Colorectal Cancer: A Review

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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

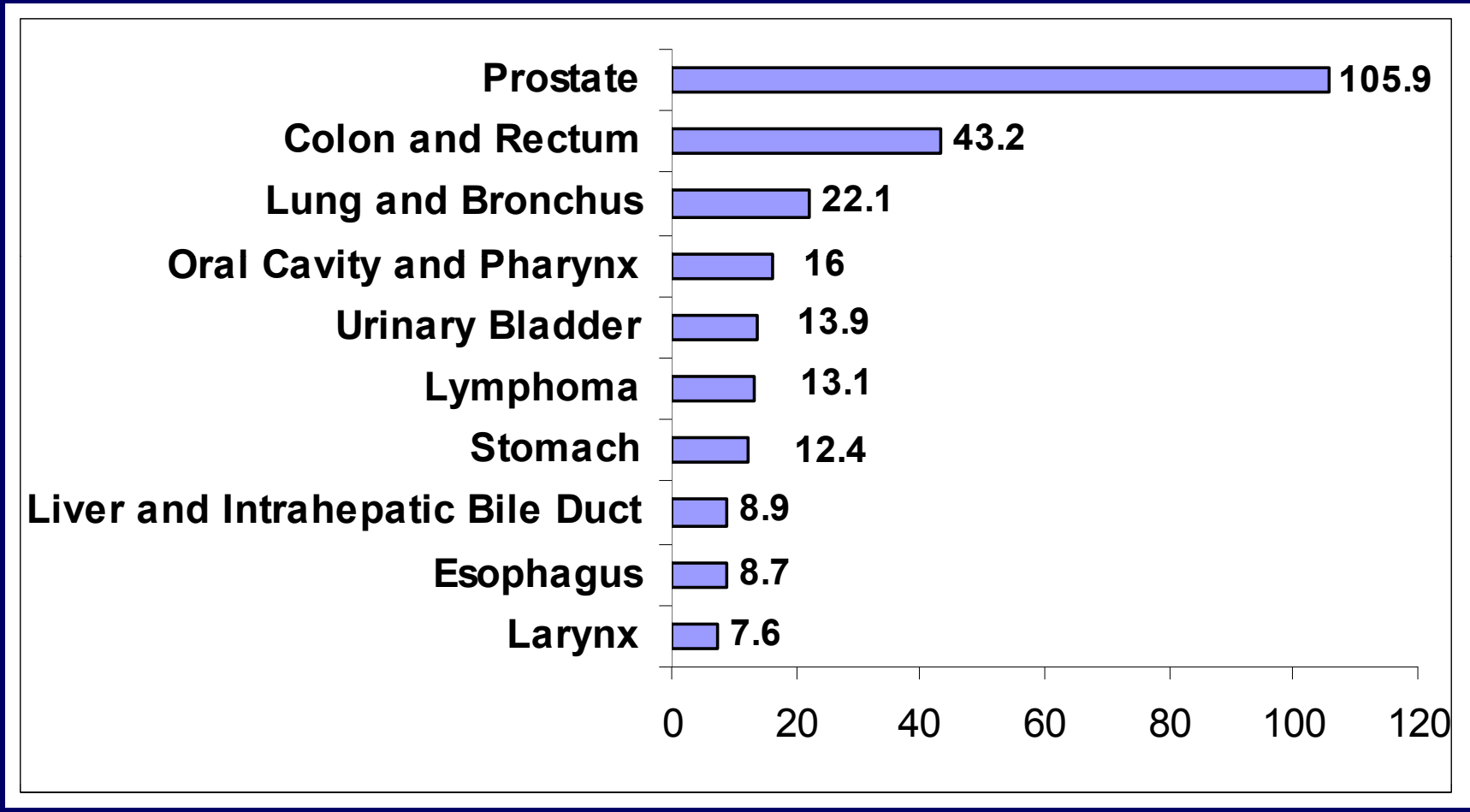
Colorectal Cancer: Epidemiology

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

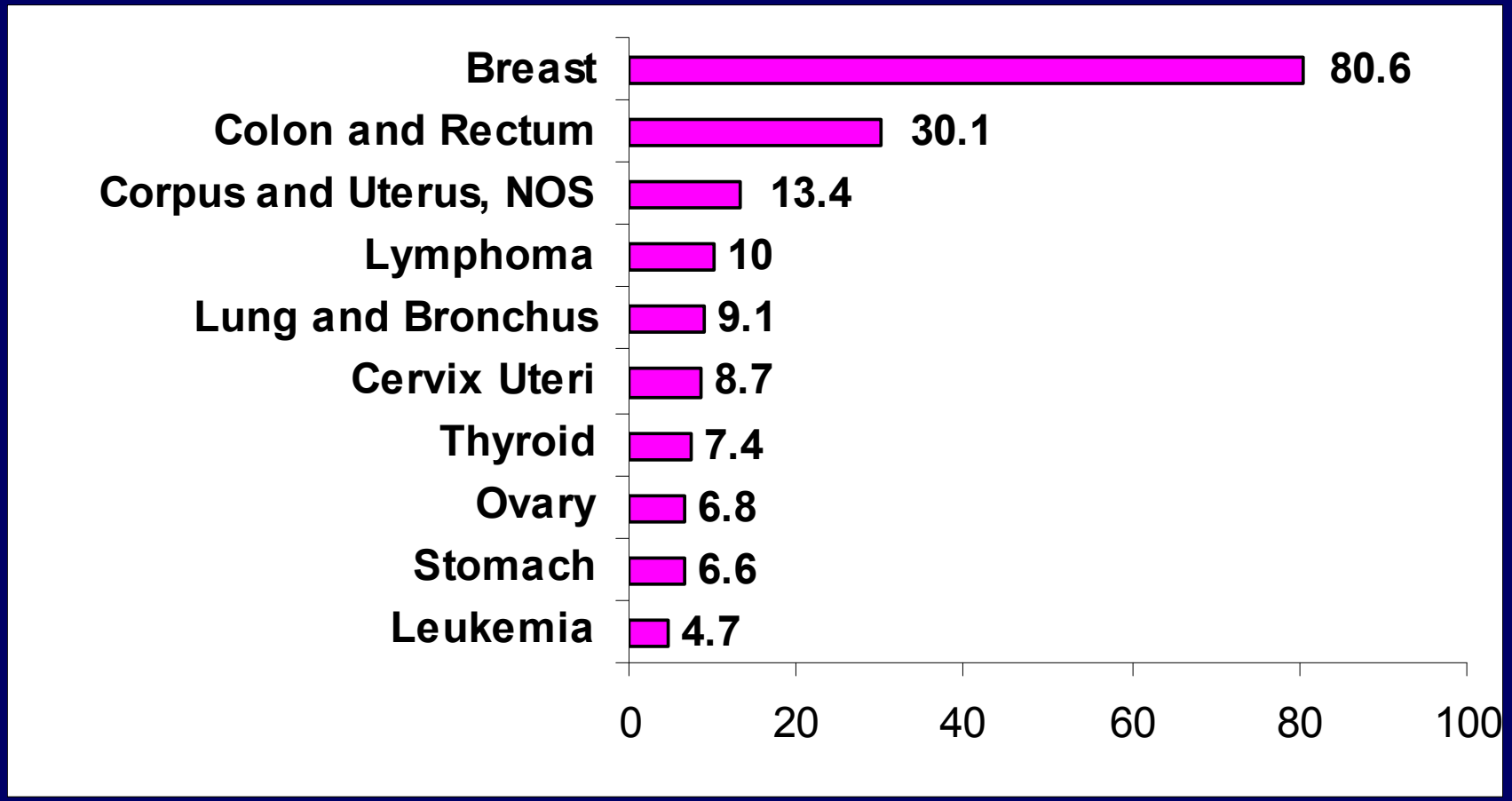
