Epidemiology of Colorectal Cancer and Overview of Screening Modalities

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American University of Beirut Medical Center, Lebanon
Question

Which of the following is best suited for population-based screening for CRC?

1. Colonoscopy
2. CT colonography
3. Videocapsule colonoscopy
4. Stool guaiac test
5. Fecal DNA test
6. Fecal immunochemical test (FIT)

*Per 100,000, age-adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.


American Cancer Society, Surveillance Research, 2006

*Per 100,000, age-adjusted to the 2000 US standard population. †Uterus cancer death rates are for uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Incidence of Colon Cancer

Data from Surveillance, Epidemiology, and End Results (SEER) Program, 1973-1992.

Life-time risk
~5-6%
Incidence of Types of Colon Cancer

About 10% of the population aged 30–70 has at least one first-degree relative with CRC.

- **50-60%**: Sporadic colon cancer
- **1%**: Genetic polyposis
- **3-5%**: Non-polyposis syndromes
- **30-40%**: Familial colon cancer

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Family History & Colon Cancer

- FDR: First degree relative
- SDR: Second degree relative

Probability (%)

- General Population
- 1 FDR (>60y)
- 1 FDR (<60y)
- 2 FDR
- 2 SDR
- 1 SDR
- 1 FDR with adenomatous polyp

Burt RW. Gastroenterology 2000;119:837-53
Johns LE, Houlston RS. Am J Gastroenterol 2001;96:2992-3003
Colorectal Cancer Risk Factors

- Age
- Gender
- Race/Ethnicity
- Personal history of IBD, adenomatous polyps or colon cancer
- Family history of adenomatous polyps, colon cancer and genetic syndromes
Other Risk Factors

- Diet (red or processed meat RR 1.2)
- DM & insulin resistance (RR 1.3)*
- Acromegaly
- Renal transplantation
- Smoking, heavy alcohol use

Webster et al. *Am J Transplant*. 2007;7(9):2140
Incidence of Colon Cancer

Data from Surveillance, Epidemiology, and End Results (SEER) Program, 1973-1992.

Life-time risk
~5-6%
The Ideal Screening Test

• Safe
• Widely available
• High sensitivity & specificity
• Acceptable to Population
• Cheap
• Cost-effective
Need a Simple & Safe Test suitable for Population Screening

• *NOT* ...
  - Selective... what you can afford!
  - ad hoc...enthusiastic ‘GPs’ or ‘motivated patients’
  - at risk... family history, predisposing disease
  - symptomatic... blood in stool, etc.

• *Everyone* within a selected age group
Screening for Colon Cancer

- Fecal occult blood testing
- Barium enema
- Fecal DNA testing
- Flexible sigmoidoscopy
- Colonoscopy
- CT colonography
- Others

*Sensitivity of ACBE is 48%*

Guaiac-Based Fecal Occult Blood Testing

- Cheap & simple
- Widely available
- Sensitivity 30-50%
- PPV 3-10%
- Yearly FOBT
  - ↓ CRC deaths by 33%*
  - After 30 years still 32%**
- Biennial FOBT:
  - Both 13* and 30** years about 22%

Guaiac – Fecal Occult Blood Test

England’s Program
2 yearly (2006-April 2013)

<table>
<thead>
<tr>
<th>Dukes Stage</th>
<th>Symptomatic</th>
<th>England Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>11%</td>
<td>36%</td>
</tr>
<tr>
<td>B</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>C</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>‘D’</td>
<td>29%</td>
<td>4%</td>
</tr>
</tbody>
</table>

60-74 year olds invited
Test Kits Out 20.0 million
Test Kits In 11.6 million
+ve Screens 214,000

Colonoscopies 210,000
Cancers 17,114 (PPV 8.2%)
Advanced Adenomas 19,384

Early cancer detection
Cancer Prevention

From Halloran S. UEGW 2013 PG Course
Mean Blood Loss from Adenomatous Polyps

Only 24% of patients with advanced neoplasia have a positive FOBT.


