Colorectal Cancer Screening

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Why?
Primary Goal is to Prevent Deaths from Colon Cancer

Estimated new cancer cases
U.S. 2011

Estimated New Cases

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon &amp; rectum</td>
<td>141,210</td>
</tr>
</tbody>
</table>

CA Cancer J Clin volume 61; number 4; july/august 2011

Estimated cancer deaths
U.S. 2011

Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon &amp; rectum</td>
<td>49,380</td>
</tr>
</tbody>
</table>

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**Colorectal Cancer Prevention**

- Most cancers develop from adenomatous polyps
- Progression takes ~10 years
- Screening and polyp removal reduces risk of developing CRC by ~90%
  - Cost effectiveness of CRC screening is consistent with other preventive measures

**Colorectal Cancer Survival Rates**

<table>
<thead>
<tr>
<th>Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2002-2006, All Races, Both sexes</th>
<th>Stage Distribution (%)</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to organ/tissue)</td>
<td>29</td>
<td>93.1</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>37</td>
<td>69.2</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>20</td>
<td>11.7</td>
</tr>
<tr>
<td>Unknown (unclassified)</td>
<td>5</td>
<td>33.3</td>
</tr>
</tbody>
</table>

(Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2002-2006. Available online at http://seer.cancer.gov.)

**Colorectal Cancer: Early detection**

- Early detection associated with improved survival rates
- 5 year survival is ~90% for early stage CRC

**Colon Polyps**

- Two thirds of polyps are adenomas
- Adenomas are found in ~25% of colonoscopies performed in people age 50 and in ~45% of people age 70
- Risk of CRC increases with adenoma size, number, villous histology
Polyp Histology

- Tubular adenoma
- Villous adenoma
- Colon cancer

Colorectal Cancer Screening

Who?
- Men and women
- Average person has a ~5% lifetime risk of developing CRC - 90% of these occur in people >50 years old
- Begin at age 50 for average risk

The Downside of CRC Screening Effectiveness

- Only about half of people 50 years or older undergo screening
- Only 4/10 cancers are detected at an early stage
- Lack of public or professional awareness
- Financial barriers

Age specific incidence of colorectal cancer

Colorectal Cancer Screening

Who?
• Increased risk groups begin screening before age 50 and/or are screened more often
• Personal history of CRC or adenomatous polyps
• Personal history of IBD (UC or CD)
• Family history of CRC or polyps (especially first degree relative, multiple relatives, age 60 or younger)
• Family history of hereditary CRC syndrome

How? CRC Screening for Average Risk Individuals

• Begin at age 50 for average risk individuals
• Colorectal cancer prevention should be the primary goal


Primary Care Physician Practices

• 99% of physicians recommend CRC screening to patients (majority colonoscopy)
• Only 61% reported that their practice had implemented guidelines to ensure that eligible adults were offered screening
• Only 30% reported use of any reminder system (eg chart flags or computer prompts)
• Only 12% reported receiving a report about CRC screening rates for their patients
• FOBT performance issues (in-office testing, difficulty with tracking test completion)

Tests that find polyps and cancer

• Flexible sigmoidoscopy every 5 years
• Colonoscopy every 10 years
• Double-contrast barium enema every 5 years
• CT colonography (virtual colonoscopy) every 5 years


## Tests that mainly find cancer

- Fecal occult blood test (FOBT) every year
- Fecal immunochemical test (FIT) every year
- Stool DNA test (sDNA) interval uncertain

**Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology**

## Screening and Surveillance of Increased Risk Patients

- small rectal hyperplastic polyps --- average risk
- 1-2 small (less than 1 cm) tubular adenomas --- colonoscopy at 5-10 years
- 3-10 adenomas or a large (over 1 cm) adenoma or any adenomas with high grade dysplasia or villous features --- colonoscopy at 3 years

**Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology**

## CRC Screening Caveats

- For FOBT and FIT use take-home multiple sample method NOT DRE and stool test [misses >90% of colon abnormalities]
- The best test is the one that the patient will take
- Among all guidelines, there is least consensus on the role of CT colonography and stool DNA testing
- Waning role of barium enema

**2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology**

- Cancer PREVENTION tests preferred over cancer DETECTION tests
- Colonoscopy is the preferred CRC prevention test
- Colonoscopy every 10 years beginning at age 50 is preferred strategy; alternatives for patients who decline colonoscopy are flexible sigmoidoscopy or CT colonography
2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- Screening for African-American persons should begin earlier -- begin at age 45 because of high incidence of CRC and a greater prevalence of right-sided polyps and cancers in this population
- New recommendations for bowel preparation to enhance quality of the exam (split dosing)

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- CT colonography performed every 5 years is an alternative for patients who decline colonoscopy
- Barium enema is not recommended for CRC screening/prevention
- Fecal testing is a cancer DETECTION test, not a PREVENTION test; fecal immunohistochemical testing (FIT) replaces the older guaiac-based fecal occult blood test (FOBT)
- Screening recommendations related to family history are modified from the 2008 guidelines.