American Cancer Society. *Cancer Facts & Figures 2008.* Atlanta, GA: American Cancer Society; 2008

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



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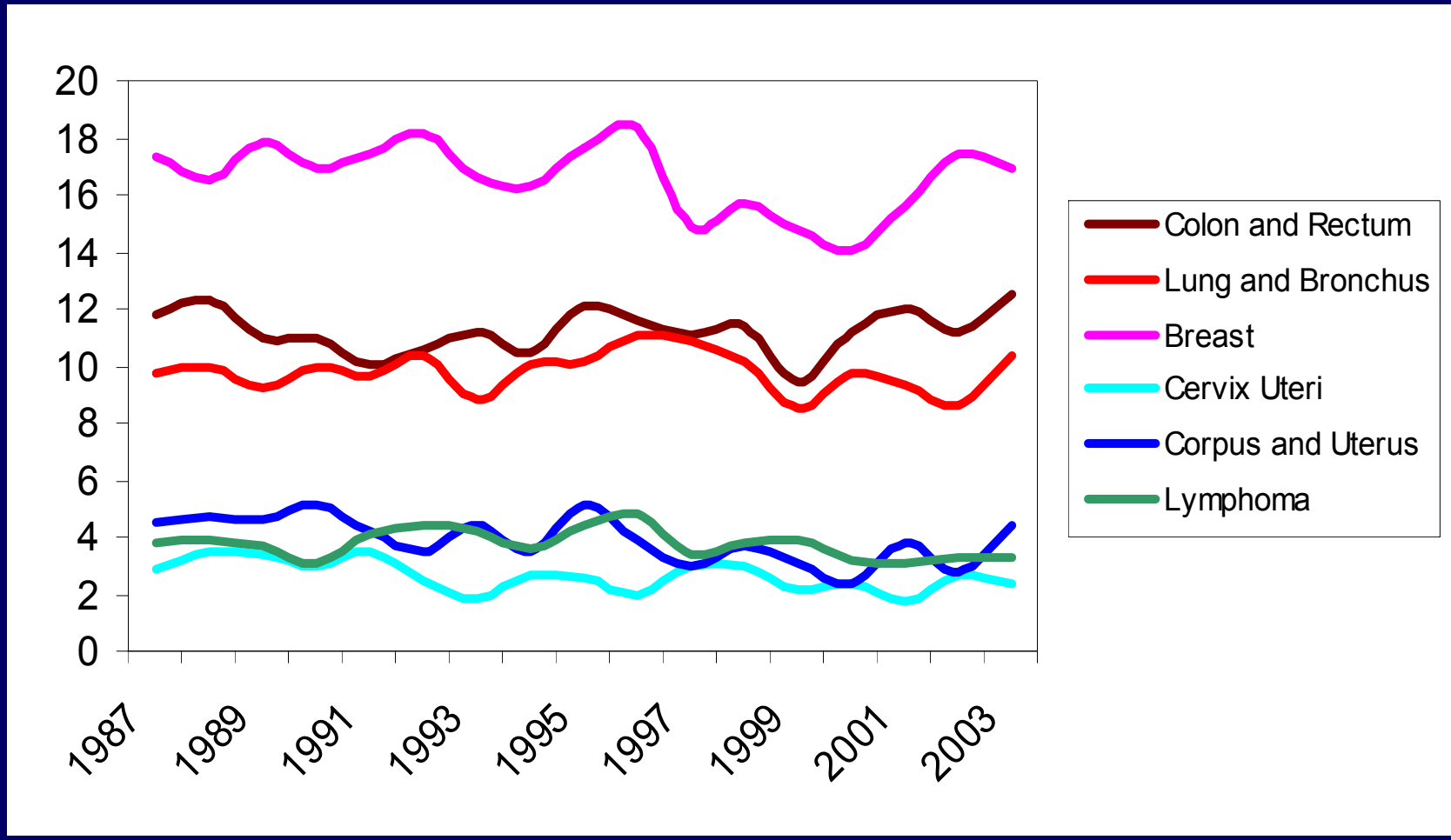
Age-Adjusted Mortality Rates for the Top 6 Sites in Females, 1987-2003