# Guaiac Test vs. Fecal Immunochemical Test (FIT)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Cancer</th>
<th>Advanced Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard gFOBT (3 stool samples)</td>
<td>33-50</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sensitive gFOBT (3 stool samples)</td>
<td>50-75</td>
<td>20-25</td>
<td></td>
</tr>
<tr>
<td>iFOBT (FIT) (1 to 3 stool samples)</td>
<td>60-85</td>
<td>20-50</td>
<td></td>
</tr>
</tbody>
</table>

## Study relation OC Sensor FIT concentration and outcome at colonoscopy

Hemoccult-II and OC-SENSA MICRO

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patient Outcomes</th>
<th>Positive gFOBT</th>
<th>Mean FIT Conc. ng/ml</th>
<th>Positives at 75ng/ml Cut-off</th>
<th>Positives at 100ng/ml Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>479 (62.2%)</td>
<td>35 (7.3%)</td>
<td>51 (5-100)</td>
<td>36 (7.5%)</td>
<td>35 (6.9%)</td>
</tr>
<tr>
<td>All Adenoma</td>
<td>219 (28.4%)</td>
<td>14 (6.5%)</td>
<td>69 (22-116)</td>
<td>24 (11.2%)</td>
<td>20 (9.3%)</td>
</tr>
<tr>
<td>Adv. Adenoma</td>
<td>59 (7.7%)</td>
<td>8 (13.6%)</td>
<td>404 (183-624)</td>
<td>22 (37.3%)</td>
<td>20 (34.5%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>13 (1.7%)</td>
<td>4 (30.8%)</td>
<td>846 (447-1262)</td>
<td>12 (92.3%)</td>
<td>11 (84.6%)</td>
</tr>
</tbody>
</table>

From Halloran S. UEGW 2013 PG Course
Study relation OC Sensor FIT concentration and outcome at colonoscopy

<table>
<thead>
<tr>
<th>Endoscopic Classification</th>
<th>No. of Patient Outcomes</th>
<th>Positive gFOBT</th>
<th>Mean FIT Conc. ng/ml</th>
<th>Positives at 75ng/ml Cut-off</th>
<th>Positives at 100 ng/ml Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGD</td>
<td>276 (99%)</td>
<td>21 (7.6%)</td>
<td>134 (75-194)</td>
<td>44 (15.9%)</td>
<td>39 (14.1%)</td>
</tr>
<tr>
<td>HGD</td>
<td>2 (0.7%)</td>
<td>1 (50.0%)</td>
<td>986</td>
<td>2 (100%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>222 (80%)</td>
<td>15 (6.8%)</td>
<td>58 (9-224)</td>
<td>24 (10.8%)</td>
<td>20 (9.0%)</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>56 (20%)</td>
<td>7 (12.5%)</td>
<td>493 (246-740)</td>
<td>22 (39.3%)</td>
<td>20 (36.4%)</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 Adenoma</td>
<td>203 (73%)</td>
<td>18 (9.0%)</td>
<td>71 (23-118)</td>
<td>25 (12.6%)</td>
<td>20 (10.0%)</td>
</tr>
<tr>
<td>≥3 Adenoma</td>
<td>75 (27%)</td>
<td>4 (5.3%)</td>
<td>327 (144-510)</td>
<td>21 (28.4%)</td>
<td>20 (26.7%)</td>
</tr>
</tbody>
</table>
Effect of Test Cut-off on Number needed to Scope to detect CRC

Dutch Recommendations
January 2010

Start January 2014

Biennial single-sample FIT testing:
for all 55-75 years old using 15ug/g cut-off

€2,200 per life-year gained
(€ 11,300 cervical screening )
FIT: What Cut-off & Sample Number?

