVetiQ+wHQ9bW6Mg4uNlgTjQ5WzlX
1XXgJxLJysl1mRSynWtmIKqlYatHX4gHdTX1lfr8UPYkSJl1xgeExDgDRk3qXr8hXXYvHCw4NATFRrIZJJKdgSh7YvZG9KmbOj
0fwo40+EE2CD/gnTwBJMO+OWNhOi8/EQioPLURwlhUWvvfbalN9N/t3kyUn+w+bjRrkLQSNPzOdZ
MCORhYMCKNiLCEsg49fS0tLVq1e//vrTz311IcfthUX9w+QmUZGUm/Vo4DByFUh6P1Qyx7PQZwsBAwbs
vffee+65+467bJ+RZQPGcOQeTNBfYBM0obdHOdeEMb4aRCLNed/qeg9ZY0CdNncDtW+bkFa1Z
swZIevXqBTB4ZvTct29fIP/ss8/f...

BQNPHc8d2n/JfKVXu3Qn4ccJsxbCY2wiA1Ai++67L+jzfqukDvhleNg65JKJoSg+JJPOy04Z7zI4
BK4fv9wxpuYvfvELNPLdd/0Ntd3U6IK9poidamtKPPPUjGnTrlvw5cIhgzcJhyKNtY3EdQlxe98o
6CR1g/kkUJlXwK/pgTICbD5vv/XWr774wmzZhoZLL774n/ffX1xQCNYaG+rxLLIyIjhefF2xfNkR
RxxxyimnYF3tt99+X3zxBYNldJqr3qS54YYbyLZzhccxurPPPpuf0GhwraQmj15PEQBYd8Yyn2AH
AAjiV1VU9u3dBwNp2pSpSxYszcnJaqqLXXnVZWQWmOEKO0gKyDfiKxbXUUcdhfGKgSuicxQwqVrj
qYNKB1599dU4WxZ1zAgtXrDk7r/fhflED3nRHOYW5Eyd+Tpruc7V8CzICahXFQxxICbNV199hWAD
Ptl8EFt0Qonce++9hP0wz5nxeoY8CWnDdOHDqCJMde655+hes6jIyIVCRUWFcz+cgxW1bOlS2R8+
+tie27rBf4wXYUy3Fmt0TiI+B6N7/LHH5nz0EdeZ9Oeed96PfvSj3ByLOOJecIIkakm0WJi3rnbG
jBnPP/cct0OeTz75hPg+5+BBE0wsJQ2IQrz44otpxsVVq1bh08DlzHBkD4+WxdIh3jA2XMLPdKVP
qcNS3CKFg5EAf2A9N9THLr7kQpibfqAUjZGOPBFQxUBcJ4qEAMb+wflIYtulWzVbpL56FZec9JMT
z/nV2SHM8Ujoyy8WPPzgQ4yCX72kTJfEbdqvk38SV17nMnEVTOdh+GuLv1rcTLAxESKeycyDEXfe
cae33nhzwl579+3Tt6iwyNSCyx1akBG3xP2lC1w0J4fH4Y8TUOxVUsQkp1yBTlwsMIRZDQuuWL68
T+/e2PJIPyGrzZHuQzX7oQoYYNQW4onHwTIi//nnn7dfW1p23mUXmGbsmLF8RedK75A0xAIm/Ysu
Xsc0LnNeWV5BeoCUMAhpiTfz2VBHBtLOBw8afMF55+87YR+CWfHGGPxH/S8MBBt5EdjFECCShD2+
DhwpqQajw0/Tn3yqcg3MFNruB1tfcfnlSEQsbNl5sgE4YfbqhCfiJnOuNvC0XXdmrBExFK6sqEDX
MQ8Jse2z714hbmoJPfnkk19+/kUec0/j2uAjSUKvK3UirSE/7rrrrps/d34yrhAK1dXXge4dd9gR
95788cBBg6qJhLUeQG+a18L6ycmUFoSMuV///tzy00mTHnnkkZFbbRGNZhXkw/E2j5E2z06fAcHA
F+JWsfsOj7QeSmPEg0xyxck5QP0zT09HPjElKJuA+Qb0H4BqamxKuur1DfW0BxVNMVNnGEYjho/A
JafBoIGDiN8io0ila4bwSSf1rhqIc8Z4/vnnMzSwii2BU4JYYkQwk+R61/AHjV06p0/yGQ8//DBR
ERi+qMisTwQbUhm9hKJnIklkqsSd4CUC5aKLLiJ3gBa+4oorMH5uu+02BpssMXGPp09YgROU8mWX
XcaMy8nNrK9pfPDBB5kn2JrAnC6e27ePlA4uPfjgg5l8wr7wJcOF0ANFqg/c80BeUV6sIZZbkEO8
m6qOXXfe5emnnhpYWmppsVgsB28IMYkrgEWiiKs/0pSAxAvAJyDUVFaNHD1mwt4TXnjxxZUrv3b5
ojqKcuh4wcLF/fr133bb7crL12Y47dzm8Oojdex424hbFJJAKtx8002MujkWP/qooy+68CKwU1Nd
Q6SNpKKzvcKcMD5kIOb/sE2H4fsTGt91p53POP30gw45xLoiRQhbO33HQVgBjDXU1nJl+IgRK1Ys
++DDD7n+7epvCfPigcENjBTV5p3TNkOwEDSasRm1nwy8w/EI46ryimlTrgOc5jhzKUbP99xz34wZ
z/Qq6UPeD4edfmT8/fOf/yQWM3PmzI8//ljVwdjuBDWJqxNzGTpkyJhRoyAixm6EYLYzHuCzUSO3
