Colorectal Cancer:
Guidelines & Controversies

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Objectives

1. Recognize the common presenting signs and symptoms of colon cancer.
2. Describe the various management options available for colorectal cancer.
3. Discuss the current screening guidelines for colon cancer.
4. Consider the benefits and limitations of each screening method potential impact on patient outcomes

Colorectal Cancer Facts

- Fourth most common malignancy behind breast, prostate, and lung
  - Second most common cause of cancer-related death behind only lung
- Estimated 153,020 new cases in 2023
- Estimated 52,550 deaths in 2023
- 5-year survival: 65.0%

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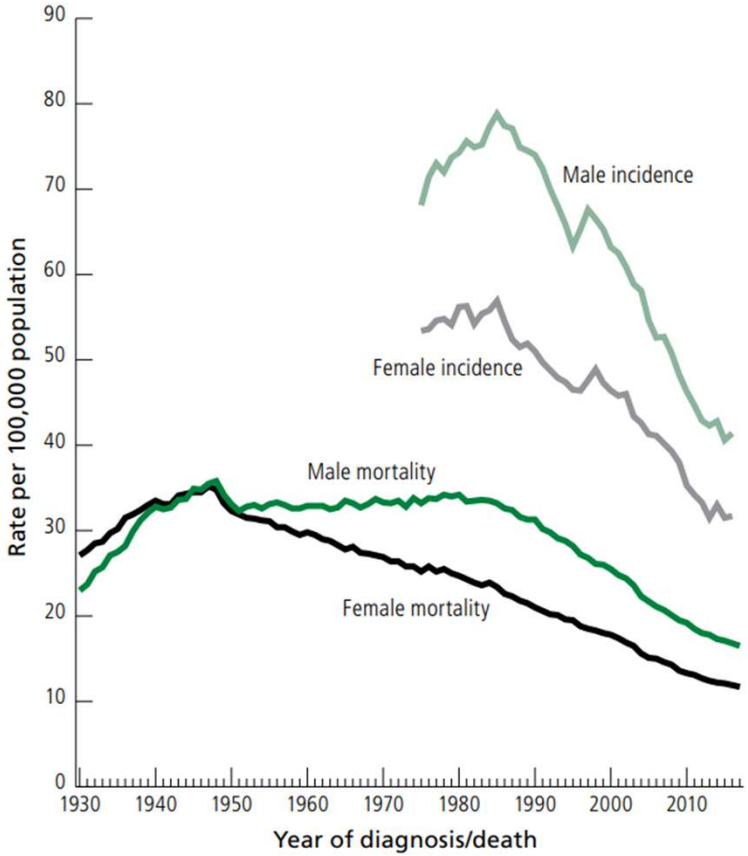
National Cancer Institute. SEER. 2023

Colorectal Cancer Trends



- Consistent decline in rates since 1990s.
- Dramatic decline in late 2000s predominately reflects an increased uptake of screening
  - 20% in 2000 to 61% in 2018

