Genetic Factors Affecting Colorectal Cancer Risk

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GENE 210
Colorectal cancer overview

SNPs/Genes associated with colorectal cancer risk

Conclusions
Colorectal Cancer Overview

- Cancer primarily in the large intestine (colon) or the rectum (end of colon)
- 95% are colon adenocarcinomas
  - Rare: lymphoma, carcinoid, melanoma, sarcoma, gastrointestinal stromal tumors (GIST)
Colorectal Cancer Death Rate

3rd leading cause of cancer death in US!

Leading New Cancer Cases and Deaths – 2012 Estimates

### Male
- Prostate: 241,740 (29%)
- Lung & bronchus: 116,470 (14%)
- Colon & rectum: 73,420 (9%)
- Urinary bladder: 55,600 (7%)
- Melanoma of the skin: 44,250 (5%)
- Kidney & renal pelvis: 40,250 (5%)
- Non-Hodgkin lymphoma: 38,160 (4%)
- Oral cavity & pharynx: 28,540 (3%)
- Leukemia: 26,830 (3%)
- Pancreas: 22,090 (3%)
- All sites: 848,170 (100%)

### Female
- Breast: 226,870 (29%)
- Lung & bronchus: 109,690 (14%)
- Colon & rectum: 70,040 (9%)
- Uterine corpus: 47,130 (6%)
- Thyroid: 43,210 (5%)
- Melanoma of the skin: 32,000 (4%)
- Non-Hodgkin lymphoma: 31,970 (4%)
- Kidney & renal pelvis: 24,520 (3%)
- Ovary: 22,280 (3%)
- Pancreas: 21,830 (3%)
- All sites: 790,740 (100%)

### Male
- Lung & bronchus: 87,750 (29%)
- Prostate: 28,170 (9%)
- Colon & rectum: 26,470 (9%)
- Pancreas: 18,850 (6%)
- Uterine corpus: 15,500 (6%)
- Liver & intrahepatic bile duct: 13,980 (5%)
- Leukemia: 13,500 (4%)
- Esophagus: 12,040 (4%)
- All sites: 301,820 (100%)

### Female
- Lung & bronchus: 72,590 (26%)
- Breast: 39,510 (14%)
- Colon & rectum: 25,220 (9%)
- Pancreas: 18,540 (7%)
- Ovary: 15,500 (6%)
- Leukemia: 10,040 (4%)
- Non-Hodgkin lymphoma: 8,620 (3%)
- Liver & intrahepatic bile duct: 6,570 (2%)
- Brain & other nervous system: 5,980 (2%)
- All sites: 275,370 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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## Colorectal Cancer Ethnic Differences

### 2005-2009 U.S. Colorectal Cancer Incidence Rates

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>54.0 per 100,000 men</td>
<td>40.2 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>53.1 per 100,000 men</td>
<td>39.2 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>66.9 per 100,000 men</td>
<td>50.3 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>44.9 per 100,000 men</td>
<td>34.2 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>45.2 per 100,000 men</td>
<td>38.0 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>45.2 per 100,000 men</td>
<td>31.5 per 100,000 women</td>
</tr>
</tbody>
</table>

### 2005-2009 U.S. Colorectal Cancer Death Rates

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>20.2 per 100,000 men</td>
<td>14.1 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>19.5 per 100,000 men</td>
<td>13.6 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>29.8 per 100,000 men</td>
<td>19.8 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>13.1 per 100,000 men</td>
<td>9.6 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>18.8 per 100,000 men</td>
<td>14.6 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.3 per 100,000 men</td>
<td>10.2 per 100,000 women</td>
</tr>
</tbody>
</table>
Risk Factors

- Age > 60
- African or eastern European (Ashkenazi Jew) descent
- Diet high in red or processed meats
- Have cancer elsewhere in the body
- Have colorectal polyps
- Have inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- Family history of colon cancer
- Heritability ~ 35%
Screening

- Colonoscopies recommended for age 50+
  - Remove polyps, check for cancer
- Lowered death rate from colon cancer
- Screening because of SNPs?
Agenda