• Is a one sample device screen adequate? Kuipers

• What ‘cut-off’ concentration is best (OC-Sensor)
  – Netherland/ New Zealand (15ug/g) Kuipers/ Rossum
  – Italy (20ug/g) Zappa Zorzi
  – Scotland Study (80ug/g) Fraser, Steele
  – England Surveillance Study (50ug/g) Atkin/ Halloran

• Different FIT sensitivity for men and women

• Adjust positively to meet colonoscopy resource

From Halloran S. UEGW 2013 PG Course
Preliminary evidence of FIT reducing CRC incidence

- Organised **biennial** single FIT screening program in Florence
- Initial screen during 1993-99
- 26,285 unscreened and **6,961 screened**
- Average **follow-up period 11 years**
- 56 cancers prevented for every 10,000 screened
- **22% reduction** of colorectal cancer incidence

Screening Colonoscopy

Aim: Interrupt the Adenoma-Carcinoma sequence
Prevalence of Adenomatous Polyps

Advanced Neoplasia

• Three large studies (Veterans Affairs CSP-380 study\textsuperscript{1}, Women study\textsuperscript{2}, Polish study\textsuperscript{3})
• End-point: prevalence of advanced neoplasia (adenomas $\geq 10$ mm, villous histology, high-grade dysplasia, CIS, or invasive cancer)
• All 3 studies did not exclude individuals with FH of CRC or adenomatous polyps

Advanced Neoplasia on Screening

Prevalence
4.9% to 10.5%\textsuperscript{1-3}

Number Needed to Screen (95\% CI)

Efficacy of Screening Programs

FS = flexible sigmoidoscopy

Cost Effectiveness

• CRC screening is cost-effective or even cost-saving when compared with no screening
• Is colonoscopy the most cost-effective?

The costs of CRC screening per added year of life is comparable to that of hypertension screening & less than that of mammography & cholesterol testing

Colonoscopic Polypectomy and Prevention of CRC Deaths

# Fecal DNA Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old stool DNA test (1 stool sample)</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>New stool DNA test (1 stool sample)</td>
<td>&gt;80</td>
<td>40</td>
</tr>
</tbody>
</table>

# CT Colonography Trials

<table>
<thead>
<tr>
<th>Size</th>
<th>&lt; 6 mm</th>
<th>6-9 mm</th>
<th>&gt; 9 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (range)</td>
<td>0.48 (14-86)</td>
<td>0.70 (30-95)</td>
<td>0.85 (48-100)</td>
</tr>
</tbody>
</table>

Markov CE analysis: CTC $24,586 per life-year saved vs. $20,930 for colonoscopy*


Colon Capsule Endoscopy

A colon capsule for colorectal cancer screening is in clinical trials in Europe, but its role is still uncertain.

Bowel preparation is required prior to the examination.

Patients with lesions detected during the examination typically require subsequent colonoscopy.
## Colon Capsule Endoscopy

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Significant Polyp</th>
<th>Any Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>69%</td>
<td>73%</td>
</tr>
<tr>
<td>Specificity</td>
<td>86%</td>
<td>89%</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Second Generation</th>
<th>Polyps &gt;6mm</th>
<th>Polyps &gt;10mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>84%</td>
<td>88%</td>
</tr>
<tr>
<td>Specificity</td>
<td>88%</td>
<td>95%</td>
</tr>
</tbody>
</table>

CCE compared to Colonoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Gossum et al. 2009</td>
<td>PillCam Colon (n=328)</td>
<td>• Polyps ≥ 6mm: Sens (64%), Spec (84%)</td>
</tr>
<tr>
<td></td>
<td>8 European sites</td>
<td>• Adv. Adenoma: Sens (73%), Spec (79%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cancer: 14 out of 19 (sens = 74%)</td>
</tr>
<tr>
<td>Sachet-Huvelin et al. 2010</td>
<td>PillCam Colon (n=545)</td>
<td>• Polyps ≥ 6mm: Sens (39%), Spec (88%), PPV (47%), NPV (85%)</td>
</tr>
<tr>
<td></td>
<td>multicenter France</td>
<td>• Cancer: detected 3 of 5 CRC</td>
</tr>
</tbody>
</table>

