



Colorectal Cancer Screening and Surveillance: Is It as Effective as Advertised?

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2009 Headline: Colonoscopy Does Not Reduce Colon Cancer Death from Right-Sided CRC!!

- Canadian administrative claims data on 10,292 colon cancer deaths 1996-2003 and 51,460 matched controls
- Prior complete colonoscopy was associated with a 67% reduced risk of colon cancer death from left-sided CRC (OR 0.63, $p < 0.001$)
- Prior colonoscopy was not associated with a reduced risk of death from right-sided CRC (OR 0.99)

Colonoscopies

BIGGEST SECRETS
FINALLY REVEALED



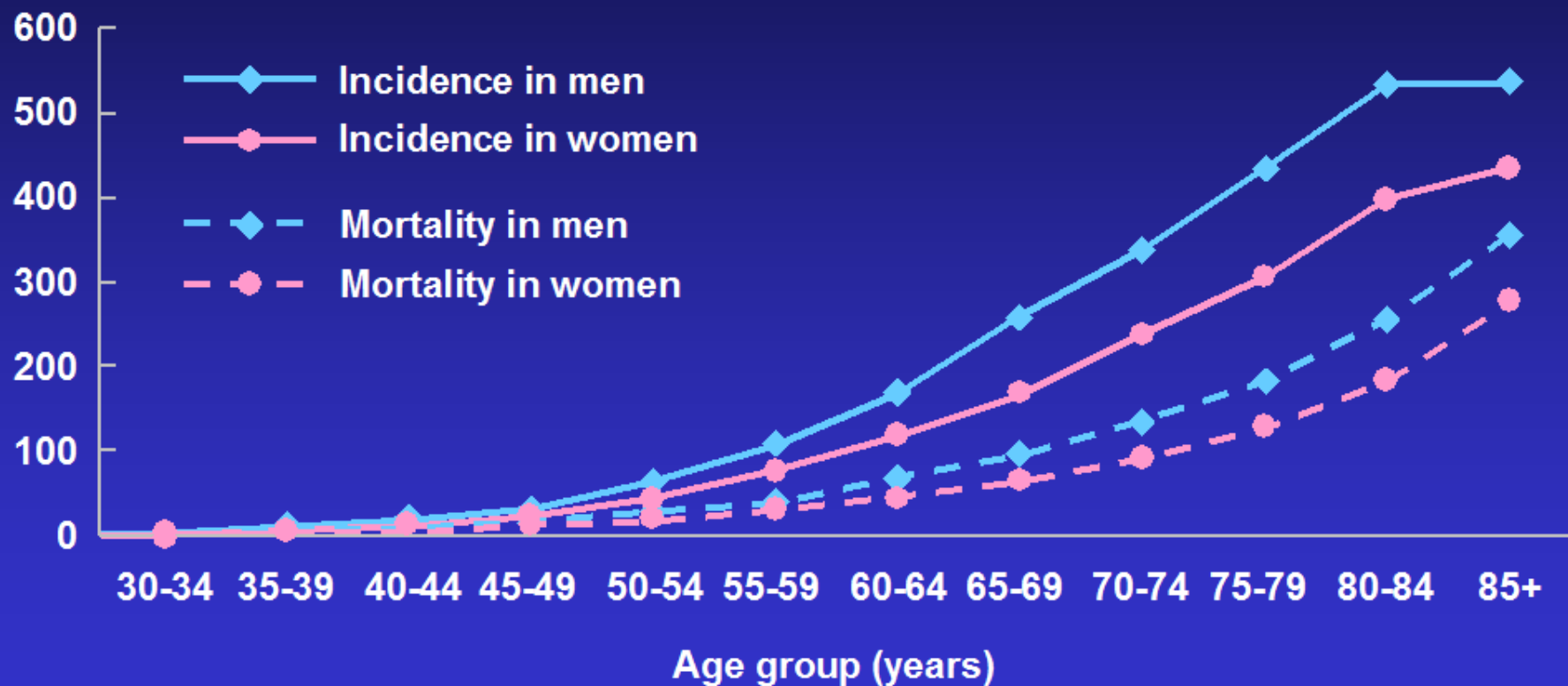


CRC Screening: Statistics

- **Colorectal cancer is the third most common cancer in California, estimated 14,415 cases in 2005**
- **The second deadliest cancer in men and women 5210 deaths in 2005 (breast 4060; lung 14,450)**
- **Screening for colonic adenomas appears to significantly reduce the incidence of and risk of dying from colorectal cancer**
- **The incidence of CRC has been declining over the last 2 decades**

Average Annual Age-Specific US Incidence and Mortality Rates of CRC, 1992-1996

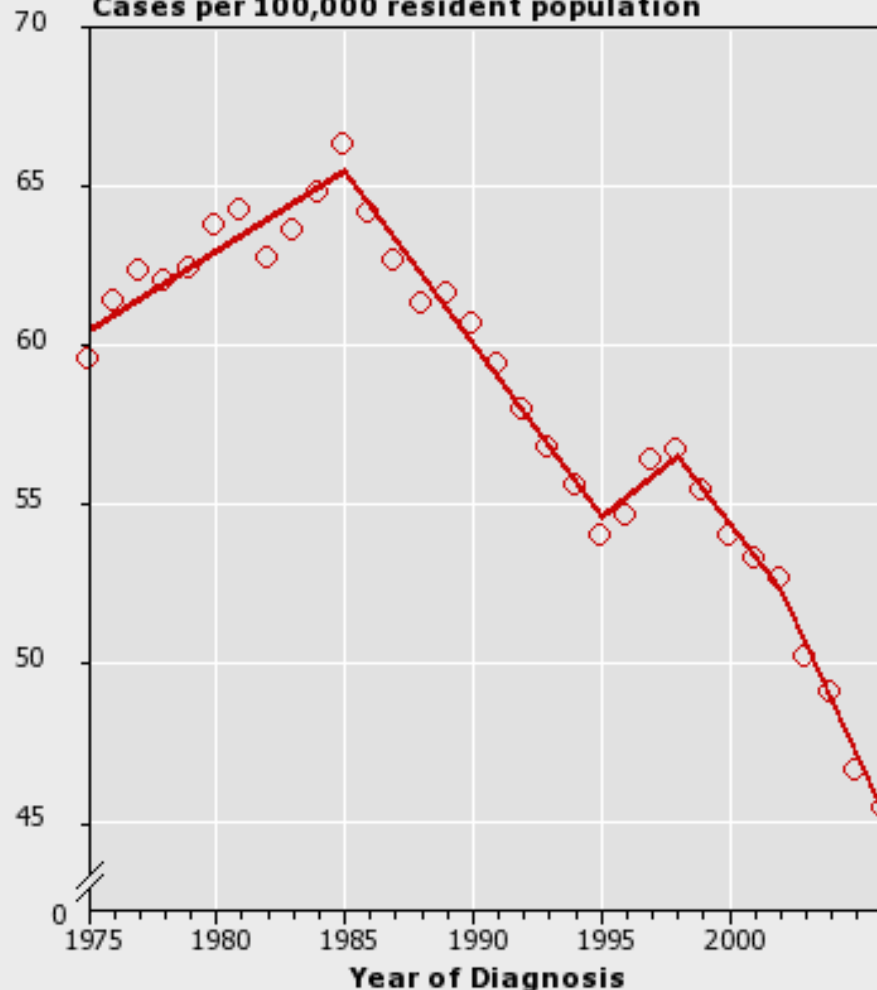
Number / 100,000 population



Historical Trends (1975-2006)

Incidence, SEER 9 Registries Colon & Rectum, All Races (incl Hisp) Both Sexes, All Ages

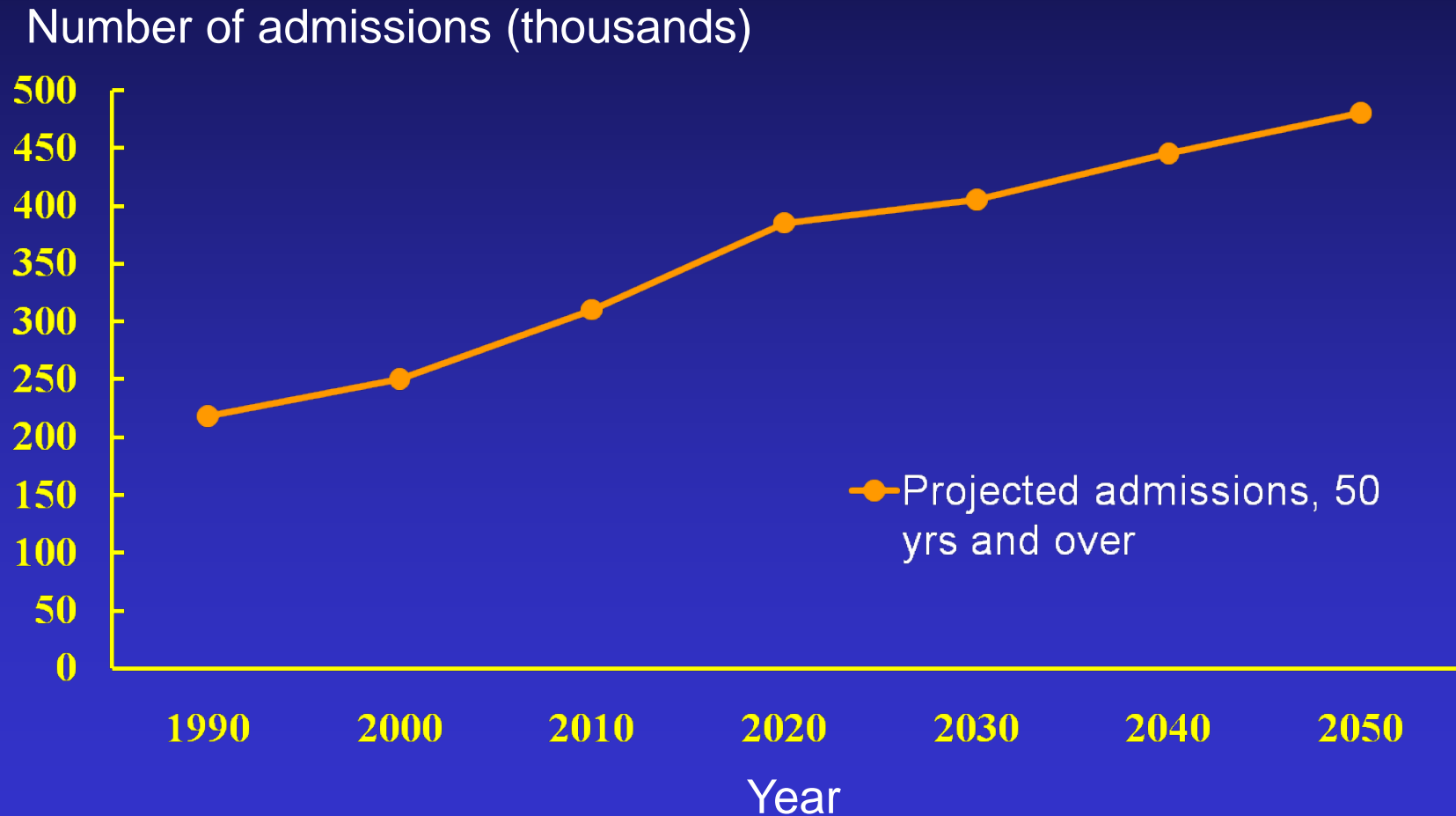
Cases per 100,000 resident population



Key
Incidence
SEER 9 Registries
Colon & Rectum
All Races (incl Hisp)
Both Sexes
All Ages

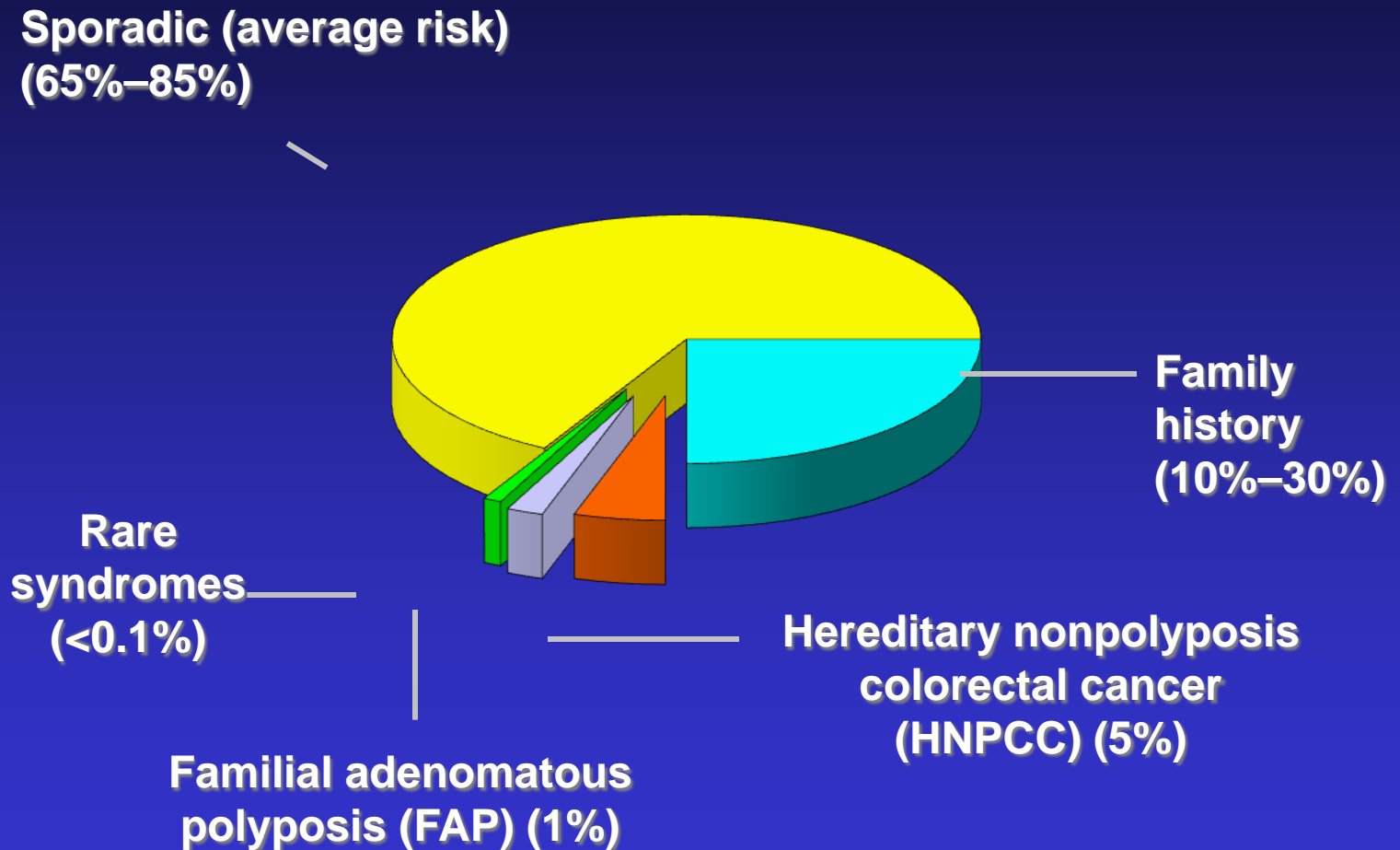


Projected Annual Hospital Admissions for Colon Cancer in the US: 1990-2050



CRC Risk Factors

Colorectal Cancer





Risk Stratification in Screening

Usual Risk Factors in Clinical Practice

average risk (age > 50)

high risk (family history)