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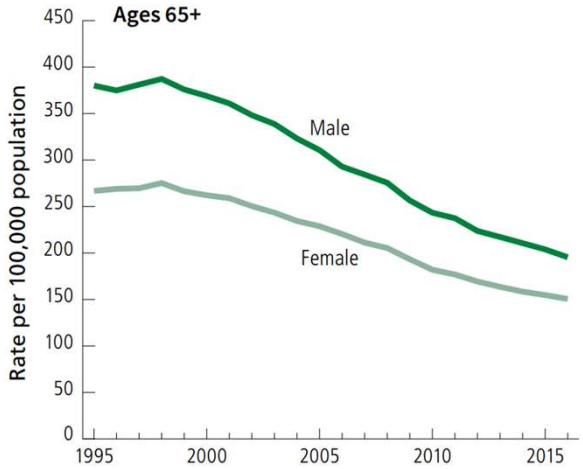
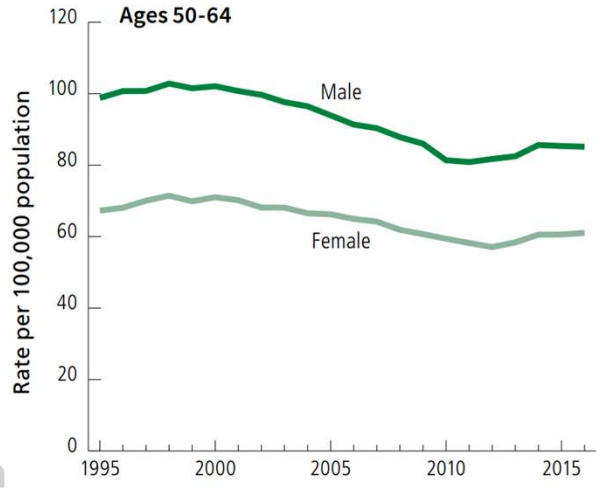
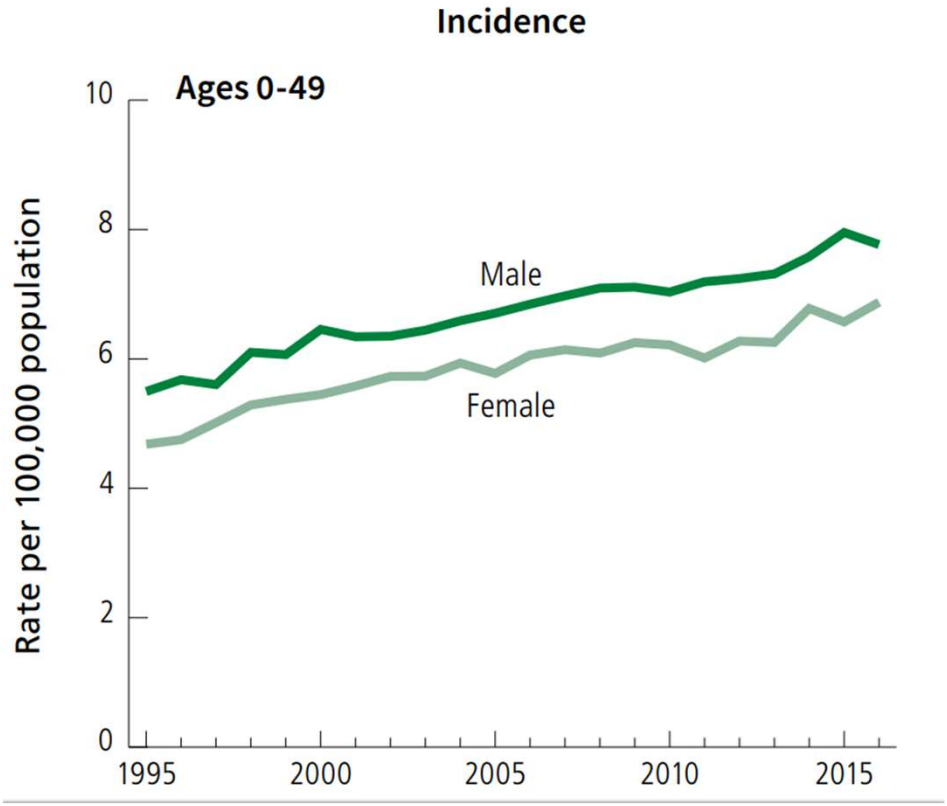
American Cancer Society. 2022







American Cancer Society. 2022

Risk Factors

- Lifestyle Factors
  - Low fiber & high fat diet
  - Low intake of fruits/vegetables
  - Sedentary Lifestyle
  - Alcohol Consumption
  - Smoking
  - Obesity
- Age
- Family History
  - First degree with CRC
  - Inheritable conditions
    - HNPCC/Lynch syndrome
    - FAP
- History of adenoma / polyps
- Inflammatory Bowel Diseases

