Colorectal Cancer Screening

Bernard Levin, M.D.
November 13, 2006

- Epidemiology
- Screening methods
- Public policy
- Cost-effectiveness
- Barriers
- Conclusions
### Number of New Cases and Rates of Colorectal (Bowel) Cancer, UK, 2002

<table>
<thead>
<tr>
<th></th>
<th>England</th>
<th>Wales</th>
<th>Scotland</th>
<th>N. Ireland</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>15,371</td>
<td>1,050</td>
<td>1,824</td>
<td>469</td>
<td>18,714</td>
</tr>
<tr>
<td>Females</td>
<td>13,207</td>
<td>887</td>
<td>1,627</td>
<td>454</td>
<td>16,175</td>
</tr>
<tr>
<td>Persons</td>
<td>28,578</td>
<td>1,937</td>
<td>3,451</td>
<td>923</td>
<td>34,889</td>
</tr>
<tr>
<td><strong>Crude rate per 100,000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>63.9</td>
<td>74.5</td>
<td>75.0</td>
<td>56.7</td>
<td>65.2</td>
</tr>
<tr>
<td>Females</td>
<td>52.2</td>
<td>59.0</td>
<td>62.0</td>
<td>52.3</td>
<td>53.4</td>
</tr>
<tr>
<td>Persons</td>
<td>57.9</td>
<td>66.5</td>
<td>68.2</td>
<td>54.4</td>
<td>59.1</td>
</tr>
<tr>
<td><strong>Age-standardised rate (European) per 100,000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>53.3</td>
<td>57.5</td>
<td>63.8</td>
<td>57.5</td>
<td>54.5</td>
</tr>
<tr>
<td>Females</td>
<td>34.4</td>
<td>36.4</td>
<td>41.4</td>
<td>41.9</td>
<td>35.3</td>
</tr>
<tr>
<td>Persons</td>
<td>42.8</td>
<td>45.8</td>
<td>51.0</td>
<td>48.5</td>
<td>43.8</td>
</tr>
</tbody>
</table>

*From: Cancer Research UK (2006)*

### Number of Deaths and Mortality Rates, Colorectal Cancer, UK 2004

<table>
<thead>
<tr>
<th></th>
<th>England</th>
<th>Wales</th>
<th>Scotland</th>
<th>N. Ireland</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths from colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7,036</td>
<td>525</td>
<td>851</td>
<td>232</td>
<td>8,644</td>
</tr>
<tr>
<td>Females</td>
<td>6,181</td>
<td>408</td>
<td>717</td>
<td>198</td>
<td>7,504</td>
</tr>
<tr>
<td>Persons</td>
<td>13,217</td>
<td>933</td>
<td>1,568</td>
<td>430</td>
<td>16,148</td>
</tr>
</tbody>
</table>

|                      |          |       |          |            |          |
| **Age-standardised rate (European) per 100,000 population, colorectal cancer** |         |       |          |            |          |
| Males                | 23.1     | 27.0  | 28.5     | 26.9       | 23.8     |
| Females              | 14.3     | 14.1  | 16.0     | 16.2       | 14.5     |
| Persons              | 18.2     | 19.8  | 21.3     | 21.0       | 18.6     |

*From: Cancer Research UK (2006)*
Objectives of Colorectal Cancer Screening

- Prevent cancers by detection and resection of adenomatous polyps
- Detection of surgically curable colorectal cancers (Stages 1, 2)
Methods of Screening for Colorectal Neoplasia

- Fecal occult blood tests
- Endoscopic techniques
  - CT colonography
  - Stool-based molecular markers
  - Gene markers in plasma

Approaches to Colorectal Cancer Screening

<table>
<thead>
<tr>
<th>Where?</th>
<th>How?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based</td>
<td>Europe, UK</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>USA</td>
</tr>
</tbody>
</table>
Screening Strategies

One-Stage Screening
Colonoscopy

Two-Stage Screening
FOBT
Flex Sig.
DC Barium Enema
Virtual Colonoscopy
Stool DNA Mutations

Colonoscopy


Screening Targets During Carcinogenesis

Normal

Adenoma: early

Adenoma: advanced

Cancer: curable

Cancer: advanced

Endoscopy or Virtual Colonoscopy
Stool DNA
Stool Blood Test

5 - 12 Years
2 - 4 Years

From: Levin, B: Clinical Cancer Research, 2006
**Blood Products (Analytes) in Feces**

**Hemoglobin**
- Heme
- Globin

Guaiac; peroxidase.