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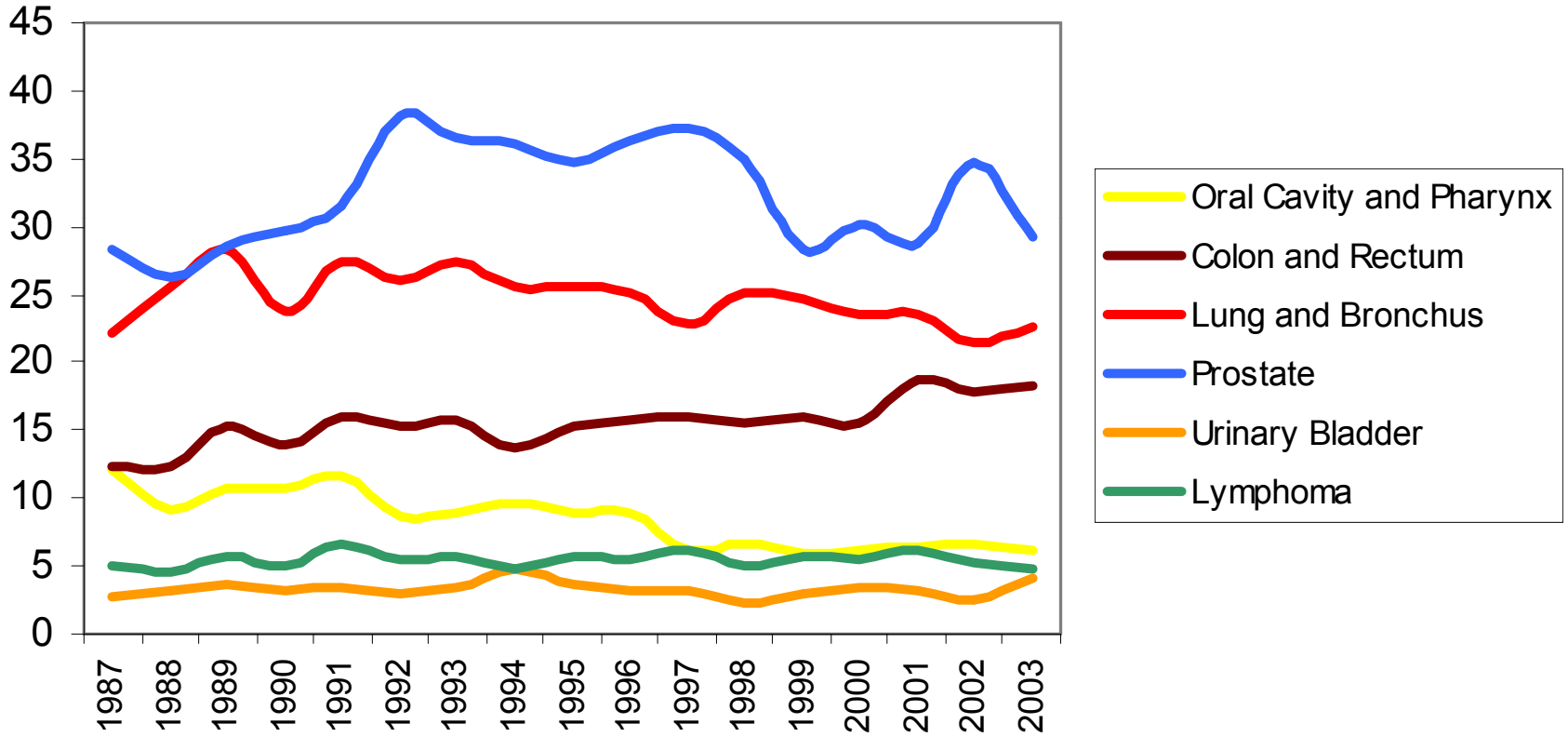


Source: Puerto Rico Central Cancer Registry, Department of Health, August 2006

Rates are per 100,000 and age-adjusted to the 2000 PR population.

