# Screening For Colorectal Cancer

**Francis A. Farraye, MD, MSc**
**Clinical Director, Section of Gastroenterology**
**Boston Medical Center**
**Associate Professor of Medicine and Epidemiology**
**Boston University School of Medicine**

Center for Digestive Disorders
BOSTON MEDICAL CENTER

BOSTON UNIVERSITY SCHOOL of Medicine

# Colorectal Cancer

- Second most common cancer in the United States
- Overall mortality rate approaches 60%
- Approximately 5% of the US population will develop CRC in their lifetime and half will die of the disease
- Estimated 145,290 new cases of CRC and 73,470 deaths in 2005
  - Massachusetts-3560 new cases and 1380 deaths

# Average annual age-specific US incidence and mortality rates of CRC, 1992–1996


*Natl Cancer Inst, SEER Cancer Statistics Review 1973–1996*

# Colorectal Cancer

- Average age of diagnosis in symptomatic patients is 67
- Five-year survival rate is 90 percent when CRC is detected in an early localized stage
- Only 1/3rd of patients with CRC are diagnosed in the earliest stage
- ~ 93% cases occur in persons $\geq$ age 50

# Screening for Colorectal Cancer

- Screening: testing asymptomatic individuals for disease
  - sensitive, specific, affordable, acceptable to asymptomatic patients, and able to reduce mortality and morbidity
- Surveillance: interval testing in high risk patients
- Diagnosis: evaluation of patients with symptoms or with positive screening tests

# Screening for Colorectal Cancer

- Substantial evidence exists to suggest that most, if not all, colorectal carcinomas arise from preexisting adenomas
- Time course from normal colonic mucosa to polyp and then to carcinoma probably requires 7-15 years
- Mortality rate for CRC declining over past 20 years
    - Combination of decreased incidence and advances in detection and treatment

# Screening for Colorectal Cancer

- **Suitable disease for screening**
  - **common malignancy with a long asymptomatic preclinical phase**
  - **high survival rate if detected in its early stage**
- **Good screening tests exist**
  - **Several options are available**
  - **Not screening is no longer an option**
- ***Prevention of CRC should be achievable by identifying and removing adenomatous polyps from asymptomatic patients***

# Screening = Early Detection and Prevention

- Early detection of CRC $\longrightarrow$ decreased mortality
- Prevention ( removal of adenomatous polyp $\longrightarrow$ decreased incidence

# CRC Awareness is Increasing

- **Medicare Funding**
- State laws mandating insurance
- "Couric Effect" – Today Show
- National awareness campaigns
- Endorsement by guideline groups
  - ACG, AGA, ACS, ASCRS, ACR, AAFP
  - US Preventive Services Task Force

# Medicare Funding for CRC Screening

- Effective 1/1/98 for Medicare patients over 50
  - Annual FOBT for average risk patients
  - Screening FS every 4 years for average risk patients
  - Colonoscopy every two years for high risk individuals
- Effective 7/1/01 for Medicare patients over 50
  - Colonoscopy every 10 years for average risk patients

