

Colon cancer update for the internist

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Learning objectives

- To understand the current recommendations for colon cancer screening
- To understand how to risk stratify patients for appropriate colon cancer screening
- To understand the pros/cons of the multiple options for colon cancer screening

CRC Epidemiology

- 4th most common malignancy in US (136,000 cases/yr)
- 2nd most common cause of cancer death (50,000 cases/yr)
- Cumulative lifetime risk of CRC is 4-5%
- Slight male predominance
- Average age of diagnosis: 65 yo
- 75% of cases occur in people without identifiable risk factors
- Prognosis is directly related to stage of disease

Colon cancer arises from a defined precursor lesion



Tubular adenoma

**Tubulovillous
Adenoma***

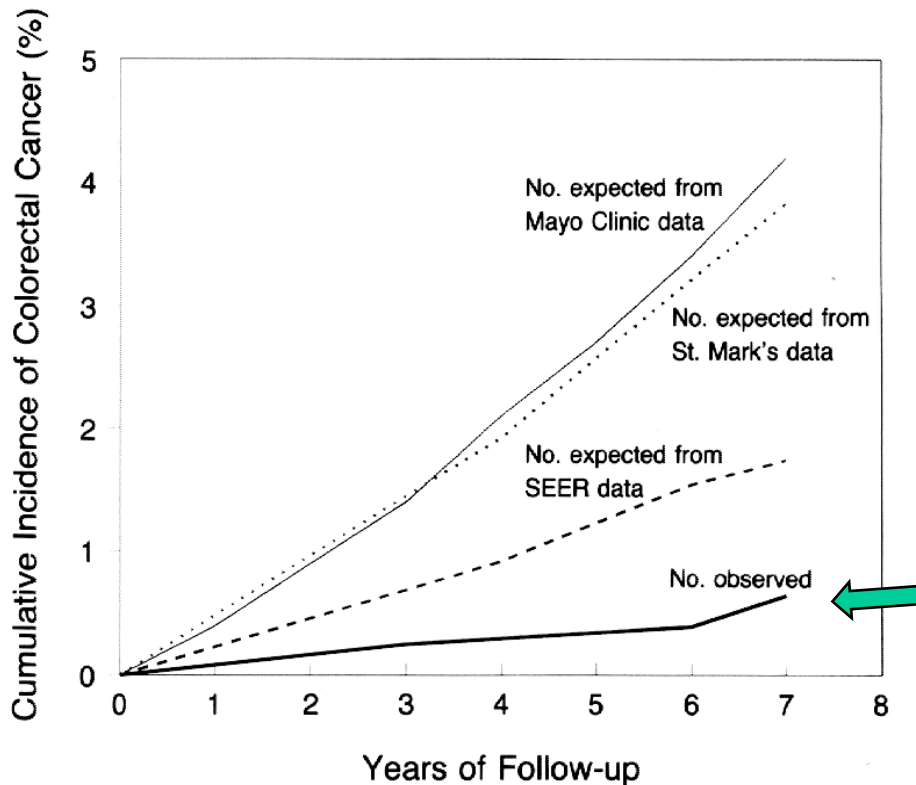
**High grade dysplasia
(Carcinoma-in-situ)***