mv/ppwsXLWxqjC9bsRRDf9DggShuWqSO5K78jzbyD3kO8wEiLm1mTqbEYX1NA3N99912JxJmQXNn
Aho6LIiftBuSzAc7ojjhyFRj+8lRiF3rqqvJnHIyZuxYpCCQMFR1VQh5KistFLdgATDgi/SI/JNJ
JKMHkmALfvrpp7VVdRoOskpyC4NELWnjl1AAhvzKPfbY46Ybb8TD+PExxxisZFdzc02bYzSDInxh
d6/xlnvQOeecU1BUCHprKmqI+jL5kU+pGM3t5R8ueZLFyfhmhRHZPHD+/PmwGnE7ij0hJc/FjkeS
oallvnsuR5jxlaevXL4c7hcqSCJg9TI0VDZXLv71r4WE5liCaCg/6q4NPDq2/3gqwP32t79F5ceb
rGJUj4lmR5GIQ4cNIxjBFOGKcJqU262JE6uXYq53wz+yKEYiz9npVU68jxs77snHn2CoQpl0/eKF
C4mBK1LQI/afXC4ZuzpRllQDrx8S+p/Eo0EXAdLiJJ5BuOy00zCVLr/88gvOPfeUSZPw2D6eM4dZ
yh8I8VrV5i3J67q6UaNHI0jEu1QGIGYYkQLynRHVilks5G8H9W1mhLme0aQIv3gsseMO2+OAU4fA
Txig9EMmDVWLbw7nERdcvHgxF7E38KXQuaQAXn75Zc6x83CMiIoXlpSw/IyZg/AzV8yBh7Gx3bbb
sUiDc0j03jvvEMLcQM7T7aZ/Dzn4MFjd6tgoSzTFkhhYOvifDz4w87lZhHpy8nJj9U1IY5yiV19+
degmmyAG8D+yXY105dq1pn991KY1yYaicXyZHpDMObiWTCShCwwvzEFyhfiGiD3C1PTGr6AfpMz/
+OPd9tgNbdUaOkgKBT0vFSkShEzzTVFJGB3j74a/3GANEqELzr+AogEkIm3kn8r3pA0iEHZBRcB2
2FtUJLz++htvvv0WMbM58+a98cbr6MaDDzwQyHBZDSGtigL+hbrkSWpqqp+ZPoOI+tryNfvvvz/R
Bsw1nxbzEBpNBI2bbgpvGZ1ciBH+++N1f8Y2yc+PMgduufmWww4/DLy960J3mIB4b7ALpUl45ea4
ZGbCbRid8BPjInN4wAEHHHTQQeSZMFKNaABsdpSlkWwykGezXE6irGzNu+++3VDXBLfsN3FirCmO
7k+dwB3rX0rcqEhuqMftp7dsKu8o76Nu7LFH/lVdXkXxW0NtAwNvboxPvWba9jvugMrgkdk50dqa
GjzBYjx/pxpVuiw8WUlzK/NZrjAQJe4CXJM92VkWf87NxYonkVVUUmzOWEYY6UKwSv4jzpc5OBmR
226+pW+fPkwGGaywAvQrKytTDkpUdP5c8pDo6vDwXqRuITuO4NcxZswY6SmJJZGcE57LOc/iiWJ3
VBLVOtj5IBpDDeZbuHiRW3nlngtmjKiuU/cJzNCd0TU3xCLhzEULFhMxNhK0sExHpVac2h+Fd+6k
pYkW4QTkjyPrwommuK3XQfiJOWtrGw88CLszY8stRl4zZdrCRUuuuuoq2QmYDT4KCJzE/G699VaY
UiEhphypYZkWBl1mJsqNR1EISKWjc+ht8dwOO+xUWVED8OXlVcuXf92rF0GfZODQmwQ66YLKbX4i
kpfrZjYTkto18wEL8otemDlzwRcL4KfGhiYSLYwN8Uv4XiASd+Azv9DqzOASe17YsM+5kOvPYT7F
NUQhLAyZF656r+1SU2hPe4uOhg0j8oH8SjmMMIo1uEgPAMyB4kNtqRxQBhkTHYQGe/aKMqgx22PH
R53oh0GZcnEs0n/AAOK3Wg0jLlbcToyou/iqYDuH/GhbvQDfW9wmwHytbBdkQSIgA/sP5Jd4Qwz3
U1q+DXgqOCVNZzxt5onV/nDQmCfSnlHrloJCFjegi6gIo6Q0H8mHBYUViMkEeynJDqgMB+yhlAlf
4PnieeAgK5Va31pagX1lSyPIYmdb/ZsjX8bgwUNLBw5UlG3Vt2VwS+p81lnLZDmnMAjuVMCC1Y+G
dYMxic9FSlEoKVBAVQMQc1gSVkX57hD761z3GnIpXXFoRWbI56JnTsRGQaRz0UrwKS9wpZRWm6uC
mnicLAsGStAxrK6qIeqrgYkzYE34TwlNHYKha+bzcDIQKWKLRBjNQ5Bw6NChIrZEowYb1O/+KfpJ
vQX9uS7suYL8AlSh7kKOSlZ1IT80k/VE2QO6UT0wP0kucyIsgW0+ifNNmjSJUDMBGjwk7rK8mWtA
IAZ3mPwnVTxk6jB5qSJTV5hA6HWde3uA/qna4gqFKkxR+SUbeCSxCUCQmScheHD9MGVAIVUtSEVG
