Genetic Factors Affecting Colorectal Cancer Risk

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GENE 210

Agenda

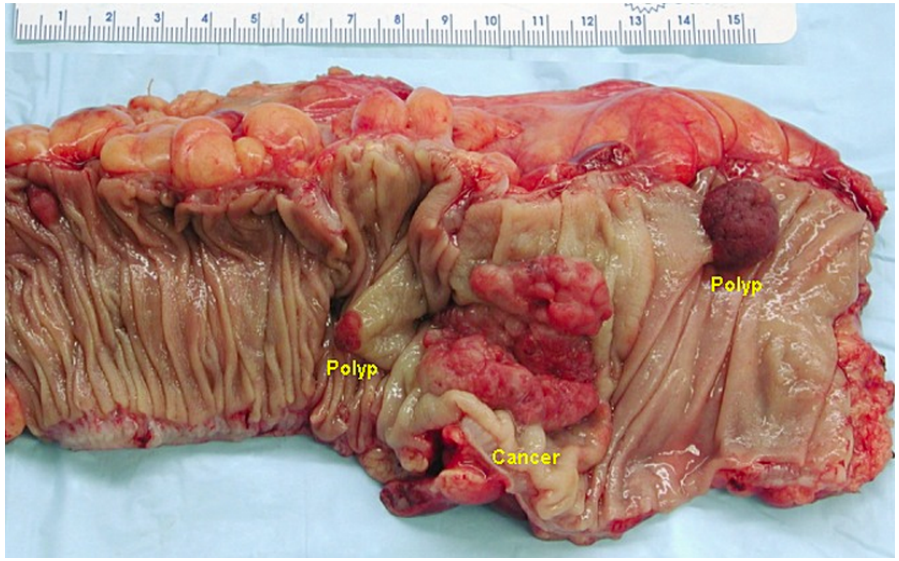
Colorectal cancer overview

SNPs/Genes associated with colorectal cancer risk

Conclusions

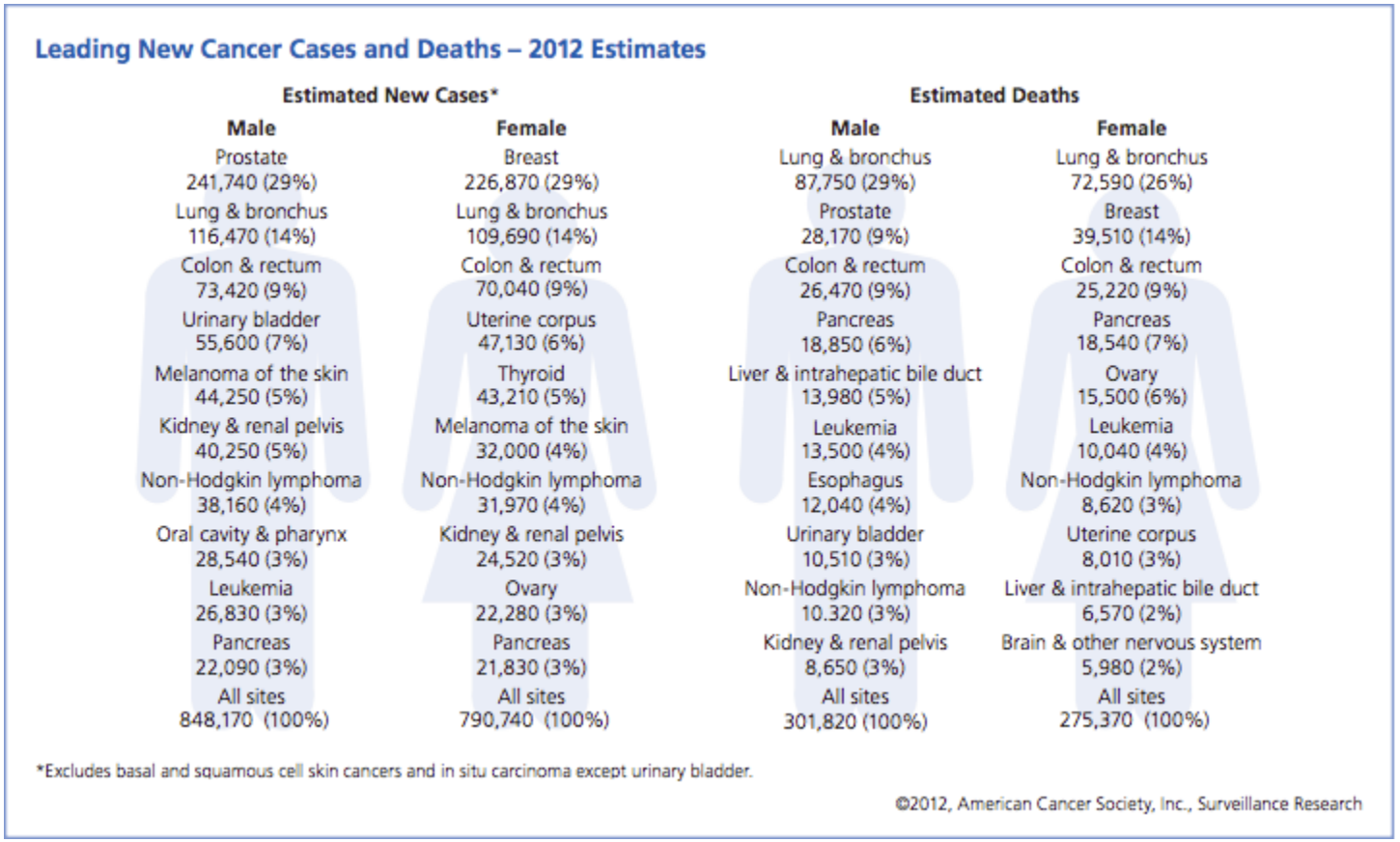
Colorectal Cancer Overview

- 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

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 241,740 (29%)	Breast 226,870 (29%)	Lung & bronchus 87,750 (29%)	Lung & bronchus 72,590 (26%)
Lung & bronchus 116,470 (14%)	Lung & bronchus 109,690 (14%)	Prostate 28,170 (9%)	Breast 39,510 (14%)
Colon & rectum 73,420 (9%)	Colon & rectum 70,040 (9%)	Colon & rectum 26,470 (9%)	Colon & rectum 25,220 (9%)
Urinary bladder 55,600 (7%)	Uterine corpus 47,130 (6%)	Pancreas 18,850 (6%)	Pancreas 18,540 (7%)
Melanoma of the skin 44,250 (5%)	Thyroid 43,210 (5%)	Liver & intrahepatic bile duct 13,980 (5%)	Ovary 15,500 (6%)
Kidney & renal pelvis 40,250 (5%)	Melanoma of the skin 32,000 (4%)	Leukemia 13,500 (4%)	Leukemia 10,040 (4%)
Non-Hodgkin lymphoma 38,160 (4%)	Non-Hodgkin lymphoma 31,970 (4%)	Esophagus 12,040 (4%)	Non-Hodgkin lymphoma 8,620 (3%)
Oral cavity & pharynx 28,540 (3%)	Kidney & renal pelvis 24,520 (3%)	Urinary bladder 10,510 (3%)	Uterine corpus 8,010 (3%)
Leukemia 26,830 (3%)	Ovary 22,280 (3%)	Non-Hodgkin lymphoma 10.320 (3%)	Liver & intrahepatic bile duct 6,570 (2%)
Pancreas 22,090 (3%)	Pancreas 21,830 (3%)	Kidney & renal pelvis 8,650 (3%)	Brain & other nervous system 5,980 (2%)
All sites 848,170 (100%)	All sites 790,740 (100%)	All sites 301,820 (100%)	All sites 275,370 (100%)

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

Colorectal Cancer Ethnic Differences

2005-2009 U.S. Colorectal Cancer Incidence Rates

Race/Ethnicity	Male	Female
All Races	54.0 per 100,000 men	40.2 per 100,000 women
