Colorectal Cancer: Screening & Prevention

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Learning Objectives

1. Review principles of colon adenoma/cancer biology that permit successful prevention regimes

2. Describe pros/cons of screening interventions (including colonoscopy, CT colography, fecal tests)

3. State current national recommendations for colon cancer screening in average risk and selected high risk populations
COLORECTAL CANCER – Scope of the Problem

• #2 cause of cancer mortality overall
• #3 in women (after lung, breast)
• #3 in men (after lung, prostate)

<table>
<thead>
<tr>
<th>New diagnosis</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>71,830</td>
</tr>
<tr>
<td>Women</td>
<td>65,000</td>
</tr>
</tbody>
</table>

U.S. 2014 incidence/prevalence (NCI/SEER)

Sieg CA Cancer J Clin 2014;64:104-17
COLORECTAL CANCER – Scope of the Problem

- Lifetime CRC risk: ~ 5%
- 5-yr U.S. survival (2009): 65% overall
  - 90% localized
- Steady ↓ in death rates since mid-1980’s:
  - ↑ screening
  - Better treatments
COLORECTAL CANCER – Risk Factors

- Age (90% ≥ 50 yrs old, avg age at dx 66)
- Obesity / physical inactivity / diabetes
- Long-term smoking
- Diet: high in red or processed meat, low in fruits and vegetables
- Personal history of colorectal cancer/polyps
- Inflammatory bowel disease
- Family history of colorectal cancer or polyps
- Inherited: Lynch syndrome, FAP

15-30% of CRC

http://seer.cancer.gov/
Oncoscience 2014; 1:400.
CRC Pathogenesis – Multiple Pathways

A. Chromosomal Instability (CIN) Pathway
- APC loss
- K-ras and other oncogenes
- 18q LOH

Normal Epithelium → Early Adenoma → Late Adenoma → Cancer

B. Microsatellite Instability (MSI) Pathway
- APC loss
- Failure of MMR genes
- TGFβRII, BAX and other mutations

Normal Epithelium → Adenoma → Cancer

C. Serrated Pathway
- BRAF mutation
- DNA methylation
- TP53, p16 inactivation, LOH

Normal Epithelium → Serrated Adenoma → Cancer
Can We Prevent Colon Cancer Deaths?

Benign Polyps
Colon Cancers
Primary Prevention of Colorectal Cancer

“Doc, Can I Just Eat Better?”

- Diet (less red meat, more fiber)
- Regular exercise, stop smoking
- Medications: aspirin / NSAIDs
  - calcium
  - post-menopausal HRT
  - statins
  - anti-oxidants (no)
- Bottom Line: Not Ready for Prime Time
## Screening Tests for Colorectal Cancer

<table>
<thead>
<tr>
<th>Tests That Detect Cancers</th>
<th>Test That Detect Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Early Cancer Detection)</em></td>
<td><em>(Cancer Prevention)</em></td>
</tr>
<tr>
<td>Fecal testing for blood</td>
<td>Colonoscopy</td>
</tr>
</tbody>
</table>
| Fecal DNA testing | CT colography  
  *(virtual colonoscopy)* |
| | Air-contrast barium enema |
| | Flexible sigmoidoscopy |
Colonoscopy

• Introduced 1969
• Most widely used colon cancer screening test
• 14 million performed annually
  • ~ 50-70% CRC screening/surveillance
• Allows visualization of rectum, entire colon ± distal TI
• When properly performed . . . safe, accurate, and well tolerated by most patients
Colonoscopy

- Gold standard for colon cancer screening since Medicare coverage 1998
- IV sedation / full bowel prep
- Flexible lighted tube with camera
- Examines entire colon
- Polyps removed during procedure – “one-stop shopping”
Polyp Removal During Colonoscopy
So Does Colonoscopy Really Work? (prevent cancer, save lives)

