Colorectal Cancer: A Review

Marcia Cruz-Correa, MD, PhD, AGAF, FAGE
Associate Professor of Medicine, Biochemistry & Surgical Oncology
Objectives

• Review the epidemiology of CRC
• Review common hereditary colorectal cancer syndromes
• Review current CRC screening guidelines
• Discuss evidenced-based data for each CRC screening recommendation
CRC Epidemiology
Colorectal Cancer: Epidemiology

Colorectal Cancer Is:

- Prevalent: 154,000 new cases estimated in United States for 2008
- Deadly: 52,000 annual deaths
- Expensive: One of most expensive cancers to treat
- Treatable: 95% survival rate when detected early
- Detectable: Screening allows for early detection

Incidence Rates for Cancer Sites in Males
PR 2004

Source: Puerto Rico Central Cancer Registry, Department of Health, August 2006
Rates are per 100,000 and age-adjusted to the 2000 PR population.
Incidence Rates for Cancer Sites in Females
PR 2004

Breast: 80.6
Colon and Rectum: 30.1
Corpus and Uterus, NOS: 13.4
Lymphoma: 10
Lung and Bronchus: 9.1
Cervix Uteri: 8.7
Thyroid: 7.4
Ovary: 6.8
Stomach: 6.6
Leukemia: 4.7

Source: Puerto Rico Central Cancer Registry, Department of Health, August 2006
Rates are per 100,000 and age-adjusted to the 2000 PR population.
Age-Adjusted Mortality Rates for the Top 6 Sites in Females, 1987-2003

Source: Puerto Rico Central Cancer Registry, Department of Health, August 2006
Rates are per 100,000 and age-adjusted to the 2000 PR population.
Age-Adjusted Mortality Rates for the Top 6 Sites in Males, 1987-2003

Source: Puerto Rico Central Cancer Registry, Department of Health, August 2006
Rates are per 100,000 and age-adjusted to the 2000 PR population.
Natural History of Colorectal Neoplasia

- Normal
- Hyper-proliferation
  - Adenoma: early
  - Adenoma: late
  - Adenoma: Intermediate
- Cancer: curable
- Cancer: late

5 - 10 years
3 - 5 years

From: Rozen, Young, Levin, Spann (2002)
Hereditary Colorectal Cancer
CRC Hereditary Syndromes

- Familial adenomatous polyposis (FAP)
- MYH-Associated Polyposis (MAP)
- Hereditary nonpolyposis colorectal cancer (HNPCC)
- Juvenile Polyposis
- Peutz-Jeghers syndrome
Familial Adenomatous Polyposis
Epidemiology

- Includes Gardener syndrome, attenuated FAP, Turcot syndrome
- Autosomal dominant disease
- 1/10,000 individuals
- Equal gender distribution
- CRC 100%; average age of CRC is 39 y
Colectomy specimen with multiple polyps.
Cancers in FAP

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lifetime Risk(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>100</td>
</tr>
<tr>
<td>Duodenal</td>
<td>5-11</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
</tr>
<tr>
<td>Brain (medulloblastoma)</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>&lt;1% (&lt; 5y/o)</td>
</tr>
</tbody>
</table>
FAP Genetic Defect

- Germline mutation APC gene in 5q21
- APC is a tumor suppressor gene
- Encodes for 2843 AA protein
- More than 825 different mutations
- >90% mutations results in protein truncation
- Genotype-phenotype variation
MYH-Associated Polyposis

- *Autosomal-recessive* inherited syndrome
- Clinically undistinguishable from FAP
- Multiple colonic adenomas (median 40)
- Age 45-60 years
- Extracolonic manifestations
  - Gastric cancer, duodenal polyposis, Osteomas
MYH-Associated Polyposis

- Biallelic germline mutation of MYH-gene on chromosome 1p
- Base excision repair gene, involved in repairing oxidative damage to DNA
- 2 most common MYH mutations: G382D and Y165C (85% MAP)*
- Commercially available testing

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

- Autosomal dominant
- Incidence 1/200 to 1/2000
- 70% to 80% CRC lifetime risk
- CRC diagnosis 44 y/o
- 1%-6% of all CRC cases
- 60%-80% tumors proximal SF