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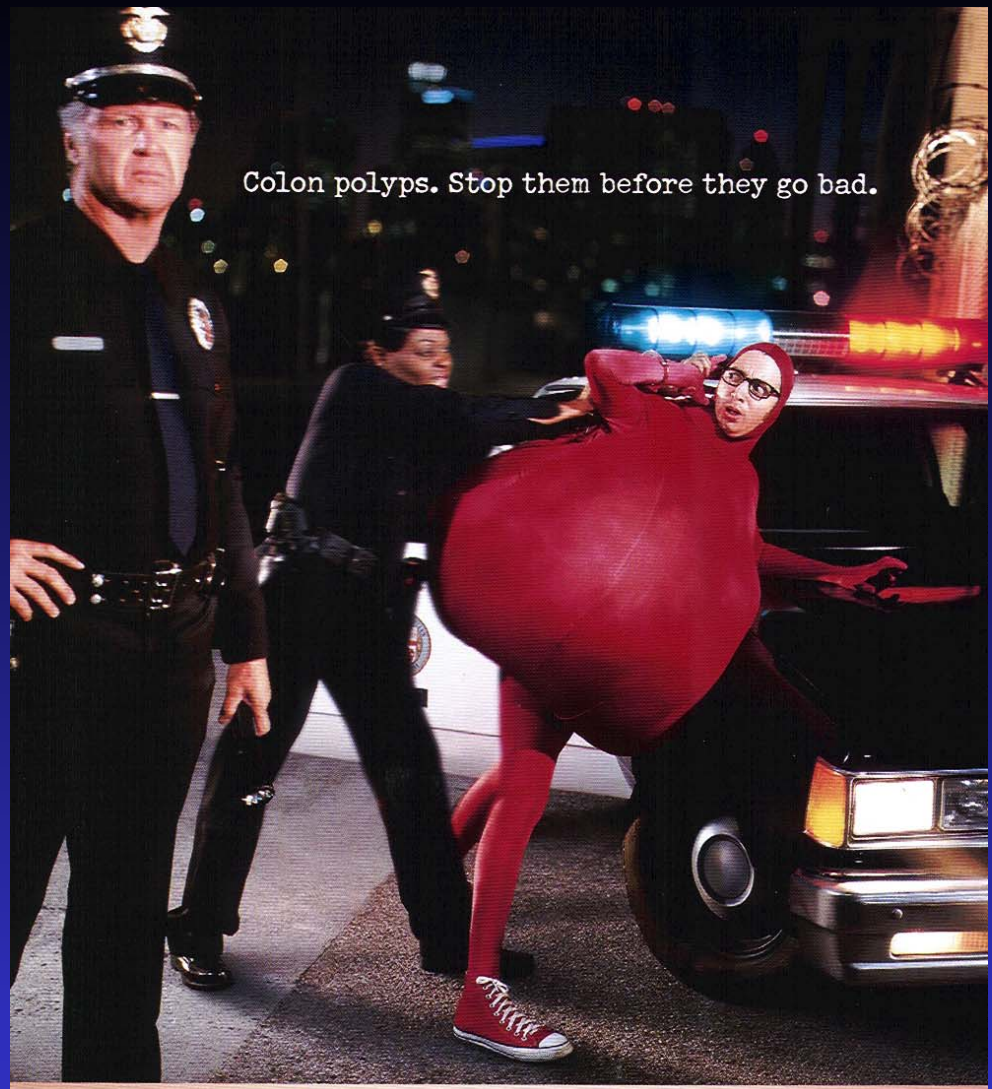


Colon cancer almost always starts with a polyp. Get the polyp early and stop colon cancer before it even starts. And that's for both men and women. Just get a test from your doctor. 1-800-ACS-2345 or cancer.org

Ad Council

Colon cancer. Get the test. Get the polyp. Get the cure.

American Cancer Society

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# US Preventive Services Task Force

- **Grade A Recommendation for colorectal cancer screening**
- **Optimal method of screening not clear**
  - **Pignone, *Ann Int Med* 2002;137:129**

# Cost-Effectiveness (Cost/Year Life Saved)

- Mandatory motorcycle helmets $2,000
- Colorectal cancer screening $25,000
- Breast cancer screening $35,000
- Dual airbags in cars $120,000
- Smoke detectors in homes $210,000
- School bus seat belts $1,800,000