Interference by Meat, vegies, vitamin C, NSAIDs.

Detects bleeding from Stomach, small & large intestine.

Immunochemical.

NO Interference.

Detects bleeding from large intestine.

**gFOBT**

**FIT**

*From: G. Young (2005)*

---

**Fecal Immunochemical Testing**

Examples:
- FlexSure OBT®
- InSure®
- Hemeselect®
- MagStream 1000/HemSP®
- And Others

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>Adenomas &lt; 1cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>59% - 66%</td>
<td>20% - 37%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*From: Allison, J (2005)*
*Morikawa, T (2005)*
Comparison of Insure\textsuperscript{\textregistered} With Hemoccult II Sensa\textsuperscript{\textregistered}

- Screening cohort (2351 individuals)
- Symptomatic diagnostic group (161 individuals)
- Insure: Brush-sampling FIT
- Hemmocult II Sensa: sensitive guaiac test

<table>
<thead>
<tr>
<th></th>
<th>Positivity %</th>
<th>InSure</th>
<th>HO II Sensa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (24)</td>
<td>87.5</td>
<td>54.2</td>
<td></td>
</tr>
<tr>
<td>Adv. Adenoma (61)</td>
<td>42.6</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Stage I Cancer</td>
<td>12/13</td>
<td>4/13</td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>3.4</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>41.9</td>
<td>40.4</td>
<td></td>
</tr>
</tbody>
</table>

From: Smith et al Cancer, 2005

Sensitivity vs Positivity Rate: InSure

From: G. Young (2005)
Fecal Immunochemical Tests: Current Status

- User friendly (e.g. brush technique)
- Automated reading
- Higher sensitivity than guaiac FOBT; acceptable specificity
- Positivity cut-off rate can be adjusted
- More data needed on adenoma detection

UK Screening Pilot
£2M to Screen 1M Population

- FOBT UPTAKE 60%
- FOBT Pos 1.6-2.1%
- 85% colonoscopy

- 40% normal
- 30% Polyps
- Polyps 5.8-8/1,000
- 11% Cancer
- Cancer 1.26-1.99/1,000

From: O’Morain (2006)
NHS Bowel Cancer
Screening Program in Progress

Eligibility: Ages 60-69

• Three year “rollout”

• Five program hubs will send out FOB test kits, analyse samples, dispatch results

• Up to 20 screening centers around each hub will provide endoscopy services and referrals to local hospital multidisciplinary teams

Anticipated Outcomes

98/100: Normal
2/100: Abnormal
98/100: Normal
2/100: Abnormal
3/10 at colonoscopy: Normal
4/10 at colonoscopy: Polyp
5/10 at colonoscopy: Polyp
1/10 at colonoscopy: Cancer
1/10 at colonoscopy: Cancer
Bleeding: 1/150
Perforation: 1/1500
Death: 1/10,000
Death: 1/10,000
Colorectal Cancer Mortality Reduction
By Sigmoidoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Colorectal Cancer Mortality Reduction</th>
<th>Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser Permanente, USA</td>
<td>Retrospective, Case Control</td>
<td>30%</td>
<td>Selby, NEJM 1992</td>
</tr>
<tr>
<td>Univ. Wisconsin, USA</td>
<td>Retrospective, Case Control</td>
<td>40%</td>
<td>Newcomb, JNCI 1992</td>
</tr>
</tbody>
</table>


Once-Only Flexible Sigmoidoscopy Trial: U. K.

Findings:
- Randomized to screening: 170, 432
- Incidence of Adenomas: 12%
- Incidence of significant adenomas: 6% (referred for colonoscopy)
- Incidence of cancer: 0.3% (62% were Stage A)

Complications:
- Perforation rate: 0.002% - sigmoidoscopy
- 0.17% - colonoscopy

Impact on mortality awaited

From: Thompson et al Dis. Colon and Rectum (June 2006)
New Stool-Based Tests for Screening for Colorectal Neoplasia

- Markers based on gene mutations*
- Markers based on epigenetic mutations*
- Markers based on DNA integrity
- Protein-based stool markers

*Also serum based

From: Haug and Brenner, Int. J. Cancer 117, 169, 2005

Why Gene-Based Testing?