White	53.1 per 100,000 men	39.2 per 100,000 women
Black	66.9 per 100,000 men	50.3 per 100,000 women
Asian/Pacific Islander	44.9 per 100,000 men	34.2 per 100,000 women
American Indian/Alaska Native [a]	45.2 per 100,000 men	38.0 per 100,000 women
Hispanic [b]	45.2 per 100,000 men	31.5 per 100,000 women

2005-2009 U.S. Colorctal Cancer Death Rates

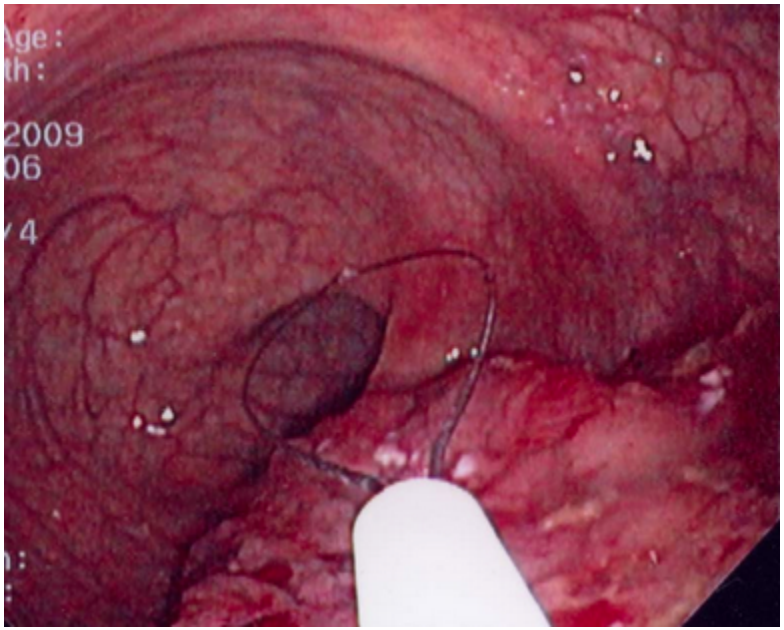
Race/Ethnicity	Male	Female
All Races	20.2 per 100,000 men	14.1 per 100,000 women
White	19.5 per 100,000 men	13.6 per 100,000 women
Black	29.8 per 100,000 men	19.8 per 100,000 women
Asian/Pacific Islander	13.1 per 100,000 men	9.6 per 100,000 women
American Indian/Alaska Native [a]	18.8 per 100,000 men	14.6 per 100,000 women
Hispanic [b]	15.3 per 100,000 men	10.2 per 100,000 women

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?



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Genes linked in CRC

Table 1. Main genetic abnormalities of CRC

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

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.

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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 2.57×10^{-7}

LOC727677 cont.

- 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 chromomose 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 chromsome 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)

SMAD7

- 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

SMAD7 cont.

- 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 x 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 x 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 x 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, $p = 1.08 \times 10^{-12}$

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

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