Colorectal cancer screening: Is total prevention possible?

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UCSF Primary Care Update 2010

Just the facts - colorectal cancer

• 2009 NCI estimates for US:
  • 146,970 new CRC diagnoses
  • 49,920 CRC deaths
• 3rd leading cause of cancer in men and women
• 2nd leading cause of cancer death in men and women
• Over 90% 5-year survival when caught early
• Under 40% are caught early


Something for everyone

• Gender
• Age
• Lifestyle
• BMI
• Ethnicity
CRC incidence rates 2002-2006

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>57.3 per 100,000 men</td>
<td>42.8 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>55.0 per 100,000 men</td>
<td>42.1 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>60.1 per 100,000 men</td>
<td>53.5 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>46.9 per 100,000 men</td>
<td>34.6 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>42.1 per 100,000 men</td>
<td>41.2 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>46.3 per 100,000 men</td>
<td>32.2 per 100,000 women</td>
</tr>
</tbody>
</table>

Overall CRC incidence: 50 per 100,000 per year


More about gender

- Men with slightly higher CRC incidence and mortality
- Women with lower adenoma detection rates than men
- Women with more proximal adenomas and colon cancers
- Women are diagnosed with CRC at older ages by average 1.9-3.4 years

We’re doing something right

- CRC incidence and mortality declining
  - Influence of treatment?
  - Influence of diet and lifestyle?
  - Influence of screening?
- Overall 5-year survival about 65% (SEER data)
  - 30-35% in China and Eastern Europe
Colorectal cancer incidence has decreased by 30% since 1985.

Colorectal cancer mortality has declined by 36.5% since 1985.

Colorectal cancer mortality has declined by 36.5% since 1985.

What happened here?
The Katie Couric effect

The impact of a celebrity promotional campaign on the use of colon cancer screening: the Katie Couric effect.

Cram P, Fendrick AM, Inadomi J, Cowen ME, Carpenter D, Vijan S

The rate of colonoscopy screening went up 20-40% after her nationally televised colonoscopy.

What are we doing right?

Estimated influences on declining CRC mortality

- Screening
- Modified risk factors
- Improved treatment

Edwards BK, Cancer, 2009
CRC screening v1.0

- Stool occult blood testing
  - Only method proven in randomized trials to decrease colorectal cancer incidence and mortality
  - 33% decrease in mortality with annual use
  - 20% decrease in colorectal cancer incidence with annual use
  - Detects cancers at earlier stages than controls
  - Limited in test characteristics and adherence


CRC Screening v2.0

- Flexible sigmoidoscopy
  - Case-control data show 60% decrease in mortality from colorectal cancer
  - Mortality benefit confined to distal colon
  - 30% of proximal advanced adenomas missed
  - Assumes L colon pathology predicts R colon pathology
  - In women miss up to 2/3 of lesions this way

Selby J, et al. NEJM, 1992
Lieberman DA, et al. NEJM, 2000
Schoenfeld P, et al. NEJM, 2005

CRC screening v3.0

- Colonoscopy
  - More sensitive than other tests (>90%)
  - One stop shopping
  - National Polyp study
    - 75-90% reduction in CRC relative to expected rate
  - Higher complication rate than other tests
  - Most costly of all the screening tests

Winawer SJ, et al, NEJM 1993
### Colon cancer mortality reduction

<table>
<thead>
<tr>
<th>Modality</th>
<th>Odds ratio Distal colon cancer Mortality</th>
<th>Odds ratio Proximal colon cancer Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible sigmoidoscopy¹</td>
<td>0.41 (0.25-0.69)</td>
<td>0.96 (0.61-1.50)</td>
</tr>
<tr>
<td>Colonoscopy²</td>
<td>0.33 (0.28-0.39)</td>
<td>0.99 (0.86-1.14)</td>
</tr>
</tbody>
</table>

¹Selby JV, et al. NEJM, 1992
Endoscopy is really good. However, it may fall short.
Tale of 2 tunnels

• Even colonoscopy appears to be limited in the proximal colon relative to the distal colon
• Why the difference?
  ▫ Technical difficulty of inspection in R colon
  ▫ Inferior bowel prep
  ▫ Inferior practitioners
  ▫ Flat polyps
  ▫ Gender differences
  ▫ Separate biology

normal mucosa → adenoma → carcinoma

R colon > L colon
Flat/depressed > polypoid

normal mucosa → adenoma → carcinoma
Where do we go from here?