- High specificity
- Non-invasive
- No dietary restrictions or bowel prep
- Large scale screening theoretically possible
- Genetic abnormalities inherent to tumorigenesis
Multicenter Studies

Stool DNA Mutation Testing

Average risk (age 50-80); colonoscopy as standard; 3 guaiac vs 1 PreGen Plus

<table>
<thead>
<tr>
<th>Funding</th>
<th>n</th>
<th>HO Developed by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXACT*</td>
<td>4404</td>
<td>Local MD</td>
</tr>
<tr>
<td>BVD**</td>
<td>2503</td>
<td>Central lab</td>
</tr>
</tbody>
</table>

*N Engl J Med 2004; 351:2704
**Gastroenterology April 2005, DDW 2005

From: Ahlquist (2005)

Stool DNA Mutation Testing

<table>
<thead>
<tr>
<th></th>
<th>Exact Study</th>
<th>NIH Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreGen Plus</td>
<td>HO</td>
</tr>
<tr>
<td>Specificity %</td>
<td>94.4</td>
<td>95.2</td>
</tr>
<tr>
<td>Sensitivity %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer/HGrDys</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity %</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>Sensitivity %</td>
<td>30</td>
<td>35</td>
</tr>
</tbody>
</table>

Modified from: Ahlquist (2005)
Detection of Colorectal Cancer by Stool DNA Testing

<table>
<thead>
<tr>
<th>Markers</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long DNA plus methylated Vimentin gene</td>
<td>87.5% (77.4-97.6)</td>
<td>82.0% (75.2 - 88.8)</td>
</tr>
</tbody>
</table>

Number of Patients:
- 140 Normal
- 40 CRC

From: Itzkowitz et al, DDW, 2006

Future Advances in Stool-Based Molecular Testing

- Sensitivity by more efficient DNA extraction
  - new technology
- Sensitivity by targeting additional markers
  - Methylation of non-expressed vimentin gene
- Adenoma markers
Effect of Colonoscopic Polypectomy on Incidence of Colorectal Cancer

- U.S. National Polyp Study: 76–90%
- Italian Multicenter Study Group: 66%


Screening Colonoscopy Studies

<table>
<thead>
<tr>
<th>Gender</th>
<th>NCS</th>
<th>VA</th>
<th>CONCERN</th>
<th>Lilly</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td>Women</td>
<td>Women</td>
</tr>
<tr>
<td>Adenomas or Cancer</td>
<td>18%</td>
<td>37.5%</td>
<td>21%</td>
<td>11% (distal)</td>
<td>14%</td>
</tr>
<tr>
<td>Advanced Neoplasia</td>
<td>6%</td>
<td>11%</td>
<td>5%</td>
<td>5%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

NCS – Winawer et al. DDW 2002 (Gastroenterology)
VA – Lieberman et al. NEJM 2000
CONCERN – Schoenfeld et al. DDW 2001, 2002 (Gastroenterology)
Lilly-Imperiale et al. – NEJM 2000, 2002
Regula-NEJM 2006
Screening by Colonoscopy in USA

Effective, Yet Imperfect

Pragmatic Issues

• ~ 8,000 U.S. gastroenterologists/endoscopists
• ~ 80,000,000 Americans 50 years of age or older
• ~ 30-40% prevalence of adenomas in Americans greater than 50 y.o.
• ~ 45-60% of persons screened - by any means, including suboptimal measures - within last 10 years
• Cost, acceptability, access, risk
• Colonoscopy may not be the most effective nor most cost-effective screening strategy (IOM, USPTF)

Modified From: NCI/DCP/GOCRG 1/05

CT Colonography
(Virtual Colonoscopy)
1? CTC screening

2,202 patients
Mean age: 57.1 yrs
M/F: 995/1,207

OC rate = 7.1%

Advanced
Adenomas = 74
Prevalence = 2,996
(130 6-9 mm polyps)

Invasive Cancers = 5

Total # of Polypectomies = 325
(233 if diminutive lesions excluded)

1? OC screening

2,210 patients
Mean age: 58.1 yrs
M/F: 967/1,243

OC rate = 100%

Advanced
Adenomas = 75
Prevalence = 3,096

Invasive Cancers = 3

Total # of Polypectomies = 1,696

Current UW CTC Screening Results in Over 3,000 Asymptomatic Adults

Large polyp (> 10 mm)
(“Immediate” OC)

4%

1-2 small polyps (6-9 mm)
(OC vs. CTC surveillance)

8%

No polyps > 5 mm
(Routine screening in 5 years)

88%

CT Colonography

What is a positive test by polyp size?

