Colorectal Cancer Screening and Aspirin for Prevention

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Trends in Incidence and Mortality For Colorectal Cancer

Outline

• What’s the best colorectal cancer screening test?
• Aspirin chemoprevention
• Are endoscopy and aspirin complementary?
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• What’s the best colorectal cancer screening test?
• Aspirin chemoprevention
• Are endoscopy and aspirin complementary?
# U.S. Preventive Services Task Force Recommendations for CRC Screening

<table>
<thead>
<tr>
<th>Adults Age 50-75 Years</th>
<th>Adults Age 76-85 Years</th>
<th>Adults Older than 85 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen with high-sensitivity FOBT (annual), Sigmoidoscopy (5 years) + HS-FOBT (3 years), or Colonoscopy (10 years)</td>
<td>Do not screen routinely</td>
<td>Do not screen</td>
</tr>
<tr>
<td>Grade: A</td>
<td>Grade: C</td>
<td>Grade: D</td>
</tr>
</tbody>
</table>

For all populations, evidence is insufficient to assess the benefits/harms of screening with CT colonography and fecal DNA testing

Grade: I (Insufficient evidence)
# Effect of Screening Intervention on Reducing Mortality from Colorectal Cancer

<table>
<thead>
<tr>
<th></th>
<th>Fecal Occult Blood Test</th>
<th>Sigmoidoscopy</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>RCTs</td>
<td>Case-control studies; RCTs</td>
<td>Case-control studies, RCTs in progress</td>
</tr>
<tr>
<td><strong>Magnitude of Effects</strong></td>
<td>15%-33%</td>
<td>About 60%-70% for left colon</td>
<td>About 60%-70% for left colon; uncertain for right colon</td>
</tr>
<tr>
<td><strong>Invasiveness</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

http://www.cancer.gov/cancertopics/pdq/screening/colorectal/HealthProfessional
The Effect of Screening Intervals on Cancer Detection

Fast-growing cancers

Slow-growing cancers

Years

0 1 2 3 4 5 6 7 8 9 10
Outcomes for the Recommendable Set of Screening Strategies/MISCAN

Beginning tests at age 50, ending tests at age 75, per 1,000 people

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Colonoscopies</th>
<th>Life Years Gained per 1,000 people</th>
<th>Incidence Reduction</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>4136</td>
<td>230</td>
<td>51.9%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Hemoccult SENA</td>
<td>3350</td>
<td>230</td>
<td>49.7%</td>
<td>66.0%</td>
</tr>
<tr>
<td>FIT</td>
<td>2949</td>
<td>227</td>
<td>47.2%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>1911</td>
<td>203</td>
<td>46.8%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Flexible Sig + SENA</td>
<td>2870</td>
<td>230</td>
<td>51.2%</td>
<td>65.7%</td>
</tr>
</tbody>
</table>

Zauber, *Annals of Internal Medicine*  
4 Nov 2008
The most effective colorectal cancer screening test is the one you are willing to take.
Compliance to FIT vs. Colonoscopy: First Round of a Spanish Randomized Trial

- Households randomly assigned to either biennial FIT or 1-time colonoscopy
- Randomization performed before invitation
- Invitation letters sent with reminders at baseline, 3 months, and 6 months
- 57,404 Randomized, 1st Round

Compliance/Acceptance Rates
- FIT 34.2%
- Colonoscopy 24.6%
- OR=0.63  p <.001

Quintero, N Eng J Med, 23 Feb 2012
# Colonoscopy vs. FIT: First Round Detection in the Spanish Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Colorectal Lesion</th>
<th>Colonoscopy (N = 26,703)</th>
<th>FIT (N = 26,599)</th>
<th>Odds Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects no.</td>
<td>Rate %</td>
<td>Subjects no.</td>
<td>Rate %</td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
<td>0.1</td>
<td>33</td>
<td>0.1</td>
</tr>
<tr>
<td>Advanced adenoma‡</td>
<td>514</td>
<td>1.9</td>
<td>231</td>
<td>0.9</td>
</tr>
<tr>
<td>Advanced neoplasia§</td>
<td>544</td>
<td>2.0</td>
<td>264</td>
<td>1.0</td>
</tr>
<tr>
<td>Nonadvanced adenoma</td>
<td>1109</td>
<td>4.2</td>
<td>119</td>
<td>0.4</td>
</tr>
<tr>
<td>Any neoplasia</td>
<td>1653</td>
<td>6.2</td>
<td>383</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* The diagnostic yield was calculated as the number of subjects with true positive results divided by the number of subjects who were eligible to undergo testing. Subjects were classified according to the most advanced lesion.
† Odds ratios were adjusted for age, sex, and participating center. CI denotes confidence interval.
‡ Advanced adenoma was defined as an adenoma measuring 10 mm or more in diameter, with villous architecture (>25%), high-grade dysplasia, or intramucosal carcinoma.
§ Advanced neoplasia was defined as advanced adenoma or cancer.