Factors Associated With CRC

Risk factors

Strong (RR > 4.0)

Advanced age
FAP / HNPCC
Long-standing ulcerative colitis

Moderate (RR 2.1 - 4.0)

High red meat diet
Previous adenoma or cancer
Pelvic irradiation

Modest (RR 1.1 - 2.0)

High fat diet
Smoking and alcohol consumption
Central Obesity/Insulin resistance/DM
Cholecystectomy
African American Race

Protective factors

Moderate (RR < 0.6)

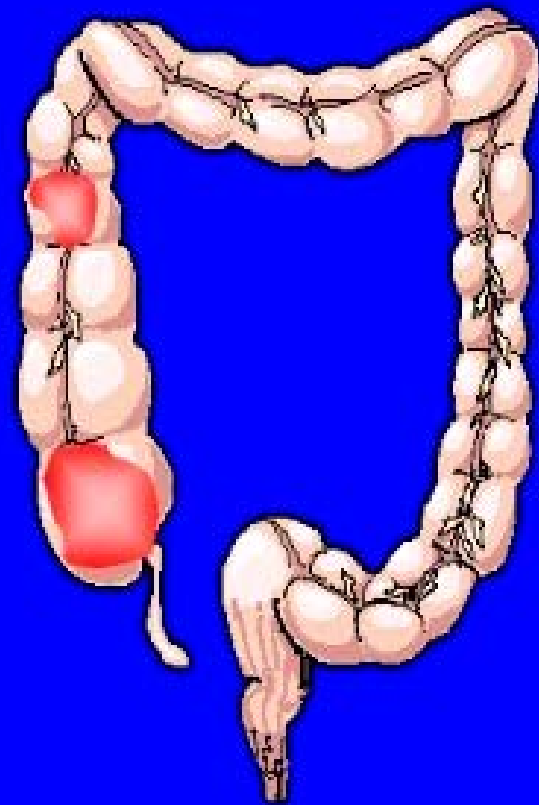
High physical activity
Aspirin / NSAIDs use

Modest (RR 0.9 - 0.6)

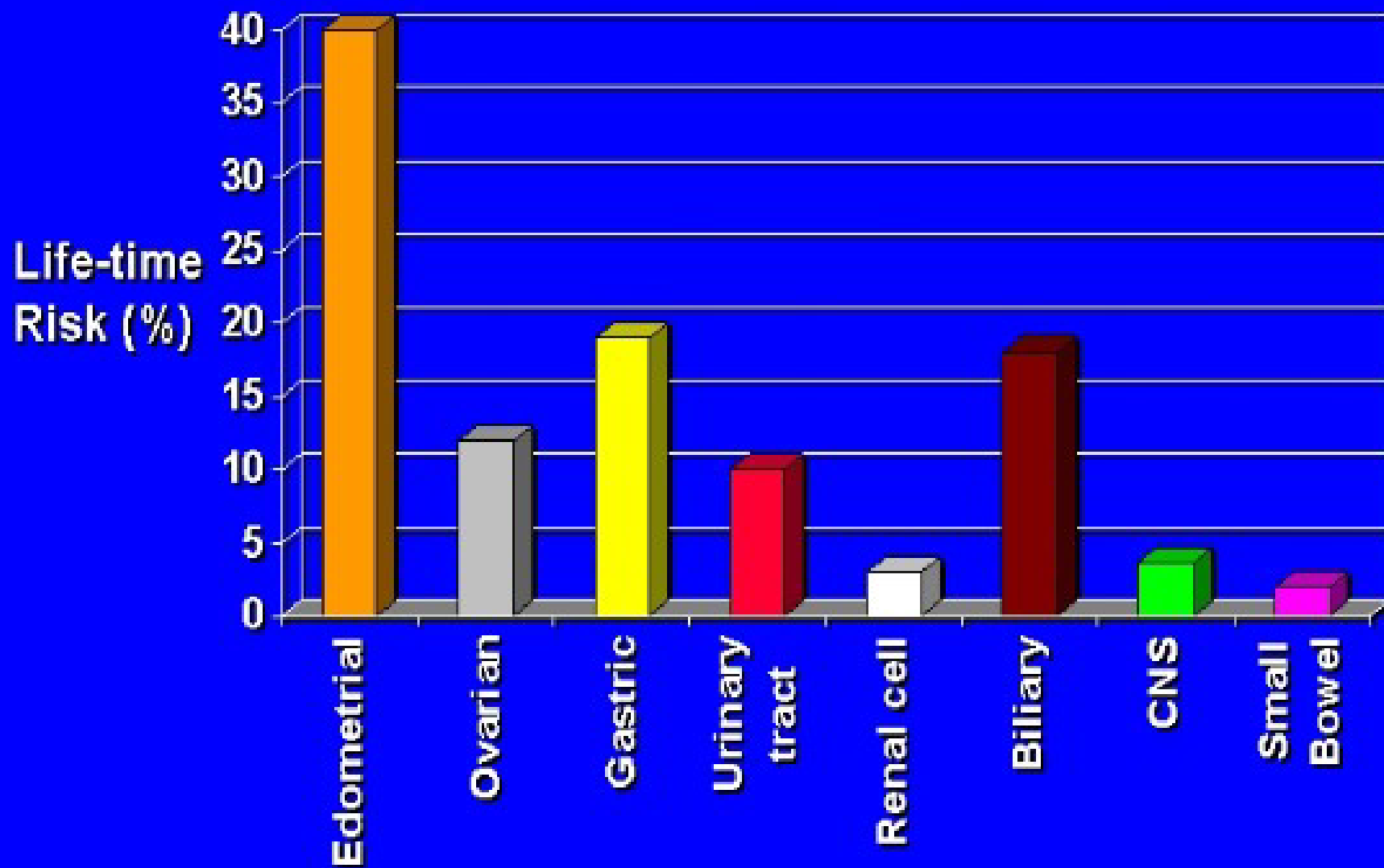
High vegetable / fruit diet
High fiber diet
High folate / methionine intake
High calcium intake/ Vitamin D
Postmenopausal hormone therapy

HNPPC

- Few adenomas
- 80% CRC risk, mean 44 yrs
- More proximal colonic
- Frequent synchronous and metachronous CRC



HNPPC, Extra-Colonic Cancers



HNPPC – Clinical Features

- Suspect HNPPC if two relatives with colon, one under the age of 50
- **Modified Amsterdam Criteria**
 - 3 relatives with HNPPC related cancer (CRC, uterine, small bowel, renal pelvis or ureter)
 - 2 generations affected
 - 1 person diagnosed at age < 50 y
 - 1 person is a first degree relative of the other two
- HNPPC should be screened every one to three years beginning between the ages of 20 and 25.

Screening



Definitions

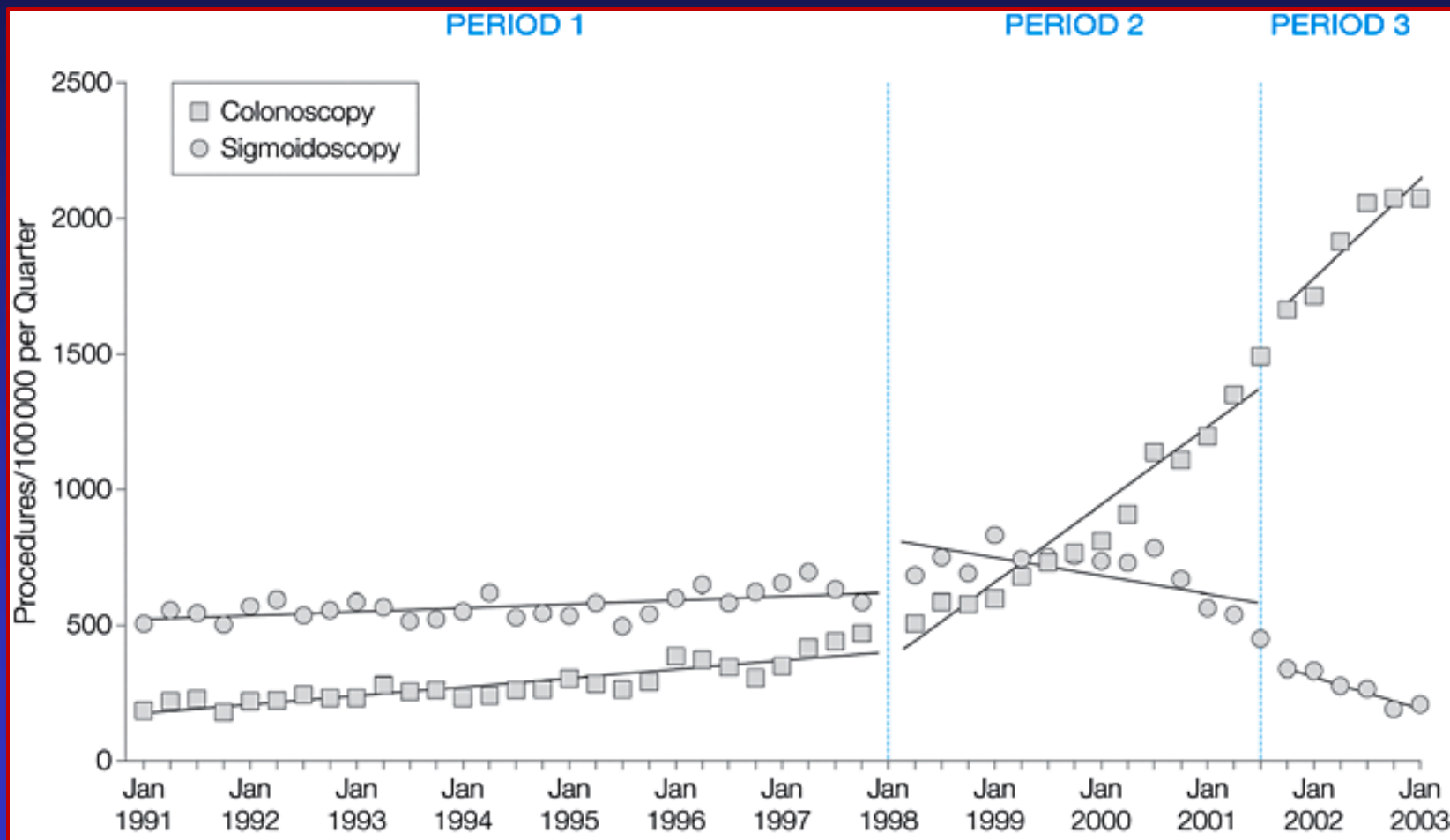
- **Screening** – search for neoplasia in persons with no symptoms and no personal history of CRC neoplasia
- **Surveillance** – follow up of persons with previous adenomas or CRC cancer; interval exams in CUC and Crohn's colitis

History of CRC Screening

- **<1990: No evidence from RCT that CRC screening reduced CRC mortality**
- **Early 1990's: 3 RTC showing annual FOBT reduce CRC mortality by 33% and bi-annual by 15%**
- **1992: case-control study showing sigmoidoscopy reduced CRC mortality by up to 60% for lesions within the reach of the scope**
- **1996: USPSTF officially endorses CRC screening with sigmoidoscopy**
- **January 1, 1998, Medicare required to pay for colon cancer screening tests including fecal occult blood testing, barium enema, and sigmoidoscopy.**
- **July 1, 2001: Medicare coverage for colonoscopy**

Use of Colonoscopy and Flexible Sigmoidoscopy Among Medicare Fee-for-Service Beneficiaries

Procedures per 100 000 beneficiaries from a piecewise linear regression model.