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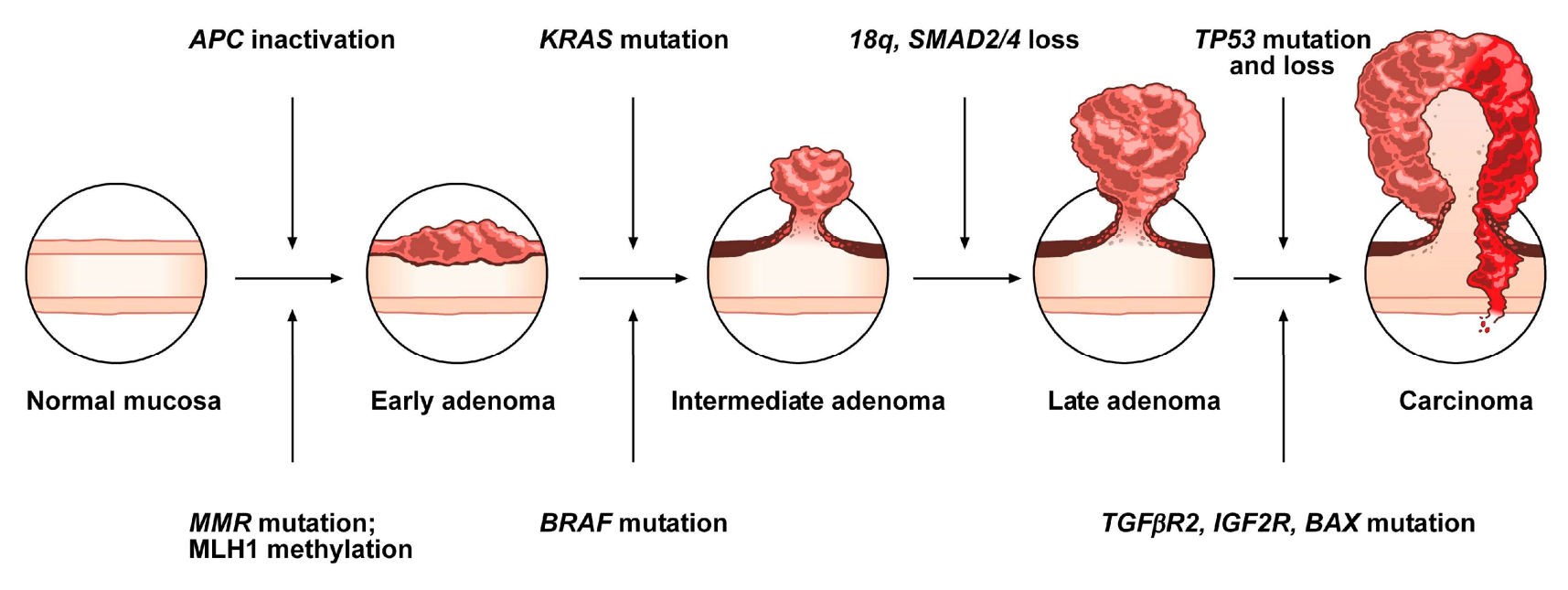
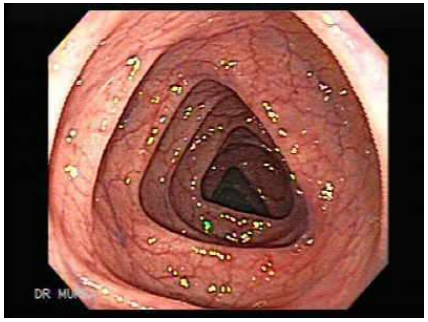
Islami et al. *CA Cancer J Clin*. 2018
Kohler et al. *Cancer Epidemiol Biomarkers Prev.* 2016.