y0QhvWsPdhNOMHGIh1SrLAFgks+FcMXNQr0yb7JUtL+CJJY64YQeNDt5lroCd3AemOKr9zRxGOVz
KD3DCWXc8IqSrVwUf3RGvy640PNrG/nHV5FKwka41gB9b34W6Veuy0D00rELCqFZbCCuZzAgW6IL
4zU4uqD8IyWOP4I0lT4FJCEB0Sho4RUoCLqeeOIJ4gly5riuemwy76RP8bTuueuur1yNDyYQ8g+C
ARW9AZWSk3CzYSMex4lOS892hgTjEmEKYaaEx0svvaQwMvfwK1dOPPFEJAHRKZrBE3owP4nDEGZg
nBAJjEsOl4MTFxyyakJacouY29NSUpPb6ZNICgkrDqID4i2u4wwyclIyiochEVXI7h/NyZpVZXhw
eCESTmJZZRHaHxs4U9vcrqHxUNlVsgvFdpppphohbF9737KPb9yYd4iU9XzXDYUdxM4CBQNgRBCJc
Jk+ebJUEjqUQmapOoM2pPz8Vk3H2yy8T5OIuSObtDRCLb+S9eFtmkH5+tT3kJs+9UpM1zUoOFD+u
KB4oeGVfhGOPPZY7GQwI1dI4n9wEDqJB1FzhTBGAZQ5xcMJXLiL2GSS3IbBSRKB3E4agwZsBQIi
yBZQIISGZWqCGkIGzFdJSg5llqVN8O904gdPjaeEn1Sw/FM/zqDM60L+efNZKti0WOvKAWFcik/d
ei3pjQ3Pi2bwuUMcKe70NGuPffw1y0m49qrJ9Sq+Q5b1yteDxKONLjgJLaaIZQsCrbSBurVyXZdN
pSXX0SHnnXceO/7gEZNwhzpe1pBLfPiRh3GHDzvssPvuvVerMgQJ99KPFSvg2EUihLWlizbwMECl
RsVYuH5YowJdGofQkRKFomtQRSK9CH0R5KQEgYoP4JPm5YSvXMRpxc7FURDHqBOkPd4+oSZCKlrr
zki4BfTBecw/omJ33HGH5p9WLcilQKYSiiNV4FUhF7WyQWYyo5Ah64WfAPaCoTNkabxSvgCZtMnC
IXqmHtOr9aBylFHLsxD/MmeDndNS1z0fdPho1lskbc1QCCRrmF3ME69zhRwxOjeq86+//lroogeh
SN6bio/Uhp+Ut4TvERMkUVE7+Hb6FS4mxEu3r7/x+qSTJ1HX/Yc//AGWoOySX5keYMNyXfE4Ukmu
5AYeVvOskSigAHMgu9G/1LqRr+ST4CTDELohMM8Dp4yBqYZ7BbvANJ7wKE0OBi+DDxDJB1AFRBsu
IldQzfAQwSeV/ajKBsHOuQQb8BAjpWqNag56gBXUObRBzwIGxqiqvIwG2Zll35SBdOFXVR7dsEsk
q0TdoPxbRUnikiVKm/qp5Q0+MQpgw2ciqoghpkRgqOo7KI/bUIspB8lNpdEoIw2alR3SVfJP0Eok
S/65nGWohjLx1uwFt9MGqLBkhCuQrIGImiojUrXimWeeicAzyKnfRnEnWjjJiebM+3gemeKtt96a
cnf8aDJ1a9eswepHKyuzvIHMZ0+kF/ga+iFdoCulyEo6qdSKiBpuL+BKOgZduWuvvZYyYLGjclD8
iou00047MTYZQ6CGi9RoTZ06lZZMo7POOktzlFtoAEZowAg5QBN5DmkKMTcS1JjMRfKAEHxxjjEA
wIoEUR3O0lQMGkkaTQzZy0Gx59VrZ/jidnGeVLm8PFfGk4E1rEpvOoRy0layZcVwDA0ZBgllgXGF
gSD4sdDJEwoYLmqFK4cPD9EeI8TmquNdTBHxrl+N0B5aASne4kT2BhFKi1QQBMsIkdj1BpWMZnmp
+BlSMvgZ1GVxr1YkyZ9gGqCjbAYmWrCFfvmLX3IXUbaS4hJ+hRZUbiM1WG+AriQ7wh+WUo/UfyTX
HIm3gNJCXwpBOSFOUhyWUiBGrKDxMxtw1y0t69DNtCOMTp0w1hj5HFwQsk9cB3T4ZtiwYeQwaInY
Yw4p1MQtNKBgk+WbMD2re7iXZ/GTAgRW4N4vWeCuSS9fmIv8qjChyAkYMp9FmM6YbL3XFaTl6Qja

nXffmaI3nos1zBSFBSVcGX77yOV6e1ZxMkPmRCFMMRl5W3NTmppgPiQK0ohRyLXv4ggqaI139OjR
7ASACfjoo48KD0KyZg4iEAryRArbkGeQCXKgYahsQjtdeuml2ELoHOmQ3/zmN7fcfjs2/fnnne+T
3TyFX7GpbGVZRsb4bbdlivZI/UtyLS1ASwRKHegAEURfXY5r3SFhjlQARHEkV1CsBEd++tOfUmXO
UNndjXgSVgVzjvFQUsonzVDEqDOkrEwWfBSmFNXCsBTPYicEpi/iEz+X9C7sSLwKsaEnesITkNOs
xcyj/IBtLhA/Mj25GLTQ18sWvoGSNBKxipmTRbXempuZGFrvIqor6pR6z2opF0SmNiegCCRoymm2