Medicare Screening Reimbursement and Stage at Diagnosis for Older Patients With Colon Cancer

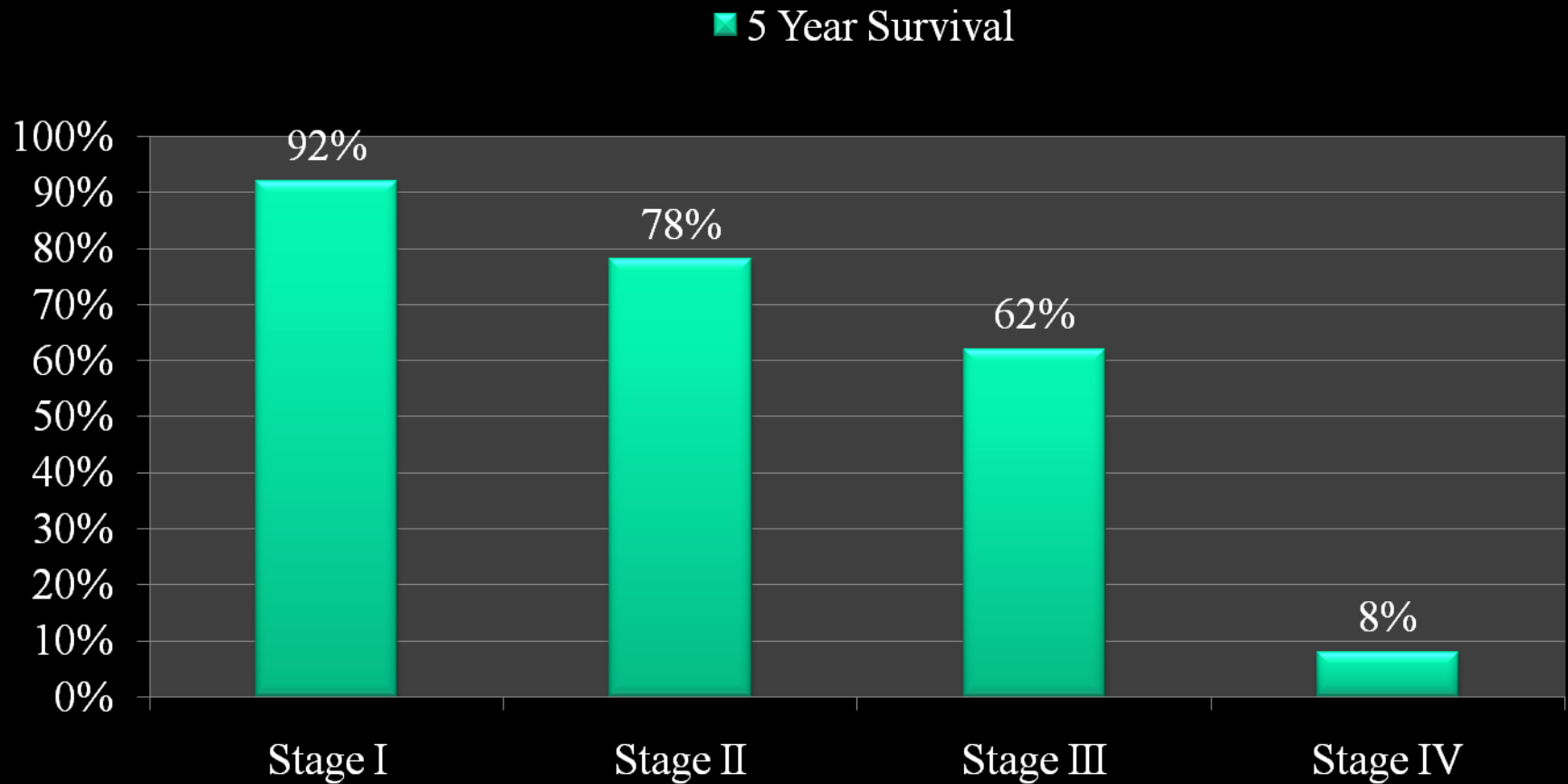
- Colonoscopy use increased from an average rate of 285/100 000 per quarter in period 1 to 889 and 1919/100 000 per quarter in periods 2 ($P<.001$) and 3 (P vs 2 $<.001$), respectively
- The proportion of patients diagnosed at an early stage increased from 22.5% in period 1 to 25.5% in period 2 and 26.3% in period 3 ($P<.001$ for each pairwise comparison).
- The changes in Medicare coverage were strongly associated with early stage at diagnosis for patients with proximal colon lesions, but weakly associated, if at all, for patients with distal colon lesions

CRC Screening: Statistics

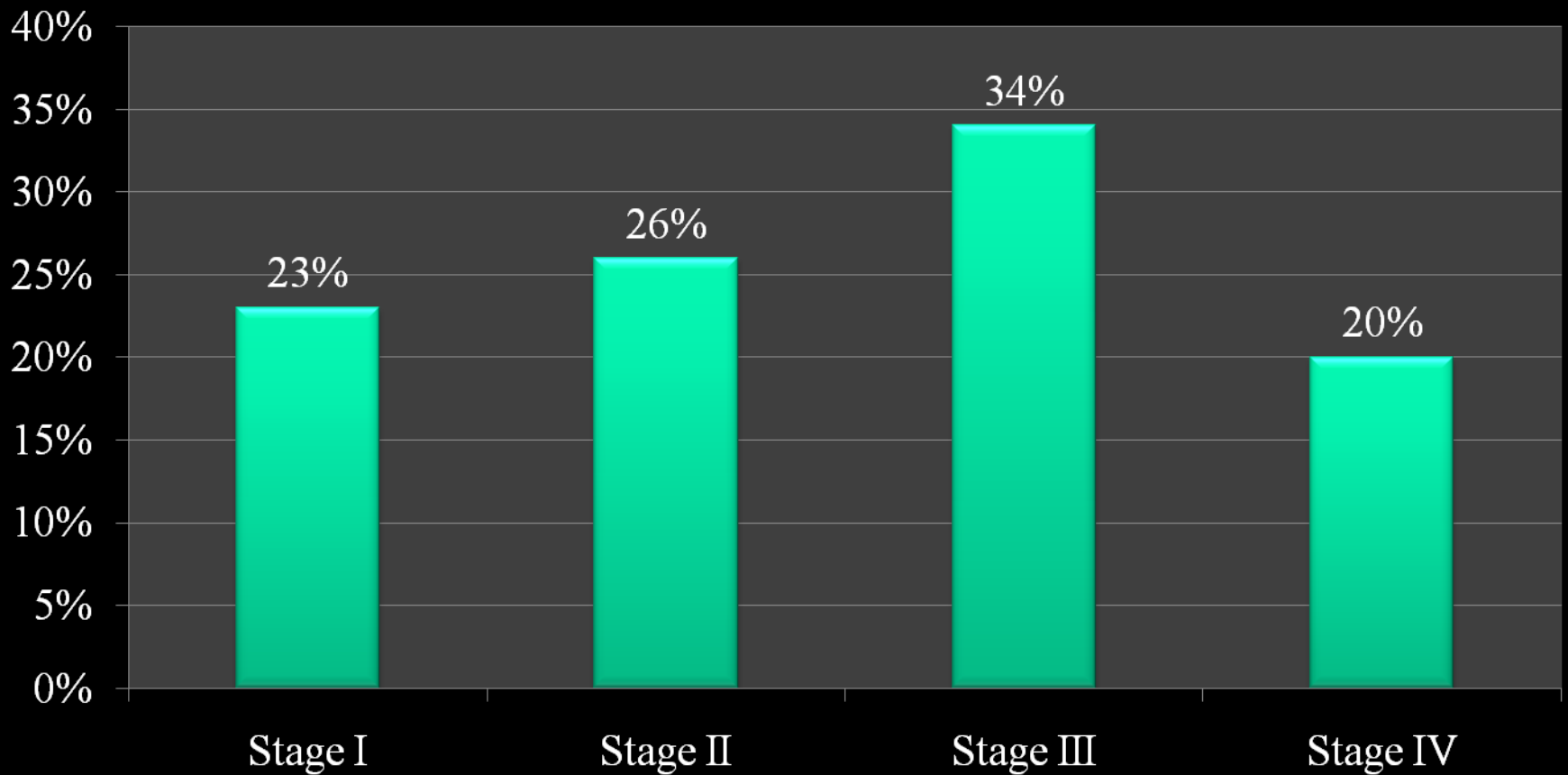
- The use of colonoscopy for screening has increased steadily over the last decade
- Estimates 15 million colonoscopies performed each year in US
- Support for the role of colonoscopy in CRC prevention derives entirely from indirect evidence and observational studies
- No randomized, controlled trials have tested whether colonoscopy reduces the incidence of colon cancer.

Rationale for Screening

Benefits of Screening: Earlier Stage = Improved Survival

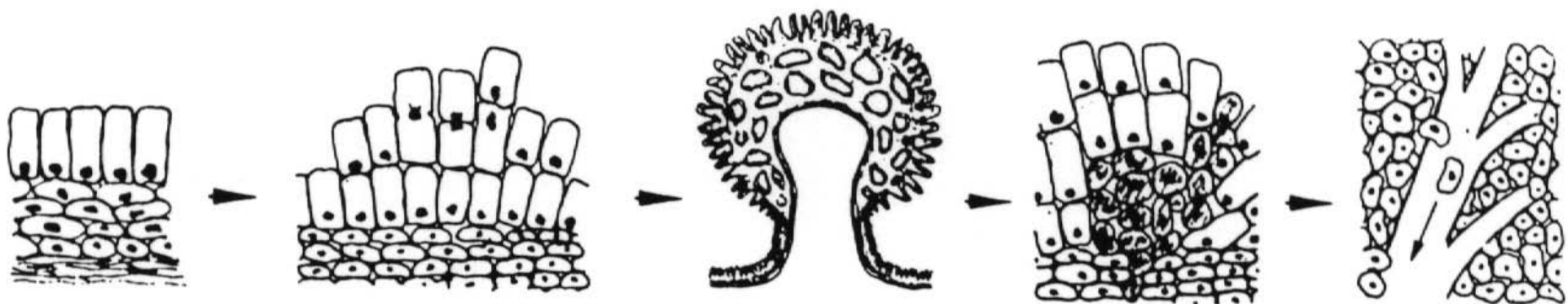


Current Distribution of Cancer Stages at Time of Diagnosis



Rationale for Screening

- Removal of advanced adenoma (over 10 mm, or associated with villous features) reduces the incidence of invasive CRC
- Cancers discovered by screening tend to be less advanced and associated with greater probability of curative resection
- Estimated 85% of colon cancers develop through a polypoid adenoma (>10 years) “Polyp-Cancer Sequence”



**NORMAL
COLONIC
MUCOSA**

**HYPERPROLIFERATIVE
EPITHELIUM**

ADENOMA

CARCINOMA

METASTASIS

5q21 allele inactivation
DNA hypomethylation

ras point mutation

17p/p53 inactivation
18q inactivation

further accumulation of
chromosomal abnormalities

5 - 10 years

3 - 5 years

Summary of Molecular Pathogenesis of Colorectal Cancer

Pathway 1: Accounts for FAP and 80% of sporadic CRC (10-15 yrs)

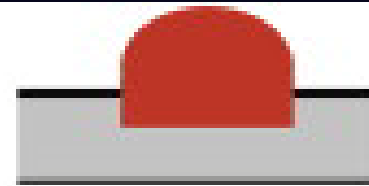
APC → $Kras^{LOH}$ → Chrom 18 → p53

Pathway 2: “Microsatellite Instability”
Accounts for HNPCC and 15-20% of sporadic cases (3-5 yrs)
MSI

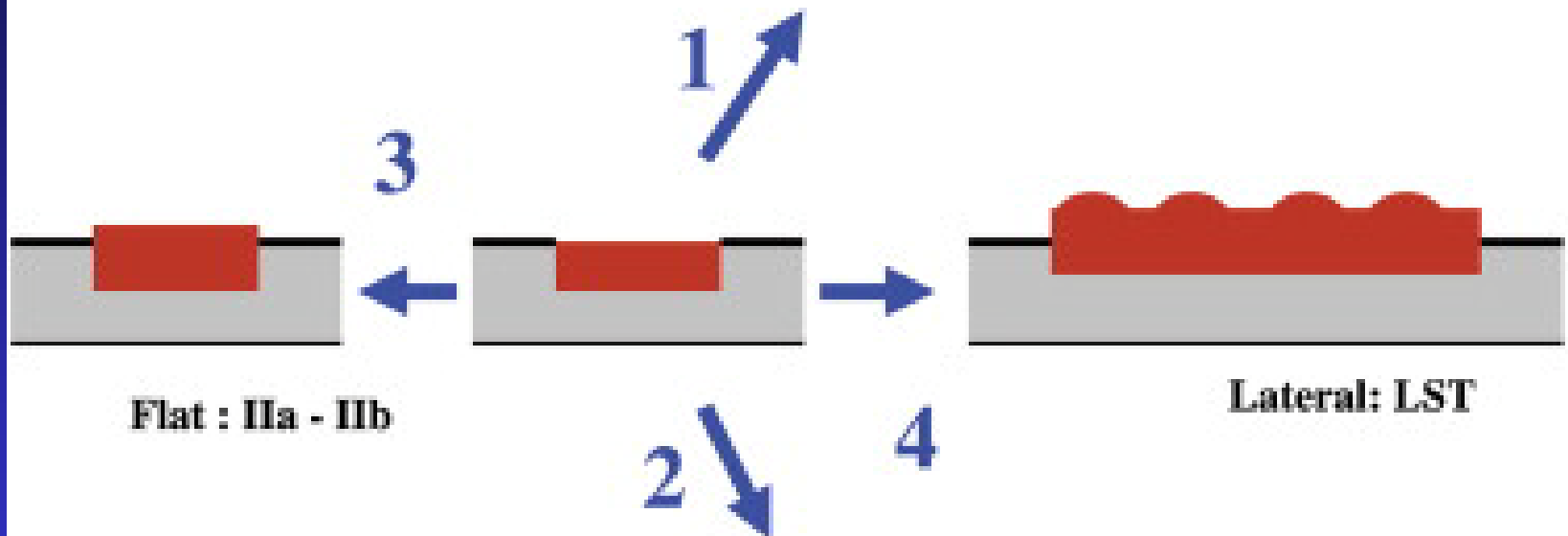
MMR mutation → $TGF_{\beta RII}$, BAX, *Wnt 1*

Pathogenesis of Colorectal Cancer

- The polyp-cancer sequence appears more complex than previously thought
- It is clear that colorectal cancer can develop through multiple pathways
- 3 types of adenomatous lesions are now recognized:
 - Polypoid
 - Non-polypoid
 - Depressed

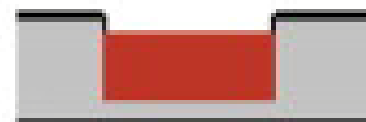


Protruding: I_p - I_{sp} - I_s



Flat : I_{IIa} - I_{IIb}

Lateral: LST

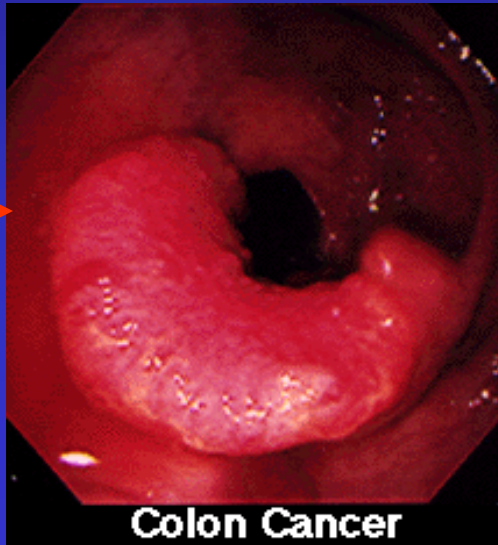
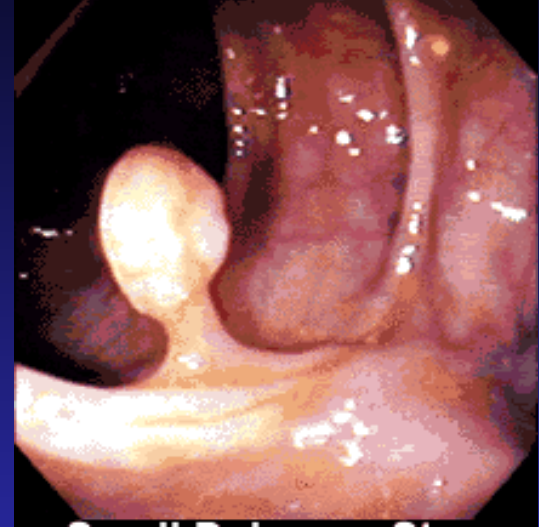