Adenoma-Carcinoma Sequence

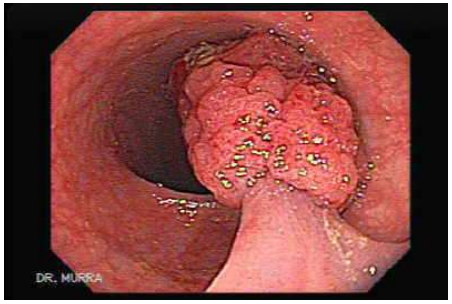


De Palma et al. *Cancers*. 2019

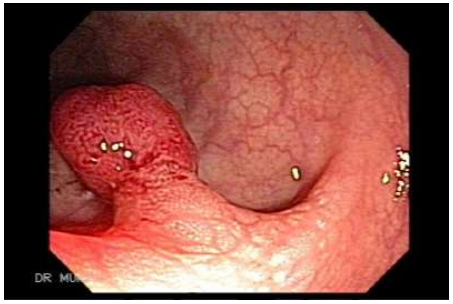
Colonoscopy Findings



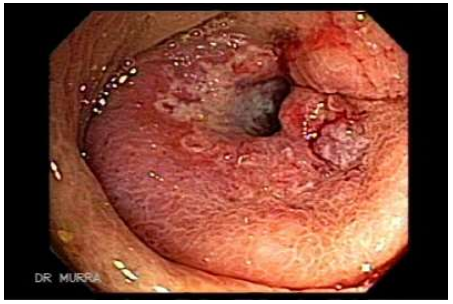
Normal Colon



Polyp



Adenoma



Circumferential Adenocarcinoma

Clinical Presentation

- Most common in the 5th, 6th and 7th decades of life
- Most often asymptomatic/insidious (~70%), obstruction (~15%), or perforation (7%).
- Presenting symptoms:
  - Change in bowel habits
    - Constipation
    - Diarrhea
  - Abdominal Pain
  - Abdominal Distention

Colorectal Cancer Screening

- *Screening* tests are performed before a person develops symptoms of colon cancer
  - Detects disease which may be present but silent
  - To prevent or more effectively treat the disease

- Colorectal Cancer Screening = Prevention & Early Detection
  - Polyp removal → Decreased Incidence
  - Early detection → Decreased mortality

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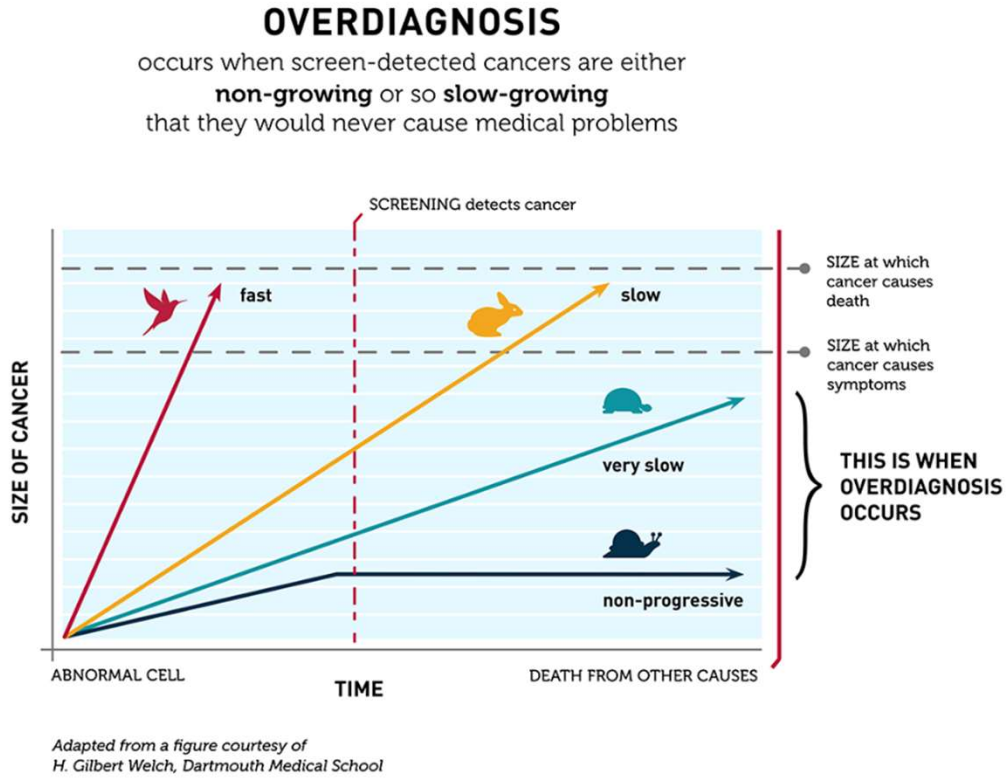
Basics of Screening