Hendricks et al. Gastroenterology 2004
## Cancers in HNPCC

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lifetime Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>80</td>
</tr>
<tr>
<td>Endometrial</td>
<td>39-60</td>
</tr>
<tr>
<td>Stomach</td>
<td>12-19</td>
</tr>
<tr>
<td>Ovarian</td>
<td>9</td>
</tr>
<tr>
<td>Ureters/renal</td>
<td>4-10</td>
</tr>
<tr>
<td>Brain (glioblastoma)</td>
<td>4</td>
</tr>
</tbody>
</table>
Genetic Defect

HNPCC

- Mutation in any one of 5 mismatch repair (MMR) genes
- MMR genes function to maintain fidelity of DNA replication by correction of base-pair mistakes
- Germline mutations of hMSH2 and hMLH1, account > 90% of the mutations
CRC Screening
Colorectal Cancer is Suitable for Screening

- Common, lethal disease
- Long preclinical phase (5-15 years)
- Safe, accurate diagnostic tests available
- Early detection (including precursor lesions) and treatment improve survival
- Screening tests available
Major Modes of Prevention

• Screening/Surveillance
  – Clinical testing of individuals who have no symptoms or signs of disease

• Chemoprevention
  – Use of a specific chemically defined agent whether synthetic or natural to reverse, suppress or prevent progression of carcinogenesis

• Nutrition, lifestyle habits
  – Diet, physical activity, avoidance of obesity, tobacco, etc
Colon Cancer Can be Prevented: National Polyp Study Cohort

Cumulative incidence of colorectal cancer (%)

No. expected from Mayo Clinic data
No. expected from St. Mark’s data
No. expected from SEER data
No. observed

Years of follow-up

0 1 2 3 4 5 6 7 8

### Behavioral Risk Factors Surveillance System

#### Race/Ethnicity CRC Screening

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Endoscopic Screening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>59</td>
</tr>
<tr>
<td>African-American</td>
<td>54</td>
</tr>
<tr>
<td>US Hispanics</td>
<td>47</td>
</tr>
<tr>
<td>PR Hispanics</td>
<td>38</td>
</tr>
</tbody>
</table>

*Morbidity and Mortality Weekly Report, 2008*
CRC Guidelines

- American Cancer Society and The US Multi-Society Task Force (March 2008)
- US Preventive Services Task Force (Nov 2008)
- American College of Gastroenterology (Jan 2009)
Update American Cancer Society and US Multi-Society Task Force on CRC

Updated guidelines released 2008*

Screening issues

– Prevention versus Detection
– New Technologies
  • iFOBT (immunochemical tests)
  • sDNA – Stool DNA
  • CT Colonography (“virtual colonoscopy”)

Testing Options for Early Detection of CRC & Adenomatous Polyps for Asymptomatic Adults Aged 50 Years and Older

Tests that Detect Adenomatous Polyps and Cancer
- Flexible sigmoidoscopy every 5 years
- Colonoscopy every 10 years
- Double-contrast barium enema every 5 years
- Computed tomographic colonography every 5 years

Tests that Primarily Detect Cancer
- Annual guaic-based fecal occult blood test
- Annual fecal immunochemical test
- Stool DNA test, interval uncertain
## Screening for Colorectal Cancer

**Clinical Summary of U.S. Preventive Services Task Force Recommendation**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults Age 50 to 75 Years*</th>
<th>Adults Age 76 to 85 Years*</th>
<th>Adults Older Than 85 Years*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Screen with high-sensitivity FOBT, sigmoidoscopy, or colonoscopy</td>
<td>Do not screen routinely</td>
<td>Do not screen</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>A</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

**For all populations, evidence is insufficient to assess the benefits and harms of screening with computed tomographic colonography and fecal DNA testing.**

**Grade: I (insufficient evidence)**

### Screening Tests

- High-sensitivity FOBT, sigmoidoscopy with FOBT, and colonoscopy are effective in decreasing colorectal cancer mortality.
- The risks and benefits of these screening methods vary.
- Colonoscopy and flexible sigmoidoscopy (to a lesser degree) entail possible serious complications.