E4FD5EijBa3bNg/q0DQE5t12242EEY0/+nAO81lw8slUYSwqFOBxrJcFn1yB0MhmisrOPfdciOJJ
eeYZZ+II0nir0aP/+Kc/kVQku6jyfUSJbd2CjUQ15M47A0k35mF7vJmpLpopfyDlaIeTN4pnSvbo
sgYGZPoqjKAC8KQ4Z7YxuZGjcC0siIcF5+Er0QNpIoSfkKKQKX7WD37wA05gelEdG+ixxx4jpIJr
LGMF3IkenipckX/g7QHdDmDSs+0Hud4rgCTtCYtIDyBRSvqY5kJskD8AM7Kl1ttVhw1gONkwjALa
y3QjAyb/oHTwYKYi40Vcde0ve4S3kihpWTBRWYLCRVIgiDSF7hmUQlHCJOtyKP3H89NIGRFg+OId
JALhfYhV5Jh17erViDpy/eQdpk+fTj7CTCmKx+rre/frh4Pog9jdQ4i/y6K13qswR93BqkOWuAxz
CSGNn2ezKodz4QuCISY1yTQk6WuEPOJQ/AoVibbLBhKLQIw999xTv2Jlir2YZzCu4AF33OXzb0FD
XuLTcxs2g1wHXexQSHSNJrEdz+JeYIBFEMksNeIurmMeII85V/FwN+Y93TIWoVrqFdOWQzBDTowN
pDjYBoYuplAbu9YjgQo/GIuvkIZiPsxKzuXYSbOBeb5S4kCRH1bQJZdcQjgaSBAWu++++y9/+Uv2
AKKwdMCgQUT5uBcmM1PPWTUYBrLjRRf0lfaB6IYeaE8F4z/PW8mT1kA/z4bSEjNe/MjaMz+8NQjH
TyhcvjJavzqJr9BJrh9ig8Fr8xQrY25VZKqL1OzUgfhEZSs6D2CcMI+9Pe7Pxd/EAVQd5HMnnHeD
+bhLgW5JQQknHk1iivwvSAcq6v4l8runf+lEWx4CHqOARdB6cDkEprQHBcevKqjh0V3QtTP9SzAB
44ea0HjM0mu4bmgb+lSIDpiRDjLmYCZkLUFWigL5FYMbZsW9ZW8Qhs+mDgTDFI+sqa4GJPCASiRN
LMeA3R2Ylt4o6npWp/Lrd3YGT97QqsJEBl2UduNElr7UsQivnBu/Mp5gTSK/ygpGbCDVmN+04aJk
FSQXRnRo3iNQ9SAfbhTNgtKXxsnJADhUvmYl07ICTxIilZEH20gy0a0EFbyoNUFEJRQVIloLC/LZ
Pf0u+OmfgygdoSVsYq6w0wXuPBat6u+htzytzuD38k8NvAZAImDkoEC5COSE9PDKrYrnu9Nb8X/5
xZKLXCE05kNm+c7WZ1ZjRdk2F0VFrE0h5k9XEIugGggBWua/tsVJF8/t2xspHTmVwNHIceVdHME2
wm9wIm3dSjaaaadAkVkSjgEADSQUX4qcNBPxJOEkAxS2gB6gQL6O9JHkIrcrsaNuZQwppKfRSl97
dhQAoqvG5k/SQg0Q8lzoQW/iPyxUeOLEE08YM2aURoENNHXqNS6jqiUgwknws9NnypbQgeChDpSm
jJfIwNHHHW1ppzWrUGraLtabHOpONKEYz51YHVT7x/QfWLp42VLLWxx+KGGBPv163/m3O6+ZOkW0
EOroVlu9cM6IuIjahbdgXEkZqdeqqnIYk50Z6ae2rvraP1z32OOPERik9J0immNPOBbM1DfUypFP
C8nJ4YhMjEWlelh8cAt7QvLJ/pBW48mqhtYpuGbNauSUwzJEN+aQ3JJdyP0CggknNa2LACdG4Ss4
Vb0McWMlEL0cJbQhmOia9pqawRiHHEbljsXuoo20f2aWc/GabN1/cmxOenXJgq54qN0fgo8cAZYI
1h0nfM3LM9OWIV9w0fmjx46yBWGR0COPPnbgwQes/GYF2+OR76cckQV6nPB5ys9/NuvFmYyIJXP4
yxjy3mwQzNAYnch2Irai1h1DNhl69ZSrqynzb6jNL8zjhP0U2ZATWkAe98cml/ZHOaE7yWBvS7dd
B8iwdXD8aR/YmrpqYMgvyj/iyCNGjt1qzZq1rNG98847DjvicB4qHErbeKiwrKiIJr2B8W2kdbGt
xnhDfnGhbZaZnfnVkgVnnXf23XffxV2gZfT4Uaf84pQs+CTMRnhNnLCLoRsHdEnpz9aPur/gYYkK
Bmy4Tri9FnOzqDokkkk9N58wu9WcUX4WJvab1IMgFJNF45HFRmGtFApjUDSbc2KEGLxyHnkK2R7F
QsXBdEI8SdknVVvBbYBBUTjBW4rSxJcwK73BvpJ5EkVS69g6JguaTb/LehNlvjO+DfhCgSfbnSAe
jj/+2JGjtqitsY185s79iLG/+urLy1csB0DyBBKBbHez3777YFohhMiA408IVEWqOSEIj42FH6Ov
eGxnn31mErr1bQHTuuFap0PTrK6oqhw2fLNJPzt5sy03a2owIc1kABhizuAQDGO3qdRAlPLyQr4d