- For a screening test to be most useful:
  - Impact
  - Detection Period
  - Cost
  - Safety
  - Sensitivity / Specificity

Harms Associated with Screening

- Test-Specific Harms
- False Positives
- Overdiagnosis



https://prevention.cancer.gov/sites/default/files/uploads/news_and_event/overdiagnosis_2018.jpg

Colorectal Cancer Screening Guidelines

USPSTF Recommendations

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Test Options

- Stool Based Tests
  - Guaiac fecal occult blood tests (gFOBT or FOBT)
  - Immunochemical FOBT (FIT)
  - Multi-target stool DNA
- Endoscopic Tests
  - Flexible sigmoidoscopy
  - Colonoscopy
- Radiology
  - Double contrast barium enema
  - CT colonography ("virtual colonoscopy")

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Stool Based Tests

- Guaiac FOBT
  - Detects peroxidase activity of heme
    - In presence of heme and developer, guaiac acid turns blue
  - False Positives:
    - Red meat (nonhuman heme)
    - Broccoli (peroxidases)
    - Non-GI blood (epistaxis)
    - ASA, NSAIDs, anticoagulation
  - False Negatives:
    - Vitamin C (antioxidant)
- Fecal Immunochemical Test
  - Antibodies to hemoglobin
    - Specific to bleeding from colon, as globin does not survive passage through upper GI tract
  - False Positives:
    - Use of ASA, NSAIDs, anticoagulation

Mathews et al. *J Hosp Med.* 2017.

Guaiac FOBT Evidence

	Mandel (1993)	Mandel (1999)	Hardcastle	Kronborg
Frequency	Annual	Biennial	Biennial	Biennial
Duration	18	18	8	13
% requiring colonoscopy	30%	30%	5%	5%
Mortality Reduction	33%	21%	15%	18%
Incidence	20%	17%		

Mandel et al. *N Engl J Med.* 1993.
Mandel et al. *J Natl Cancer Inst,* 1999.
Hardcastle et al. *Lancet.* 1996.
Kronborg et al. *Lancet* 1996.

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FIT Test Characteristics

Condition Detected	Sensitivity	Specificity
Cancer	68.8 – 90.9%	94.4 – 95.6%
Advanced Adenoma	22.2 – 40.3%	97.4 – 91.3%

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Lin JS et al. AHRQ Publication No. 14-05203-EF-1. 2015.

Stool Based Testing

Advantages

- Inexpensive
- No specialized resources
- Can be done at home
- FIT specific for human blood
- No dietary restrictions with FIT
- Proven CRC mortality reduction

Disadvantages

- Annual testing
- Dietary restriction for gFOBT
- Decreased sensitivity for adenomas
- FIT test variation

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Stool Based Testing

- Mortality reduction depends on program of annual FOBT
  - ***Test*** sensitivity compared to ***Program*** sensitivity

- Positive FOBTs **must** be followed up with colonoscopy
  - Do not repeat positive FOBTs
  - If colonoscopy negative, next screen in 10 years

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Multi-Target Stool DNA

- Brand name: Cologuard®
- Tests stool for presence of known DNA alterations in adenoma-carcinoma sequence and human hemoglobin with FIT
- Requires relatively large stool specimen
- Sensitivity: 92.3%
- Specificity: 84.4%

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Flexible Sigmoidoscopy

- Test Statistics
  - Estimated sensitivity for CRC: 58-75%
  - Estimated sensitivity for advanced neoplasia: 72-86%
- Adenoma miss rate
  - 20% overall polyps any size (14% polyps >10 mm, 19% >6mm)
- Refer for colonoscopy if adenoma
  - Risk of proximal adenoma 2x greater with adenoma any size in distal colon