Invasive cancer

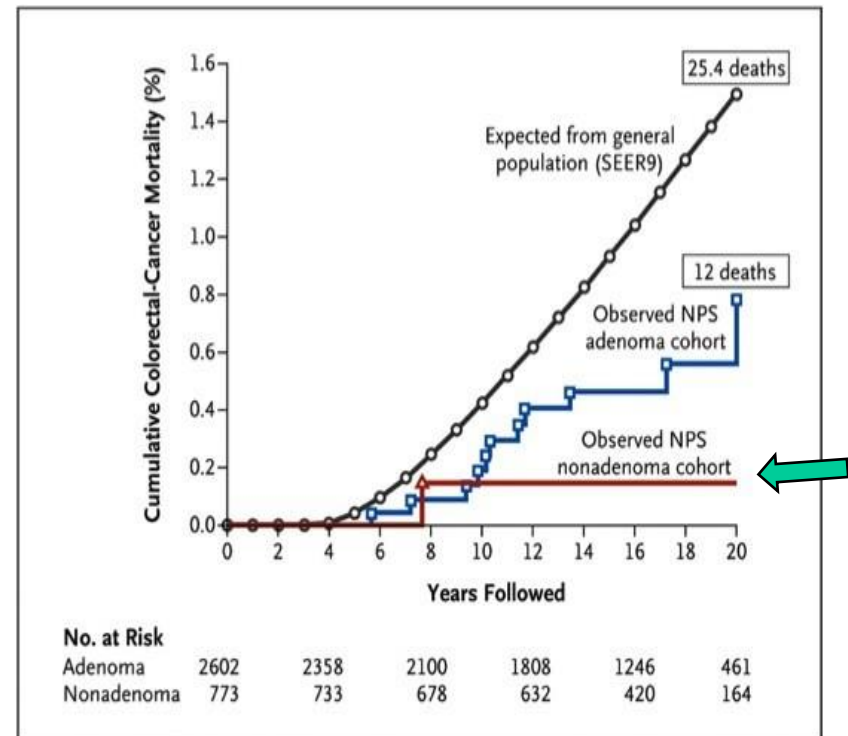
Time -----> **7-10 yrs**

* “Advanced Adenoma”: Villous, high grade dysplasia, or > 1 cm

National Polyp Study: *polypectomy reduces the incidence and mortality of CRC*



Winawer, NEJM, 1993



A Zauber, NEJM, 2012

Colorectal cancer screening

1. Who to screen?

- Average risk 75%
- Moderate risk 20%
- High risk 5%

2. How and how often to screen?

- Colonoscopy
- FIT/Cologuard
- Flexible sigmoidoscopy
- Virtual colonoscopy
- Molecular/genetic testing

Quality parameters for colonoscopy

- Adenoma detection rate (ADR)
 - 20% for women
 - 30% for men
- Cecal intubation rate
 - >95% for screening exams
- Bowel prep quality is critical
 - Split preps are now standard

CRCs can arise soon after a clean colonoscopy ("Interval Cancers")

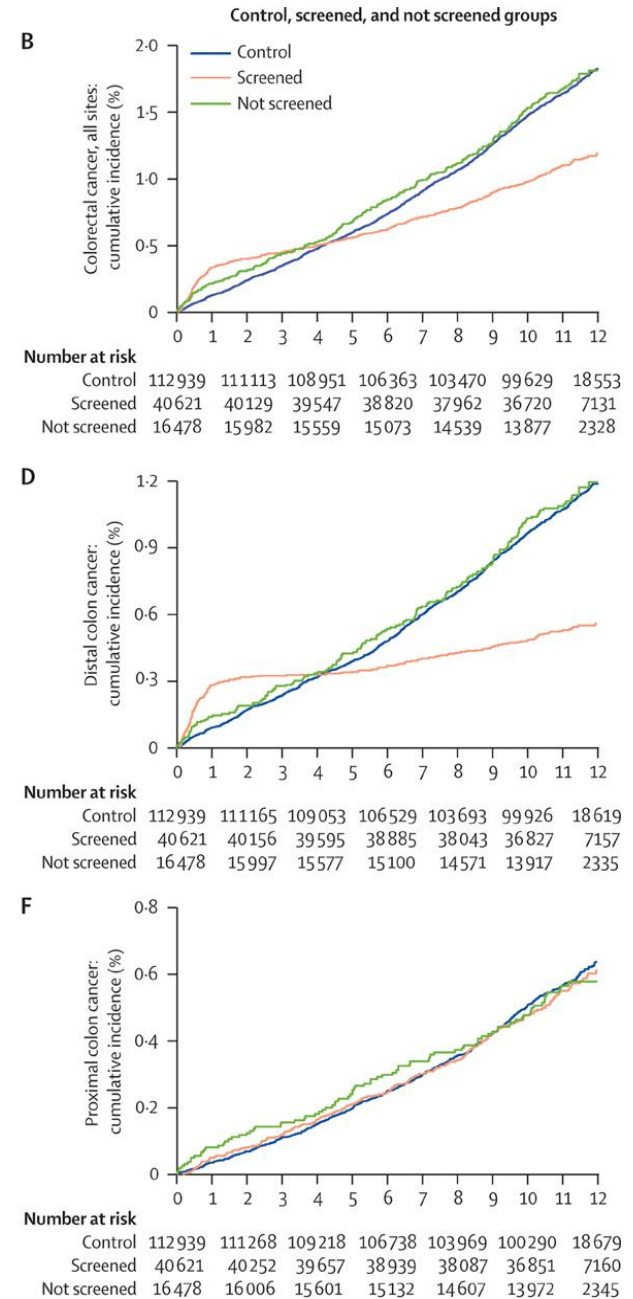
| Reference | Country | Years studied | Number of iPCCRC/number of CRC cancers examined | Relative prevalence of interval CRC (%) | Percentage of interval cancers that were right sided (N) | Percentage of interval cancers that were left sided (N) | Comments |
|----------------|-------------|---------------|---|---|--|---|---------------|
| Singh (7) | Canada | 1992–2008 | 388/4,883 | 7.9 | 58 (225) | 38 (147) | 6–36 Months |
| Bressler (12) | Canada | 1997–2002 | 430/12,487 | 3.4 | 55 (238) | 45 (192) | 6–36 Months |
| Baxter (5) | Canada | 2000–2005 | 1,260/14,064 | 9.0 | 54 (676) | 46 (584) | 7–36 Months |
| le Clercq (14) | Netherlands | 2001–2010 | 147/5,107 | 2.9 | 60 (87) | 40 (60) | <60 Months |
| Erichsen (9) | Denmark | 2000–2009 | 982/38,064 | 2.6 | 45 (441) | 44 (433) | 12–60 Months |
| Cooper (6) | USA | 1994–2005 | 4,192/57,839 | 7.2 | 68 (2,851) | 30 (1,253) | 6–36 Months |
| Samadder (15) | USA | 1995–2009 | 159/2,659 | 6.0 | 55 (88) | 40 (63) | 6–60 Months |
| Arain (10) | USA | 1989–2004 | 63/1,323 | 4.8 | 63 (40) | 37 (23) | <60 Months |
| Corley (8) | USA | 1998–2010 | 712/8,730 | 8.2 | 60 (427) | 38 (267) | 6–120 Months |
| Brenner (11) | Germany | 2003–2007 | 78/1,945 | 4.0 | 56 (44) | 41 (32) | 12–120 Months |
| Ferrandez (13) | Spain | 2003–2005 | 27/386 | 6.7 | 22 (6) | 78 (21) | <36 Months |