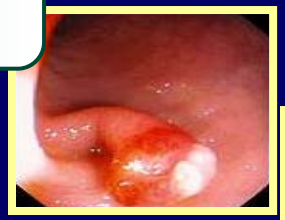
Natural History of Colorectal Neoplasia

Normal

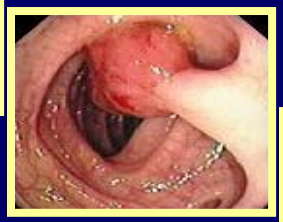
Hyper-proliferation

5 - 10 years

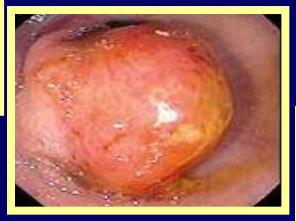
Adenoma: early



3 - 5 years



Adenoma: late



Adenoma: Intermediate

Cancer: curable

Cancer: late

From: Rozen, Young, Levin, Spann (2002)

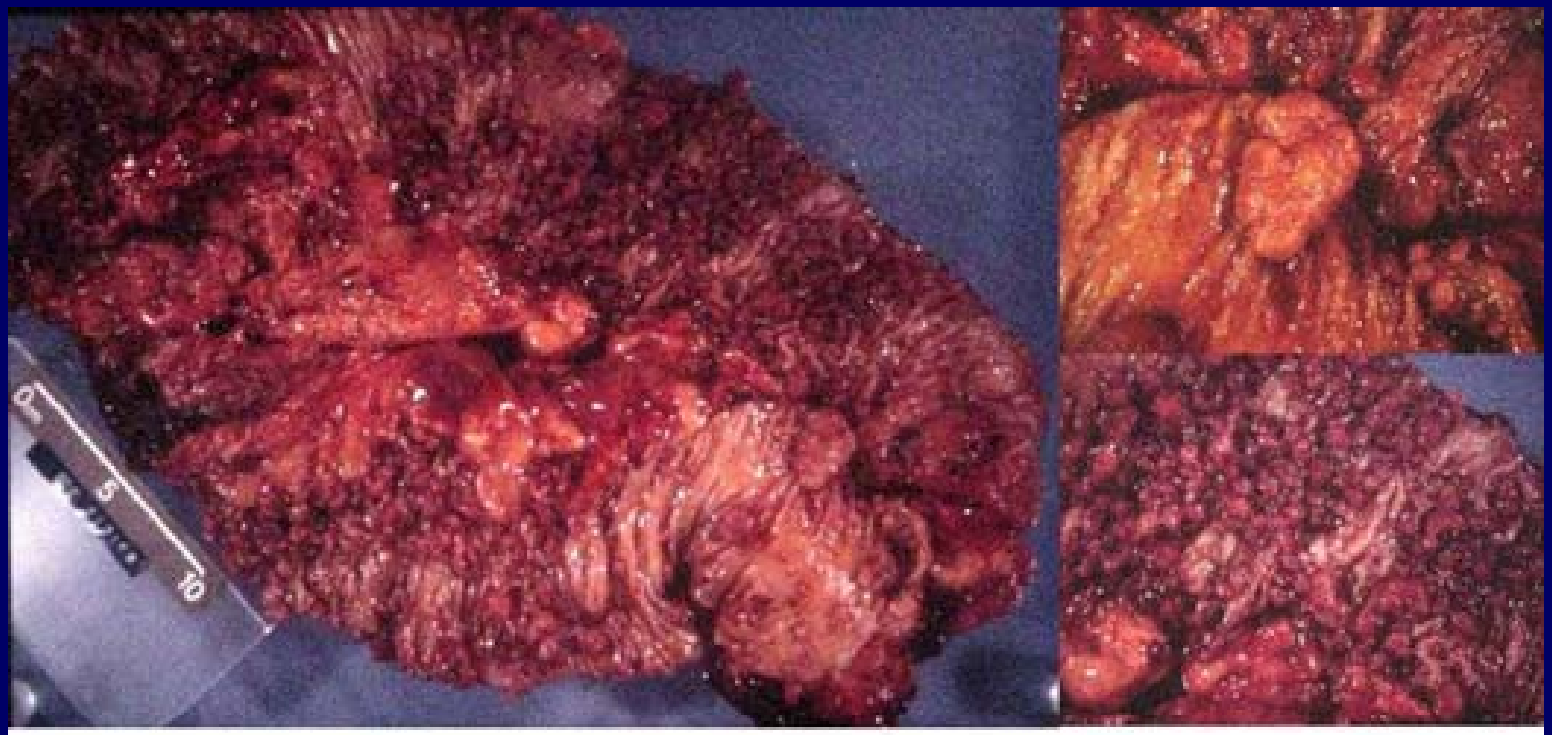
Hereditary Colorectal Cancer

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

Cancer	Lifetime Risk(%)
Colon	100
Duodenal	5-11
Pancreatic	2
Thyroid	2
Brain (medulloblastoma)	< 1
Hepatoblastoma	<1% (< 5y/o)