### Screening Test Intervals

**Intervals for recommended screening strategies:**

- Annual screening with high-sensitivity FOBT
- Sigmoidoscopy every 5 years, with high-sensitivity FOBT every 3 years
- Screening colonoscopy every 10 years

### Balance of Harms and Benefits

- The benefits of screening outweigh the potential harms for 50- to 75-year-olds.
- The likelihood that detection and early intervention will yield a mortality benefit declines after age 75 because of the long average time between adenoma development and cancer diagnosis.

### Implementation

- Focus on strategies that maximize the number of individuals who get screened.
- Practice shared decision making; discussions with patients should incorporate information on test quality and availability.
- Individuals with a personal history of cancer or adenomatous polyps are followed by a surveillance regimen, and screening guidelines are not applicable.

### Relevant USPSTF Recommendations

- The USPSTF recommends against the use of aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer.
- This recommendation is available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov).
ACG Guidelines 2009
Colonoscopy Screening

- Preferred Colorectal Cancer Prevention Test
  - Colonoscopy Every 10 Years
- Second examination at five years?
  - Might not substantially impact CRC
- Start Screening
  - 50 y in average-risk persons (men/women)
  - 45 in African-Americans

Am J Gastroenterol 2009;104:739-750
# High Risk CRC Screening

<table>
<thead>
<tr>
<th></th>
<th>Start</th>
<th>Test, Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single FDR age ≥ 60</td>
<td>50 y</td>
<td>Same as AR</td>
</tr>
<tr>
<td>Single FDR age &lt; 60 or multiple FDR</td>
<td>40y or 10y before youngest FDR</td>
<td>Colonoscopy q 5y</td>
</tr>
<tr>
<td>HNPCC*</td>
<td>20-25y</td>
<td>Colonoscopy q 2y until 40, then q 1y</td>
</tr>
<tr>
<td>FAP*</td>
<td>10-11y</td>
<td>Sigmoidoscopy q 1y</td>
</tr>
</tbody>
</table>

*Consider Genetic Testing*
Current Screening Methods: Evidence-Based Data
Types of Stool Testing

- **Guiac-Based**
  - Detects blood in stool through *peroxidase* activity in Heme/Hemoglobin
- **Immunological**
  - Detects *human globin*, protein that constitutes Hemoglobin
- **DNA**
  - Detecting molecular markers associated to advanced neoplasia/cancer
Guiac-FOBT

**Benefits**

- Safest & least expensive
- Efficacy (Prospective RCT)
  - Mortality reduction 15-33%
  - Incidence reduction 17-20%

**Limitations**

- Low sensitivities for CRC
- Variable Sensitivity (37%-79%)
- Only 1/3 of patients with positive FOBT undergo colonoscopy
- Requires annual testing
- Dietary and drug restrictions

Mandel et al., NEJM 1993; Mandel et al., NEJM 2000
High-Sensitivity G-FOBT

- Hemoccult –SENSA
- Diagnostic accuracy improved
  - Sensitivity for CRC  64.1% - 79.4%
  - Specificity for AN/CRC  87.0% - 98.1%
- Requires dietary restrictions
- Requires 3 BM testing/yearly evaluation
- Minimal increase cost compared to low-sensitivity gFOBT

Allison JE et al.  NEJM 1996
# Fecal Immunological Testing (FIT)

<table>
<thead>
<tr>
<th><strong>Benefits</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use antibodies specific to human hemoglobin</td>
<td>• No data from RCT</td>
</tr>
<tr>
<td>• Specific to human blood</td>
<td>• Higher cost than gFOBT</td>
</tr>
<tr>
<td>• Not affected by necessity of dietary and drug restrictions</td>
<td>• Similar diagnostic profile to Hemoccult-SENSA</td>
</tr>
<tr>
<td>• More specific to lower GI track source (globin digested by digestive enzymes)</td>
<td></td>
</tr>
</tbody>
</table>
Why a Stool-Based DNA Assay for Colorectal Neoplasia?