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Flexible Sigmoidoscopy: Evidence

- Case Control Studies
  - Selby 1992
    - Rigid sigmoidoscopy with polypectomy
    - 60% reduction in mortality from distal CRC over 10 years
    - Death from proximal cancer same in both groups
  - Newcomb
    - 79% mortality reduction for CRC with sigmoidoscopy
- Randomized control trial
  - Atkin
    - One time flex sig between age 55-65 year
    - Incidence of CRC in people attending screening reduced 33%
    - CRC mortality reduced 43%
    - Incidence of distal CRC reduced by 50%

Selby et al. *NEJM*. 1992.
Newcomb et al. *J Natl Cancer Inst*. 1992.
Atkin et al. *Lancet*. 2010

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Flexible Sigmoidoscopy

Advantages

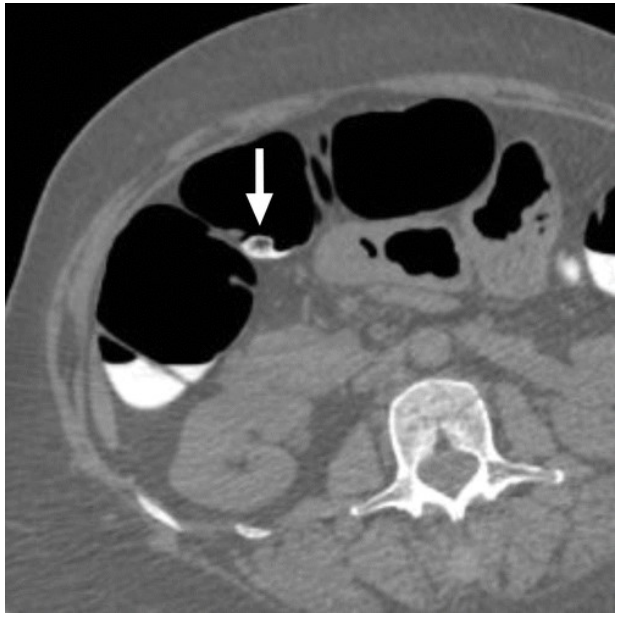
- Office based
- No sedation
- Simplified bowel preparation
- Every 5 years
- Evidence to support incidence & mortality reduction

Disadvantages

- Complications
- Quality
- Invasive
- May miss isolated proximal adenomas/cancers

CT Colonography

- Following bowel preparation and colon insufflation, computed tomography images of the bowel allows for direct visualization of polyps
- Identification requires follow up colonoscopy



CT Colonography

Concerns

- Radiation exposure
- Extracolonic findings
- Management of small polyps
- Sensitivity for flat adenomas

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Colonoscopy

- Indirect evidence of colonoscopy screening effectiveness
  - Observational studies: 60-90% reduction in CRC incidence after polypectomy
  - National Polyp Study
    - 76-90% reduction in observed CRC incidence over 6 years after polypectomy
- Effectiveness highly dependent on quality of colonoscopy
  - Dependent on skill of endoscopist
  - Quality metrics important to monitor
    - Adenoma Detection Rate
    - Cecal Intubation Rate
    - Quality of Bowel Preparation

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Colonoscopy

Advantages

- Most accurate test as single application
- Detection and removal of polyps in single procedure
- If negative, once every 10 years

Disadvantages

- Bowel preparation
- Sedation
- Invasive
- Potential for complication
- Expensive

Colonoscopy: Evidence

Until 2022, no randomized controlled trial had demonstrated reduction in CRC mortality by colonoscopy screening

- Nordic-European Initiative on Colon Cancer (NordICC) trial
  - 85,585 patients between 55-64 years
  - Randomized to receive an invitation to undergo one-time colonoscopy screening or to receive no initiation
    - 42% of patients receiving invitation underwent screening
  - End points: risk of colon cancer and CRC-related death at 10 years