0ykzK3t1eVldU+3Ml2btO3Gff9x1TySHgv/QsC2G/fTkSaPGjCSozlYfpnzjXc/zzvDuQhmtLMjk
iQwYUnrEYYfLnYEtXpj1Att0OvjMKURin3TiSebksrLPlJ2pQg54CIT6KaVZhWWAzUQ/jAeL4fe/ /z3VPogEKs+YZHJa+arZxjmJZiwJpLpy2zyPyAuxUKp
NsCgEJ+DIUiz09AnCbyF1D0+ZC8hJPCWI7caMnTo0uVLVq9aTbS4vqn+vnsf+GrRgr79+yHDyF/U
syMq5RpZlC7bc2QQaxJivGM1oukIizCZGQs/UXJB4G3b7bZhI4vU99/oYghya2RCEHPAef/626/L
vi1zu4O0EBEksIquJ3VOJ7LChU8/XWnWFGtcvaZsydLFCO/LLr6MnU9sSXc80be0L/UKJKiAHLRj
4tMDztN64+TtATaZDvO4/ddenz17rwkTIn1K+/7wiCMU34LbPnj//UULFrlNGJIVy1QvMmngPxb9
M08Ana+kX6htQQ96U0z1FMwPnDui0wTZicUzUegZvPNUlheAILIjvl4XMUbkEwWBCUwZAR1SrKAy
YDQ1li/4IkZDM54otxR82TYdd99t7kKmbcoMoAcfejDY0WsjlEOTitdJF+b8epmyuKgYmcGQyQMR
EWQx5vIVy5rqYwXF+Z/MnX//ffc/+dQTrErkoYairEwW58OOzC4ineSH7r//frawYB7aHqluWwiA
QSCRhCRiWramzCmk9UKx/gYy4Bi+MivkoohIoDTZrIcKduABwwRWqTbVPk8qmFAanRkCqoH2ueef /c1ll06ZMnX+vPkmgEwTtuy+9+6k+LGdmPYQD
1ttvuSO5btK2Aoq8+soru+y8CwCxJgMzyVudMBmyio3LUTQwh2L3CrTK4uGc6QKgRJjgGFx9WpL2
QRLQxm/jQEuVWimUyInpgkQCXiTt6DOYnghELghfWV7VbdYG/W685UYCsCAIjKg8UV6ki1raEWDB
9KLTyDWtSQM2FDGkpWYHQpZ92xqlRzS7XQAKSwoIbbBwQ/NE1XIqfLSJbKXzYZQAS62pJ8LVgOo0
iOZF2+znvH5e66gFokhrh3k6Xh1cAjCrvvn2vbffw56hLiE3L6e+zsy14pIirVKgMQQCMxCLAdo2
w7Hm7LyspoZYToGVUUILDAalFfiqXXs5F57RS1xM19ppCVmZXHL/58mTr5w8OTJ0+CaHHXIoaAJ0
oKmtqZ0184Xktka28CMxfPhmaDd5/uhfDZ9eSFlCG8QVqUNu14uTtDhDbRQ1RL0Sdkd40DlXsAgZ
LaahgoJws4LY4hIOyTCyeWSQQZBKSs3edh4u/YNQot9JuRsO9R7Q+4QTTqClosdiOOFlw+VfU2Ny
n1YgJDnLGBkOGSpbEBRqKa8sZ6N7O8LsCBMrZ6/WNRXla8sryitYqU7sHKtVZQGlpQOYhDibhx56
KMMXCVlhZCnEnpB/PuwAlpT5ABv5BfnbjN+GRCJWPTRiPrLADCuWSdvY0FhVWbXGKofWVlRQ6mvG
Nz4Hu45nRK14h2j2lClTqL+iBZwHzKrNVnBAglPzPK0J04H+3WTEpvtPnKi+LOFRXDzzhZlsVmKi
xeGuurqKSCwrFZytbfU5ShUABy4FjMU8xpOAS2QFMn7VUdMbKTgC7ion4Qo3wnaU4GKg0BilQD/g
zrMszVBMpMnRUIqdikfF/XzF0cZ/RP6bSHNe17htxhH3UvhQcs4jZcP5r0/fvmvZfZXCnN69iXav
LlsNrL379Nljzz1GjxkzYvMROfk5cGFjfaMJuXVBqiRRiooLd91tV3KJSBESWWCM8jOQg1licVA2
+eoh/gO3qmQztnNBLiYqFKmprAbVsD4pFpKWUIoVn7ZbodtJwmSErTFKbsqLJN5xp+2POfYYJj/6
hNuZcoq30zmPoE++IrxlIPnYcOos2IH+5f0f106ZKgFDv7yekMzMJ3PMAjBa2q52oXnzPqQmwGzn
Jisp008+RMw50wvFhPcgEYWcIEpOwhFFIM9Lw9At4EgpcCxFEvCQBP5DtvMTj2aPTh9P0bTzw6MZ
oQ2fFmNLAV4hctgRhyIpEcOK4EiKyx/ccP2LDFPRIUNQ9haQAAMJAcZUTmwyZC11cWuQajVVtWz/
TUv8ML17kEpqDvBUhye1xUEAq6a+LpLVQTAvdXL6lkIyIPFoOBsScIIKBh7WzYFweIWv4IRMCfKM
XCgWFyqbK/ArUFmN0tAhBIDExHQiQ4g+fR5LHKI4g9znoOBIBez2+je81bajHrj3PmDikbZWubKK