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

**Jones S, et al. Hum Mol Genetic 2002*

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

Cancer	Lifetime Risk (%)
Colon	80
Endometrial	39-60
Stomach	12-19
Ovarian	9
Ureters/renal	4-10
Brain (glioblastoma)	4

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

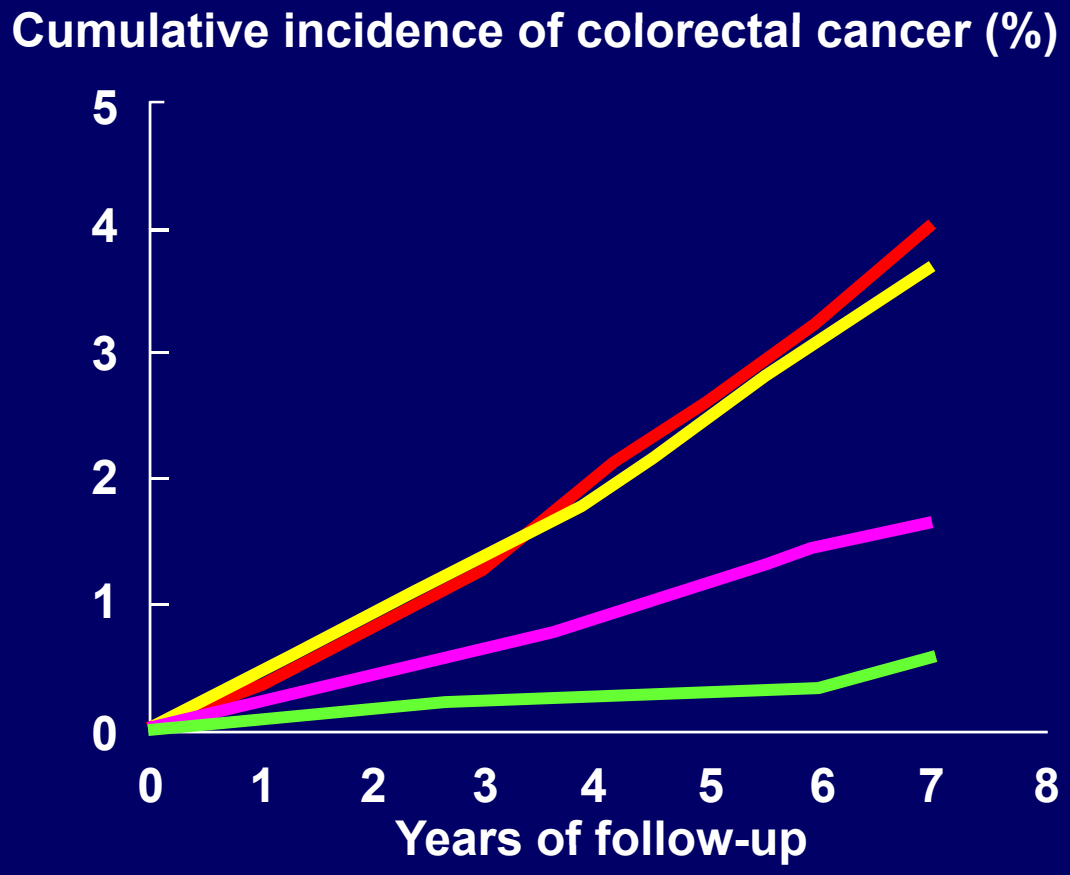
Colorectal Cancer is Suitable for Screening

- 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



No. expected from Mayo Clinic data

No. expected from St. Mark's data

No. expected from SEER data

No. observed

Winawer et al, New Engl J Med 1993; 329: 1977

Behavioral Risk Factors Surveillance System Race/Ethnicity CRC Screening

	Endoscopic Screening (%)
Whites	**59**
African-American	**54**
US Hispanics	**47**
PR Hispanics	**38**

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”)

**CA Cancer J Clin January 2008, Gastroenterology March 2008, Radiology September 2008*

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

Annals of Internal Medicine

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

USPSTF

SCREENING FOR COLORECTAL CANCER
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adults Age 50 to 75 Years*	Adults Age 76 to 85 Years*	Adults Older Than 85 Years*
Recommendation	Screen with high-sensitivity FOBT, sigmoidoscopy, or colonoscopy Grade: A	Do not screen routinely Grade: C	Do not screen Grade: D
	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.	

