StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-.

Colon Cancer Screening

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Last Update: September 10, 2024.

Definition/Introduction

Colorectal carcinoma (CRC) is the third most common non-skin cancer in the United States (US) after lung cancer in both men and women, with an annual incidence of 42.9 per 100,000 people. CRC accounts for 8% of cancer-related deaths in the US alone.[1] The prevalence and incidence of CRC vary worldwide, with Australia and New Zealand having the highest incidence, followed by North America and Europe. Africa and South-Central Asia have the lowest incidence. Such a pattern only extrapolates that CRC incidence is attributed to dietary factors along with genetic and environmental factors. This condition also displays a strong correlation with increased age, with the maximum rate at the age above 75 years and the lowest below 40 years. Men are affected more than females. Blacks have the highest incidence, and Asian Pacific Islanders have the lowest. Screening is the process of looking for cancer in patients who have no symptoms. Several tests are available to screen for colorectal cancer. These tests can be divided into stool-based tests and visual exams. Any abnormal test result should be followed up with a colonoscopy. If cancer of the colon is caught early, the patient usually has a better outcome.

Issues of Concern

With the advent of newer and better screening tools, the CRC-related mortality rate has decreased, on average, by about 2.7% between 2004 and 2013. This number is expected to decrease further to about 38% for 50 to 74-year-olds and about 45% for those older than 75 by 2030.[2] However, for unknown reasons, data from the United States Surveillance, Epidemiology, and End Results (SEER) database suggests that the incidence has been increasing among younger adults below 50 years of age.[3] Rates have increased constantly at a rate of 2 percent yearly from 1992 through 2013.[3] Hence, delivering more effective and robust screening is the best preventive instrument.

Recently, a gradual shift towards right-sided or proximal colon cancers has been seen both in the United States and internationally.[4][5] Mostly, the incidence of cecal primary malignancies has increased.[6] This can be attributed to the anatomic distribution of CRCs as well as to improvements in diagnosis and treatment by screening and removal of adenomatous polyps in the distal colon. Cancer biology also seems to play a role in this recent shift since serrated adenomas, which exclusively have *BRAF*-V600E mutations, cause lesions that are flatter and difficult to visualize endoscopically and are more common in the right colon.[7] Wide-spread, compliant, and flexible screening is the best step to prevent CRC mortality in the near future, given the present epidemiological evidence.

Pathogenesis

Most CRCs begin as protuberances tethered to the inner surface of the colon or rectum, clinically known as “polyps.” These are mainly of two types: flat or raised, relative to the inner-epithelial lining. Raised polyps show two distinctive growth patterns of mushroomed growth:

- Without a stalk (sessile polyps)

About 10% of patients with CRC carry 1 or more pathogenic “non-Lynch syndrome mutations,” including mutations in high-penetrance genes such as *APC*, bi-allelic *MUTYH, BRCA1, BRCA2, PALB2, CDKN2A*, and *TP53*.[8] Right-sided CRCs tend to be diagnosed in advanced stages compared to left-sided, as the cecum and right colon have a larger caliber, and stool is more liquid, causing fewer symptoms of partial obstruction such as pain, swelling, and constipation. Blood in stools (hematochezia or melena) isn’t readily observed and comes much later as compared to the left side, making screening tools pivotal in management for early detection and therapy.[8][7]

Risk factors for CRC

Risk factor assessments help to categorize the patient as high, average, or low-risk. Aggressive multiple interval-based testing starts as early as the teenage years in patients with a positive family history or co-existing genetic cancer syndromes. A relaxed approach toward screening and further management can be seen in the majority of cases who are at average risk.[9][10]

Family history (especially first-degree relatives)

- Colorectal carcinoma
- Pre-cancerous adenomas

Genetic cancer syndromes

- Familial adenomatous polyposis (FAP) (and its variants Gardner and Turcot syndrome)
- Lynch syndrome
- Hereditary non-polyposis colorectal cancer (HNPCC)
- Peutz-Jeghers syndrome
- Juvenile polyposis

Medical history

- Previously resected or diagnosed adenomatous colorectal polyps; or any of the above-mentioned genetic cancer syndromes
- Cystic fibrosis [11]
- Inflammatory bowel diseases like Crohn disease or ulcerative colitis
- Diabetes mellitus and insulin resistance [12]
- Abdomino-pelvic radiation for an earlier cancer in childhood or adolescence (as suggested by Children Oncology Group)
- Human immunodeficiency virus infection in men [13]

Personal history

- Chronic alcohol use disorder
- Smoking

- Obesity
- Poor diet (low fiber; high amounts of red and processed meat consumption)