- Colorectal cancer results from an accumulation of mutations in genes that control cell growth and normal cell death
- The DNA alterations are known
- Cells with mutated DNA continuously shed into the feces (DNA is stable in stool)
- The DNA changes identified are fundamental to the neoplastic process and serve as biomarkers of risk or disease
Advantages of a molecular approach to CRC Screening

- No dietary restrictions or bowel preps
- Non Invasive
- Allows for large scale screening
- The DNA changes identified are fundamental to the neoplastic process
- Entire colorectum is evaluated
# Fecal DNA Testing (Prospective Trial)

<table>
<thead>
<tr>
<th>Most Advanced Finding at Colonoscopy</th>
<th>Total No.</th>
<th>Positive Fecal DNA (%)</th>
<th>Positive FOBT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>K-ras</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>31</td>
<td>51.6</td>
<td>16.1</td>
</tr>
<tr>
<td>Advanced adenoma</td>
<td>403</td>
<td>15.1</td>
<td>4.5</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>40</td>
<td>32.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Other</td>
<td>363</td>
<td>13.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Minor polyps</td>
<td>648</td>
<td>7.6</td>
<td>2.9</td>
</tr>
<tr>
<td>No polyps on colonoscopy</td>
<td>1423</td>
<td>5.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Imperiale et al, NEJM 2004*
Objective: To compare stool DNA and FOBT for detection of screen-relevant neoplasia (curable stage cancer, HGD or adenomas >1 cm)

Blinded, multicenter cross-sectional study

SDT-1 23 marker assay: point mutations on K-ras, APC, p53; BAT-26, long DNA

SDT-2: point mutations on K-ras, scanned mutator cluster region of APC, vimentin methylation
# Summary of Test Performance

<table>
<thead>
<tr>
<th>Index Test</th>
<th>Screen-Relevant Neoplasia, n*</th>
<th>Positive Test Result, n</th>
<th>Sensitivity (95% CI)</th>
<th>No Screen-Relevant Neoplasia, n</th>
<th>Negative Test Result, n</th>
<th>Specificity (95% CI)</th>
<th>Positive Likelihood Ratio (95% CI)</th>
<th>Negative Likelihood Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoccult (n = 2497)</td>
<td>157</td>
<td>17</td>
<td>11 (6-16)†</td>
<td>2340</td>
<td>2297</td>
<td>98 (98-99)‡</td>
<td>5.9 (3-10)</td>
<td>0.9 (0.9-1.0)</td>
</tr>
<tr>
<td>HemoccultSensa</td>
<td>157</td>
<td>33</td>
<td>21 (15-27)§</td>
<td>2340</td>
<td>2258</td>
<td>97 (96-97)‖</td>
<td>6.0 (4-9)</td>
<td>0.8 (0.8-0.9)</td>
</tr>
<tr>
<td>SDT-1 (n = 2497)</td>
<td>157</td>
<td>31</td>
<td>20 (14-26)</td>
<td>2340</td>
<td>2246</td>
<td>96 (95-97)</td>
<td>4.9 (3-7)</td>
<td>0.8 (0.8-0.9)</td>
</tr>
<tr>
<td>SDT-2 (n = 217)</td>
<td>142</td>
<td>66</td>
<td>40 (32-49)¶</td>
<td>75</td>
<td>NA**</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available; SDT = stool DNA test.

* Includes curable-stage cancer, high-grade dysplasia, and adenomas ≥1 cm.
† $P = 0.02$ for STD-1 vs. Hemoccult.
‡ $P < 0.001$ for STD-1 vs. Hemoccult.
§ $P = 0.80$ for STD-1 vs. HemoccultSensa.
‖ $P = 0.40$ for STD-1 vs. HemoccultSensa.
¶ We calculated the weighted sensitivity for SDT-2 with the following equation: reweighted sensitivity = (% [colorectal cancer + high-grade dysplasia] \( \times \) PR) + (% adenomas ≥2 cm \( \times \) PR) + (% adenomas 1–2 cm \( \times \) PR) = (0.13 \( \times \) 0.49) + (0.18 \( \times \) 0.57) + (0.68 \( \times \) 0.34). PR = proportion of participants for that category of screen-relevant neoplasia in the entire population with screen-relevant neoplasia. See “Comparison of Stool DNA Tests” for statistical comparisons of SDT-1 and SDT-2 in participants who had both DNA tests performed.
** We did not calculate formal specificity because SDT-2 was not performed on all subsets without screen-relevant neoplasia.
# Summary Stool Testing