Images provided courtesy of Dr. Douglas Rex of IUPUI.

FIT Test Kit

Images provided courtesy of Dr. Douglas Rex of IUPUI.
2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- Key emphasis on QUALITY of colonoscopy
  - Trained examiner
  - Cecal intubation
  - Adenoma detection rate [target 25% in men and 15% in women]
  - Withdrawal times [6 minutes with no biopsies or polypectomies]

- Polyp removal techniques
  - Piecemeal resection requires close follow up
  - After complete exam and adequate prep, follow screening and surveillance intervals
  - Detection rate is not 100%
  - Risks: perforation rate is <1 in 1,000

Specific Screening Tests

- Stool DNA
  - Requires submission of an entire bowel movement (on ice) in customized kit
  - Expensive
  - False negatives do occur
  - Significance of “false positives” unknown (positive screen and negative colonoscopy)
Specific Screening Tests

- CT Colonography
  - Multiple CT images
  - Bowel prep required to reduce false positives created by residual stool
  - Colonoscopy recommended for polyps >6 mm
  - Air insufflation required
  - Diagnostic yield for cancers and polyps over 10 mm is similar to colonoscopy
  - Disadvantages include potential miss of flat polyps, radiation exposure, extracolonic findings

CRC Screening Summary

- Be familiar with and follow consensus recommendations
- Colonoscopy is the preferred screening test
- Any screening is better than no screening
- Screening is not a "one shot" endeavor
- Build system methods to capture the eligible cohort
- Ask about family history
Colon Cancer Screening: Family History Implications

Heather Hampel, M.S., CGC
Professor, Division of Human Genetics
Genetic Counselor
The Ohio State University Comprehensive Center
Arthur G. James Cancer Hospital & Richard Solove Research Institute

Hereditary susceptibility to CRC

Adapted from Burt RW et al. Prevention and Early Detection of CRC, 1996

Flowchart for Hereditary Colon Cancer differential diagnosis

Flowchart for Hereditary Colon Cancer
differential diagnosis

Presence of >10 polyps

Yes

No

Type of polyps

Lynch syndrome

Familial Colorectal Cancer
syndrome type X

MUTYH-Associated Polyposis

Hamartomatous

Adenomatous

Juvenile Polyposis

Peutz-Jeghers syndrome

Hyperplastic Polyposis syndrome

Cowden syndrome/BRR

Familial Adenomatous Polyposis

Attenuated FAP

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Lynch Syndrome

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile duct, sebaceous skin tumors

Lynch Syndrome Management

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1-2 y beginning at age 20-25 (MLH1 &amp; MSH2), or 30 (MSH6 &amp; PMS2)</td>
</tr>
<tr>
<td>Endometrial sampling</td>
<td>Every 1 y beginning at age 30-35</td>
</tr>
<tr>
<td>Transvaginal U/S</td>
<td>Every 1 y beginning at age 30-35</td>
</tr>
<tr>
<td>Urinalysis with cytology</td>
<td>Every 1-2 y beginning at age 25-35</td>
</tr>
<tr>
<td>History &amp; Exam w/ review of systems</td>
<td>Every 1 y beginning at age 21</td>
</tr>
</tbody>
</table>


Lynch Syndrome Cancer Risks (to 70)

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>MLH1&amp; MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer (men)</td>
<td>40-80%</td>
<td>10-30%</td>
<td>20%</td>
</tr>
<tr>
<td>Colon cancer (women)</td>
<td>40-80%</td>
<td>10-30%</td>
<td>15%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>30-60%</td>
<td>15-30%</td>
<td>15%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;13%</td>
<td>&lt; 3%</td>
<td>6%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12-24%</td>
<td>1-11%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Lynch Syndrome Prophylactic Surgery Options

- Options include subtotal colectomy, hysterectomy, and oophorectomy
- Subtotal colectomy does not eliminate cancer risk
- Hysterectomy eliminates risk of endometrial and ovarian cancer
- Expert panels made no recommendation for or against surgery due to unproven efficacy

The Family History Is Key to Diagnosing Lynch Syndrome – or is it?