Race

- Higher incidence and mortality among Blacks particularly men. CRC occurrence is higher in Black individuals less than 50 years of age. Hence earlier screening, starting from the age of 45 years, is recommended by the US Preventive Services Task Force (USPSTF).[1]

Clinical Significance

Screening Tools

The various modalities for early detection of CRCs are as follows:

Stool-Based Tests

- Fecal immuno-chemical test (FIT)
- Guaiac fecal occult blood test (gFOBT), also known as HSgFOBT (high-sensitivity guaiac-based fecal occult blood test)
- Stool deoxyribonucleic acid (DNA) test (FIT-DNA): also known as multi-targeted-stool DNA test (MT-sDNA)

Visualization-Based Tests

- Sigmoidoscopy
- Colonoscopy
    - Optical: standard
    - Virtual: radiological; CTC and capsule colonoscopy
- Barium enema

Blood-Based Test

- Methylated *SEPT-9*

Age to Initiate Screening

The USPSTF and many other expert councils recommend initiating screening for average-risk patients at 45 years of age due to high early-onset incidence.[1] For those with high-risk attributes (positive family history or cancer syndromes), screening can be initiated as early as the teenage years.[9] Screening for those with a positive family history is recommended to start 10 years before the age of diagnosis of the family member. USPSTF doesn't recommend routine CRC screening in adults 86 years and older.

Contraindications for Screening

Contraindications might vary depending on the screening method. Most stool-based tests can be carried out easily. However, other screening methods involve sedation, consumption of contrast, and further instrumentation of the colon. Bowel preparation is a vital prerequisite, using either a laxative or non-laxative method. The type of bowel

if there is a concern for bowel perforation. Care should be taken for the following conditions:

- Active colonic inflammation (eg, acute diarrhea, active inflammatory bowel disease)
- Symptomatic colon-containing abdominal wall hernia
- Recent acute diverticulitis
- Recent colorectal surgery
- Recent deep endoscopic biopsy/polypectomy/mucosectomy
- Known or suspected colonic perforation
- Symptomatic or high-grade bowel obstruction
- The patient is unwilling to give consent
- The patient is uncooperative or unable to achieve sedation
- Risk of colonic perforation in patients undergoing colonoscopies, such as those with toxic mega-colon and fulminant colitis [14]
- Other contraindications limited to colonoscopy include inadequate bowel preparation, recent myocardial infarction, arrhythmias, or medically unstable patients

Evidence of Effectiveness of Various Screening Tests:

Guaiac FOBT vs F ecal Immune-chemical Test

- FIT is more sensitive than gFOBT for colon lesions.[15]
- High-sensitivity gFOBT has a sensitivity of 62% to 79% and a specificity of 87% to 96% for detecting colorectal cancer.[16]
- FIT has a sensitivity of 79% to 88% and a specificity of 91% to 93%.
- Evidence suggests a decline in the mortality rate by 15% to 33% when gFOBT/FIT is performed every 1 to 2 years in people 50 to 80 years.[16]
- FIT has high sensitivity (80%) for detecting CRC, while only 25% to 56% sensitivity is for detecting advanced adenomas.[16][17]

Stool DNA Test

- The sensitivity and specificity were 92% to 95% and 84% to 95%, respectively. This test's sensitivity to detect advanced precancerous lesions such as advanced adenomas and sessile serrated polyps measuring less than 1 cm was 42% and its specificity to detect "all nonadvanced findings," including non-neoplastic findings, was 87%.[18]
- This test displays a higher sensitivity than FIT (92% vs 74%), with more false positives. However, it detected less than half of advanced adenomas (42%), limiting its preventive role due to its low specificity (87% to 90%). [19]
- No evidence of mortality reduction currently exists.

- Evidence suggests that regular screening with sigmoidoscopy alone after 50 years (55 to 64 years) significantly lowers mortality related to rectal or lower colonic cancer by 60% to 70%.[20][21]
- There is a reduction of CRC incidence by 33% to 42% through various randomized controlled trials.[20][22]