Epidemiology of Colorectal Cancer in Lebanon
Colorectal Cancer in Lebanon

• CRC is the second most commonly reported cancer in females and the fourth most commonly reported cancer in males in Lebanon in 2012

• CRC is diagnosed in an average of 630 individuals annually in Lebanon

• No vital statistics or information about burden of disease in terms of morbidity & mortality
**Time-Trend for CRC in Lebanon**

The ASR for colon cancer:
1998: 8.71/100,000
2007: 15.28/100,000

The ASR for colon cancer:
1998: 8.87/100,000
2007: 10.29/100,000

ASR= age-standardized rate

Colorectal Cancer in Lebanon

• There is no national CRC screening strategy or education awareness program
• Screening with fecal occult blood testing is rarely practiced
• Gastroenterologists recommend and perform screening colonoscopy on an erratic and opportunistic basis
## Screening Colonoscopy Studies

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Journal</th>
<th>Number</th>
<th>Adenomas</th>
<th>Advanced Neoplasia</th>
<th>Positive FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman et al. (USA)</td>
<td>NEJM 2000</td>
<td>3,196 96.8% ♂</td>
<td>37.5%</td>
<td>10.5%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Schoenfeld et al (USA)</td>
<td>NEJM 2005</td>
<td>1,463 ♀</td>
<td>20.4%</td>
<td>4.9%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Regula et al. (Poland)</td>
<td>NEJM 2006</td>
<td>43,042 Age 50-66</td>
<td>14.9%</td>
<td>5.9%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Kim et al. (USA)</td>
<td>NEJM 2007</td>
<td>6,283 CTC vs. OC study</td>
<td>• Not reported per patient • Polyps &lt;6mm on CTC not evaluated</td>
<td>3.3%</td>
<td>?</td>
</tr>
</tbody>
</table>

*Only HNPCC/FAP excluded*
### Screening Colonoscopy in *True Average Risk*

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Journal</th>
<th>Number</th>
<th>Adenomas</th>
<th>Advanced Neoplasia</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rex et al. (USA)</td>
<td>GIE 2000</td>
<td>121</td>
<td>35%</td>
<td>4.8%</td>
<td>African Americans</td>
</tr>
<tr>
<td>Scott et al. (Australia)</td>
<td>AJG 2005</td>
<td>184</td>
<td>Unclear from report</td>
<td>8.7%</td>
<td>FH of 1\textsuperscript{st} degree relative excluded</td>
</tr>
<tr>
<td>Chiu et al. (China)</td>
<td>GIE 2005</td>
<td>1741</td>
<td>15.4%</td>
<td>3.0%</td>
<td>FH of 1\textsuperscript{st} degree relative excluded</td>
</tr>
<tr>
<td>Strul et al. (Israel)</td>
<td>AJG 2006</td>
<td>994</td>
<td>21.3%</td>
<td>6.7%</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Graser et al. (Germany)</td>
<td>Gut 2009</td>
<td>311</td>
<td>36.8% <em>CTC (+3%)</em></td>
<td>9.6%</td>
<td>One 1\textsuperscript{°}&lt;60 or two 1\textsuperscript{°} at any age excluded</td>
</tr>
</tbody>
</table>
SCREENING COLONOSCOPY IN AVERAGE-RISK ADULTS IN LEBANON

- Patients with ANY known family history of CRC or large adenomas were EXCLUDED
- Potential risk and protective factors for developing adenomatous polyps & advanced neoplasia
- Withdrawal time & adenoma detection recorded
- 1000 patients enrolled
- Complete data analysis on 980 patients
RESULTS (n=980)

All Adenomas = 42.8%
Advanced Neoplasia = 5.1%
Cancer = 0.8%

Mean age = 61.1 y
n = 249 (51.9%)*

Male (n=479)
Adenomas = 45.5%
Advanced Neoplasia = 6.5%

Mean age = 60.6 y
n = 170 (33.9%)

Female (n=501)
Adenomas = 30.1%
Advanced Neoplasia = 3.8%

•Sharara AI, et al. Gastroenterology 2013 (Abstract)
Prevalence of Adenomas by Age and Gender

