COLON CANCER
Risk Factors &
How much is in the GENES?

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Colorectal Cancer

- Common and preventable
- Third leading cancer in the US
- Leading cause of death in non-smokers
- 10% of all cancer deaths

Screening for colorectal cancer:
- Prevents cancer
- Reduces cancer related deaths
# New Cancer Cases and Deaths

United States, 2015

## Estimated New Cases

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>220,800 (26%)</td>
<td>231,840 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>115,610 (14%)</td>
<td>105,590 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>69,090 (8%)</td>
<td>63,610 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>56,320 (7%)</td>
<td>54,870 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>42,670 (5%)</td>
<td>47,230 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>39,850 (5%)</td>
<td>32,000 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>38,270 (5%)</td>
<td>31,200 (4%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Pancreas</td>
</tr>
<tr>
<td>32,670 (4%)</td>
<td>24,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>30,900 (4%)</td>
<td>23,370 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>25,510 (3%)</td>
<td>23,200 (3%)</td>
</tr>
</tbody>
</table>

**All Sites**: 848,200 (100%)

## Estimated Deaths

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>86,380 (28%)</td>
<td>71,660 (26%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>27,540 (9%)</td>
<td>40,290 (15%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>26,100 (8%)</td>
<td>23,600 (9%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Pancreas</td>
</tr>
<tr>
<td>20,710 (7%)</td>
<td>19,850 (7%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Ovary</td>
</tr>
<tr>
<td>17,030 (5%)</td>
<td>14,180 (5%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>14,210 (5%)</td>
<td>10,240 (4%)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>12,600 (4%)</td>
<td>10,170 (4%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>11,510 (4%)</td>
<td>8,310 (3%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>11,480 (4%)</td>
<td>7,520 (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>9,070 (3%)</td>
<td>6,380 (2%)</td>
</tr>
</tbody>
</table>

**All Sites**: 312,150 (100%)

Sporadic (~75%)
Familial colorectal cancer (~20%)
Inherited colorectal cancer syndromes (~5%)
Age is the Strongest Risk Factor for CRC in the general population

*Increasing incidence of colorectal cancer with age* The age-specific incidence of colorectal cancer in the general population was measured between 1988 and 1992 in men and women of all races. (Data from Surveillance, Epidemiology, and End Results (SEER) Program, 1973-1992.)
# Factors Associated With CRC

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong (RR &gt; 4.0)</strong></td>
<td><strong>Moderate (RR &lt; 0.6)</strong></td>
</tr>
<tr>
<td>Advanced age</td>
<td>High physical activity</td>
</tr>
<tr>
<td>FAP / Lynch syndrome (HNPCC)</td>
<td>Aspirin / NSAID use</td>
</tr>
<tr>
<td>Long-standing UC/Crohn’s colitis</td>
<td><strong>Moderate (RR 2.1 - 4.0)</strong></td>
</tr>
<tr>
<td>High red meat diet</td>
<td>High vegetable / fruit diet</td>
</tr>
<tr>
<td>Previous adenoma or cancer</td>
<td>High fiber diet</td>
</tr>
<tr>
<td>Family history of adenoma or cancer</td>
<td>High folate / methionine intake</td>
</tr>
<tr>
<td><strong>Modest (RR 1.1 - 2.0)</strong></td>
<td>High calcium intake</td>
</tr>
<tr>
<td>High fat diet</td>
<td>Postmenopausal hormone therapy</td>
</tr>
<tr>
<td>Smoking and alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td></td>
</tr>
</tbody>
</table>
Colon Cancer Incidence and Meat Consumption

![Graph showing colorectal cancer cases per 100,000 women against daily meat consumption (grams). Countries are represented by their initials. The graph demonstrates a correlation between higher meat consumption and increased colorectal cancer incidence.]
Environmental Risk - Migrant Effects

Cancer in Japanese Migrants

Colorectal Cancer

Cases per 100,000

Years after migration

Stomach

Colon

Japanese diet

American diet
Does Family History of Colon Cancer matter?
Family History of CRC Increases Risk: 10 Year Shift


Cumulative incidence of CRC (cases/10,000)

- Family history (n = 11,734)
- No family history (n = 107,382)

Family History of CRC

- Risk of CRC depends on the specifics of the family history

  - CRC in 1 FDR
  - CRC in ≥2 FDR relatives

| Relative Risk | 2x (2, 2.5) | 4x (3, 6) |

*FDR= parents, siblings, children*
CRC risk increases with personal and family history of Adenomatous Polyps

Adenomatous polyps are the CRC precursor lesion
Hereditary Colorectal Cancer Syndromes

Identifying these conditions helps determine:

- Who is at risk?
- Who may benefit from genetic evaluation?
Hereditary Colorectal Cancer Syndromes

Cancer presents in two types of settings:

- Multiple polyps: Familial Adenomatous Polyposis (FAP)
- Few (if any) polyps: Lynch Syndrome

Both involve inheritance of gene mutations that are detected in the blood
Risk of Colorectal Cancer

- General population: 6%
- Personal history of Colon polyps: 15%-20%
- Inflammatory bowel disease: 15%-40%
- Lynch Syndrome: 70%-80%
- FAP: >95%

Lifetime risk (%)
Colon Cancer: Is it genetic?