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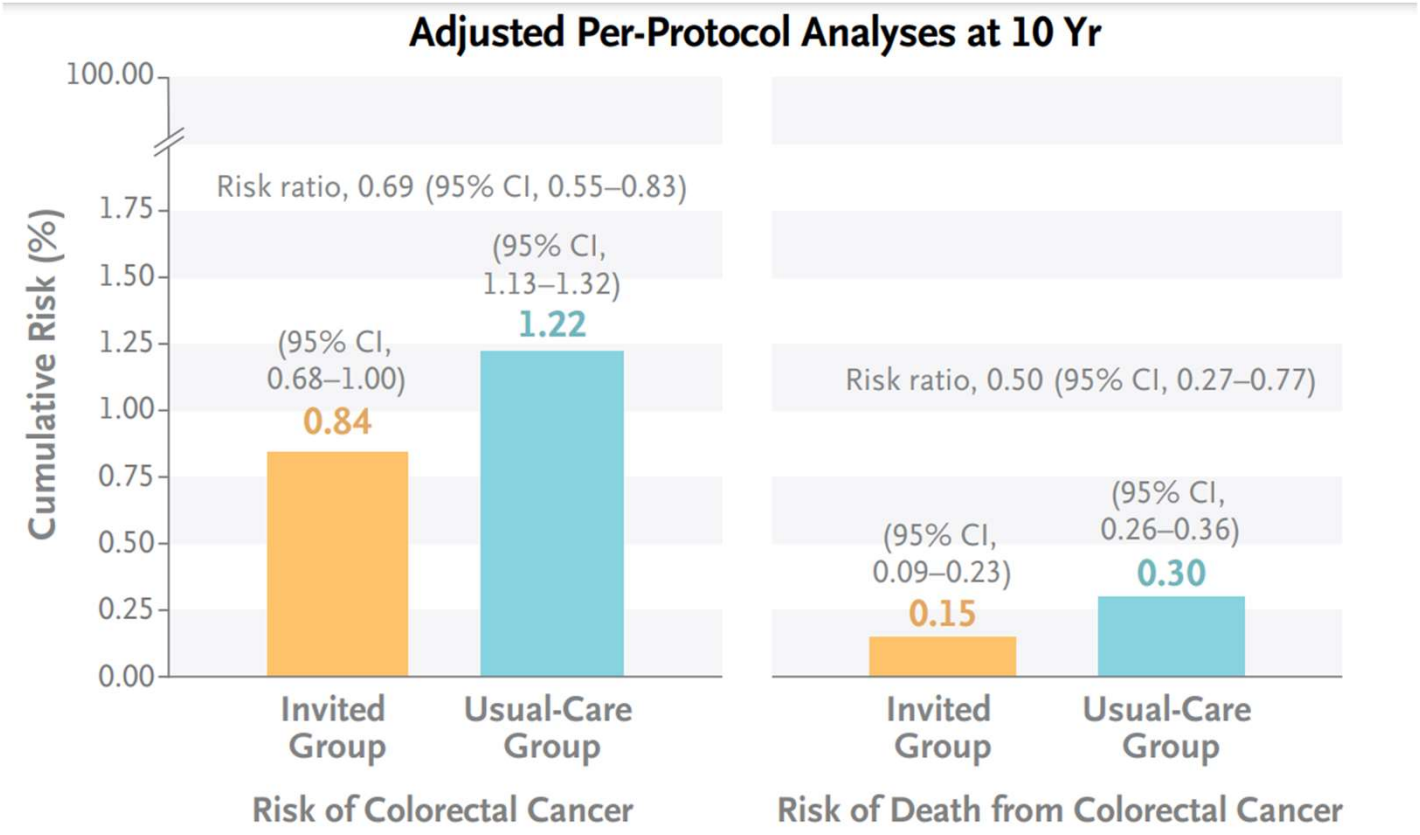
Bretthauer et al. *NEJM*. 2022