Depressed : I_{IIc} - $I_{IIc+IIa}$ - $I_{IIa+IIc}$

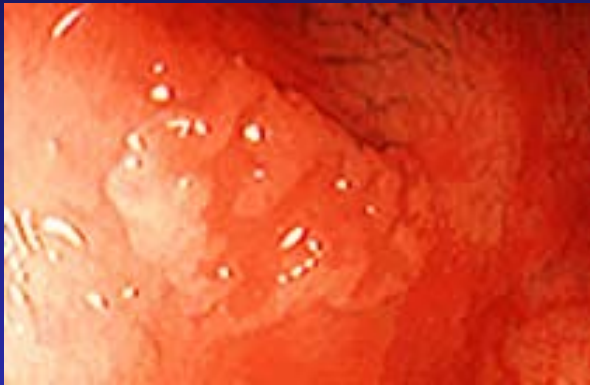
Pathogenesis of Colorectal Cancer

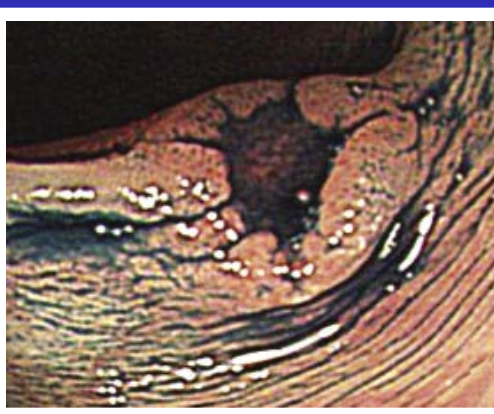
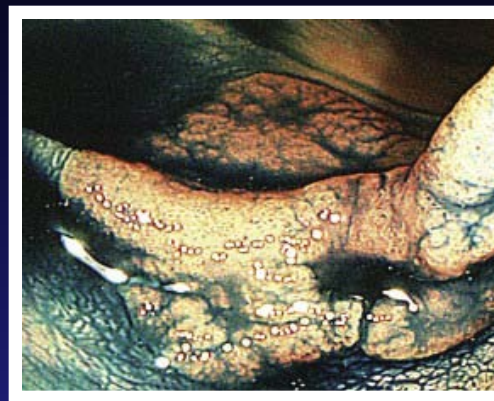
- **Polypoid** lesions grow above the surface of the mucosa, and the volume of the polypoid component appears to correlate with the histologic stage (61%)
- **Nonpolypoid** lesions may grow flat or slightly elevated and, eventually, may grow and progress to polypoid lesions or to laterally spreading tumors. (37%)
- **Depressed** lesions (2.4%) deserve special attention because of the difficulty in their detection, & increased risk of rapid progression to cancer, independent of size.
- Nonpolypoid, depressed lesions progress in depth rather than above the surface of the mucosa, and submucosal invasion is frequent, even for small lesions

Classic Adenoma-Cancer Sequence

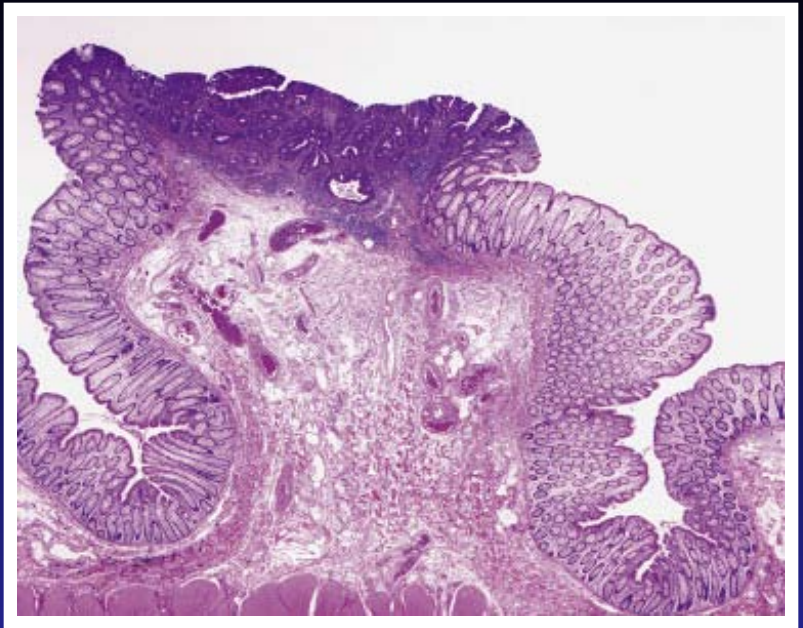
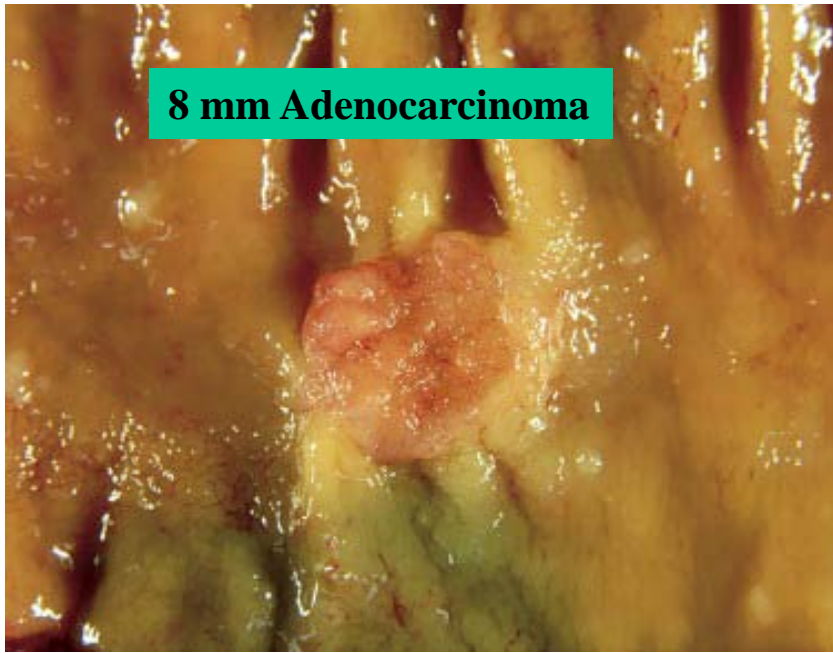


Flat Adenomas: Easily Missed

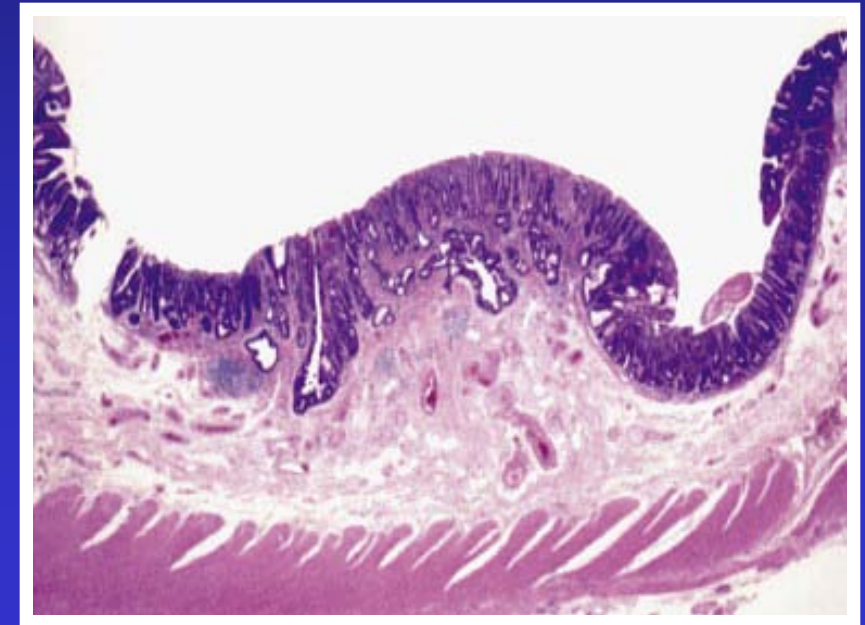




8 mm Adenocarcinoma



5 mm Adenocarcinoma



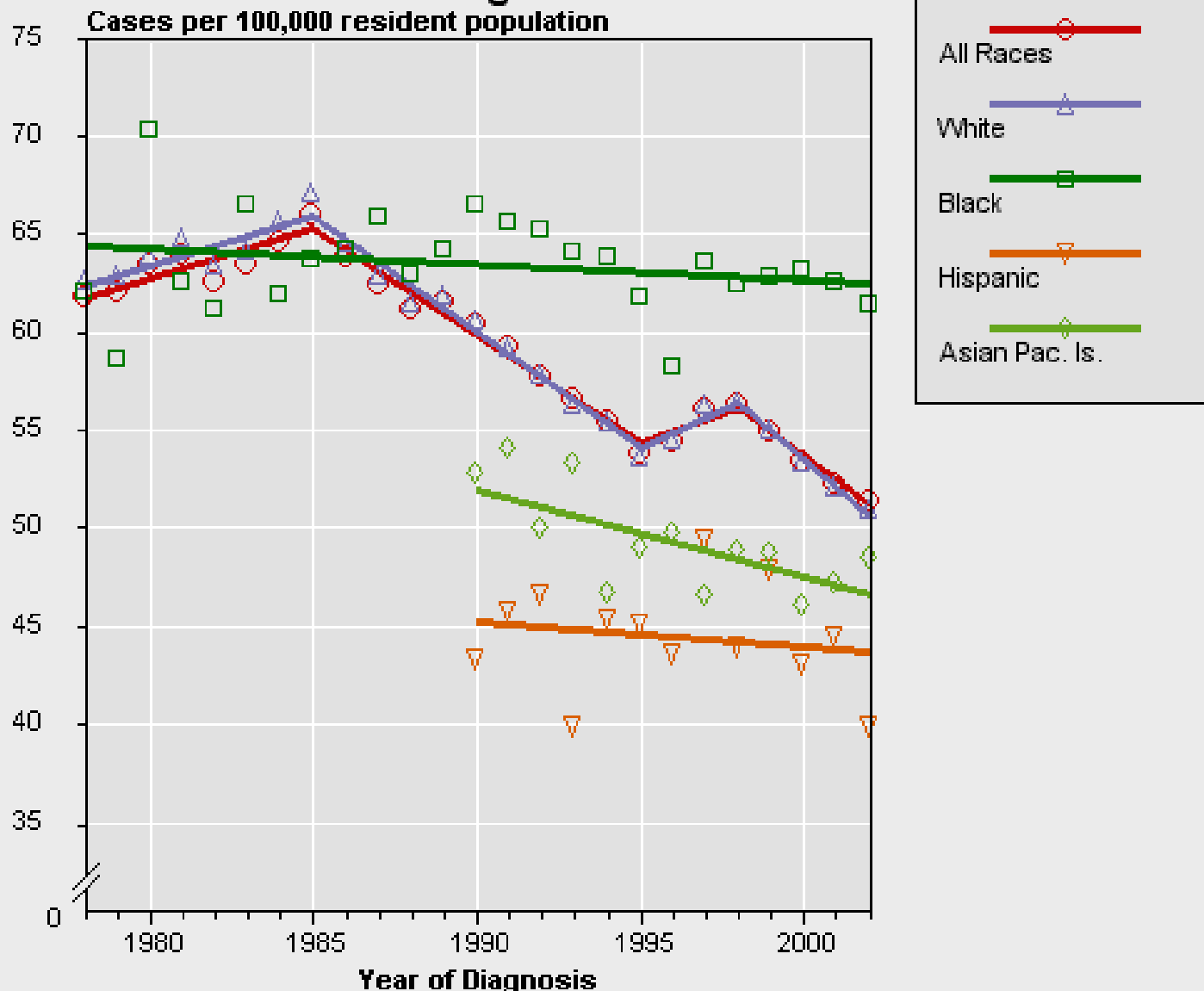
CRC Screening: How Well Does It Actually Work?