3.7%

Adler, Robertson, AJG, 2015

UK Flex Sig Trial

- One time Flexible Sigmoidoscopy between ages 55 and 64
- 33% reduction in incidence of CRC
- 50% reduction in incidence of distal CRC
- 43% reduction in CRC mortality



Immunochemical tests for fecal hemoglobin (FIT)

- More sensitive than guaiac based assays
 - Pooled sensitivity of 79% for cancer (Spec = 94%)
 - Sensitivity between 6-56% for advanced adenoma
- No dietary restrictions necessary, only one stool sample required
- Variable performance depending upon kit, storage conditions, and cut-off values

FIT vs. colonoscopy for screening

- RCT of colonoscopy vs. FIT in average risk individuals in Spain

| | <u>Colo</u> | <u>FIT</u> |
|---------------------|-------------|------------|
| Participation | 24.6% | 32.4% |
| Colon cancer | 0.1% | 0.1% |
| Advanced adenoma | 1.9% | 0.9% |
| Nonadvanced adenoma | 4.2% | 0.4% |

Stool DNA testing

- Based upon principle that colon tumor cells are shed into the stool.
 - Tumor DNA can be isolated from stool
 - Tumor-specific gene mutations can then be detected
- “Cologuard”: fecal DNA + FIT
- Covered by Medicare q 3 years.

Prospective evaluation of fecal DNA testing

N = 9989 subjects referred for screening colonoscopy

| | <u><i>Sensitivity</i></u> <i>(CRC)</i> | <u><i>Sensitivity</i></u> <i>(Advanced Adenoma)</i> | <u><i>Specificity</i></u> |
|------------------|---|--|---------------------------|
| <i>Fecal DNA</i> | 92.3% | 42.4% | 86.6% |
| <i>FIT</i> | 73.8% | 23.8% | 94.9% |