- National Polyp Study (NPS)
  - 1417 patients with $\geq 1$ adenoma removed
  - Mean follow-up of 5.9 years
  - 76, 88 & 90% reduction in colon cancer incidence vs. three reference groups
- 16-yr follow-up of 2602 NPS center patients 53% reduction in colon cancer mortality after removal of 1 or more adenomatous polyps

Impact of Screening Colonoscopy

• 2001-2010
  • Colorectal cancer incidence ↓ 3.4%/year

| Screening Colonoscopy Utilization in U.S. Adults Aged 50-75 |
|---------------|-----|
| 2000          | 19% |
| 2010          | 55% |

Siegel CA Cancer J Clin 2014;64:104-17
Limitations of Colonoscopy

- Invasive
- Potential for physical discomfort
- IV sedation (miss work, need chaperone)
- Most expensive method of screening
- Patients don’t like bowel prep
- Small risk of serious complications (bleeding, perforation)
- Not perfect: up to 10% polyps > 1cm missed
Colonoscopy. . . not everybody seems to want one

- Screening rates historically low (<breast / cervical)
  - 63% of adults > age 50 screened by any means
- Public uninformed and/or resistant
- Concerns about ... bowel prep, pain, indignity
- Too many options in guidelines?

CDC Behavioral Risk Factor Surveillance Survey 2008
Limitations of Colonoscopy
We may not be as good as we think we are . . .

• “Interval cancers” after screening colonoscopy
  • Canadian administrative claims study
  • Colonoscopy decreased death from CRC in left colon but not the right
  • Most CSP performed by non-gastroenterologists

• It matters who does your colonoscopy (operator-dependent)
  • Cancer miss rates: 3% for GI vs. 13% for non-GI
  5% one GI group vs. 1% all other GI
• Intensified awareness of flat/subtle/atypical right-sided polyps
• Renewed emphasis on scrupulous prep and technique
Emphasis on Quality Indicators in Colonoscopy
Thorough Inspection = Increased Lesion Detection

• High-quality bowel preps
• Cecal intubation ≥ 95% in screening cases
• Mean withdrawal time without intervention ≥ 6 minutes . . .*don’t rush!*
• Adenoma detection rate (ADR) in asymptomatic screening patients
  >age 50, adenomas should be detected in:
  ≥ 25% men
  ≥ 15% women

Froelich Gastrointest Endosc 2005 Mar;61(3):378-84
Alternative Screening: Barium Enema

- Once common, now rarely performed
- Examines entire colon, cheaper than colonoscopy, less complications
- Colonoscopy needed for all positive studies
- Poor sensitivity
  - For cancer (83%)
  - For polyps > 1cm (50%)
- Not proven to prevent colon cancer
Alternative Screening: Flexible Sigmoidoscopy

- Examines lower third of colon
- No sedation / enema prep only
- Can be done by ML or PCP
- CRC mortality
  - ↓ 67% in examined area
  - ↓ 80% if polyps prompt colonoscopy
- Usage plummeted with screening colonoscopy
CT Colography

• CT scan w/ extensive 3D image reconstruction
• Equals traditional colonoscopy for detecting cancers and polyps > 1cm
• Still not covered by Medicare
• Current indications:
  • Failed colonoscopy
  • Patients unable to undergo colonoscopy

## CT Colography (vs. Colonoscopy)

<table>
<thead>
<tr>
<th>Cons</th>
<th>Pros</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still requires bowel prep and enema tube</td>
<td>Image acquisition takes few seconds only</td>
</tr>
<tr>
<td>Poor detection small- and medium-sized polyps</td>
<td>Less invasive</td>
</tr>
<tr>
<td>Colonoscopy still required if medium/large polyps found</td>
<td>No IV / sedation</td>
</tr>
<tr>
<td>Cost-efficacy unproven</td>
<td>Safer (but not without risk)</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>Cheaper</td>
</tr>
<tr>
<td>Extra-colonic findings</td>
<td>Patient Preference</td>
</tr>
</tbody>
</table>
Alternative Screening: Fecal Tests

• Stool guaiac
  • 3 stool samples
  • 32% ↓ CRC mortality over 30 yrs with annual testing
  • High false positive rate ➔ many unnecessary tests