Percent (%) vs Age group (years)

- Female
- Male
Prevalence of Advanced Neoplasia by Age and Gender

![Bar graph showing the prevalence of advanced neoplasia by age and gender across different age groups.](image-url)
### Number Needed To Screen to Identify Adenomas &/or Advanced Neoplasia

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Adenomas (95% CI)</th>
<th>Advanced Neoplasia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>2.7 (2.5-2.9)</td>
<td>18.2 (14.4-24.8)</td>
</tr>
<tr>
<td>50-59yo</td>
<td>3.3 (3.0-3.6)</td>
<td>24 (19-36.4)</td>
</tr>
<tr>
<td>60-69yo</td>
<td>2.3 (2.2-2.9)</td>
<td>14.1 (11.5-18.3)</td>
</tr>
<tr>
<td>≥70yo</td>
<td>2.1 (1.9-2.2)</td>
<td>14.9 (12.1-19.6)</td>
</tr>
</tbody>
</table>
## Multivariate Logistic Regression Model Predicting the Risk of Advanced Neoplasia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>( \beta \pm \text{S.E.} )</th>
<th>p-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.035 ± 0.018</td>
<td>0.048</td>
<td>1.036 (1–1.073)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>0.794 ± 0.417</td>
<td>0.057</td>
<td>2.211 (0.978–5.003)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.265 ± 0.447</td>
<td>0.005</td>
<td>3.544 (1.475–8.514)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>&lt;40 pack-years</td>
<td>0.697 ± 0.353</td>
<td>0.048</td>
<td>2.01 (1.01–4.01)</td>
</tr>
<tr>
<td>≥40 pack-years</td>
<td>1.376 ± 0.385</td>
<td>0</td>
<td>3.96 (1.86–8.42)</td>
</tr>
<tr>
<td>Daily red meat</td>
<td>0.702 ± 0.4</td>
<td>0.079</td>
<td>2.017 (0.921–4.419)</td>
</tr>
</tbody>
</table>

Model for Predicting Advanced Neoplasia according to Risk Factors against BMI

Sharara AI, et al. Gastroenterology 2013 (Abstract)
Age: 65
Weight: 68
Height: 170
Packs/day: 0
Years of smoking: 0
Red meat: None
 Calculate risk
Risk of Advanced Neoplasia
2.0 %

[Graph showing advanced neoplasia risk across different age groups with and without red meat consumption]
Age: 65
Weight: 74
Height: 170
Packs/day: 1
Years of smoking: 20
Red meat: [ ] None  [X] Daily  [ ] Once a week  [ ] 3 times/week

Calculate risk

Risk of Advanced Neoplasia: 14.0%

Overweight (BMI 25-29.9 kg/m²)

- age only
- + daily red meat (RMₜ)
- +RMₜ + 40 packyrs
- +RMₜ + ≥40 packyrs

Graph:

Age (years)
Accuracy of Model for Predicting Advanced Neoplasia

AUC=0.722

•Sharara AI, et al. Gastroenterology 2013 (Abstract)
Proposed Algorithm

High Risk (positive FH) → Colonoscopy

Average Risk Age 50-70 → Multivariate Colon Cancer Risk Score (Age, BMI, Smoking, Red meat)

Multivariate Colon Cancer Risk Score → High Risk Score
High Risk Score → Positive FIT
Average Risk Score → Annual or biennial FIT (cut off TBD) Stop at age 70

Surveillance according to existing guidelines
Colorectal Cancer in Lebanon

• CRC is common in Lebanon and appears associated with a significant burden
• The prevalence of colon adenomas and advanced neoplasia is similar to rates published in Europe and North America
• Risk factors may help stratify risk, chief amongst these are BMI and heavy smoking

• *A national screening strategy is a priority*
Colorectal cancer is the second leading cancer killer, yet it is preventable, treatable, and beatable!
No National Program for Colorectal Cancer Screening