CRC Screening Efficacy

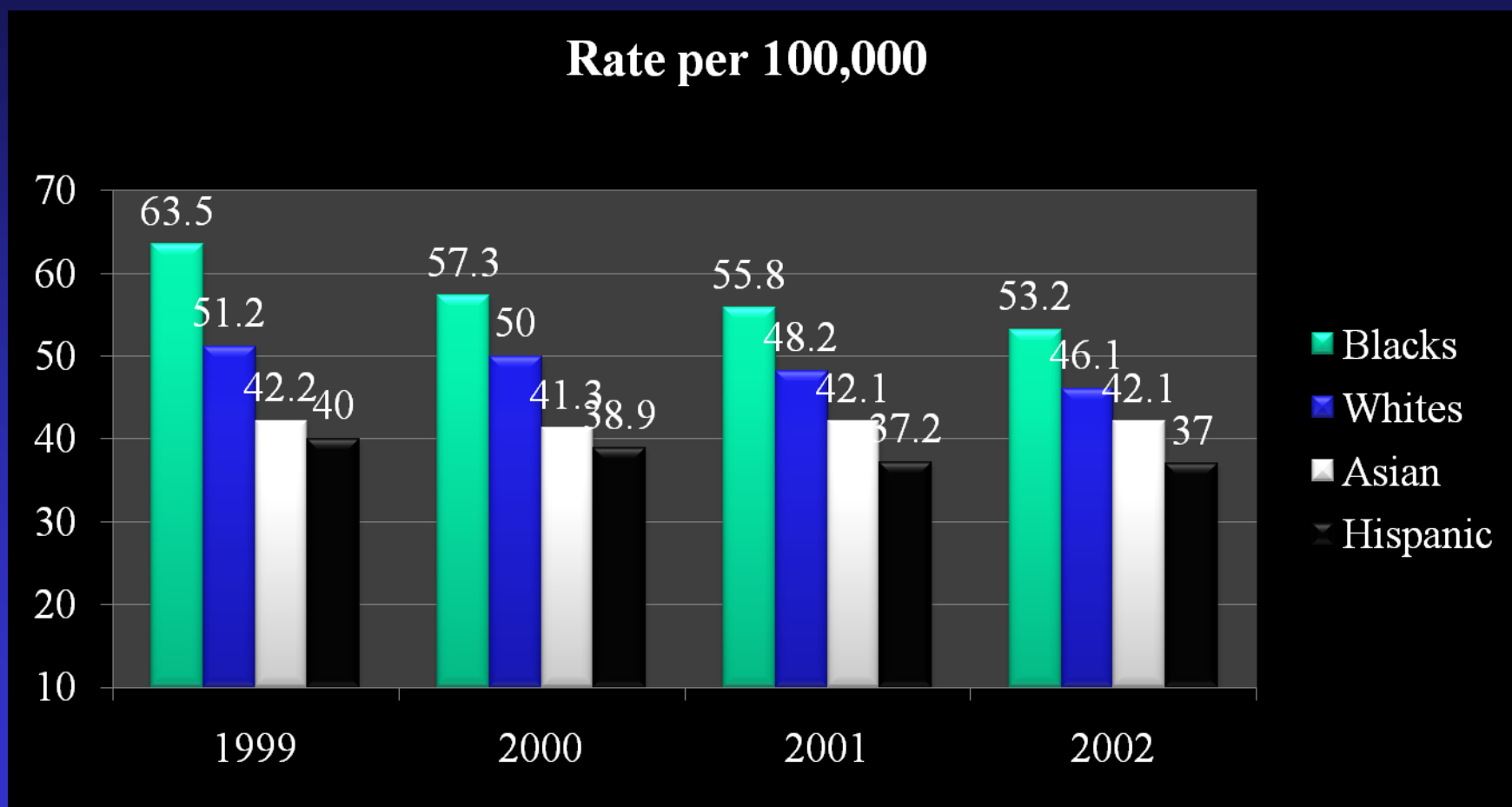
- SEER data indicate that CRC incidence rates peaked in 1985 and have declined since.
- CRC cancer rates for whites were 20-25% lower in 2000 than in 1985
- The National Polyp Study data suggest that colonoscopy and polypectomy reduces the incidence of subsequent colon cancer by 73-90%

Historical Trends (1978-2002)

Incidence, SEER 9 Registries Colon & Rectum, Both Sexes All Ages



Age-Adjusted Colorectal Cancer Rate: California 1999-2002

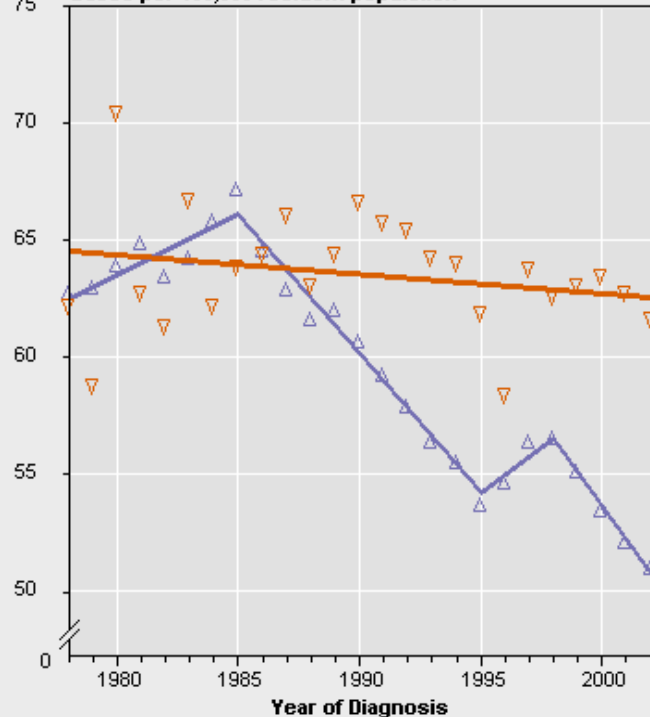


CRC Incidence: Bay Area Outperforms California

Historical Trends (1978-2002)

Incidence, Colon & Rectum Both Sexes, All Ages

Cases per 100,000 resident population

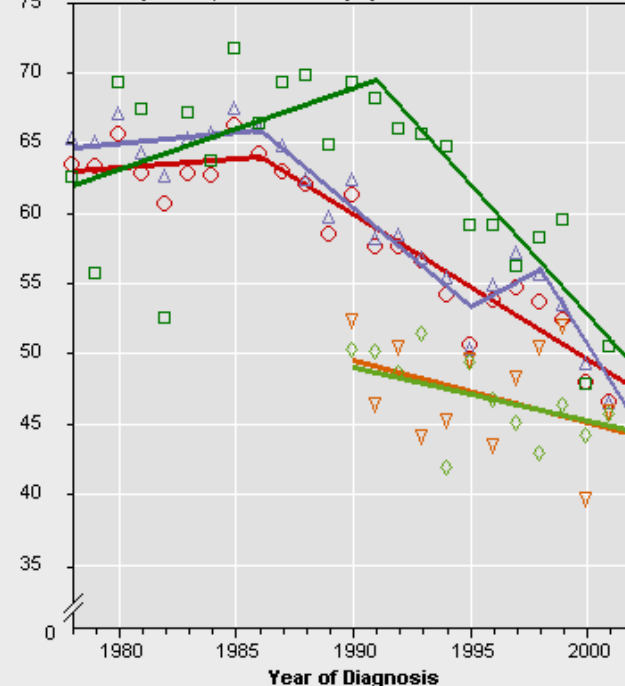


Key
Incidence
Colon & Rectum
Both Sexes
All Ages
Suppressed*
California
White
SEER 9 Registries
White
Suppressed*
California
Black
SEER 9 Registries
Black
*Suppressed to ensure
confidentiality and
stability.

Historical Trends (1978-2002)

Incidence, SF-Oakland Colon & Rectum, Both Sexes All Ages

Cases per 100,000 resident population

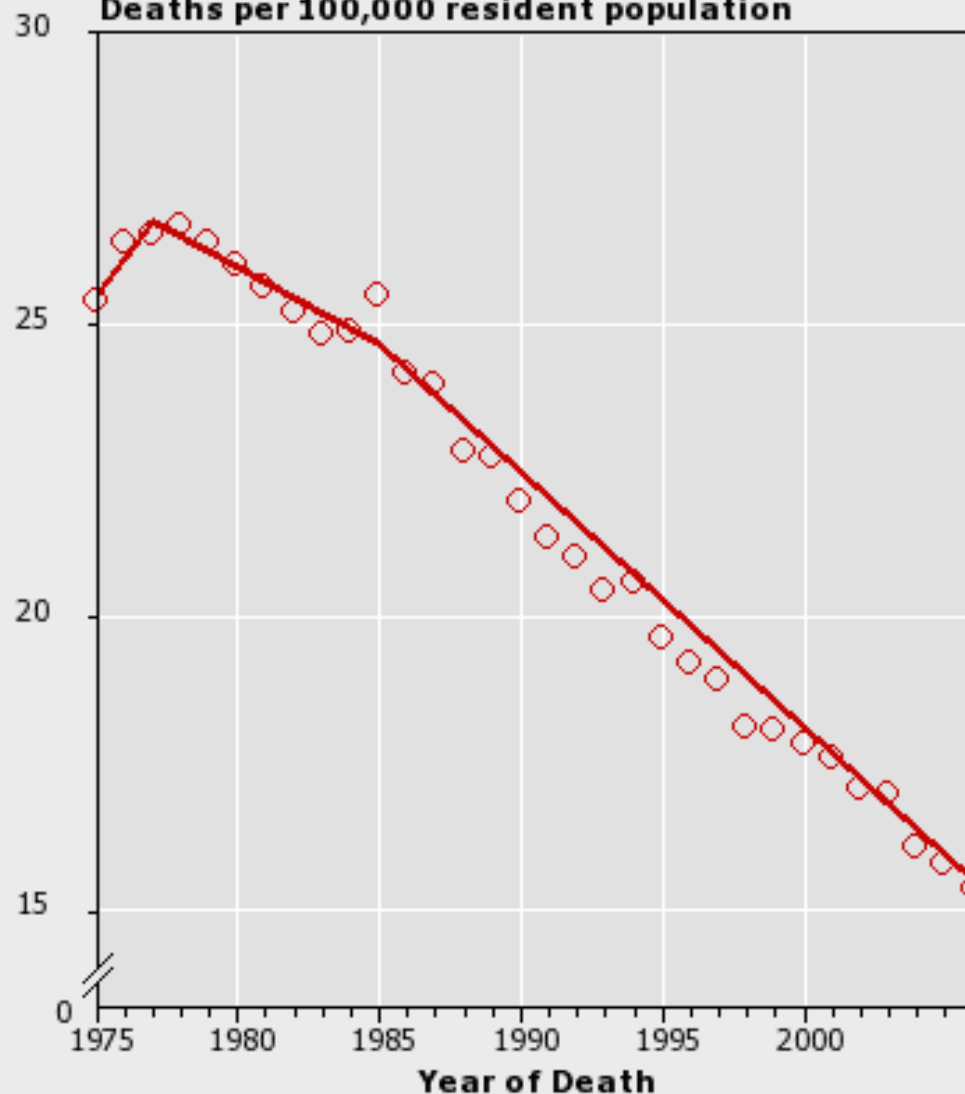


Key
Incidence
SF-Oakland
Colon & Rectum
Both Sexes
All Ages
All Races
White
Black
Hispanic
Asian Pac. Is.

Historical Trends (1975-2006)