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### Table 1. Main genetic abnormalities of CRC

<table>
<thead>
<tr>
<th>Altered genes</th>
<th>Frequency</th>
<th>Normal Function</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>70–80%</td>
<td>Tumor suppressor</td>
<td>Mutations linked to FAP and sporadic CRC</td>
</tr>
<tr>
<td>DCC (SMAD2/4)</td>
<td>~10%</td>
<td>Tumor suppressor</td>
<td>? Relation to advanced disease and poor prognosis. SMAD4 is linked to juvenile polyposis syndrome</td>
</tr>
<tr>
<td>Src</td>
<td>~80%</td>
<td>Oncogene</td>
<td>Overexpression/mutations lead to Akt/PI3K pathway overactivation</td>
</tr>
<tr>
<td>MSH2, MSH6, MLH1 and other MMRs</td>
<td>~15% sporadic cases, &gt;95% HNPCC</td>
<td>DNA MMR, microsatellite stability</td>
<td>Mutations linked to HNPCC (Lynch syndrome). Microsatellite unstable tumors (MSI) related to poor response to adjuvant CT but better prognosis</td>
</tr>
<tr>
<td>TP53 (p53)</td>
<td>~50–60%</td>
<td>Tumor suppressor</td>
<td>Mutations associated with poor prognosis</td>
</tr>
<tr>
<td>KRAS</td>
<td>~40–50%</td>
<td>Oncogene</td>
<td>Overexpressed mutations lead to resistance to EGFR mAbs</td>
</tr>
<tr>
<td>BRAF</td>
<td>~5–12%</td>
<td>Oncogene</td>
<td>Mutations lead to resistance to EGFR mAbs</td>
</tr>
<tr>
<td>PTEN</td>
<td>18–40%</td>
<td>Tumor suppressor</td>
<td>Loss of activity related to poor response to EGFR mAbs is linked to Cowden's syndrome</td>
</tr>
</tbody>
</table>

Abbreviations: APC, adenomatous polyposis coli; CRC, colorectal cancer; CT, chemotherapy; EGFR, epidermal growth factor receptor; FAP, familiar adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal carcinoma; mAbs, monoclonal antibodies; MMR, mismatch repair; MSI, microsatellite instability.
LOC727677: Rs6983267

- **SNP on chromosome 8q24**
- Many studies in Europeans, some studies in Asians (Chinese and Japanese)
  - Limited research on African Americans
- Increased risk for other cancers (prostate)
- **Odds ratio = 1.50** (95% CI: 1.29-1.75)
  - OR for (G;T) = 1.39 (CI:1.03-1.88)
  - OR for (G;G) = 1.68 (CI:1.21-2.33)
  - Allelic p-value of $2.57 \times 10^{-7}$
• Transcriptional enhancer for nearby MYC, which has role in other cancers
• G allele linked to increased binding of transcription factors in cancer signaling pathways
• Involved with formation of polyps
rs2273535 in the AURKA gene

● SNP on the AURKA gene on chromosome 20 (a serine/threonine kinase involved in mitotic chromosome segregation)

● Meta-analysis of three colorectal cancer studies showed an *increased risk in homozygotes (TT) (OR=1.50; 95% CI of 1.14-1.99)* for colorectal cancer (Caucasian population)

● Homozygotes have also been linked to increased risk of breast cancer (Caucasian & Chinese) and lower risk of lung cancer (Caucasian population)
Rs7903146 in the TCF7L2 Gene

- Transcription factor (TCF7L2) gene on chromosome 10 - originally linked to higher Type II diabetes risk [rs7903146(C;T) rs7903146 (T;T)] for multiple ethnicities

- A study of over 13,000 individuals initially free of cancer and followed over 10+ years found that the rs7903146(T) allele was associated with increased risk of colorectal cancer
  ○ Adjusted OR of 1.25 (CI:0.85-1.83) and 2.15 (CI:1.27-3.64) for the (C;T) and (T;T) genotypes, respectively [Caucasians and African-Americans]