**CRC screening may in fact be cost saving**

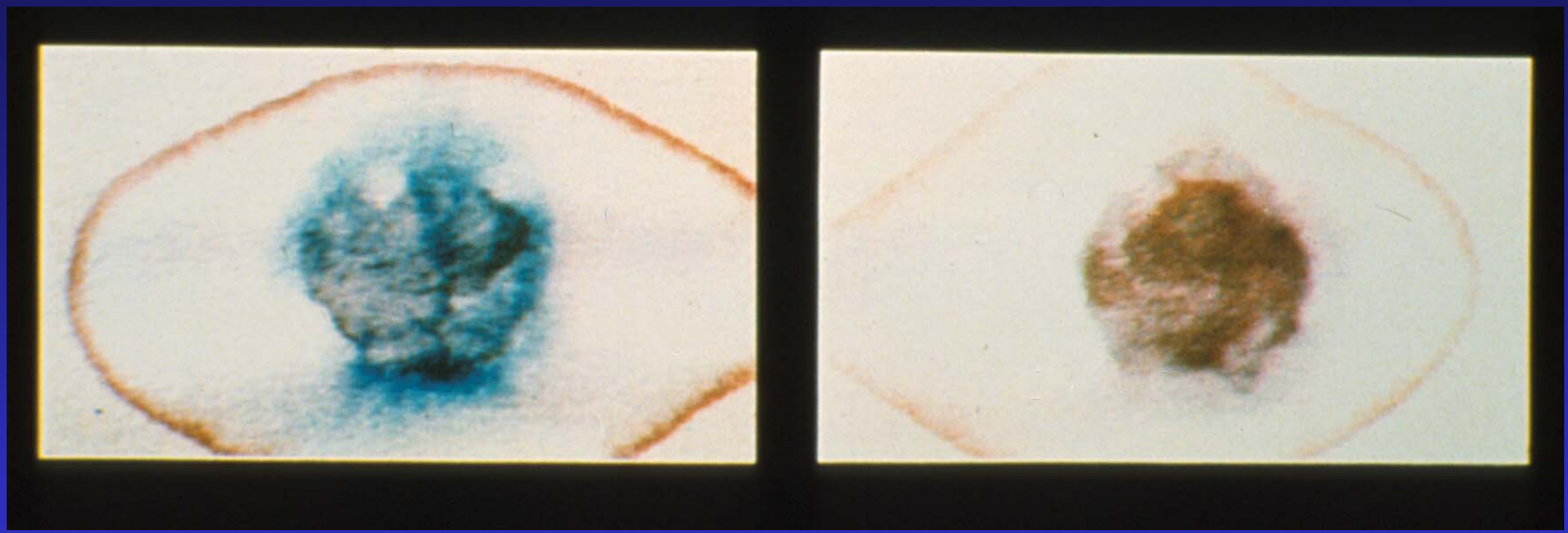
# Average Risk Asymptomatic Patients Starting at Age 50

- Annual FOBT
- Flexible Sigmoidoscopy every 5 years
- FOBT and Flexible Sigmoidoscopy
- DCBE every 5-10 years
- Colonoscopy every 10 years

# Average-Risk Options Are Not Equivalent

- Effectiveness
- Up front costs
- Risk
- Acceptability

# Fecal Occult Blood Test



# Fecal Occult Blood Test

**Pros:**

- Proven effective in randomized trials
- Non-invasive
- Cost-effective

**Cons:**

- Mortality reduction low (15-33%)
- Compliance with annual testing unlikely in community practice
- Evaluation of positive tests often inadequate

Mandel et al, *N Engl J Med* 1993;328:1365; Jorgensen et al, Gut 2002;50:29; Scholefield et al, Gut 2002;50:840; Lurie, Welch, *J Natl Cancer Inst* 1999;91:1641

# Flexible Sigmoidoscopy

## Pros

- Easier prep
- Performed by PCPs
- Inexpensive
- No Sedation

## Cons

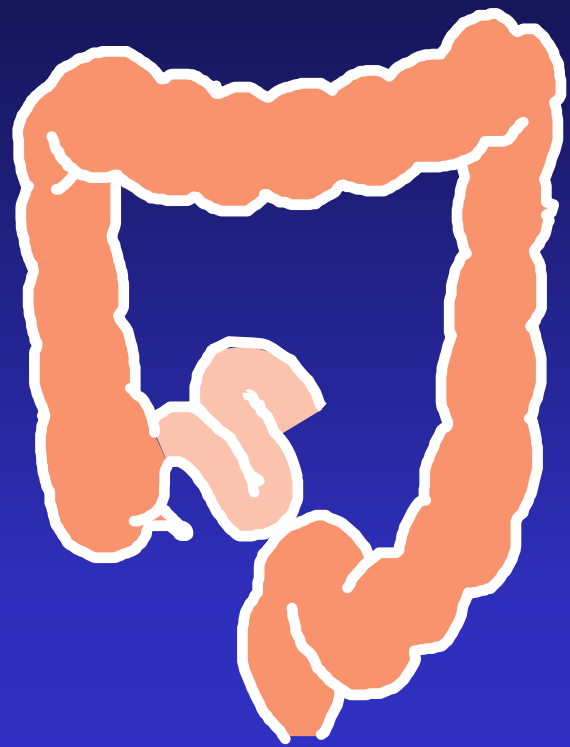
- Prep often limits insertion
- Miss rates higher
- Reduced willingness to repeat
- Does not examine right colon