CRC Screening: Average risk patient

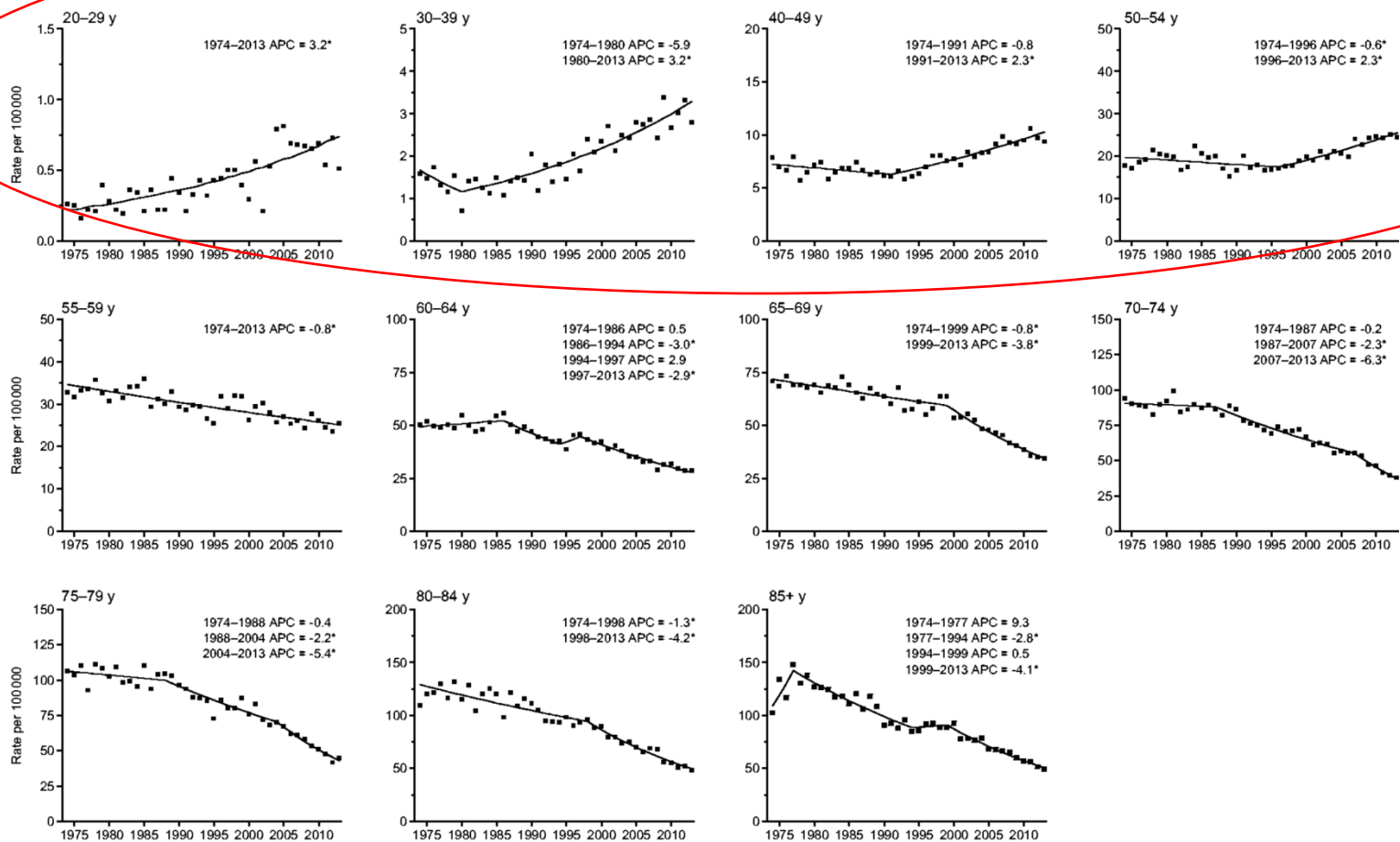
- Men and women over age 45
- No symptoms (bleeding), no occult blood in stool
- No risk factors for CRC (Fam Hx, IBD, adenoma)

Tier 1 (detection of adenomas and CRC)

- Colonoscopy every 10 yrs
- Annual FIT

Tier 2

- CT colonography every 5 years
- FIT-fecal DNA (Cologuard) every 3 years
- Flex Sig every 5-10 years



From: Colorectal Cancer Incidence Patterns in the United States, 1974–2013

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CRC Screening: *Moderate risk patient*

History of adenomas

- Colonoscopy surveillance interval based upon specific features of prior adenomatous polyps:

| | |
|---|--------------------|
| $n > 10 :$ | 1 yr |
| $n=5-10, \geq 10 \text{ mm, villous} :$ | 3 yrs |
| $n= 3-4 :$ | $3-5 \text{ yrs}$ |
| $n= 1-2 :$ | $7-10 \text{ yrs}$ |