<table>
<thead>
<tr>
<th></th>
<th>gFOBT</th>
<th>HS-FOBT</th>
<th>FIT</th>
<th>sDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Accuracy</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Dietary Restrictions</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Annual Evaluation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>???</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++++</td>
</tr>
</tbody>
</table>
## Sigmoidoscopy

### Advantages
- Reduction 60-80% mortality
- 20% reduction in incidence
- Can be performed by PCP
- Low risk

### Limitations
- Examines 1/3 colon
- No randomized clinical trials
- Adenomas in right colon can occur without adenomas in the left colon
Barium Enema: Advantages

- Widely available
- Safer and less expensive than colonoscopy
- Does not require sedation
Barium Enema: *Limitations*

- National Polyp study in U.S. BE had **50% sensitivity for polyps ≥ 1cm**
  - low sensitivity!
- Need for colonoscopy if lesions are found
- Radiation exposure
Colonoscopy: \textit{Advantages}

- Only test that allows examination of the entire colon & provides ability for \textit{removal} of polyps
- Although no controlled trials several cohort, observational and 1 case-controlled study → reduction in CRC mortality
Colonoscopy Related Risk Reduction of CRC

- Canadian study (administrative database)
  - Risk reduction for 14 yrs for distal CRC
  - Risk reduction for only 7 yrs for proximal CRC
- Canadian study (administrative database)
  - Population based case-controlled study
  - Risk reduction left sided CRC (OR 0.33)
  - No risk reduction right sided CRC (OR 0.99)

Clin Gastroenterol Hepatol 2008;6:1117-1121
Colonoscopy: **Limitations**

- **Cost**
- **Complications**
  - Perforations - 1:1000
  - Death 1-3 in 10,000
- **Incomplete procedure 5-15%**
- **Miss 5-10% of adenomas > 1cm**
- **High level of expertise**
CT Colonography ("virtual colonoscopy") for CRC screening

- Reconstructed spiral CT images of colon
- Non-invasive
- Still requires preparation as for colonoscopy
- No sedation given
- New data indicates that may be an acceptable screening strategy in average risk individuals
8 mm sigmoid polyp
## CT Colonography

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No Subjects</th>
<th>Tech Method</th>
<th>Polyp Sensitivity ≥10 mm (%)</th>
<th>Polyp Specificity ≥10 mm (%)</th>
<th>Cancer Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson</td>
<td>2003</td>
<td>703</td>
<td>2-D, 3-D, problem solving</td>
<td>63</td>
<td>95</td>
<td>NA</td>
</tr>
<tr>
<td>Pickhardt*</td>
<td>2003</td>
<td>1233</td>
<td>3-D-fly-through</td>
<td>94</td>
<td>95</td>
<td>--</td>
</tr>
<tr>
<td>Cotton**</td>
<td>2004</td>
<td>600</td>
<td>2-D</td>
<td>55</td>
<td>96</td>
<td>75</td>
</tr>
<tr>
<td>Rockey**</td>
<td>2005</td>
<td>614</td>
<td>2-D</td>
<td>59</td>
<td>96</td>
<td>78</td>
</tr>
</tbody>
</table>
Comparison of results from primary CT colonography (n=3120) and optical colonoscopy (n=3163) screening programs

Main outcomes: detection of advanced neoplasia and total number of harvested polyps

CT colonography (CTC) followed by optical colonoscopy

Primary Endpoint: Detection by CTC of histologically confirmed large (≥ 10mm) adenomas or carcinomas
Virtual Colonoscopy - Issues

- What needs to be detected/removed?
- Interval (interval for small polyps)?
- Training Standardization
- Cost effectiveness/ insurance coverage CPT
- Flat lesions
- Impact on compliance
- Extracolonic findings
- Logistics of same day colonoscopy
- Bowel preparation
- Radiation exposure
Summary

- CRC is a highly prevalent and deadly cancer
- Screening for CRC reduces incidence and mortality of CRC
- Screening adherence continue low, specially in Puerto Rico
- Evaluation and screening for Hereditary CRC requires different guidelines than AR people
- Several options available for CRC screening based on detection of adenomas or cancer
- Colonoscopy only method that provides diagnosis and treatment (not perfect, risk)