<table>
<thead>
<tr>
<th>Modality</th>
<th>Interval</th>
<th>ACS-MSTF</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoccult II</td>
<td>1 year</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>High-sensitivity Hemoccult or fecal immunochemical test</td>
<td>1 year</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>5 years</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CT colonography</td>
<td>5 years</td>
<td>Yes</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>10 years</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stool DNA testing</td>
<td>5 years</td>
<td>Yes</td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>


Stool testing

- Fecal occult blood testing (FOBT)
- Fecal immunochemical testing (FIT)
- Fecal DNA

“Cancer detection tests”
FOBT

- Detects heme within stool
- Poor sensitivity for cancer (25-38%)
- Low positive predictive value (under 5-15%)
- Dietary restrictions
- Positive with occult bleeding from anywhere in GI tract
- Cost – low
- Convenience/safety – high
- Evidence – high

An aside - no DRE for CRC

- Digital rectal exam is not an established colorectal cancer screening test.
- FOBT obtained on DRE has high false positive rate
- Though digital exam can be useful as part of a physical exam in men (prostate exam), a digital exam should not be used as a proxy for formal colorectal cancer screening

FIT

- EIA for fecal globin (the protein of hemoglobin)
- Good sensitivity for cancer (61-91%)
- Excellent specificity (91-98%)
- Not affected by diet
- Specific for bleeding in lower GI tract
- Cost - low (higher than FOBT)
- Convenience/safety - high
- Evidence - low

Fecal DNA

- PCR test that checks for mutations in DNA found in stool
- Fair sensitivity for cancer (50%)
- Excellent specificity
- Cost - moderate (higher than FOBT or FIT)
- Convenience/safety - high
- Evidence - low

Endoscopy

- Flexible sigmoidoscopy
- Colonoscopy

“Cancer prevention tests”
Flexible sigmoidoscopy

- Exam to splenic flexure
- Ability to detect, biopsy, and remove polyps
- Specificity high
- Sensitivity 90-100% L colon, 70% overall (with reflexive colonoscopy if polyp found)
- More sensitive in men than women
- Cost – moderate
- Convenience/safety – moderate
  - 0.34 serious complications/1000 pts
- Evidence – moderate
Colonoscopy

- Whole colon exam
- Specificity high (nearly 100%)
- Sensitivity high (90% for advanced adenomas)
- Cost – high
- Convenience/safety – low
  - 2-4 serious complications/1000 patients

Ko CW et al Clin Gastroenterol Hepatol, 2010
- Evidence – moderate

Whole colon imaging

- Double contrast barium enema
- CT colonography (virtual colonoscopy)
Double-contrast barium enema

- Low sensitivity (48% adenomas >1cm)
- Unsedated
- Radiation exposure
- No longer recommended for routine screening
- Exceptions:
  - Nothing else available
  - No other imaging feasible or reasonable

Winawer SJ et al. NEJM 2000
CT colonography

- Total colon study
- Comparable to colonoscopy
  - 90% sensitive for polyps >1cm
- Requires follow-up testing
- Optimal intervals?
- Will not detect “flat polyps”
- Radiation risk – cancer from 1/1000 exposures?
- Extracolonic findings – 7-16%

CT colonography

- Cost – high
- Convenience/safety – moderate
  - Bowel preparation required
  - Air insufflation/discomfort
  - Radiation
  - Perforation rate low but not zero
- Evidence – low
Is total prevention possible?

• Identify who is at risk
• Effective treatment for pre-cancer
• Overcoming barriers
• Improving colonoscopy
• Optimal screening study
• Optimal screening intervals

Impact of family history on risk

• Average risk 5.2% lifetime risk

<table>
<thead>
<tr>
<th>Family members affected</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative, any age</td>
<td>1.91 (1.82-2.00)</td>
</tr>
<tr>
<td>First degree relative &gt;50</td>
<td>2.02 (1.93-2.11)</td>
</tr>
<tr>
<td>First degree relative &lt;50</td>
<td>3.31 (2.79-3.89)</td>
</tr>
<tr>
<td>2 first degree relatives, any age</td>
<td>3.01 (2.66-3.38)</td>
</tr>
<tr>
<td>Second degree relative only, no 1st degree</td>
<td>1.05 (0.99-1.11)</td>
</tr>
</tbody>
</table>

“Dose response”: your risk associated with number, age, and “degree” of your affected relatives

Taylor et al, Gastroenterol, 2010

Impact of family history on risk

• Only 15% of patients with colorectal cancer have an affected 1st or 2nd degree relative
• Do we need to be more inclusive?
  • HNPCC: endometrial, gastric, pancreatic, small bowel, biliary, ovarian, urothelial, brain, skin
  • Family history of polyps?
    • Advanced adenomas in 1st degree relative RR=2
    • Non-advanced adenoma in 1st degree relative NO increased risk

Cottet, Gastroenterol, 2007
Lifestyle risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect on CRC risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Increased</td>
</tr>
<tr>
<td>Alcohol &gt;2 drinks per day (men) or &gt;1 drink per day (women)</td>
<td>Increased</td>
</tr>
<tr>
<td>Diet high in red meat or processed foods</td>
<td>Increased</td>
</tr>
<tr>
<td>Diet high in fruits and vegetables</td>
<td>Decreased</td>
</tr>
<tr>
<td>Active lifestyle</td>
<td>Decreased</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Disease risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect on CRC risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of polyps or CRC</td>
<td>Increased</td>
</tr>
<tr>
<td>Family colon cancer syndrome</td>
<td>Increased</td>
</tr>
<tr>
<td>Ulcerative colitis or Crohn’s disease</td>
<td>Increased</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity</td>
<td>Increased</td>
</tr>
<tr>
<td>Prior pelvic irradiation</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Can symptoms help?