CRC Screening: Moderate risk patient

History of CRC

- Personal history of resected colon cancer:
 - Full colonoscopy within 1 year of surgery*
 - If negative, follow-up colonoscopy in 3 years, thereafter every 5 years

CRC Screening: Moderate risk patient Inflammatory Bowel Disease

- 8 years of pan-ulcerative colitis or
15 years of left-sided colitis:

Colonoscopy every 1-2 years

- Crohn's colitis

CRC Screening: Moderate Risk Patient

Family History of CRC/advanced adenomas (1)

- CRC or advanced adenoma in 1st degree relative < 60 or two 1st degree relatives of any age:

Colonoscopy at age 40, or 10 yrs before youngest case. Then every 5 years.

- CRC or advanced adenoma in 1st degree relative \geq 60 or two 2nd degree relatives of any age :

Average risk recommendations, but start screening at age 40

CRC Screening: Moderate Risk Patient

Family History of CRC/advanced adenomas (2)

- CRC or advanced adenoma in 1st degree relative at any age:

Colonoscopy at age 40, or 10 yrs before youngest case. Then every 5 years.

When to stop screening?

US Preventive Services Task Force (USPSTF):

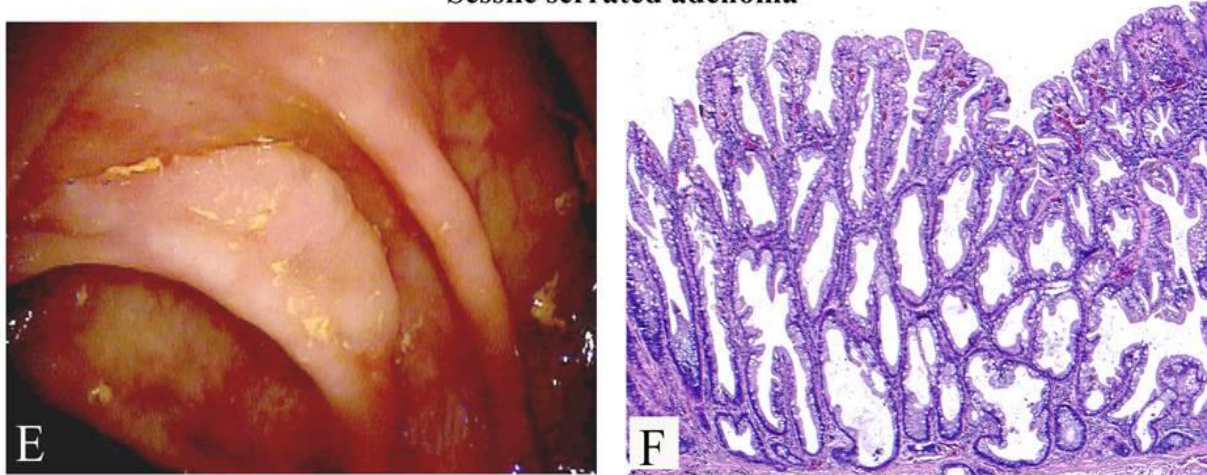
- * Recommends screening until age 75 yrs
- * Advises against screening age 76-85 yrs,
but this should be individualized
- * Recommends against screening after age 85 yrs

These guidelines do not apply to:

- * Surveillance
- * High risk individuals

What about “sessile serrated polyps”?

Sessile serrated adenoma



- Sessile serrated polyps/adenomas are pre-cancerous and should be managed like tubular adenomas.
- More common in right colon and in elderly patients
- Likely responsible for “interval cancers”
- Surveillance guidelines as per typical adenomas

Screening tools on the horizon

- AI/computer aided detection of polyps during colonoscopy. First device approved by the FDA in 2021.
- Colon capsule endoscopy. FDA approved for incomplete colonoscopy or those at major risk with routine colonoscopy.
- Blood assays for circulating cell-free tumor DNA under investigation

High-risk patients: Hereditary Colon Cancer families

- Lynch syndrome
- Autosomal dominant inheritance
- CRC: 60% lifetime risk
early age of onset (40's)
multiple primary tumors
- Few adenomas
- Strong association with endometrial cancer
(50% lifetime risk)
- Genetic testing available (MSH2, MLH1, MSH6,
PMS2, EPCAM genes)