RNPFF1xCd9EcdtCBoqGDDjrgmekWEMHGVTGStCFjFhypPDuVNhJgUqDBMJ6cHoBEI+AdJ0eO/sqO
PPLYwxCb7JC0PzyB0SntoKjNhth/9sqKjg6pCyAEknUHuZiI2TeyZXXI51DMpf2RfB1KKqhxbdKN
rne2t7lWbGmK+k87SXfDlJQhV8O6BpMLvYqK8Tun/f73V119tSl70JSMqMVZi56HBCrpVZiVnQHz
EQXEMIDkM55NrnRU5kNpNBVjpglDV82lZ731JkLyIIX3/v3vf2M4cr8EJLpDe8l725GL8CiS5jts
EfhCPz1yeCYDKlAB9piW1XW1ayvKeboMJn7yE8lL4jYn6aLOs/UGnthrFNwhYazEDGJPkaONd6D3
OJRnMuOXnEXp0IEH7L+/kt8mMJqbkYJs8/jJJ1bhQnAfB44S6YaGOhw3tCgYVLhSHgBddMMO7Rrv
ngt9jIoT6IrvjOfBALT5M8Ll/04/bYstt5COQEDKcZaakOzREaB68Lwzrlh3vbPWwGDRUZeVCU4Y
XvZmPhtOhUtPYO/rz19pTVsk8xfqZCMebnus9n/uPRn2JxvaQyWXceMd9lIKyrYzbYnFG7Nn77n3
3sZJiBCtYJB4h3LYy2wj51ShKUSYlbgd0SxwrWCEOE/bGKTrBHXBfNIFahA85yvVSqqsFJCIwL79
+tg2ey6iC0hahswBI0qP6/DgeV7Z8BMPoddi4llxpAdefmgXckW/pn54j2oDTyThNEW9iRK0mNc/
NbvVAuUJp2G/mRehV2t5UBAqQAAG8QzwNogU4HzwHgS3l2S4oqIGhxz1pxy2kg0yI9JVIqm0p1vB
Q2NwhLnAHj+6EX0Bh2HysypZBfpwJOKQxiKkhQYDh2Zzt2c2Vl77P9uD2Rxw99ZP1zt/XrPrWUG5
2JlESQUVG6ONYPNQCeCgON/wKdphD6rQU7WHNjRx653cxJViBg6mBRYMscdBg2w1BtEjVDDh/UWL
lhEKh/DiCU10L656BE1CiuSHarE4J0xDNRGBex/6xljBXyOu4aNTZkm4xnwCkrdgGAvnsiODbkEq
9lPTOi+iq+br9DvbR1MNEZArkr5dqLN0yewtig088eKzW1Ks+zd5vbFOO22z63Y3/uV65bgsbNHc
YoVo1TUE68lbEzqGy+A/wgjU1SMOSQ6y1kvriWT496wLIvvSw8dLeVip4GtGIJhsWGbC/gdOxOQn
C6JScsV3FIURB/tDU4VPJRVTPNy7lTr2IG36th5B/Y79pxo2/0Svjjt6KLGi9OK36Zo69k6c9mHJ

70oND6opkjThSRGTvlkibP4DGwST7oOC1MmGNx+z+WWXXr52bVlRUUlNDZtmZG87fhyfrPNih2oS
MHM/mpeVHWmot0AMUoaZxxaLpDXpVKE+BUe6AkXFXql8EnCOsxmZvceap1HQcfNfb7r8ist1L9lY
Xj7GrrcTD9j/umnX8l6uBlc89tVXC/E+BTPbeXEOnEIyv9qqVgqY3JW0rAXRwriw3ftzqY/z7891
OyYSnLZP9sbyU1zP0mdnWoKdBFx7FdGs/5OcbYot1Rt5mg7p0hk8vAw8LXhSgTnQhiyRxa3YGJ0k /q033XTZlVcma7eyXeUff7379jnqqCOpTHniiX9RGT
zYpjcTvRuU5av7Kfn11svd7IznbuRz6/Xb1q0qmnAFIkmm2lLjlR7Q44cvSoJ6Y/Pe+Tj1965eX/
fPH5kUf9iF33LMGayVuCrWrS/uwN7R1+tlZwqo5zvX++t3CIpxQWF/hSN6of/LP8c4nf+gY5efBo
yF6LLB8TTmstk7OwswHp/zqDdkOv5+bn6EECTM/VeVFJoeChTRA2f045RWa2ee7f+aMDNnoUbrvC
c4eQ27viW++yk8m/v9p8f8vGJOxd3pTr1NdRlmwLYSZO3J9MNrOXBCIFVFJwcBsBfQQe7jCLyamE
UyguGC7nq3xkmWtEgU3CS6U6iWTn2gnUiX7W0xL00Zb5fDY0Ubua+elnn1551VWsF9RWvrqLlqxO
uP2OOyieW01NTSj04sxZFIzpfXluFEl54/bet87bfep6qn+Gk9Yt/AAS604BWgv0tLiSMCpAaeFe
w8nB/uM6sVVUcYsB2SahZt7bX2FBIYlXC57HXYbaBWo6gbM95N25wtMdqGzmbICxt4bZwQLS9jI3
pUQbPpXWoiXqhVebUHhmtVvNZlzZVzapcqC6W9yGo8776gjDXcBpvNc6ajvZZ8I+6/SFooKoV7gH
qwu245wEGhqWJC/lpQg8+FJrEDmhPo+FYUSAsRTluHCjzEG+el/BdnL19pxT4fxBGVlkpnvkcyRZ