Levin et al Gastro 2002;123:1786

Loeve et al JNCI 2000;92:557

# Anatomic distribution of colorectal cancers and polyps according to the reach of the sigmoidoscope or colonoscope

Proximal colonic lesions
( beyond reach of the sigmoidoscope)
36% of cancers
34% of Adenomatous polyps



Distal colorectal lesions
(within reach of the sigmoidoscope)
64% of cancers
66% of Adenomatous polyps

# Sigmoidoscopy to Detect Advanced Colonic Pathology

- **Half Full**
  - **Sigmoid exam detects 68-80% of all patients with advanced neoplasia**
- **Half Empty**
  - **Sigmoid exam fails to detect 52-62% of all patients with advanced proximal neoplasia**

# Screening Colonoscopy

- One of the most powerful tools in clinical medicine
- Polypectomy plus surveillance colonoscopy reduced incidence of CRC by 76-90% (NPS)
- Surveillance accounts for 20-40% of the costs for CRC
  - 90% of the benefit comes from index colonoscopy
  - Efforts must be made to decrease number of surveillance examinations

# Colonoscopy

## Pros

- Most sensitive
- Long lasting protection
- Single session diagnosis and therapy
- Comfortable

## Cons

- Perceived as invasive
- Highest risk
- Requires bowel preparation
- Imperfect sensitivity

Rex, Am J Gastroenterol 2000;95:868

# Colonoscopy – It's Not Perfect

- Inherent miss rate
- Flat and depressed lesions
- Variable Growth Rates (e.g.,microsatellite instability)

Rex, Am J Gastroenterol 2001;95:952

# Complications of Screening Tests

## Complication Rates

| Screening Test | (Perforation/Hemorrhage) | Death |
|---|---|---|
| Barium enema | 1/10,000 | < 1/10,000 |
| Sigmoidoscopy | 1-2/10,000 | <1/10,000 |
| Colonoscopy | 10-30/10,000 | 1-3/10,000 |

# CRC Screening Options
## *Detection Rates*

| | *Cancers* | *Polyps ≥ 1 cm* |
|---|---|---|
| **FOBT** | **30%** | **10%** |
| **Flex Sig** | **70%** | **70%** |
| **FOBT + FS** | **75%** | **75%** |
| **DCBE** | **85%** | **50%** |
| **Colonoscopy** | **95%** | **95%** |

# CRC Screening Recommendations

| | *FOBT* | *FS* | *FS +FOBT* | *Colon* | *DCBE* |
|---|---|---|---|---|---|
| **USPSTF** | + | + | + | + | + |
| **GI Consortium** | + | + | + | + | + |
| **ACS** | + | + | + | + | + |
| **ACG** | + | + | + | **Preferred** | + |
| **Canadian Task Force** | + | + | **Insufficient** | **Insufficient** | **Insufficient** |

# Do Something

- All persons aged 50 years and older should begin regular screening
- High-risk individuals may need to begin screening earlier
- Less than half the eligible population has had any screening
- Choice of which test is less important than initiating some screening

# The Future for CRC Screening

- Virtual colonoscopy (CT Colography)
- Stool analysis for DNA mutations

# CT Colography

- Novel imaging technique in which helical computed tomography (CT) is used to generate 2D and 3D displays of the colon and rectum

# Advantages: CT Colography

- Minimally invasive, no sedation required
- Retrograde and antegrade viewing
- Ability to traverse strictures
- Accurate anatomic localization of tumors