Mortality, California Colon & Rectum, All Races (incl Hisp) Both Sexes, All Ages

Deaths per 100,000 resident population



Key

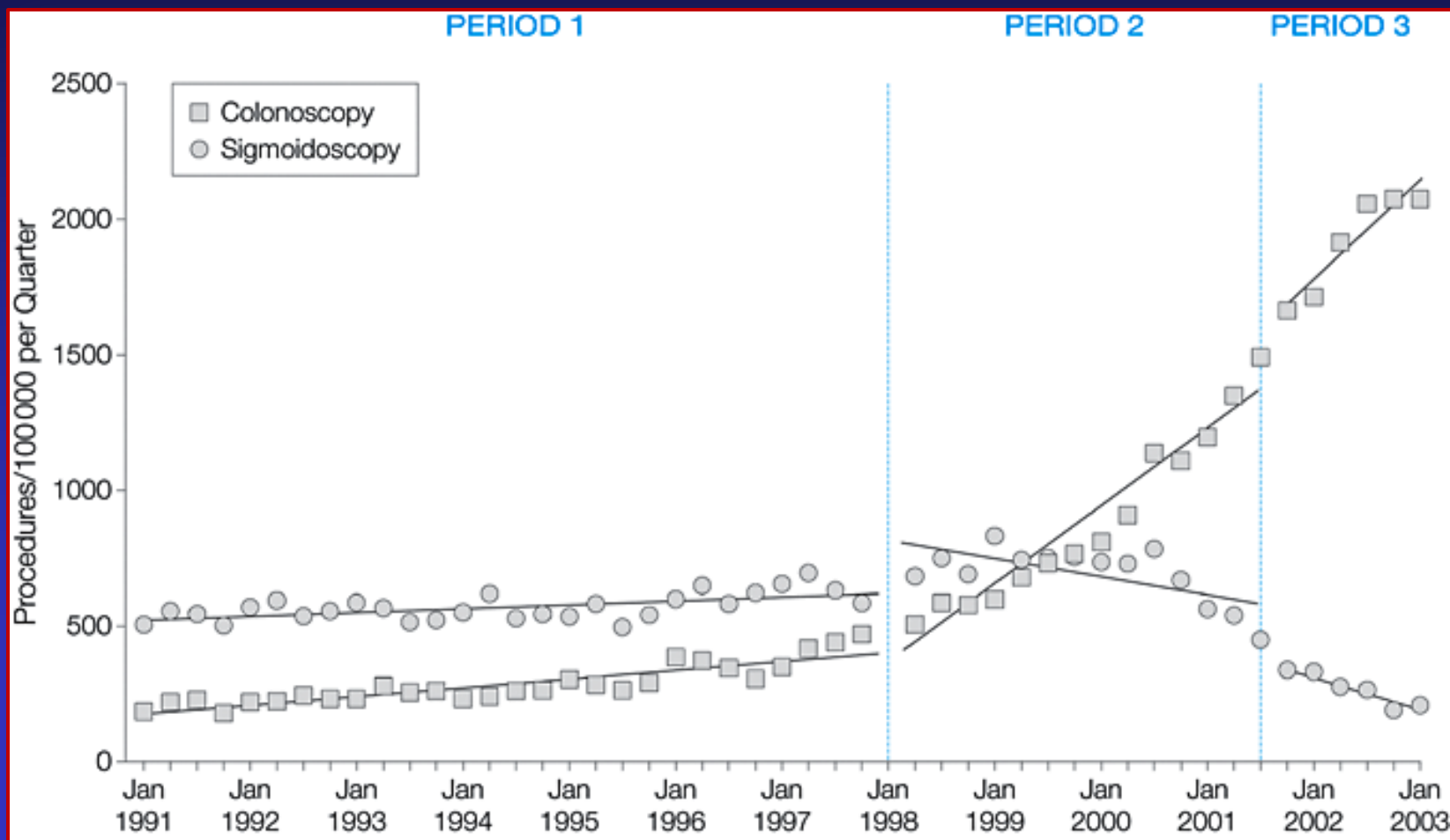
Mortality
California

Colon & Rectum
All Races (incl Hisp)
Both Sexes
All Ages

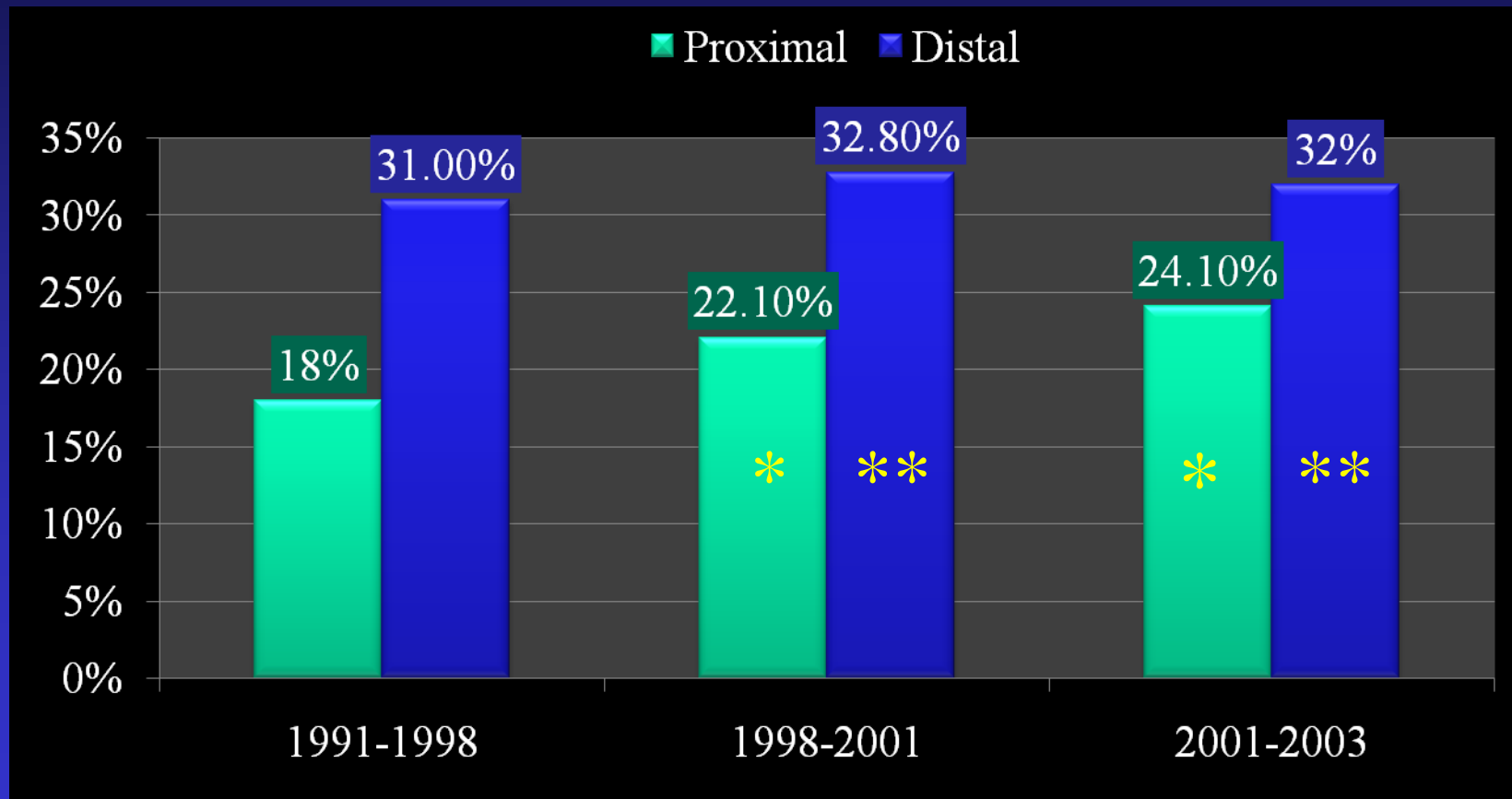


Use of Colonoscopy and Flexible Sigmoidoscopy Among Medicare Fee-for-Service Beneficiaries

Procedures per 100 000 beneficiaries from a piecewise linear regression model.



Prevalence of Stage I Colon Cancer in Medicare Beneficiaries



* P < 0.001

** P = NS

JAMA. 2006;296:2815-2822.

Colonoscopy with May Not Significantly Reduce the Risk of Proximal Colon Cancers

2009 Headline: Colonoscopy Does Not Reduce Colon Cancer Death from Right-Sided CRC!!

- Canadian administrative claims data on 10,292 colon cancer deaths 1996-2003 and 51,460 matched controls
- Prior complete colonoscopy was associated with a 67% reduced risk of colon cancer death from left-sided CRC (OR 0.63, $p < 0.001$)
- Prior colonoscopy was not associated with a reduced risk of death from right-sided CRC (OR 0.99)

Table 2. Self-designated Specialty of Endoscopist

Variable	Gastro- enterologist	General Surgeon	General Internist	Other
Total colonoscopies, <i>n</i>	1808	2303	944	695
Complete colonoscopies, %	83	79	80	66
All colonoscopies, %	31	40	16	12
Case patients, %	30	42	17	11
Controls, %	32	40	16	12

Table 3. Results of Primary Analysis: Odds Ratio for the Association Between Colonoscopy and Colorectal Cancer Death*

Model	Odds Ratio (95% CI)			
	All Cancer	Right-Sided Cancer	Left-Sided Cancer	Undefined Site of Cancer
Attempted colonoscopy				
None	1.00	1.00	1.00	1.00
Any	0.69 (0.63–0.74)	1.07 (0.94–1.21)	0.39 (0.34–0.45)	0.90 (0.75–1.08)
Completeness of colonoscopy				
None	1.00	1.00	1.00	1.00
Complete	0.63 (0.57–0.69)	0.99 (0.86–1.14)	0.33 (0.28–0.39)	0.90 (0.73–1.10)
Incomplete	0.91 (0.78–1.07)	1.35 (1.07–1.69)	0.63 (0.49–0.81)	0.91 (0.61–1.35)

* Conditional logistic regression, adjusted for Charlson Comorbidity Index score.

Failure of Colonoscopy to Prevent Right-Side CRC

- In a case-control study in the California Medicaid population involving 4458 cancer cases and 43,815 controls
- Singh et al. identified a 45% reduction in CRC incidence after colonoscopy (adjusted RR, 0.55; 95% CI, 0.46–0.65).
- Overall, the risk for right-sided tumors after negative colonoscopy was considerably higher (0.67) than that for left-sided tumors (0.16).
- Although both sexes had an 84% reduction in left-sided cancers, the reduction in right-sided cancers was 62% in men and only 18% in women.

Failure of Colonoscopy to Prevent Right-Side CRC

- 3287 adults aged at least 55 years were to undergo screening colonoscopy at 1 of 33 gastroenterology practices in Germany
- 98.5% cecal intubation rate
- 586 adults had previous colonoscopy in the preceding 1 to 10 years (mean, 5.7 years).
- Advanced colorectal neoplasm was detected by colonoscopy in 36 (6.1%) of 586 participants who had undergone a previous colonoscopy in the preceding 10 years vs 308 (11.4%) of 2701 participants with no previous colonoscopy.

Failure of Colonoscopy to Prevent Right-Side CRC

- Adjusted prevalence ratios of advanced colorectal neoplasms in patients who had colonoscopy in the previous 1 to 10 years for various anatomic sites:
 - Cecum and ascending colon, 0.99 (95% CI, 0.50 - 1.97)
 - Hepatic flexure and transverse colon, 1.21 (95% CI, 0.60 - 2.42)
 - Splenic flexure and descending colon, 0.36 (95% CI, 0.16 - 0.82)
 - Sigmoid colon, 0.29 (95% CI, 0.16 - 0.53)
 - Rectum, 0.07 (95% CI, 0.02 - 0.40)
- Advanced neoplasm = CRC, large adenoma, villous adenoma, or high grade dysplasia

Possible Reasons for Why Colonoscopy Protection is Imperfect

- Multiple explanations for interval cancers have been proposed,
 - Missed lesions during the initial colonoscopy,
 - Incomplete adenoma removal,
 - Development of new lesions, and
 - Failed detection of cancer despite biopsy.
- In one study, the rate of cancer detection at the first follow-up interval was 3.79/1000 PYO compared with only 0.96/1000 PYO for the second follow-up interval,
 - Suggesting that many of the cancers diagnosed at the first interval were missed

Possible Reasons for Why Colonoscopy Protection is Imperfect

- Poor bowel preparation
- Tumor biology (including genetic factors and environmental factors, such as diet/smoking)
- Physician
 - Procedural/motor skill deficits
 - Incomplete colonoscopy,
 - Incomplete/inadequate polypectomy,
 - Withdrawal technique

Possible Reasons for Why Colonoscopy Protection is Imperfect

- **Physician**
 - Perceptual factors (e.g., variation in color and depth perception)
 - Personality characteristics (e.g., conscientiousness, obsessiveness, impulsivity)
 - Knowledge and attitude deficits (e.g., awareness and appearance of flat lesions)
- **Organizational factors (e.g., workload pressures, level of training)**

Variation in Adenoma Detection Rates Between Gastroenterologists

- **550 consecutive screening colonoscopies, average risk individuals**
- **10 BC GI at a tertiary academic institution**
- **121 (22%) had at least one adenoma**
- **Adenoma detection rate per colonoscopy 0.09-0.82 (a nine-fold range)**
- **Mean withdrawal time 7 min (3.4-9.6)**
- **Significant inverse relationship between cecal intubation time, withdrawal time, and adenoma detection ($p < 0.01$)**

Variation in Adenoma Detection Rates Between Gastroenterologists

- 12 BC GI at ASC
- 2051 consecutive screening colonoscopies
- Mean adenoma detection 25.2% (9.5-31.5%)
- Mean withdrawal time 7.0 min (2.0-22.5 min)
- Advanced adenoma found in 6.6% if withdrawal >7 min vs 3.0 if withdrawal < 7 minutes ($p < 0.005$)

65% CRC Reduction May Be Best We Can Achieve

- **715 patients with screening colonoscopy 1989-1993
Univ. Indiana**
- **10,492 patient years of follow-up**
 - **Doctors, dentists, nurses and spouses**
 - **95% White**
- **12 cases of colon cancer/ 3 cancer deaths at average of 8
years of follow-up**
 - **8/12 cancers in proximal colon.**
- **67% reduction in cancer incidence**
- **65% reduction in cancer death**



Current CRC Screening Guidelines

2008 AGA CRC Screening Guidelines

American College of Gastroenterology

- Colonoscopy every 10 years, or
- Flex sig every 5 yrs, or
- CT colonography every 5 years replaces double contrast barium enema as the radiographic screening alternative, when patients decline colonoscopy
- Annual Hemoccult Sensa
- Fecal DNA testing every 3 years

Average Risk Screening

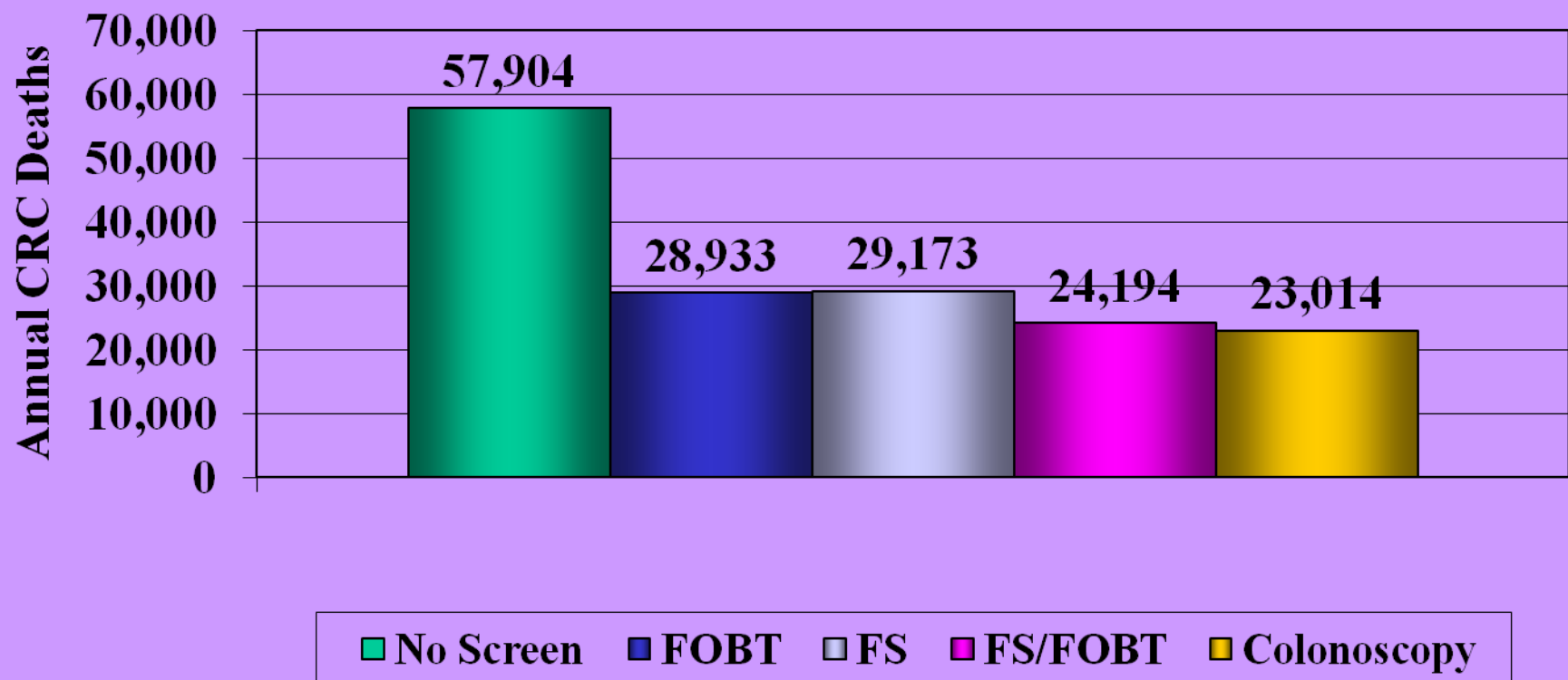
- The ACG continues to recommend that screening begin at age 50 years in average-risk persons
- The ACG recommends that screening begin at age 45 years in African Americans
- Current evidence supports a decision by clinicians in individual patients with an extreme smoking history or obesity to begin screening at an age earlier than 50 years and perhaps as early as 45 years.