Amsterdam II criteria
- 3 or more relatives with verified HNPCC-associated cancer in family
- 2 more generations
- 1 case a first-degree relative of the other two
- 1 CRC dx <50
- FAP excluded

Does not include ovarian, gastric, brain, biliary tract or pancreatic cancer

Bethesda Guidelines
- CRC dx <50
- Synchronous or metachronous CRC, or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology dx <60
- CRC with >1 FDR with an HNPCC-associated tumor, with one cancer dx <50
- CRC with >2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age

Warning: Family Histories can be Deceiving
- Family size is getting smaller
- Wider use of colonoscopy likely to prevent many colon cancers
- MSH6 & PMS2 have lower cancer risks
Lynch Syndrome Genes

- **MSH2**, **MSH6**, **MLH1**, **PMS2**

Microsatellite Instability (MSI)

- Repetitive DNA sequences 1-4 nucleotides (microsatellites) normally found genome
  - Mono: TCGAGG AAAAAAAA GGAGCT
  - Di: TCGAGG CACACACACACA GGAG
- With MMR failure, variability in repeats
- 95% of HNPCC tumors are MSI+
- 10%-15% of sporadic CRCs are MSI+

MSI testing on Genotyper

- Immunohistochemistry
  - Identify MMR proteins
  - Normally present
  - If protein is absent, gene is not being expressed (mutation or methylation)
  - Helps direct gene testing by predicting likely involved gene
  - If abnormal IHC (absent), MSI+
Immunohistochemistry

- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+

Identification of Lynch Syndrome among all Newly Diagnosed CRC Patients

- Unlikely to have good family history
- High volume
- Pathologists will know age at dx, synchronous primaries, but not likely to know all metachronous primary or family history of patients
- Must rely on screening tests for LS (MSI/IHC)

Identification of Lynch syndrome in the Genetics Clinic

- Can predict who is more likely to have LS using family history criteria (Amsterdam & Bethesda)
- Can predict the likelihood of a MMR gene mutation using on-line programs
  - PREMM1,2
  - MMRpro
    http://www4.utsouthwestern.edu/breasthealth/cagene/
  - MMRpredict
    http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php
- Can order MSI and/or IHC on tumor to screen for LS
- Can diagnose Lynch syndrome with genetic testing
Columbus-Area Lynch syndrome Study

Colorectal cancer
Total accrued N = 1600
Testing completed N = 1566

MSI positive (high & low)
N = 307 (19.6%)

Colorectal cancer
Testing completed N = 1566

MSI negative
N =1259 (80.4%)

Sequence MLH1, MSH2, MSH6
Immunohistochemistry
Methylation of MLH1 promoter

Mutation positive
N = 44* 2.8% (1/35)
*2 had MSI- tumors

Mutation result not yet interpretable
N =55 3.5%

Mutation negative or polymorphism found
N =209 13.4%


Family Studies of 35/44 CRC Probands

35 CRC probands have had genetic counseling

Degree of Kinship | Tested | Positive
--- | --- | ---
First | 99 | 52
Second | 64 | 28
> Second | 86 | 29
Total | 249 | 109


44 CRC Proband Characteristics

- Age at diagnosis – 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria
- Mutations
  - 20.5% MLH1
  - 52.3% MSH2
  - 13.6% MSH6
  - 13.6% PMS2


Familial Colorectal Cancer syndrome type X

- ~40% of families that meet Amsterdam I criteria do not have an MMR gene mutation
- Only have increased risk for CRC
- CRC risk is lower than among families with MMR gene mutation (SIR 2.3 v 6.1)
- No testing available at this time
- Colonoscopy at least every 5 years beginning 5-10 years before the earliest CRC diagnosis in the family

MUTYH-Associated Polyposis (MAP)

- Recessive – carrier frequency high (1/100)
- Biallelic mutations found in;
  - ≤ 1/3 of polyposis cases without APC mutations or evidence of vertical transmission
  - 0.2-6.7% of CRC dx <50 without polyps
- Y165C & G382D common in W.E. Caucasians
- E466X in Eastern Indian families

MAP Management

- Colonoscopy every 1-2 y begin at 25-30
- UGI endoscopy and side viewing duodenoscopy every 3-5 y begin at 30-35
- Subtotal colectomy or proctocolectomy depending on adenoma density and distribution
Familial Colorectal Cancer Risks

**Screening Recommendations**

- **FDR diagnosed <50**
  - Colonoscopy every 3-5 years beginning at age 40
- **FDR diagnosed 50-60**
  - Colonoscopy every 5 years beginning at age 40
- **FDR diagnosed >60**
  - Colonoscopy every 5 years beginning at age 50
- **Otherwise follow Average Risk recommendations**

**GINA**

- Prevents health insurers from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.
  - Group and self-insured policies
- Insurers may not request that an individual undergo a genetic test.
- Employers cannot use genetic information to make hiring, firing, compensation, or promotion decisions.
- Sharply limits a health insurer's or employer's right to request, require, or purchase someone's genetic information.

**Resources**

- Heather Hampel
  - 614-293-7240
  - Heather.Hampel@osumc.edu
- **Family HealthLink**
  - https://familyhealthlink.osumc.edu
  - Free, on-line tool that assesses family history of cancer and cardiovascular disease