- TCF7L2 variation also was associated with lung cancer incidence in Caucasians but not African-Americans (however, smoking may be a confounder)
rs4779584 in the SCG4 and GREM1 genes

- rs4779584 in ch 15q13.3 region

- A study of 7000+ UK patients with colorectal cancer identified the rs4779584 SNP that increases disease risk

- Inheriting the rs4779584(T) risk allele is estimated to increase overall risk odds by 1.26x (CI: 1.19-1.34, p=4x10e-14)
  - OR for heterozygotes was 1.23x (CI:1.13-1.33), and OR for rs4779584(T;T) homozygotes, 1.70 (CI: 1.41-2.04)
Most studies in Europeans, one in Chinese, one in African Americans
  ○ 23andme - N/A for all but Europeans

TGF-beta signaling
  ○ Normally controls colorectal cell growth
  ○ Can promote survival, invasion, and metastasis of colorectal cancer cells

More research needed
• **rs4939827** - decreased risk for C allele
  ○ OR for (C;C) = 0.73 (CI: 0.66-0.8),
  ○ OR for (C;T) = 0.86 (CI: 0.79-0.92),
  ○ Overall $p$-value = $1 \times 10^{-12}$

• **rs12953717** - increased risk for T allele
  ○ OR for (T;T) = 1.37 (CI: 1.25-1.5)
  ○ OR for (C;T) = 1.11 (CI: 1.03-1.2)
  ○ Overall $p$-value = $9 \times 10^{-12}$

• **rs4464148** - increased risk for C allele
  ○ OR for (C;C) = 1.35 (CI: 1.2-1.51)
  ○ OR for (C;T) = 1.10 (CI: 1.09-1.21)
  ○ Overall $p$-value = $7 \times 10^{-8}$
LOC120376: rs3802842

- SNP in region of chromosome 11q23
- Many studies in Europeans, some studies in Asians (Chinese and Japanese)
  - Limited research on African Americans
- Unknown function
- C allele in study of 10,000 subjects was associated with increased risk
  - OR = 1.17, CI: 1.12-1.22, p = 1.08 x 10^{-12}
Decreased risk

SNPS lowering the risk of developing colorectal cancer and also lowering the risk of its metastasis:

- **rs2306536** in the CHFR gene
- **rs1049174**, representing a haplotype of the KLRK1 gene
- **rs1864010** in the INSR gene
- **rs1801278** in the IRS1 gene
Examples of Cancer Treatments Affected by Genetics

- **Irinotecan** (chemotherapy agent) - FDA approved genetic test designed to assess a SNP in the **UGT1A1** gene.
  - Drug dosage guidelines are different for different **rs34815109** genotypes.
- **rs396991** influences progression-free survival when using **cetuximab** to treat metastatic CRC
- **K-ras Mutations and Benefit from Cetuximab** in Advanced Colorectal Cancer
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Overview - SNPs & Genes associated with Colorectal Cancer

**Major (strong evidence):**
- rs6983267 in ch 8q24
- rs2273535 in ch 20 (AURKA gene)
- rs7903146 in ch 10 (TCF7L2 gene)
- rs4779584 in ch 15q13.3 (SCG4 & GREM1 genes)
- Multiple SNPs in the SMAD7 gene
- rs3802842 in ch 11q23

**Minor (limited studies and/or weak associations):**
- rs16892766 in the 8q23.3 chromosomal region
- rs10795668 in ch 10p14
- rs3802842 in ch 11q23.1
- rs9929218 in ch 16q22.1
- rs10411210 in ch 19q13.1
- rs961253 in ch 20p12.3
- rs1047972 in ch 20
Conclusions

- Many genes and SNPs have been linked to colorectal cancer risk
- Ethnic differences are present in colorectal cancer
- More research is needed on genetic associations, especially in high-risk populations such as African-Americans
- Early screening can be offered to patients with higher genetic risk
- Certain treatment efficacies dependent on patient's genotype
References

5. https://www.23andme.com/you/journal/colorectalcancer/overview/- Colorectal cancer