Lynch: *Screening guidelines*

- Colorectal cancer

Colonoscopy q1-2 yrs from age 25

- Endometrial cancer

Endometrial aspirate +/- transvaginal ultrasound q1 yr from age ~30

- Other tumors (ovarian, gastric, urinary tract)
guided by family history

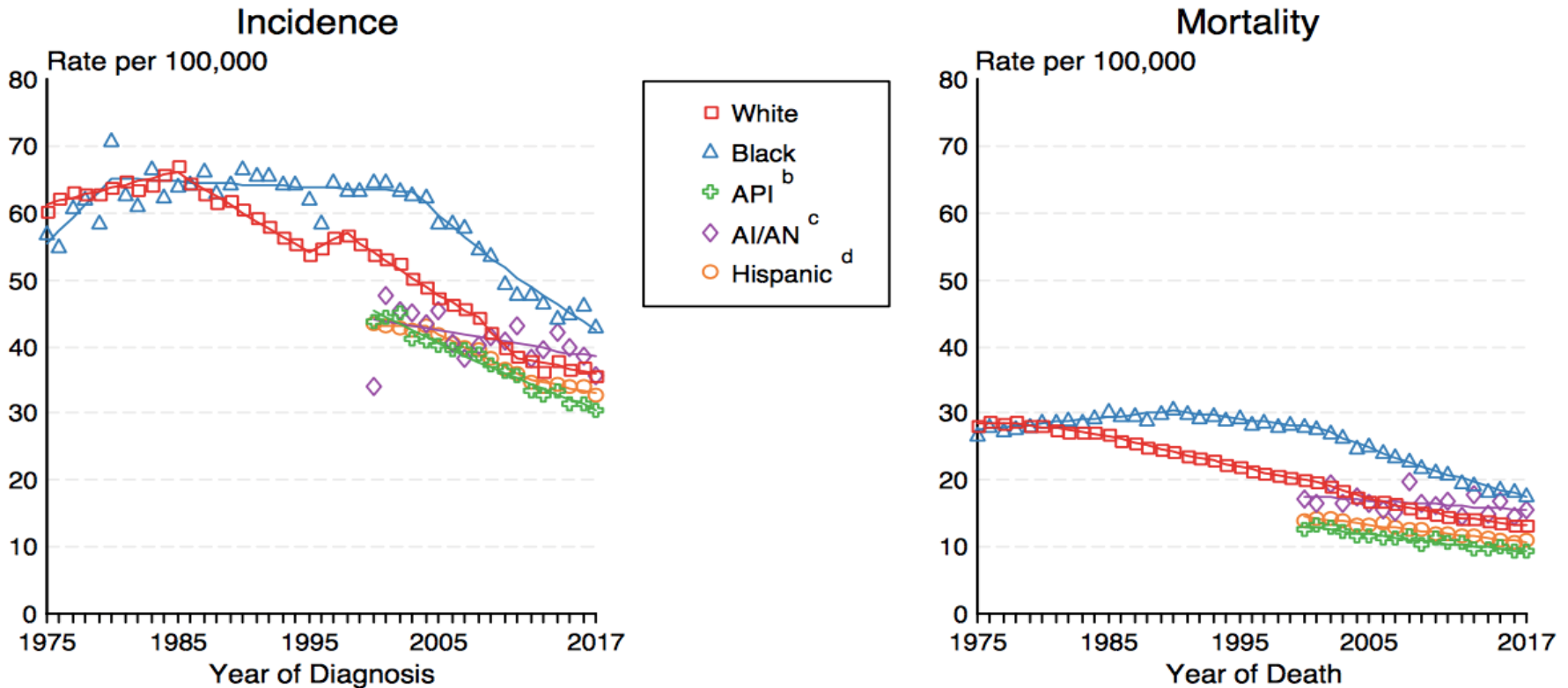
CRC incidence and mortality are falling in the US