- 10mm: 3.9%
- 8mm: 6.7%
- 6mm: 13.6%

Proportion of Small (5-10 mm) Adenomas With Advanced Histology

<table>
<thead>
<tr>
<th>Study</th>
<th>Total advanced histology</th>
<th>Carcinoma</th>
<th>Total number of small adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinya 1979a</td>
<td>15.5%</td>
<td>.5%</td>
<td>1661</td>
</tr>
<tr>
<td>NPS 1990b,c</td>
<td>7.3%</td>
<td>1.5%</td>
<td>1230</td>
</tr>
<tr>
<td>Gschwantler 2002</td>
<td>13.5%</td>
<td>.9%</td>
<td>2789</td>
</tr>
<tr>
<td>Butterly 2006</td>
<td>10.1%</td>
<td>.9%</td>
<td>921</td>
</tr>
<tr>
<td>All Studies</td>
<td>12.4%</td>
<td>.9%</td>
<td>6601</td>
</tr>
</tbody>
</table>

5 to 9 mm adenomas
6 to 10 mm adenomas
NPS data do not include villous histology


**CT Colonography Extracolonic Findings**

- Pickhardt: 4.5% (“high clinical import”)
- Pedersen:
  - 65% had extracolonic abnormalities
  - 12% additional work-up indicated

**Serious findings:**
- Ovarian cancer
- Renal cell cancer
- Lung tumors
- Hepatic lesions
- Adrenal lesions

*Note: absence of contrast enhances difficulty of diagnosis of cystic lesions*


---

**Potential Implications for Public of VC**

- More individuals may accept screening
- Overall, more significant lesions found
- More patients referred for truly therapeutic colonoscopy
- Enhanced risk-benefit ratio for endoscopic services
Reducing the Need for Colonoscopy

Average and Increased Risk Population

Initial Screen

Colonoscopy

Appropriate Sensitivity
Appropriate Specificity
Affordable Cost

Novel Endoscopic Advances

• Aero-Scope? (pneumatic, self-propelling, self-navigating, omnidirectional 'scope)
• Navigator? Endoscopy System: avoidance of looping
• Capsule Endoscopy
• "Red flag" techniques to identify abnormalities
  – Chromoendoscopy
  – Magnification and high-resolution endoscopy
  – Narrow band imaging
  – Fluorescence imaging
  – Optical coherence tomography
  – Confocal microscopy
Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality assurance procedures.
Colorectal Cancer Screening Guidelines
U.S. Preventive Services Task Force (USPTSF)*

“The USPSTF strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer. Grade A Recommendation.”

*USPSTF. Ann Int. Med. 2002

Which Screening Test is Best?

- Quality of evidence of health benefit
- Accuracy
- Magnitude of health benefit
- Harms and Inconveniences
- Cost
- Tradeoffs
- Is the ‘menu’ of options a deterrent?

From: S. Woolf
Modeling Can Help Us Link Screening, Treatment and Prevention Goals to Mortality Goals

Per 100,000

Screening/Treatment/Risk factors remain at 1999 levels


Year of Death

* Age adjusted to the SEER 2000 standard.

What are Barriers to Colorectal Cancer Screening?

Decisions are made by:

• Policy makers/legislators/third party payers
• Physicians
• Consumers

"It takes a village" ……… to eliminate colorectal cancer
Summary

• Currently available techniques, while not perfect, are under-utilized
• Fecal Immunochemical tests appear to be ready for large-scale use
• Molecular tests on stool (?blood in future) have potential but are expensive
• Novel endoscopic technology may substantially enhance the efficiency and effectiveness of colonoscopy
• Virtual colonoscopy (CT colonography) is likely to have broad appeal and if it becomes "prepless", could find major acceptability