gq2GG5548glKc5+fMcO2mdeaWW5hNVM0Sr0u9W0EjMho4aBcO3UqoFonLu0mZZdukqBDDaWLPsap
mI5X31rOHdTm0EJVPIKEX41mrbEYeXU+P04zhuAbdAHAhv/kVa10l7JqcJuvJFCGhgMgFedXhg3g
lX+jpfeT2gy5e+B5K5ZsVjJeZXzpWEfBW0IwRAjJxpIlhO1gMohNFkSlezCltp9GQCKigE95CBUK
qDSBX1XSnJR5kmG2ZM3tJ+vC38gze8MEks/xH0lHNqy9/oYbWKPP++ypYmD3SdaD2gt22UqspASL
leQv8OD2ImAohJn9yitCgWjPSc86Q+ocnIhImniK5/GVwYIWxiiPRzjkIJ2qSjCuMHtpb0omkaDs
AMbVFi0gGXT1bPSgQ26AWMr/KjJFGwAWS4FDCMpXDdDkeGsDAnVc5Ba5gxpXG++n2/M8yH/JsIXs
NtFPkwAMsoEBmw/xE/gFVtYh/+ay37AkkV15DLOFhSzR05i3+8EP2AWLOiheveKxIGGbylG+di1V
CDDfmWefpR3u0bMsfPLLUHr17YsLTFEGswJIABUD4KrLnV/i+ENRaAYmIyGVh6bSRnNS+OIpVO+x
zFFWr2KfMBOSmEIKCrYxmuEwaj8pT6QNELJkTiqFlmw2gEohAMZ+F1QqaCl0uv5sKjAH27BWl1eH
cgVgWAiB1FCZNFvAHH300YTSWFiJrJFgpsCRoBvlsSRggRNxQ9U0VZ7aMl8Y8HOs28B7PuZEXqwd
7cUGM4aDNfoglw1+wC+5r5tvvcX2FjezmhfHY8/iMEXYCBolinMweuyYy664/KO5c+zdeIkExeWm
pNr4HDgbsTirE+SCrC1bM+v5meecdfamQ92WP22sXWfhFvYqufn2275avOj5F194+/33eD/61VOn
YKQYAK2rKzzS5YmnG1frrH0QMzyLCSlJoEMygxPmJ6vatFcEVCS4wEXwRpBSwFA/rA1DWZCg2mOu
S7tt1lMkAtzGc7FStIOtnov7yEVMKSwrKSsWVlJbxHTS0CwS5w6KbSl59OgFWoUzfdQmXfg9dTj5
Dv+poyAjMlcQNiwWJP0AcJTIL12+7Nbbbxs7fhxs5za8b8cxGOSZkeGbjzjn3F89N/N53Gy4lgAy
ZT8oTUQFhemUaWE7sncWmw+xTsePzVaVE3iJZtuLhWAvx+j7HrD/62+/9eWihQ899ijM99pbb97+
97+J+bLzkgt8fA+ciLTpIqUL/gt2Tg0fJIHnkHBoBuoO2Zif9dtcxCogHi4hQWLGdktJJIhv6XbC
qHzFmCGHvoH0S2tolFrKTuVgLZIW/GMpEc9n8oj/uMLMoTRfzXitPWseqLHFBJdBz8JTve3Mo6In
+Y++bNlba++aDXx6B4K6eXZmgI2Y1i++/NLH8z95+913fvTjI40D2CMuLxdGRPiZXHTeNV8JVfAT
F0EWZY+qGaYKEjMRkcBgglwOAMnUs+dm9ZOVedGll8yd/8nsN99A8s16+aV5n87/84038FJufs1x
AligSkppCOo5LSJ10djDKbHKe4pFJKq47e1LTi8zIkQdF3mRml+Sw1oWrlCWS/SKlmg6vmpbDPUp
aHsKzs76QcmK7wU2s4WWYGzy5Ml8RclSGgyh/bgQSH63WZiSLfZoxlzCxdR1HXpc9+AP3m7yr0PQ
Pd51wmojbH+slrfeefuV11978913vli44O777t1ytC2MjebnwSv8SWIl/4g3cKXzI2j6JPdCaL0X
3jrw0EMeePihjz/79N1/f/DcC7OQfG+99+6Fl1yMLl73CGTwRj48uwgPLKFS7okMEE4GTAn92MIL
IqHmJkyY4AfFTJMug+QiNg0wDTecfmmNmHki2Yx445OyUy2Bw5hGtmEO6ivxNZqxBbffjF9wInro
AbkOL3rFEpQdaQHThmvpv1P+C3K6ztkc7fQzz/hgzkcwH9LoxVdfgTPe/+jDaX/8AzyR4SLD+vsO
I7buhNshH8pvWMeItp9axt777XvTbbfO+eTjz778ggc9/eyMf8+d8+Qz04885mj1z7NM/7rG3Rh/
Wrd0xn8sH0SocMiqg9XgQo1R8hjxhnsOp5pftXAhbfBFfJZIQ9bYN+oB60iH4oWgcznBoEeSSbAh
lQlmAQnWIQaftgPw5PAncJ7WH3qYNVJp4XQPPUKdw39d1X/TyGth9sek/oqVGTV1tYOHDoH8nBAr
nrDvPrxx6oqrrtzvoAPziossQsk7GOmcl99iijFKl5lAF5s4VPjbOS582v5BhDhdRHLzLbfAWH7w
oYdY3sZyJ2YqbhfKC48SEmKLPP7oo0ZdVr4Q1NWWRT2x/3qHE2O9FxF+jAyDFQ4jzkK0AkEowaAQ