• Fecal immunohistochemical test (FIT) for hemoglobin
  • Only 1-2 samples needed
  • Higher sensitivity/specificity
  • Higher cost

Lee Ann Intern Med 2014;160:171
Alternative Screening: Fecal DNA Testing

- 2nd generation test (Cologuard™)
- Approved August 2014
- FIT + multi-target DNA composite:
  - DNA via gene amplification
  - Hemoglobin
  - DNA methylation patterns
- Detects cancers and (some) advanced adenomas

Imperiale *N Engl J Med* 2014;370:1287
## Alternative Screening: Fecal Tests

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity for Colon Cancer</th>
<th>Sensitivity for Large Adenomas</th>
<th>Specificity for either</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>74%</td>
<td>24%</td>
<td>95%</td>
</tr>
<tr>
<td>FIT-MT DNA</td>
<td>92%</td>
<td>42%</td>
<td>87%</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>97-100%</td>
<td>90-100%</td>
<td></td>
</tr>
</tbody>
</table>
Colon Cancer Screening Guidelines

- Multiple “competing” guidelines published in 2008
- All agree: offer screening to average risk individuals beginning at age 50
- After that . . .
U. S. Preventive Services Task Force

• Simulation decision model
• Identifying premalignant lesions (prevention) not valued over cancer detection
• For adults aged 50-75, three screening strategies:
  • Annual FOBT
  • Flex Sig every 5 yrs + FOBT every 3 yrs
  • Colonoscopy every 10 yrs
• Insufficient evidence for CT colography, fecal DNA, ACBE
American Cancer Society/Multi-Society Task Force

- More inclusive list of recommended tests
  - No test unequivocally superior
  - “the best test is the one patients will take”
  - Incorporating patient preferences may ↑ rates of screening
- Stop screening when estimated life expectancy < 10 years

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<th>Strategies Endorsed for Early Detection + Prevention</th>
<th>Strategies Endorsed for Early Detection</th>
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<tr>
<td>Colonoscopy every 10 yrs</td>
<td>FOBT (guaiac) annually</td>
</tr>
<tr>
<td>CT colography every 5 yrs</td>
<td>FIT annually</td>
</tr>
<tr>
<td>Flex Sig every 5 yrs</td>
<td></td>
</tr>
<tr>
<td>ACBE every 5 yrs</td>
<td></td>
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Levin CA Cancer J Clin 2008;58:130
American College of Gastroenterology

• Endorsed all options in ACS-MSTF guideline, but . . .
• Colonoscopy designated as “preferred strategy” for screening/cancer prevention
• FIT “preferred strategy” for screening/cancer detection for patients who “decline a cancer prevention test”
• Screening ends at age 75
• Recommend begin screening at age 45 in African-Americans
American Cancer Society – May 2018 Update

• Lower age of initial screening to 45
• Screen till age 75 unless life expectancy < 10 years
• Individualize between 75-85 based on health, preferences
• No screening after age 85

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<tr>
<td>Flex Sig every 5 yrs</td>
<td>Multi-target fecal DNA every 3 yrs</td>
</tr>
<tr>
<td>ACBE every 5 yrs</td>
<td></td>
</tr>
</tbody>
</table>
# What Does Medicare Currently Cover?

<table>
<thead>
<tr>
<th>Test</th>
<th>Coverage Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal Occult Blood or FIT</td>
<td>annually</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>every 4 years, or 10 years after a previous colonoscopy</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>every 10 years, or 4 years after a previous flexible sigmoidoscopy</td>
</tr>
<tr>
<td>Barium Enema</td>
<td>every 4 years (if done instead of colonoscopy or flexible sigmoidoscopy)</td>
</tr>
<tr>
<td>Multi-target fecal DNA</td>
<td>every 3 years</td>
</tr>
</tbody>
</table>

Not covered: CT colography

www.cancer.org/healthy/findancerarely/cancerscreeningguidelines
### Follow-Up Intervals After Surveillance Colonoscopy