# 3D Trial: CT Colography

- Multicenter – military hospitals
- 1233 asymptomatic patients

| | 10mm | 8mm | 6mm |
|---|---|---|---|
| • CT Sens AD by pt | 94% | 94% | 89% |
| • CC Sens AD by pt | 88% | 92% | 92% |
| • CT Specificity | 96% | 92% | 80% |

Pickhardt, NEJM 2003; 349: 2191

# Disadvantages: CT Colography

- Performance in an average risk population highly variable
- Stringent bowel prep required
- Uncomfortable
- Flat lesions not seen
- Colonoscopy needed to confirm and biopsy
- Not endorsed by authoritative groups
- Not covered by Medicare or third-party payers

# Indications 2005: CT Colography

- Incomplete colonoscopy
  - Screening
  - Obstructing tumor or stricture
- Evaluation of high-risk symptomatic patients
- Pre-operative tumor localization and staging
- CRC screening for patients who refuse colonoscopy

# CT Colography for CRC Screening

- Under optimal conditions, virtual colonoscopy compares favorably with conventional colonoscopy for detecting clinically significant lesions
- Definition of "significant" lesion based on polyp size (?6 mm vs. 10 mm) remains highly controversial
- Marked site-to-site variation in performance precludes widespread endorsement by authoritative groups
- Not covered by Medicare or third-party payers

# Rationale: Stool-Based DNA Testing

- CRC results from an accumulation of alterations in known tumor suppressor genes (*APC*, p53) and proto-oncogenes (K-*ras*)
- CRC cells with mutated DNA continuously shed into the feces
- DNA is stable in stool

# Fecal DNA Testing

- 5 targets K-RAS, P53, APC, BAT-26, long DNA
- Sensitivity for cancer 52%
- Sensitivity of FOBT for cancer 13%
- Sensitivity for advanced adenomas 18%
- Specificity 94%

Imperiale TF, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004 Dec 23;351(26):2704-14.

# Advantages: Stool-Based DNA Testing

- "Total colon" examination
- Non-invasive, safe
- No bowel preparation
- Convenient (single sample collected at home)
- Rapidly improving technology

# Stool-Based DNA Testing: PreGen-Plus ™

- Assay system developed by EXACT Sciences
- 23 genetic markers assayed:
  - > 21 point mutations in K-ras, APC, p53
  - > 1 microsatellite instability marker = Bat-26
  - > " Long DNA" (> 200 Bp)
- Single whole stool (≥ 30 gm) required
- Specific for human DNA

# Multitarget Stool-Based DNA Testing

## Summary of Published Literature

| | *Sensitivity* | *Specificity* |
|---|---|---|
| Cancer | ~70% | 95% |
| Adenomas (≥ 1cm) | ≥ 50% | 95% |

# Prospective, Multicenter Trial Comparing Stool-Based DNA vs. FOBT*

*Sensitivity*

| | *Cancer* | | *Advanced Adenomas* |
|---|---|---|---|
| SB-DNA | 52% | *P<0.001* | 15% |
| FOBT | 13% | | 11% |

* n = 5400 average-risk subjects; 31 cancers

Imperiale TF, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004 Dec 23;351(26):2704-14.

# Disadvantages: Stool-Based DNA Testing

- Limited sensitivity (especially for advanced adenomas)
- Optimal interval not defined
- High cost ($600-800)
- Not endorsed by authoritative groups

# Recommended Screening Strategies 2005

## *Beginning at age 50: Average Risk*

- **Annual FOBT**
- **Flexible sigmoidoscopy (FS) every 5 years**
- **Annual FOBT plus FS every 5 years**
- **Annual FOBT plus FS every 5 years**
- **Colonoscopy every 10 years**

# Recommended Screening Strategies 200?

## *Beginning at age 50: Average Risk*

- **Annual FOBT**
- **Flexible sigmoidoscopy (FS) every 5 years**
- **Annual FOBT plus FS every 5 years**
- **Annual FOBT plus FS every 5 years**
- **Colonoscopy every 10 years**
- ***Virtual colonoscopy every 5 years***
- ***Stool based DNA testing every 3-5 years***

# Colorectal Cancer Screening

- Compelling rationale
- Suitable tests
- Favorable cost-effectiveness