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

	Start	Test, Intervals
Single FDR age ≥ 60	50 y	Same as AR
Single FDR age < 60 or multiple FDR	40y or 10y before youngest FDR	Colonoscopy q 5y
HNPCC*	20-25y	Colonoscopy q 2y until 40, then q 1y
FAP*	10-11y	Sigmoidoscopy q 1y

***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)

Benefits

- Use antibodies specific to human hemoglobin
- Specific to human blood
- Not affected by necessity of dietary and drug restrictions
- More specific to lower GI track source (globin digested by digestive enzymes)

Limitations

- No data from RCT
- Higher cost than gFOBT
- Similar diagnostic profile to Hemoccult-SENSA

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)

Most Advanced Finding at Colonoscopy	Total No.	Positive Fecal DNA (%)						Positive FOBT (%)
		Overall	K-ras	p53	APC	BAT-26*	Long DNA	
Adenocarcinoma	31	51.6	16.1	25.8	29.0	6.5	3.2	12.9
Advanced adenoma	403	15.1	4.5	2.7	6.7	1.2	2.0	
High-grade dysplasia	40	32.5	12.5	5.0	7.5		12.5	15
Other	363	13.2	3.6	2.5	6.6	1.4	0.6	10.2
Minor polyps	648	7.6	2.9	0.8	2.5	0.6	1.2	4.8
No polyps on colonoscopy	1423	5.6	1.5	1.1	0.8	1.1	1.3	4.8

Imperiale et al, NEJM 2004

Annals of Internal Medicine | ARTICLE

Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia

David A. Ahlquist, MD; Daniel J. Sargent, PhD; Charles L. Loprinzi, MD; Theodore R. Levin, MD; Douglas K. Rex, MD; Dennis J. Ahnen, MD; Kandice Knigge, MD; M. Peter Lance, MD; Lawrence J. Burgart, MD; Stanley R. Hamilton, MD; James E. Allison, MD; Michael J. Lawson, MD; Mary E. Devens; Jonathan J. Harrington; and Shauna L. Hillman, MS

Ahlquist, D. A. et. al. Ann Intern Med 2008;149:441-450

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 3. **Summary of Test Performance**

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

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 sensitvity for SDT-2 with the following equation: reweighted sensitivity = (% [colorectal cancer + high-grade dysplasia] × PR) + (% adenomas ≥2 cm × PR) + (% adenomas 1–2 cm × PR) = (0.13 × 0.49) + (0.18 × 0.57) + (0.68 × 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.

Ahlquist, D. A. et. al. Ann Intern Med 2008;149:441-450

Summary Stool Testing

	gFOBT	HS-FOBT	FIT	sDNA
Diagnostic Accuracy	+	++	+++	+++
Dietary Restrictions	+	+	-	-
Annual Evaluation	+	+	+	???
Cost	+	++	++	++++

Sigmoidoscopy

Advantages

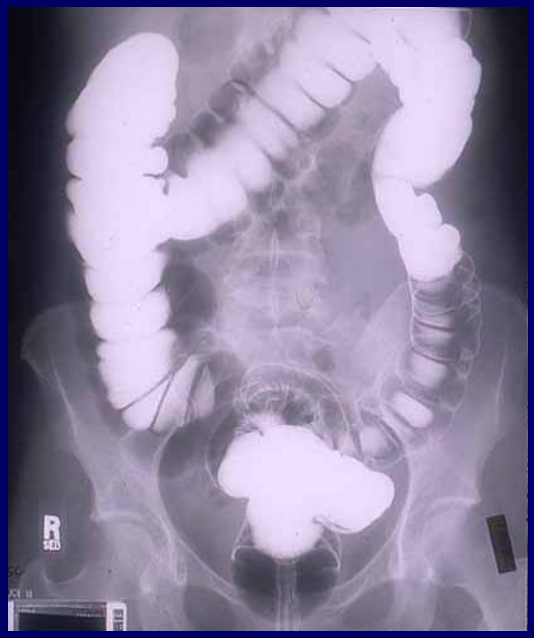
- Reduction 60-80% mortality
- 20% reduction in incidence
- Can be performed by PCP
- Low risk

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

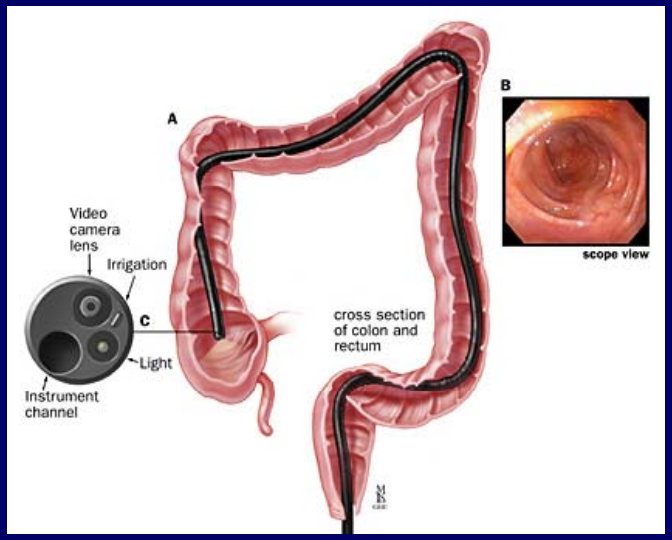


Barium Enema: *Limitations*

- 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: *Advantages*

- Only test that allows examination of the entire colon & provides ability for ***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
Ann Intern Med 2009 2009;150:1-8