Family History of Colon Cancer

- *Single first-degree relative with CRC or advanced adenoma (adenoma 1 cm in size, or with high-grade dysplasia or villous elements) diagnosed at age 60 years.*
 - **Recommended screening: same as average risk (colonoscopy every 10 years beginning at age 50 years)**
- *Single first-degree relative with CRC or advanced adenoma diagnosed at age <60 years or two first-degree relatives with CRC or advanced adenomas.*
 - **Recommended screening: colonoscopy every 5 years beginning at age 40, or 10 years younger than age at diagnosis of the youngest affected relative**

Markov Model: Estimated Reductions in CRC Deaths for Various Screening Protocols

75% of Adults Age 50-80 Screened



Gastroenterology 2005;129:1151-62

Surveillance

Postpolypectomy (good prep, exam to cecum)

Category

Interval

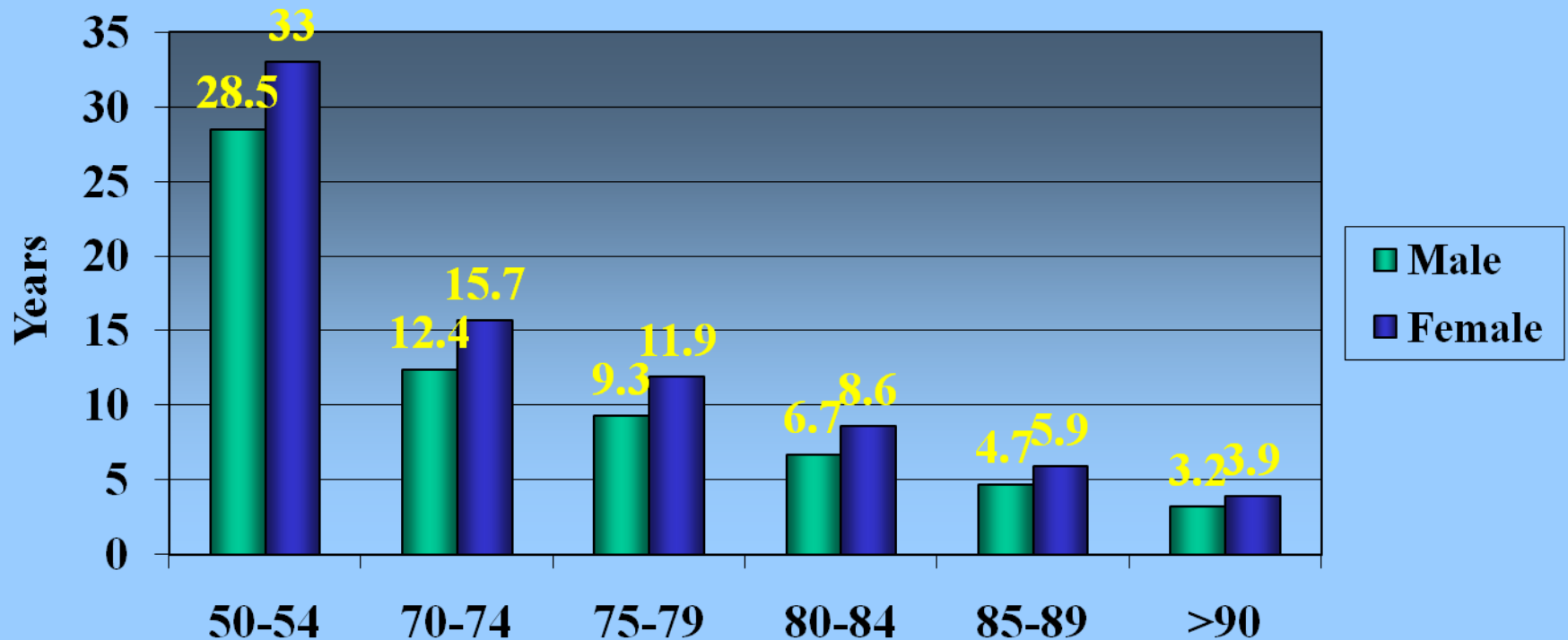
- | | |
|--|--------|
| ▪ One or two TA < 1cm | 5 y |
| ▪ > 2 adenomas, any villous component | 3 y |
| ▪ Large sessile adenoma | 2-6 mo |
| ▪ Normal follow up or only hyperplastic polyps | 5 y |

When Should We Stop Screening ?

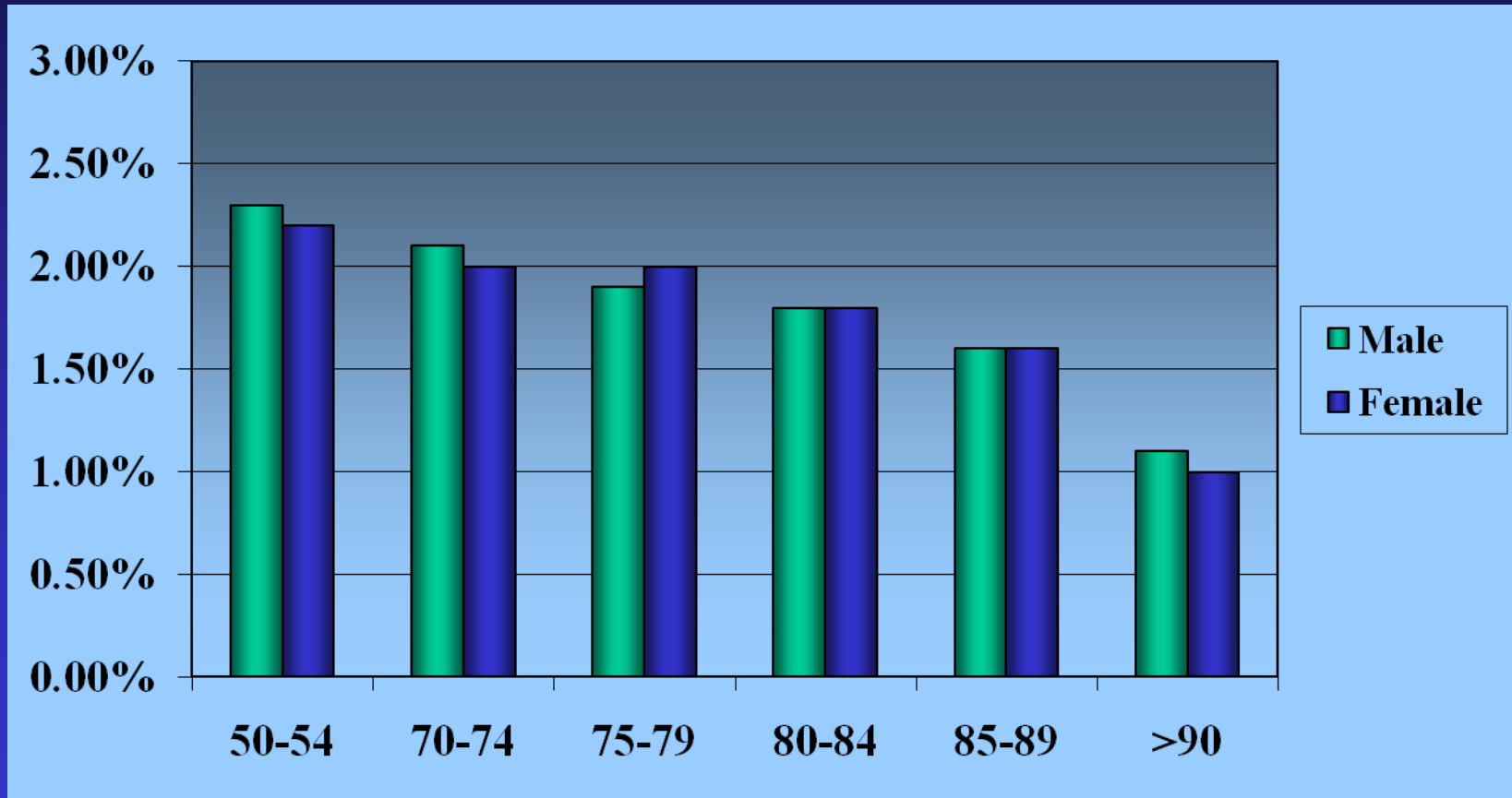
- **Randomized trial show a clear mortality benefit from CRC screening for ages 50-70**
- **There are no clear guidelines on when to stop screening**
- **Mortality benefits from screening do not accrue for 5 or more years after screening**
- **Individuals with a life expectancy of less than 5 years should not undergo screening**

Average Life Expectancy for Person of Average Health

50th Percentile of Health at All Ages

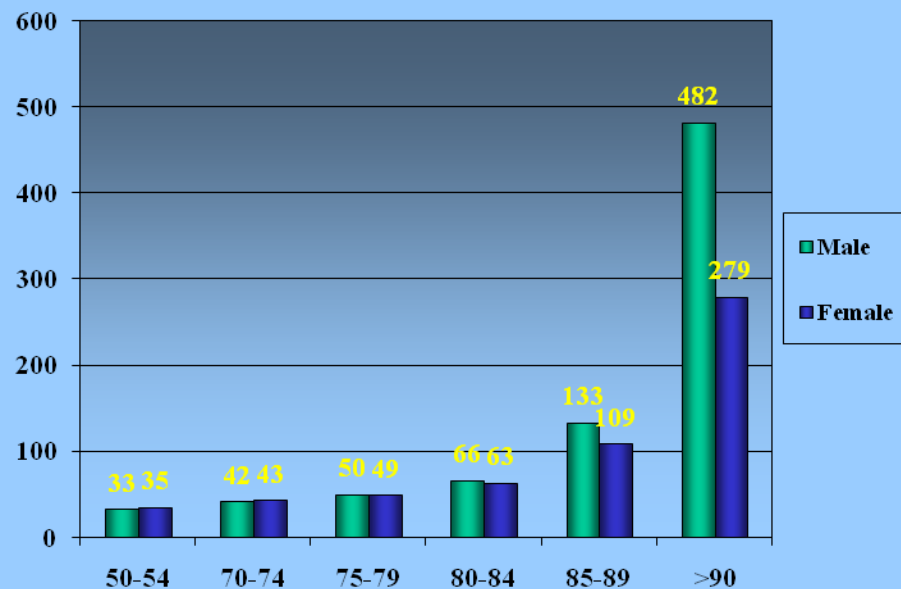


Risk of Colon Cancer Death

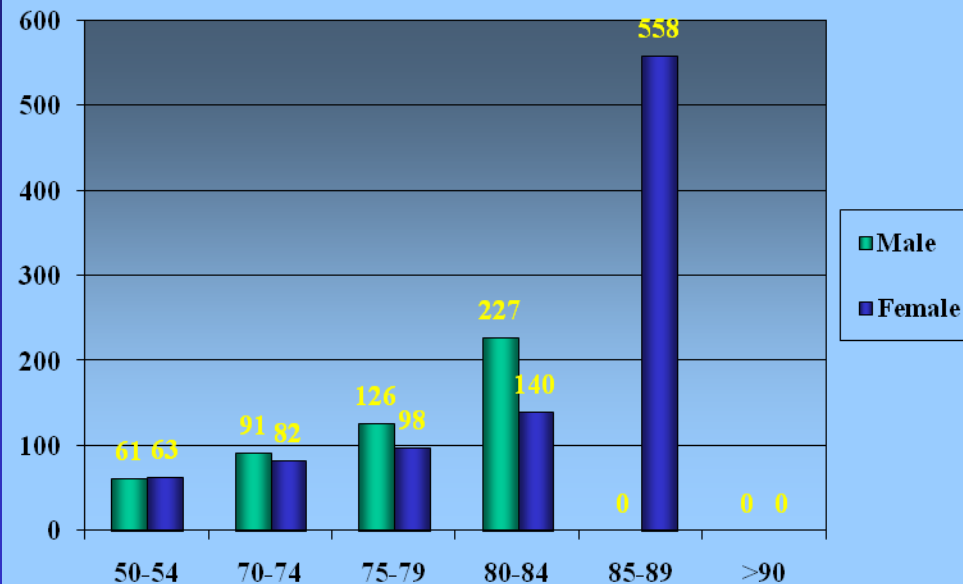


Number of Colonoscopies Necessary to Prevent One Colon Cancer Death

Top 25th Percentile of Health at All Ages



50th Percentile of Health at All Ages



Conclusions

- **Colonoscopy remains the gold standard for diagnosing and removing pre-malignant lesions.**
 - Reduction of colon cancer incidence and mortality of approximately 65%
 - Worrisome lack of reduction in proximal CRC
- **Failure of colonoscopy to reduce proximal cancers is likely driven by physician limitations and less by proximal cancer biology**
- **Sigmoidoscopy and annual FOBT may result in comparable reductions in CRC mortality**



CRC Screening and Surveillance: Unresolved Issues

- Is a 10-year screening interval too long?
- What to do with a marginal or poor bowel prep?
- When, if ever, should FOBT tests be resumed following a negative colonoscopy?
- What impact will virtual colonoscopy and fecal DNA tests have on demand for colonoscopy?
- Can we improve the skill set of the average gastroenterologist.?