Colonoscopy

- The reduction in CRC incidence and mortality was 31% and 46%, respectively, as established by 6 observational studies, which further suggested strong evidence of a reduction in incidence and mortality of both distal and proximal colorectal cancers. Sigmoidoscopy only helps in curtailing distal CRC-related mortality and incidence.[7]
- Colonoscopy is more effective in preventing left-sided CRCs than right-sided CRCs, which could also contribute to a shift in the distribution of cancers in the colon.[7]
- The sensitivity of colonoscopy after bowel preparation to detect adenomas 6 mm or larger ranged from 75% to 93%, and specificity ranged from 89% to 91%.[23]
- For adenomatous polyps 6 mm or larger, a systematic review reported the sensitivity of colonoscopy for detection varied from 75% to 93%. The miss rate for polyps of any size was 22%, with rates increasing inversely with the size of the lesion. Adenomas smaller than 5 mm were missed in as many as 25% of patients.[24][25][26]

Colon Capsule Endoscopy

Study results showed that in patients who are asymptomatic using high-quality optic colonoscopy as the standard, capsule endoscopy identified subjects with more than one adenoma of greater than or equal to 6 mm with a sensitivity of 88% and specificity of 82%, and even higher rates in larger adenomas.[27]

Computed Tomography Colonography

- Even though it's a sophisticated modality when compared to colonoscopy, multiple studies demonstrate a fluctuating sensitivity for CRC lesions, between 67% and 94%, while colonoscopy is 92% sensitive. However, CT colonography (CTC) has a very high specificity at 96% to 98%.[28]
- Patients who underwent both colonoscopy and CTC saw a surge of 14 to 15 non-rectal neoplasms, missed by colonoscopy, which were located on mucosal folds.[29][25]
- This test can still miss some flattened and small polyps (less than 8 mm).[29]

Methylated *SEPT-9*

- This can detect advanced CRC; however, relevance in early-stage detection is yet to be established. The methylated *SEPT-9* DNA assay has a sensitivity for CRC of 75% and specificity of 87%, with increasing detection rates in advanced cancers.[30]
- Due to poor sensitivity, its role as a primary screening tool is questionable. This test also has a false positive rate of 4.7%.[31][30]
- There is no evidence yet that this test can reduce CRC deaths. However, as a non-invasive testing option, it can have significantly increased compliance and participation among high-risk groups.[30]

Fecal Occult Blood Test

- Since polyps and CRCs have a high propensity to bleed, FOBT can detect occult blood.[19]
- Sample collection: The patient is given a stool collection kit or asked to get one from the pharmacy (as per local protocols) and is asked to bring in stool samples (sometimes by mail) within 24 hours of collection, as sensitivity to test declines proportionally to delay.[32][33]
- Sample processing: Don't rehydrate samples, as it may falsely increase sensitivity, leading to an increased number of false positives.[33]

Guaiac FOBT: This test uses guaiac as the main reagent, a plant that grows exclusively in the Caribbean. It detects organic heme by oxidation. Therefore, the presence of dietary heme from red meat, peroxidase from some plants, and anti-oxidants like vitamin C or E can lead to false positives. Fasting is advised before the test.

Fecal Immune-Chemical Test: This test employs antibodies to specifically detect human heme-based globin. Dietary and medication restrictions prior to the test aren't required. The test is very specific for detecting colonic/rectal bleeding.

- **Advantages**
  - Bowel preparation isn't a prerequisite.
  - Dietary or medication restrictions are not a prerequisite for FIT. Samples can be collected at home, hence convenience and higher adherence.[34]
  - Cost-effective compared to other CRC screening tests.
  - There is no risk of damage to the colon.
- **Disadvantages**
  - The test does not detect some polyps and cancers.
  - False-positive test results are possible.
  - Dietary restrictions are needed before guaiac FOBT.
  - Additional procedures, such as colonoscopy, may be needed if the results are positive.

Stool DNA Test

- Also known as the FIT-DNA test, it comes as a US Food and Drug Administration (FDA)-approved kit. This is a multi-target test that detects occult blood along with 9 DNA biomarkers of three genes associated with CRC and advanced adenoma.[8][18]
- Sample collection: Like FOBTs, the patient is provided with a stool collection kit and asked to collect a stool sample, which can be delivered via mail or personally to a laboratory/office, ideally within 72 hours.
- **Advantages**
  - No bowel preparation is required.
  - No dietary or medication restrictions as a pre-requisite.

- No risk of damage to the colon.

- **Disadvantages**
  - More expensive than gFOBT or FIT.
  - Test sensitivity for adenomas is low.
  - False-positive test results can be seen.
  - Additional procedures, such as colonoscopy, are advised if the results are positive.

Sigmoidoscopy

- Examination of the rectum and sigmoid colon using a sigmoidoscope, an instrument consisting of a flexible tube with a lens and light source for visualization and a tool for removing tissues (polyp/adenoma) or taking biopsy samples.
- The sigmoidoscope is inserted through the anus up to the splenic flexure after insufflating carbon dioxide for better visualization.