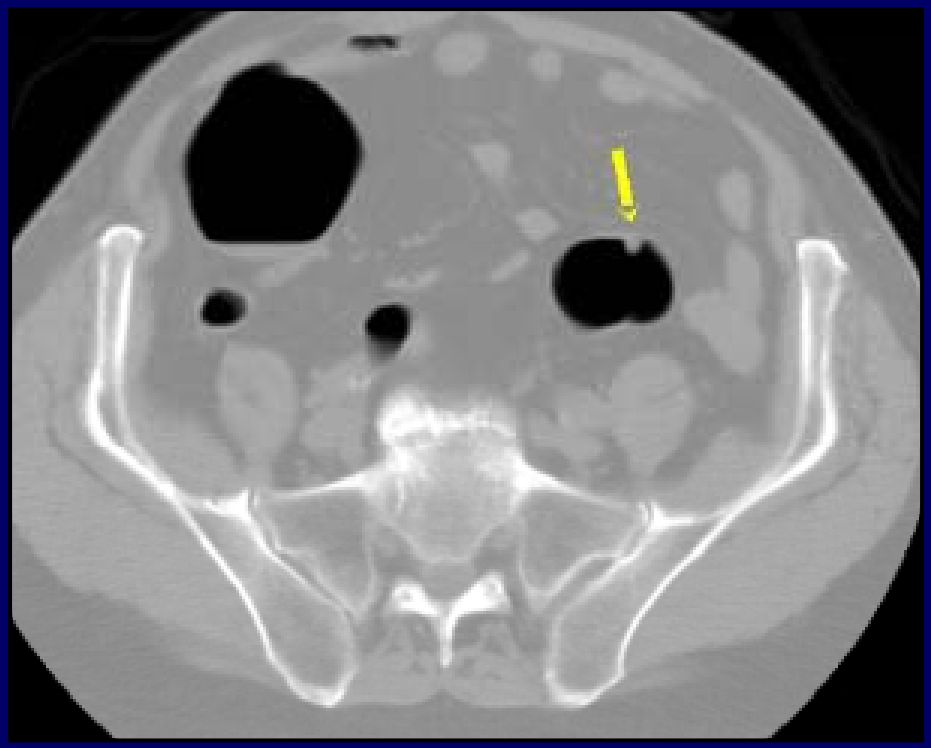
Colonoscopy: *Limitations*

- 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

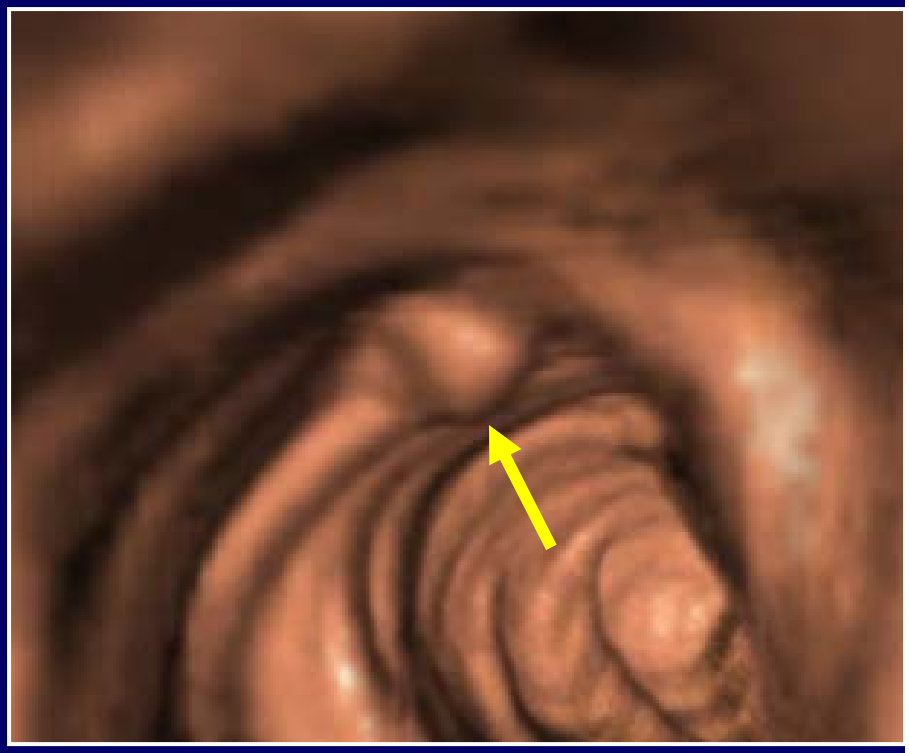
CT Colonography ("virtual colonoscopy") for CRC screening