<table>
<thead>
<tr>
<th>Baseline colonoscopy: most advanced finding(s)</th>
<th>Recommended surveillance interval (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>1–2 small (&lt;10 mm) tubular adenomas</td>
<td>5–10</td>
</tr>
<tr>
<td>3–10 tubular adenomas</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
<td>3</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>3</td>
</tr>
<tr>
<td>Adenoma with HGD</td>
<td>3</td>
</tr>
<tr>
<td>Serrated lesions</td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10 mm with no dysplasia</td>
<td>5</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) ≥10 mm</td>
<td>3</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp with dysplasia</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Serrated polyposis syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Serrated polyposis syndrome is no longer recommended as a surveillance interval.
What About After the First **Surveillance** Exam?

<table>
<thead>
<tr>
<th>Findings at Baseline Colonoscopy</th>
<th>Findings at 1st Surveillance</th>
<th>Interval for 2(^{nd}) Surveillance (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk Adenoma (LRA)</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td>- 1-2 adenomas</td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td>- &lt; 10mm in size</td>
<td>No adenoma</td>
<td>10</td>
</tr>
<tr>
<td>High Risk Adenoma (HRA)</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td>- 3 or more adenomas</td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td>- Advanced Adenoma(s)</td>
<td>No adenoma</td>
<td>5</td>
</tr>
<tr>
<td>• ≥ 10mm in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <em>high grade dysplasia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <em>villus histology</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*US Multi-Society Task Force Update*

Lieberman et al *Gastroenterology* 2012:143:844
## Surveillance – Increased Risk Patients

### Family History of Colorectal Cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age to Begin Colonoscopy</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single FDR with CRC or advanced adenoma* at age ≥ 60</td>
<td>40</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>Singe FDR with CRC or advanced adenoma at age &lt; 60 or Two FDR with CRC or advanced adenoma at any age</td>
<td>Age 40 or 10 yrs younger than youngest affected relative</td>
<td>Every 5 years</td>
</tr>
</tbody>
</table>

*Advanced adenoma = adenoma ≥ 1cm in size, or HGD, or villous histology
### Surveillance – Increased Risk Patients

**Hereditary Syndromes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age to Begin Colonoscopy</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic FAP (Familial Adenomatous Polyposis), Gardner’s</td>
<td>At diagnosis</td>
<td>Annually, until colectomy</td>
</tr>
<tr>
<td>Lynch Syndrome(s)</td>
<td>Age 20-25</td>
<td>Every 2 yrs, annually after age 40</td>
</tr>
</tbody>
</table>

*Rex Am J Gastroenterol 2009;104:739*
Surveillance – Increased Risk Patients
Inflammatory Bowel Disease

• After 8-10 yrs of colitis annual or biannual colonoscopies with multiple biopsies at regular intervals

• HGD in flat mucosa, confirmed by an expert pathologist, is an indication for colectomy

• LGD in flat mucosa may also be an indication for colectomy

• Emerging alternative: chromoendoscopy with biopsy of detected abnormalities
Surveillance – Increased Risk Patients
After Colon Cancer Resection

- Initial surveillance colonoscopy 1-yr post-op
- 2\textsuperscript{nd} surveillance colonoscopy 3 years later (4 yrs post-op)
- 3\textsuperscript{rd} surveillance colonoscopy 5 years later (9 yrs post-op)... and every 5 yrs thereafter, till surveillance not appropriate

\textit{US Multi-Society Task Force}

\textit{Am J Gastroenterol} advance online publication, 12 February 2016; doi:10.1038/ajg.2016.22
In Conclusion . . .

• Colorectal cancer is a serious national health problem and largely preventable
• Colon cancer rates are decreasing, most likely due to increased screening
• Colonoscopy is the dominant and most effective form of screening, but many patients resist having one
• Beneficial screening and cancer detection alternatives exist, and any screening is better than no screening
• Start screening at age 50, earlier in high risk patients
Thanks for your attention!