Harms/Complications in the First Round of the Spanish Randomized Trial of Colonoscopy vs. FIT

- 24 of 4,953 patients in colonoscopy group had complications (0.5%)
  - Bleeding (12)
  - Hypotension or bradycardia (10)
  - Perforation (1)
  - Desaturation (1)

- 10 of 8,983 patients in FIT group had complications (0.1%)
  - Bleeding (8)
  - Hypotension or bradycardia (2)
  (all 10 had positive FIT and received a colonoscopy)

Outline

• What’s the best colorectal cancer screening test?
• Aspirin chemoprevention
• Are endoscopy and aspirin complementary?
Effect of Low-dose (75-300mg) Aspirin Versus Control on Colorectal Cancer Incidence & Mortality

- Incidence
  - All patients: 0.75
  - Aspirin ≥2·5 years: 0.69
  - Aspirin ≥5 years: 0.62

- Mortality
  - All patients: 0.61
  - Aspirin ≥2·5 years: 0.54
  - Aspirin ≥5 years: 0.48

Data from 4 randomized trials of aspirin vs. control

Rothwell, Lancet, 20 November 2010
Effect of Aspirin on Incidence of Cancer
Daily Dose Range 75-100 mg, vs. Placebo


Data from 6 randomized trials of aspirin vs. control
Effect of Aspirin on Vascular Events, Cancers, or Fatal Extra-cranial Hemorrhage

Daily Dose
Range 75-100 mg vs. Placebo

HR 0.92 (95% CI 0.86-0.98), p=0.01

Data from 6 randomized trials of aspirin vs. control

Rothwell, Lancet, 28 April 2012
Screening vs. Prevention

• Screening may reduce the mortality from one disease.
• Prevention may be able to reduce the mortality from multiple diseases.
Effect of Aspirin on 20-Year Risk of Death Due to Common Cancers in 4 Long-Term Trials

Outline

• What’s the best colorectal cancer screening test?
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### Colonoscopy and Right- versus Left-sided Colorectal Cancer Death

<table>
<thead>
<tr>
<th></th>
<th>All Cancer</th>
<th>Right-Sided Cancer</th>
<th>Left-Sided Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attempted Colonoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Any</td>
<td>0.69 (0.63-0.74)</td>
<td>1.07 (0.94-1.21)</td>
<td>0.39 (0.34-0.45)</td>
</tr>
<tr>
<td><strong>Completeness of Colonoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Complete</td>
<td>0.63 (0.57-0.69)</td>
<td>0.99 (0.86-1.14)</td>
<td>0.33 (0.28-0.39)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0.91 (0.78-1.07)</td>
<td>1.35 (1.07-1.69)</td>
<td>0.63 (0.49-0.81)</td>
</tr>
</tbody>
</table>

Differential Efficacy of Colonoscopy

Potential reasons for difference in proximal vs. distal colorectal cancer mortality reduction

- Technical: Inadequate bowel prep
- Expertise/Experience
- Biological
  - Faster growing lesions on the right
  - Flat and depressed adenomas on the right
## Effect of Aspirin (75-1200 mg) on Right- versus Left-sided Colorectal Cancer Incidence

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Events</th>
<th>Hazard Ratios (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>397</td>
<td>0.76 (0.63-0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proximal Colon</td>
<td>69</td>
<td>0.45 (0.28-0.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Distal Colon</td>
<td>100</td>
<td>1.10 (0.73-1.64)</td>
<td>0.66</td>
</tr>
<tr>
<td>Rectum</td>
<td>119</td>
<td>0.90 (0.63-1.30)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Data from 4 trials of aspirin vs. control

Rothwell, *Lancet*, 20 November 2010
<table>
<thead>
<tr>
<th>Event</th>
<th>Events</th>
<th>Hazard Ratios (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Cancers</td>
<td>240</td>
<td>0.66 (0.52-0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Proximal Colon</td>
<td>41</td>
<td>0.34 (0.18-0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Distal Colon</td>
<td>44</td>
<td>1.21 (0.66-2.24)</td>
<td>0.54</td>
</tr>
<tr>
<td>Rectum</td>
<td>70</td>
<td>0.80 (0.50-1.28)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Data from 4 trials of aspirin vs. control

Rothwell, *Lancet*, 20 November 2010
Remaining Uncertainties in Colorectal Screening and Prevention

• Comparative effectiveness of the available screening tests?

• Mechanism(s) of aspirin action on carcinogenesis?

• Optimal duration & age range for aspirin use
  • Aspirin in Reducing Events in Elderly (ASPREE) is examining composite disability-free survival in ≥ 70 years

• Are screening and aspirin complementary, additive?