- Are there multiple relatives with CRC or other cancers?
- Were relatives diagnosed with CRC at a young age?
- How old were you when you were diagnosed with CRC?
- Did you have CRC more than once?
- Have you had multiple cancers?
Lynch Syndrome

- Most common hereditary CRC syndrome
  - 3-4% of all CRC
  - Affects 1 in 35 patients with CRC

- Lifetime risk of CRC = 70-80%
  - Risk is markedly lower if colonoscopies begin early
Lynch Syndrome Features

• Striking family history affecting multiple generations
• Early age at CRC diagnosis (mean 45 years)
• Multiple cancers
• Cancers other than the colon:
  – Endometrium
  – Ovary
  – Urinary tract
  – Stomach
  – small bowel
  – sebaceous carcinomas of skin
Lynch Syndrome Results From Failure of Mismatch Repair (MMR) Genes

Base pair mismatch

Normal DNA repair

Defective DNA repair (MMR+)

T C T A C
A G C T G

T C G A C
A G C T G

T C T A C
A G A T G
Need for Specialized Screening

1- CRC occurs at younger ages: start screening at 25 years

2- Rapid growth of polyps and tumors: repeat screening every 1-2 years or consider surgical resection

3- Most cancers happen in the right colon: colonoscopy is test of choice

4- Patients with Lynch Syndrome are at increased risk of other cancers: consideration additional screening
Surgical Management of Colorectal Cancer Risk in Lynch Syndrome

- Consider compliance with screening, efficacy of screening tests, need for surgical resection
- Subtotal colectomy should be considered if patient not candidate for optimal surveillance
- Subtotal colectomy option given risk of second CRC (20% in 10 years)
Surgical Management of Endometrial Cancer Risk in Lynch Syndrome

- Most common extracolonic cancer
- Up to 60% lifetime risk in women
- Prophylactic removal of uterus and ovaries recommended when childbearing is completed
## Associated Lynch Syndrome Cancers

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Surveillance Recommendation*</th>
<th>Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colonoscopy every 1-2 years</td>
<td>20-25 years</td>
</tr>
<tr>
<td>Endometrium/</td>
<td>Transvaginal ultrasound/Endometrial biopsy annually;</td>
<td>30 years</td>
</tr>
<tr>
<td>Ovaries</td>
<td>consider risk reducing TAH/BSO when childbearing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>completed</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>EGD every 2-3 years</td>
<td>30-35 years</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Urinalysis and cytology annually</td>
<td>30-35 years</td>
</tr>
<tr>
<td>Brain</td>
<td>No evidence to support screening</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary Tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
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<td></td>
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</tbody>
</table>
Familial Adenomatous Polyposis

- Classic FAP easily recognizable
- Inherited $APC$ gene mutation
- Risk of cancer is near 100% without surgery
- Risk of extracolonic tumors: upper GI, desmoid, osteoma, thyroid
Management of FAP

- Sigmoidoscopy at 10–12 years and every 2 years to assess polyp burden
- Colectomy
- Upper GI endoscopy for polyps in stomach and small intestine
- Genetic counseling
Prophylactic Colectomy for FAP

• Timing of colectomy:
  – Individualized
  – Depends on:
    • Polyp burden: number, size, advanced histology
    • Family history of CRC onset

• NCCN recommendation
  – Patients be managed by physicians or centers with FAP expertise

• Type of colectomy:
  – Depends on overall polyp burden and rectal involvement
Genetic Evaluation

- Requires a team of
  - genetic counselors
  - Physicians: gastroenterologists and surgeons
  - pathologists
- Draw a complete family tree of three-generations
- Patient Education
- Review medical records and tumor specimens
Rationale for Genetic Testing for Hereditary Cancer Syndromes

- Determine cancer risk
- Make a plan for individualized cancer screening (i.e. endoscopy)
- Test at-risk individuals and family members
CRC Screening in the Asymptomatic Patient: Risk Stratification

### Average Risk
- Age ≥ 50
- No risk factors
- CRC screening age 50

### Moderate Risk
- History of adenomas
- History of CRC
- Family hx of adenomas
- Family hx of CRC

### High Risk
- Inflammatory bowel disease
- Hereditary CRC syndromes

**Colonoscopy**
Polypectomy of Adenoma during Colonoscopy:

Prevents Colon Cancer
Take home message:

• Colorectal cancer is a preventable disease

• Know your family history of cancer
Thank you!

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