BtKOFaiYuVQSsXYTRQzqFPXwPN3t+MV6wfMNFGrhKytlAQANxhoo1kVoaxgVDXFCNl9xQc51hYPM
gowEflK5sX71Q+jG+t/2kHfFfwr8qNaSpxIZQVDjumPckIGAM5hbIBr3AosblwoP//Lf/na/Aw9k
2Q5Qt8RjxoKWFbAqFHufSevY9G4TNpfmDZe86vcv11+PhU6FFeoAa4NABn4PZEPA4P0gWubPmyfm
M+q6wie9dO6/daBVMfvwalknxthRZJRlUJ8GlsCYBAMLovV6HKQjxYssVFV5rCQHnz0YJ+oMD1q9
Co1sOeaqVfgWtASfOOlMG09ZprpMcDGcsgnEZbhROkrrXdyUT2Z6FITacPwnJWGbjoREGa36yTCb
zD1F2LWJOSQaMKUUL1RwFU4D3ThWeLt8fvDe+3yFPPIHtW8Sn2hzMIJ5oVem0AOYoiVRMXw0LjJB
Wb7++OOPr/r6a55u4UDtdq0FGYIK/dWa+NpwRHTYAzBbusxtbc0n9h9SjZZEAdEGuoXhUKHDniFw
GMvgtQAZHcdwKOOlGaTihECGdsOVmPE1vBsJcnXLZiBs8Yvlh2/EDn8gn+WIhFrgRXQLoOL/kkRg
5rPDAavQceq1s6PSEEwtFDcD5BaUtZIO+slzRbrwewnKSVf6l2ess8xaxbJtDscLj6qqnps+nUWZ
OCUwGaNCAUEegiywIyf4K3AYBw0YGyNnxzEOVABWCKvKsWrZZ5dZCGoQn6CDuxgn2gpribAF0ezb
br4Z5pME9cxHhghjJDnmjVP6mgpCgdkvZWCnAcbLXQgMv/eNtJ6msZQg2kqLbLhRzBeMaKTy0G60
kUkAYrWtLcRi6xKEhfwMBS/BPDzKJ+4RXKht0PkJQUCACUeKXVC0OkQAaERB3ugGYP6W9dh/UiWW
QXcvPm2oq7Xwh6s3Iaf9+KOPHHP8cT/7+alvvvP28q9X5hbk9x3Qn0KGtZUVtQ31DJvluljo2h9c
opGqBaQ93cJ5DIlZCP1Yp4jOJdSOaiAif/8999gmtY7zkPJRqVr3IlAT+iyFZBrw9b9n/1EZSUCe
jUSx2dlSiGUADAfLVZTjU1YgqFPaN8hq2mSNn76H5JvW9ACJ9gXloQCMOCDyAiKhqVYNk9xnC0rE
IchHTMCjuClIbtwXmnGOjAzuLArXwoLBpbHdZsGO9W8b5ZvUwrbfTzTOLhys3WdU/KmSxX1G8/N5
UwMKiGgfxrh2bC1k1TqFM2Q/YWKIQWMrqkjUVFVRgs1KtcVLl7JtzHsffLBi2TLb7ZXqZW2foJ75
312xd5GRiIRmLolsqHTmQWfrC7uNjjY3dqZ/lZ9UuSsYJD+EncpW3ZwzXpUXQE4Sklo0Q9iZ9dEy
pDBF5Ah7d6SnoG3fD8/FhgEA9n3DSJB5ivBjL3LMayBk5mjVNuYQFvxJJ50UfKsROhe3HSWmqSIx
FBSE3jxLfQht9G9y2bkmh7qTrdNxj8766uAImmUYsNnZDIP5gWPFRMnJtr154BV8EDJvfK5Ytryu
ob6uppZiILMqSXuw2IQ34cac75xKpWpqmeXU8bLelgwHac2IkNYyzLmFE5QahgeHdK4/YFAozVTk
Uy8yaX90g37rhTPYgLgxWhXIibDI59VuJ3hOeHiINGxWt8WeHVyHHWnPAWAYgmwoxV006yk4ve3I
DARdvADC+E/7Q/Jdzg6TO93QQIeqxBeGSCoweF/lwOO17qQNNtN9blrE6EZj6QEPtnrwJQ5So1yR
o6aZ7W8JMmKwXj8IxsYeL5AHd4cKplohPZmkHFp9IU9LvBh0PXvK2oMlhAq5YkTmLRvDwzxjBquJ
UieYJpAkqC9V4nZFHHTwVYFHWUXq3LOmyJz6E7+3ln5oqjbo7Lle83KiiiZGpDItbgnmDII9dKpn
emh4QVUmpyEYNAn+KgYIXvH1oJ1Nnu7B6B+BKUKIPoQdEOwIrdGNfWV8D2KvtCDrxi1p9d+DjQEV
9EFIfUIh7wVLbATHnnTa0sRGD0JLV2g2gQS0ivvoEGwaRWfOrBr0LDyIPe+1EAMh4mOvL7N3rbja
IQ+cF1QpnrSBUnpctrkEgz+65rYUH/d9NmtPgCCTeemoZkzdtKbfxh6IoAqCJHIEGas9wEEaSZz3
FJyCBwOa/c1wus1ikV8NV3oLBuc83dAUIKJKpHklBjikizVgDdLbUsnVBq0ldPwkQvaUndtTs1Zg
+ymkbhmUtJUOmX06hAeFTr1c6UJrezukpwBu0w+wAQYAyMQC7VzB7UX3eXqJLiKBz9Bo4LqRI11+
6Gw49EMMDoWuN6hx/D9Oey8knIH9kAAAAABJRU5ErkJggg==
</pkg:package>