- Correlation of GI symptoms and colon cancer is poor
  
  Katsalidis P. Word Congress of Gastroenterology, 2009

- Majority of colon adenomas and cancers asymptomatic
Effective treatment for pre-cancer

- Polypectomy – National Polyp Study, Winawer, NEJM, 1993
- Chemoprevention
  - NSAIDs, Chan AT, JAMA, 2005
  - Vitamins
    - Folic Acid
    - Calcium
    - Vitamin D
    - Vitamin B6
  - HRT – RCT and meta-analysis – decreased CRC
    but incr breast CA, thrombotic/embolic events

Overcoming Barriers

- Adherence
- Manpower
- Access
- Cost

Adherance

- Only 60.8% of >50 screened as of 2006
- Demystifying
  - Thank you Katie!
  - Herd effect
- Increase convenience
  - Offer a buffet of options
- Inreach/outreach
Manpower

- Who can deliver depends on type
  - FIT: anybody
  - Flexible sigmoidoscopy: Nurse, PA, non-GI MD, or GI MD
  - Virtual colonoscopy: radiologist
  - Colonoscopy: GI MD (US) or MD
- Do we have enough?
  - Estimates suggest we neither have nor are training enough GI docs to be the sole screeners

Source: Seeff LC, et al, Gastroenterol, 2004

Access

- CRC screening rates in US:
  - whites > minorities
  - High/middle income > low income
- Coverage issues
  - Insured
    - need to cover all modalities without deterrents (eg high copays)
  - Uninsured
    - Where do they get their screening?
    - Where do they get their screening followed-up?

Source: Philips KA, Med Care, 2007

Cost

- Relative cost of each modality
  - Stool testing
  - FOBT
  - FIT
  - Fecal DNA
  - Sigmoidoscopy
  - Colonoscopy
  - CT colonography
- In this country, you need insurance to be screened endoscopically
- As cost comes down, will access come down with it?
- CRC expenditures expected to decline, while overall health spending to screen could increase $0.8-2.8 billion per year

Source: Ladabaum U, Gastroenterol 2005
Improving colonoscopy

- Split-dose bowel preparations
- Practitioner quality
  - Training
  - Withdrawal time
  - Adenoma detection rate
- Improved optics
  - High-definition endoscopes/monitors
  - Narrow band imaging
  - Confocal microscopy
  - 3rd eye retroscope

Optimal screening study

- Average risk screening: the list of options approach
  - Highly sensitive fecal testing annually
  - Flexible sigmoidoscopy every 5 years
  - Colonoscopy every 10 years
  - Start age 50, stop age 75
Optimal screening interval

- 10 years too many?
  - Adenoma-to-carcinoma sequence 10 years
  - Multiple studies have now shown that the risk of cancer or advanced adenoma is extremely low
- When do risk outweigh benefits
- When to start
- When to stop


Who should we screen before 50?

- Strong family history: start age 40 or 10 yrs prior to youngest 1st degree relative, then q 5 yrs
  - 1st degree relative under 60 with CRC or advanced adenoma
  - Multiple 1st degree relatives of any age CRC/AA
- Familial colorectal cancer syndromes (various)
- Chronic inflammatory bowel disease: q 2-3 yr starting 10 yrs after disease onset
- Blacks: start age 45

Why stop?

- Risk appears to exceed benefit at some point
  - Life expectancy should be >5 years because screening doesn’t improve mortality until then
  - Screening ages >80 yields less than 1/6 the life-years gained compared to screening ages 50-54
- We overscreen sick 80+ and underscreen healthy 60-75

Lin OS, et al. JAMA, 2006

When to stop?
• Most should stop at 75 (USPSTF)
• Prior adenomas/cancer should stop at 80
• If never screened, consider single time screening
  75-80
• No screening/surveillance beyond 85

Is total prevention possible?
• Not with current setup:
  ▫ Optimal screening intervals still not clear
  ▫ No totally accurate test
  ▫ Screening not available to all
  ▫ Screening not desired by all
  ▫ Certain people inappropriate to screen
    • However, cancers still sporadically show up in
      inappropriate populations

Death from CRC should be preventable
• Very treatable if found early
• Combination of 2 different total colon studies
  (stool test and/or blood test plus total colon imaging)
• Better risk stratification
• More resources/manpower/access
CRC screening v4.0

- The “post-colonoscopy screening” era
  - Better risk stratification
  - Serum markers
  - Enhanced fecal testing for average risk
    - Fecal immunochemical testing plus fecal DNA
  - Enhanced colonoscopy
  - Capsule colonoscopy
  - Virtual colonoscopy without radiation
Can we imagine this curve?