NordICC Trial 2022



Bretthauer et al. *NEJM*. 2022

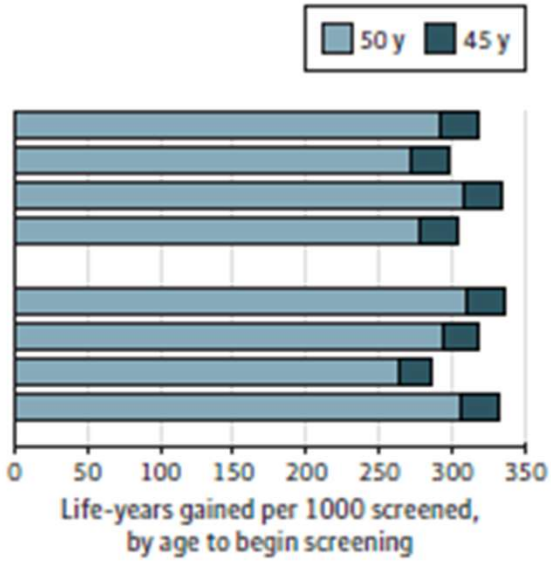
USPSTF Screening Recommendations

- Age 45-49: Screening is recommended. **Grade B**
- Age 50-75: Screening is recommended. **Grade A**
- Age 76-85: Case by case discussion. **Grade C**

- Screening modalities:
  - High sensitivity guaiac FOBT: annually
  - Stool DNA-FIT: every 1-3 years
  - CT colonography: every 5 years
  - Flexible sigmoidoscopy: every 5 years
  - Colonoscopy: every 10 years
    - Preferred given diagnostic and therapeutic capability

A Benefit: Estimated life-years gained per 1000 individuals screened[a]

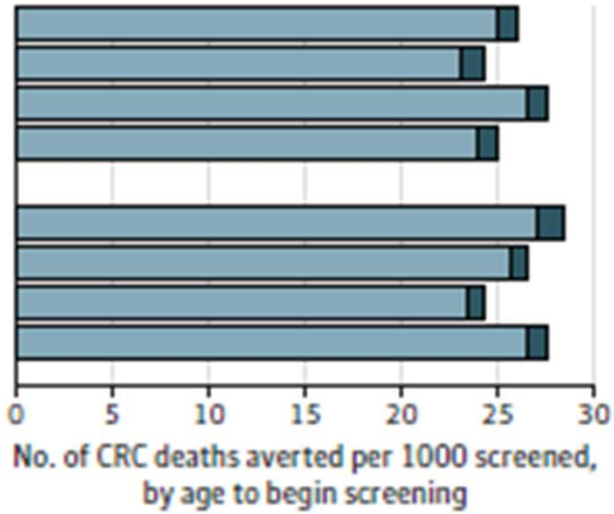
Screening modality and frequency	Mean life-years gained if start screening[b]		Additional life years gained if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 y[d]	278	303	25
Direct visualization tests			
COL every 10 y	310	337	27
CT colonography every 5 y	293	317	24
Flexible SIG every 5 y	264	286	22
Flexible SIG every 10 y plus FIT every year	306	332	26



USPSTF 2021 Recommendations

C Benefit: Estimated No. of CRC deaths averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC deaths averted if start screening[b]		Additional CRC deaths averted if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	25	26	1
HSgFOBT every year[c,d]	23	24	1
sDNA-FIT every year	27	28	1
sDNA-FIT every 3 y[d]	24	25	1
Direct visualization tests			
COL every 10 y	27	28	1
CT colonography every 5 y	26	26	0.9
Flexible SIG every 5 y	23	24	0.9
Flexible SIG every 10 y plus FIT every year	26	28	1



USPSTF 2021 Recommendations

Summary

- Multiple modalities exist to effectively screen for colorectal cancer
- Some modalities with strong randomized-controlled evidence to support reduction in CRC incidence and mortality
- Despite recent controversies surrounding colonoscopy screening – it remains the gold standard in CRC
- Ultimately – the best screening test for CRC is the one that a patient will complete

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Thank you!

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