- **Advantages**
  - Minimal discomfort and complications are rare.
  - Biopsy and polypectomy (removal of a polyp or adenoma) can be performed during the same procedure.
  - Less extensive cleansing of the colon is required than for colonoscopy, as it only probes the sigmoid colon.

- **Disadvantages**
  - Pre-cancerous or CRC lesions in the right colon will be missed due to limited visualization.
  - Bowel preparation by either enema or laxatives is a pre-requisite.
  - Medication and diet changes may be needed before the test.
  - Small risk of bleeding or perforation of the colon lining.
  - Additional procedures, such as colonoscopy, may be needed to detect synchronous lesions.

Colonoscopy

- A colonoscope is inserted through the anus and through the entire colon ending in the cecum.
- Abnormal growths can be visualized and can be either removed (polypectomy) in whole, or a small sample can be taken for biopsy in a single procedure.
- Since the procedure is more invasive than sigmoidoscopy, it requires rigorous bowel preparation and dietary modifications.[35]

- **Advantages**
  - This is one of the most sensitive and definitive methods (the gold standard) currently available for the detection of pre-cancerous adenomas and CRC.

- Biopsy and polypectomy can be done in a single procedure.

- **Disadvantages**
  - Even though this test is highly sensitive, it still may not detect all small or sessile polyps and cancers.
  - Thorough cleansing of the colon is a prerequisite.
  - Diet and medication modifications are prerequisites.
  - Some form of sedation is almost always used. Hence, the patient must have someone to accompany them. Rest and avoiding any work is advised after the procedure.
  - Small risk of bleeding or perforation of the colon; this risk increases with age, with the presence of other health problems, and when polyps are removed.[14]

Colon Capsule Endoscopy

- This is FDA-approved for use only in patients who had an incomplete colonoscopy. The patient swallows a capsule containing tiny wireless cameras that take images as the capsule traverses the colon.
- **Advantages**
  - Colon capsule endoscopy requires bowel preparation; however, it does not require sedation or dietary or medication adjustments.
- **Disadvantages**
  - It doesn't accommodate polypectomy or biopsy and is only meant for lesion visualization. This test appears to have a sensitivity and specificity similar to colonoscopy. However, it is not indicated as a primary screening tool.

Computed Tomography Colonography

- The procedure isn't invasive and doesn't require sedation. However, bowel preparation and carbon dioxide insufflation are still needed for better visualization.
- This may additionally require an intravenous catheter for glucagon administration for bowel relaxation. Images are then obtained during a single 32-second breath-hold.[28]
- **Advantages**
  - A minimally invasive procedure, hence little to no risk of damage to the colon.
  - No sedation is required.
- **Disadvantages**
  - Thorough cleansing of the colon is a pre-requisite.
  - This can miss small polyps.
  - Additional procedures, such as standard colonoscopy, are advised should CTC come back positive for lesions.

allergy.

Fecal Tagging

- It's a laxative-free CTC approach. The contrast agent is administered orally over several days before the procedure, making fecal material in the colon distinct from colon tissue by "tagging" it.
- Radiographs of the colon are then obtained.
- Sensitivity is somewhat lower than conventional CTC with laxative bowel preparation.[28]

Barium Enema

Either single- or double-contrast is rarely used, and neither is recommended by any other expert group due to its poor screening indices and the advent of better endoscopic and CTC procedures with better results.

Screening Frequencies and Ideal Intervals for Surveillance and Follow-up

Guaiac FOBT and F ecal Immune-chemical Test

Frequency of testing: Experts recommend sigmoidoscopy every 5 years for people at average risk who have had negative test results.[34]

Stool DNA Test

Frequency of testing: The current recommendation is once every 3 years. If positive on any of the occasions, endoscopic studies such as colonoscopy and sigmoidoscopy are recommended.[1]

Sigmoidoscopy

Screening frequency: Sigmoidoscopy should be performed at 5-year intervals from baseline intervention, with gFOBT/FIT every 3 years.[1][24]

Colonoscopy

Screening frequency: Patients undergoing colonoscopy should have a 10-year interval between screening colonoscopies if the examination is negative and of adequate quality.[1][36]

Computed Tomography Colonography

Screening frequency: Current USPSTF recommends CTC every 5 years from baseline CTC or optical colonoscopy.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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Disclosure: Rahul Kumar declares no relevant financial relationships with ineligible companies.

Disclosure: Catherine Lewis declares no relevant financial relationships with ineligible companies.

Bookshelf ID: NBK559064 PMID: 32644490