SEER Incidence and US Death Rates^a

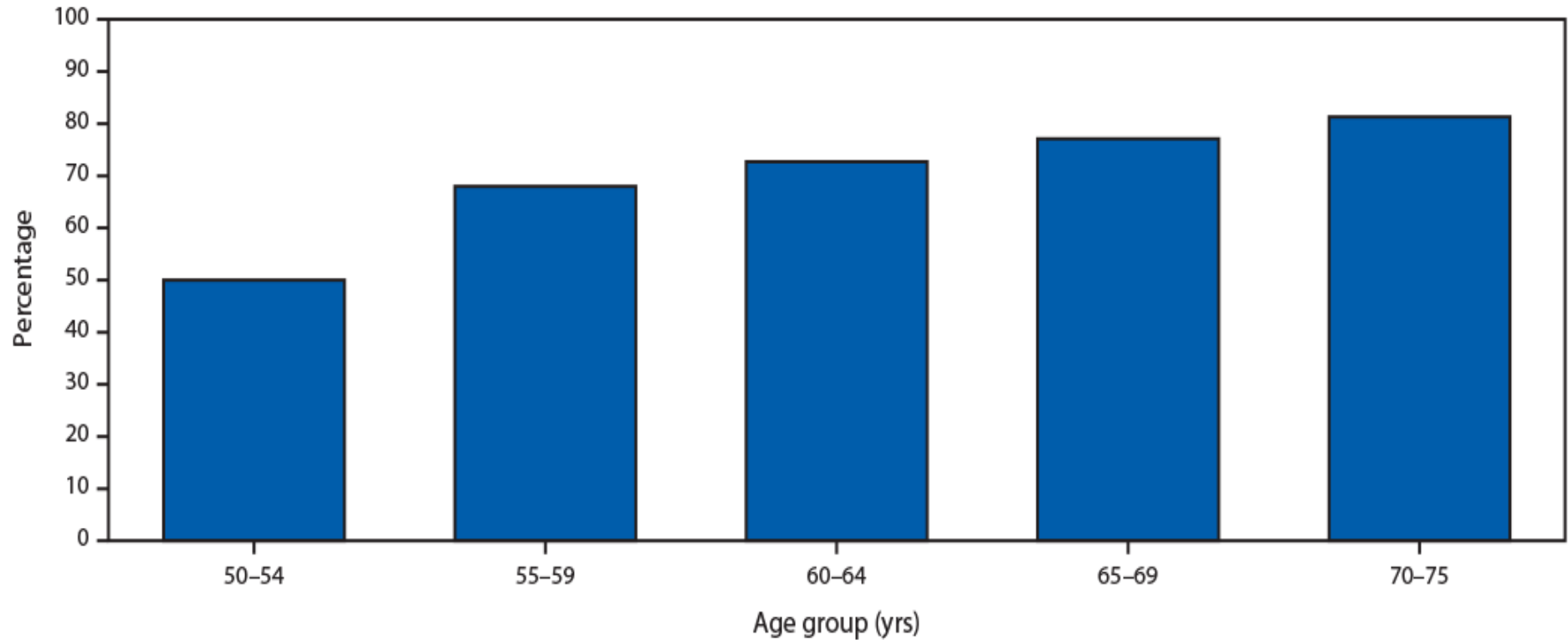
Cancer of the Colon and Rectum, Both Sexes

Joinpoint Analyses for Whites and Blacks from 1975-2017

and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 2000-2017



Participation with CRC screening guidelines



Overall rate of participation in 2018: 69%
** Highly age-dependent*

CRC screening in the COVID pandemic

- 86% reduction in CRC screening volume early in the pandemic
- Estimated 18,000 delayed diagnoses of CRC over a 3-month period
- Strategies to address the issue:
 - Create safe environment in endoscopy unit
 - Offer alternative at-home options (FIT, Cologuard)
 - Ensure that higher risk individuals do not postpone surveillance

A healthy 65 year old woman had a 3 mm adenomatous polyp removed from the right colon at colonoscopy. The prep was reported as good. Which follow-up plan would you recommend?

- A. Colonoscopy in 3 years.
- B. Colonoscopy in 5 years.
- C. Colonoscopy in 7 years.
- D. Cologuard testing in 1 year.

Which of the following is NOT a quality measure in the performance of colonoscopy?

- A. Adenoma detection rate in men > 30%
- B. Cecal intubation rate > 95%
- C. Excellent bowel preparation
- D. Low rate of post-procedure perforations
- E. Use of propofol for anesthesia

Key points

- Everyone requires colon cancer screening
- Age of initiation of CRC screening lowered to 45 yrs
- Colonoscopy and FIT are Tier 1 options for screening
- Surveillance intervals post-polypectomy have been extended
- Accurate risk stratification is key, and this depends upon a careful family history
- High quality screening exams are essential
- Refer high-risk individuals for genetic evaluation