- 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



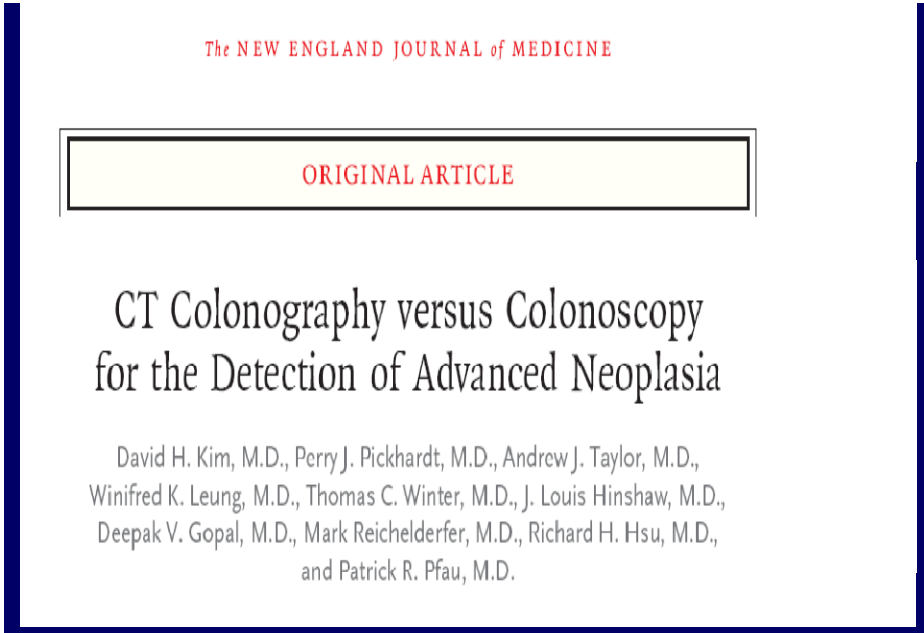
2D



3D

CT Colonography

Author	Year	No Subjects	Tech Method	Polyp Sensitivity ≥10 mm (%)	Polyp Specificity ≥10 mm (%)	Cancer Sensitivity (%)
Johnson	2003	703	2-D, 3-D, problem solving	63	95	NA
Pickhardt*	2003	1233	3-D-fly-through	94	95	--
Cotton**	2004	600	2-D	55	96	75
Rockey**	2005	614	2-D	59	96	78

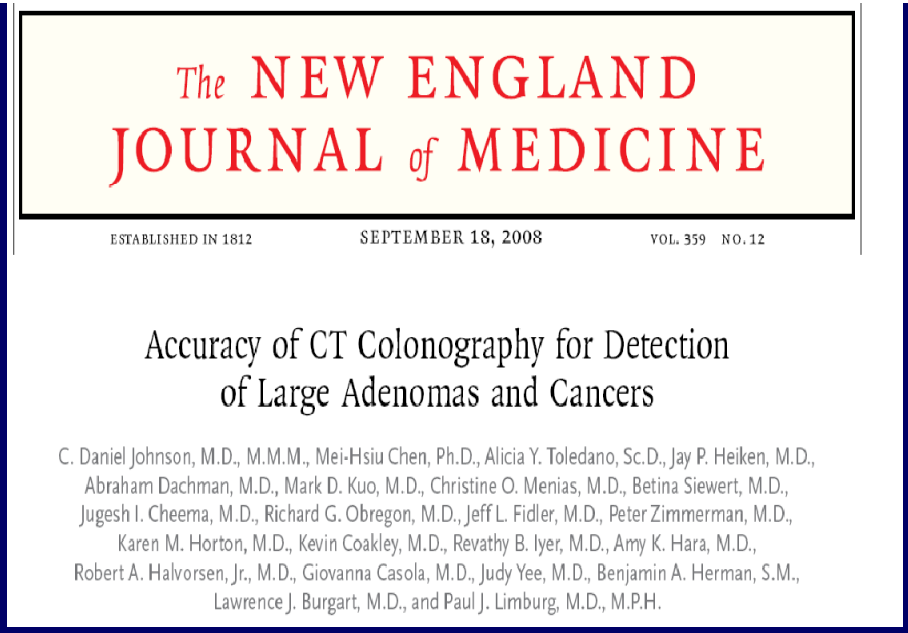


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CT Colonography versus Colonoscopy for the Detection of Advanced Neoplasia

David H. Kim, M.D., Perry J. Pickhardt, M.D., Andrew J. Taylor, M.D., Winifred K. Leung, M.D., Thomas C. Winter, M.D., J. Louis Hinshaw, M.D., Deepak V. Gopal, M.D., Mark Reichelderfer, M.D., Richard H. Hsu, M.D., and Patrick R. Pfau, M.D.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 18, 2008 VOL. 359 NO. 12

Accuracy of CT Colonography for Detection of Large Adenomas and Cancers

C. Daniel Johnson, M.D., M.M.M., Mei-Hsiu Chen, Ph.D., Alicia Y. Toledano, Sc.D., Jay P. Heiken, M.D., Abraham Dachman, M.D., Mark D. Kuo, M.D., Christine O. Menias, M.D., Betina Siewert, M.D., Jugesh I. Cheema, M.D., Richard G. Obregon, M.D., Jeff L. Fidler, M.D., Peter Zimmerman, M.D., Karen M. Horton, M.D., Kevin Coakley, M.D., Revathy B. Iyer, M.D., Amy K. Hara, M.D., Robert A. Halvorsen, Jr., M.D., Giovanna Casola, M.D., Judy Yee, M.D., Benjamin A. Herman, S.M., Lawrence J. Burgart, M.D., and Paul J. Limburg, M.D., M.P.H.

Comparison of results from primary CT colonography (n=3120) and optical colonoscopy (n=3163) screening programs

CT colonography (CTC) followed by optical colonoscopy

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

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)