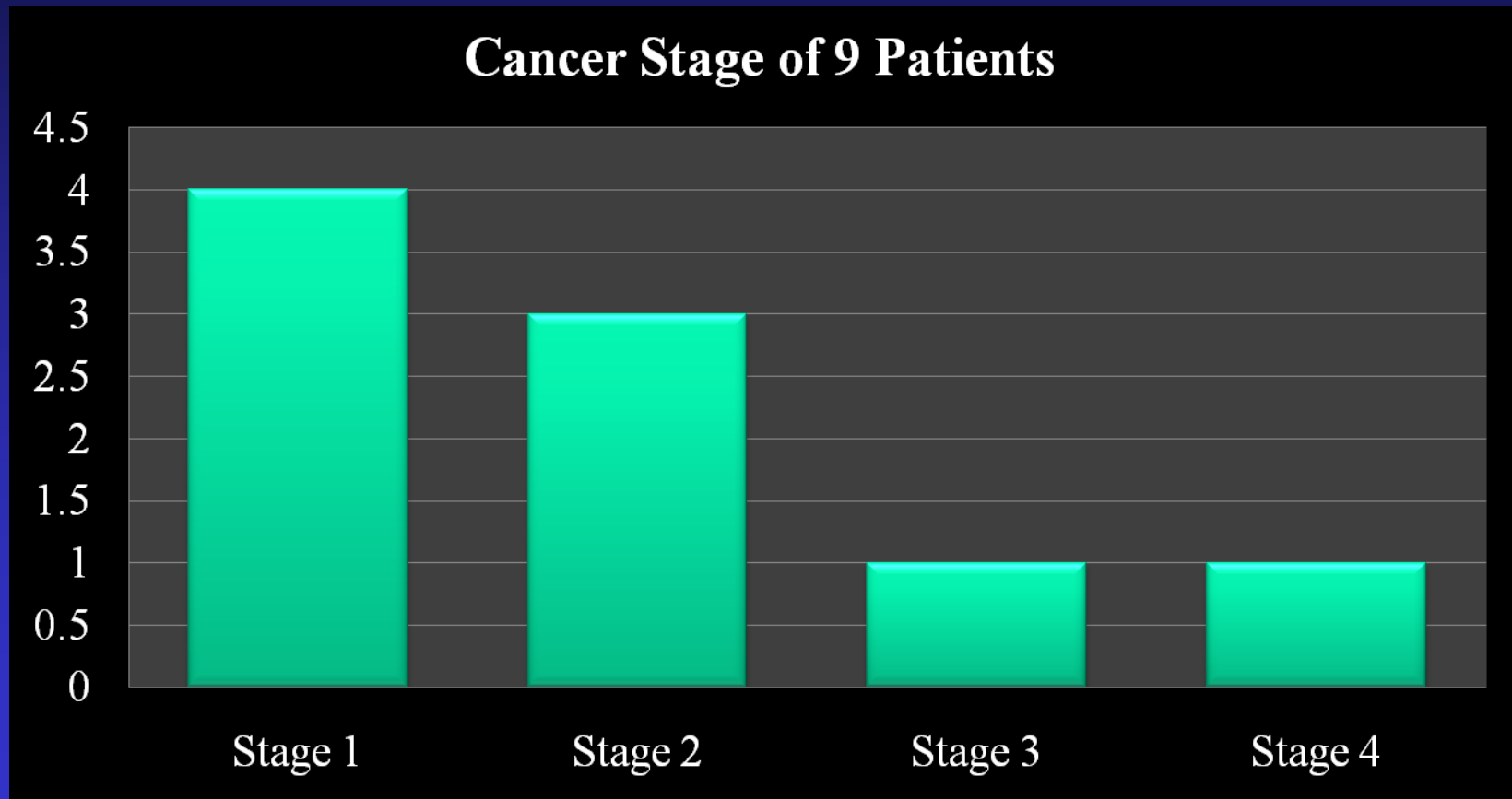
Polyp Prevention Trial-CFS

- The Polyp Prevention Trial (PPT) was a 4-year multicenter, randomized, controlled trial designed to examine the effect of a low-fat, high-fiber, high-fruit and vegetable diet on the recurrence of colorectal adenomas.
- In the trial, 13 cases of interval CRC were identified over 5810 PYO, for a rate of 2.2/1000 PYO
- Subjects underwent frequent colonoscopy including at study entry and at 1 and 4 years after enrollment, with an average of 3.1 colonoscopy examinations during the trial.
- After completion of the PPT, patients were given the option to enroll in the PPT Continued Follow-up Study (PPT-CFS).

Polyp Prevention Trial-CFU

- Followed for a median of 6.2 years after 4.3 years of median follow-up in the main PPT.
- Nine cases of CRC were diagnosed over 7626 person-years of observation (PYO), an incidence rate of 1.2/1000 PYO.
 - 8 of the 9 cancers proximal to the splenic flexure
- Including all CRCs (N = 22) since the beginning of the PPT, the observed compared with expected rate by SEER was 0.74 (95% CI, 0.47-1.05).
- Of patients in whom CRC developed in the PPT-CFS, 78% had a history of an advanced adenoma

Stage Distribution of 9 Interval Cancers in PPT-CFU Study



Fecal Immunochemical Test

- Fecal immunochemical test (FIT) may be more sensitive and specific than gFOBT and detects human hemoglobin
- Special dietary precautions to avoid false-positive tests are unnecessary.
- There are many commercial FITs
- The best tests identified only 25-27% of patients with advanced neoplasia.
- Several unresolved issues with FIT that require further study:

FIT: Unresolved Issues

- 1) How many stool samples are ideal?**
- 2) Which of the several commercially available tests has the best performance in practice?**
- 3 Is a quantitative test superior to a qualitative test?**
- 4) Can the stool sample be frozen for later analysis, or is fresh specimen required?**
- 5) Is FIT performance superior to a sensitive (and less expensive) gFOBT?**



Emerging Screening Tests

American College
of Gastroenterology

CT Colonography

2-D



3-D



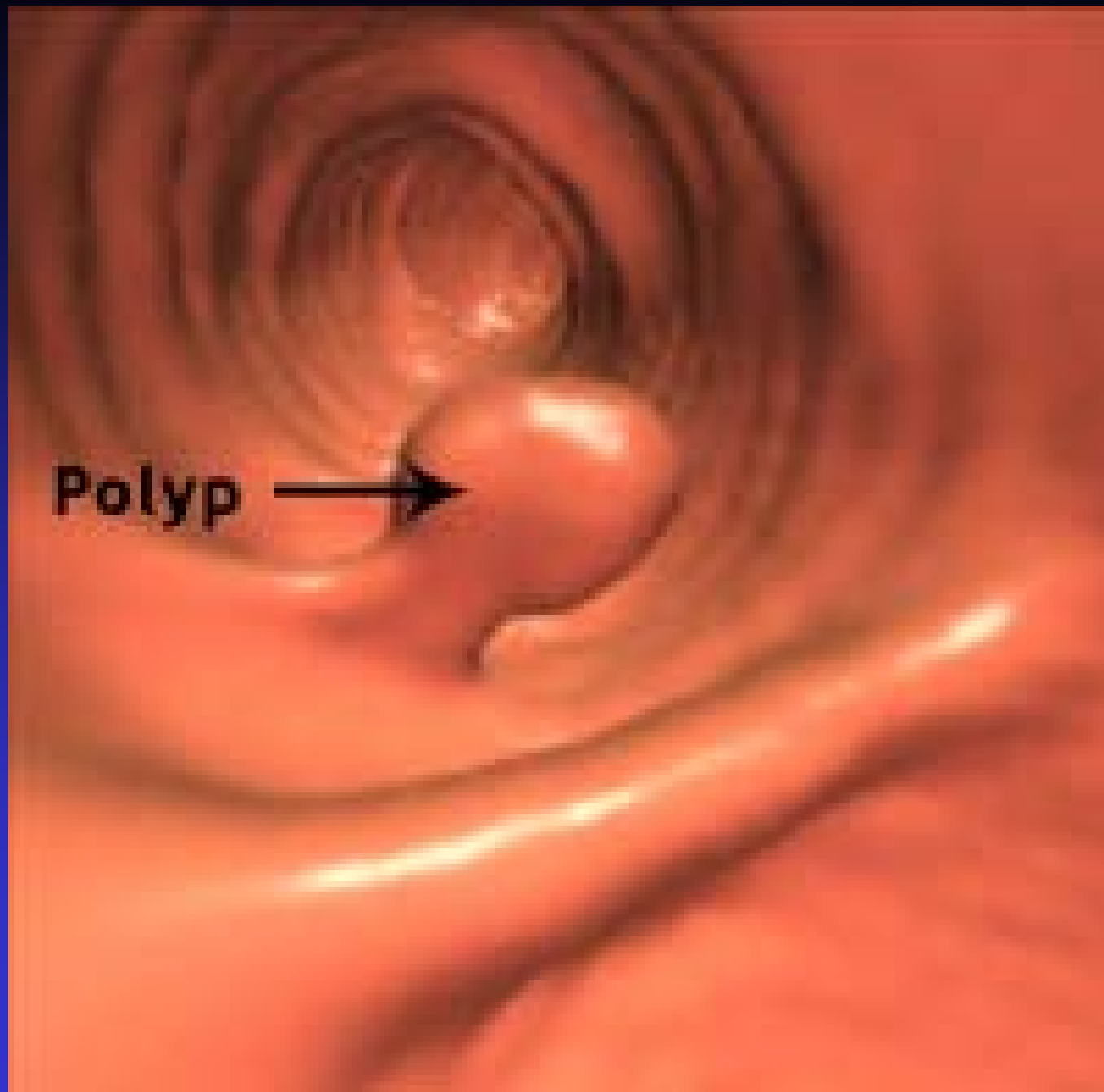
Colonoscopy



An example of a rectal mass

(Rockey et al, Lancet 2005)

Rockey, 2005



Polyp

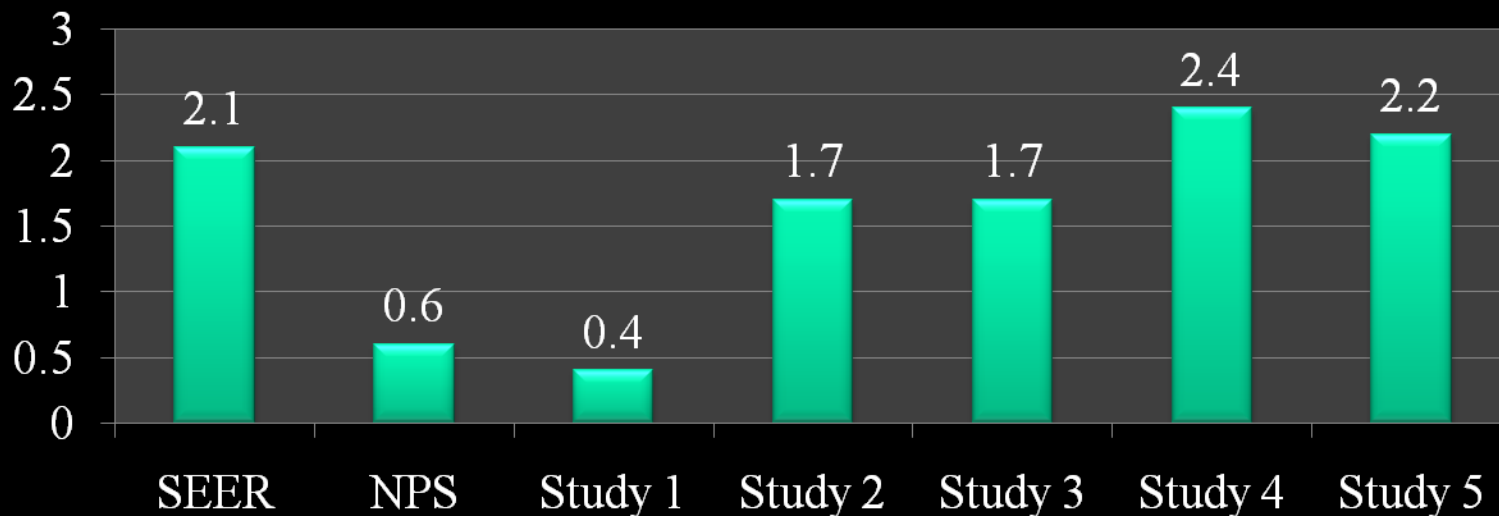
Polypectomy Does Not Eliminate Colon Cancer Risk

- **After initial colonoscopy, patients with adenomas are followed with surveillance colonoscopy to identify and remove subsequent adenomas before they progress to CRC**
- **Colonoscopy is not perfect, and interval cancers diagnosed between surveillance examinations may develop.**
- **Several studies have reported interval cancer incidence rates ranging from 1.7 to 2.4 cancers per 1000 person-years of observation (PYO) essentially the same as the unscreened population**

Annual Colon Cancer Incidence During Surveillance for Prior Adenoma

Incidence per 1000 Patient-Years

NPS=National Polyp Study (N Engl J Med 1993;329:1977–1981).



1) Gut 2001;48:812–815

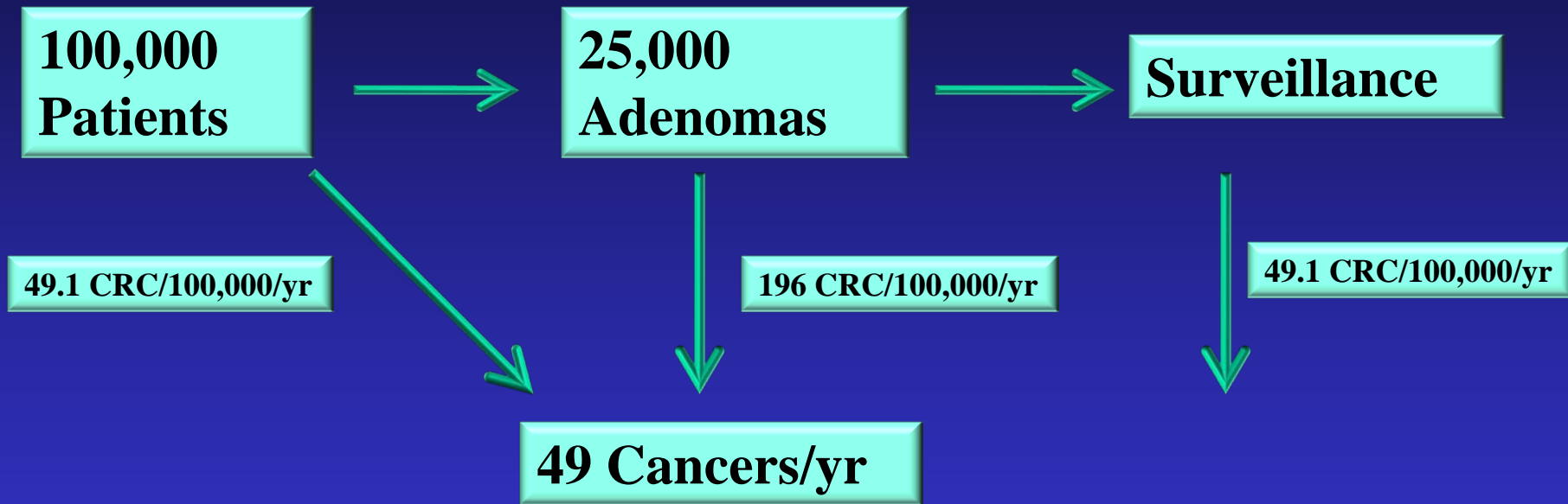
2) Gastroenterology. 2005;129:34–41

3) Gastroenterology. 2007;133:1077–1085

4) Gastrointest Endosc. 2005;61:385–391

5) Engl J Med. 2000;342:1149–1155

“Failure” of Surveillance of Adenomas to Reduce Annual CRC Incidence May Be Illusion



2006 Age-adjusted Incidence Rate CRC 49.1 per 100,000 /Year

African-Americans and CRC

- **AA have lower 5-year CRC survival**
 - **53% vs 63%**
 - **AA have a higher percentage of stage IV at presentation**
 - **Survival still lower than whites even when matched for disease stage**
- **Lower survival may be partially attributed to difference in access to health care**
- **No difference in survival between AA and whites treated in the VA system or clinical trials**
- **Initial screening colonoscopy for AA at age 45 now recommended by ACG**