Colorectal Cancer Screening

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Abstract

Colorectal cancer (CRC) is a common malignancy among both women and men, and the risk increases with increasing age. The incidence and mortality due to CRC has declined over the past several decades, likely due to screening examinations used to detect and remove premalignant colon polyps, as well as modification of risk factors and improvements in the treatment of CRC. Several professional groups have issued guidelines for screening average-risk individuals, and these guidelines incorporate both stool-based tests and structural exams. This review will address the recent incidence and mortality trends of CRC, as well as current CRC screening guidelines and the various screening methods available.

Key words: colon cancer, screening, colonoscopy, CT colonography, fecal DNA

Introduction

Colorectal cancer (CRC) is the third most common cancer in women and men, and is the second leading cause of cancer death in the United States, accounting for approximately 9% of all cancer deaths.[1] In average-risk individuals, the risk of CRC increases with age, such that the likelihood of individuals younger than age 40 years developing CRC is 1 in 1200, as opposed to 1 in 25 for individuals over age 70.[2] About 85% of CRC cases occur after age 55.[3] Because average-risk individuals are unlikely to develop sporadic CRC before the age of 50, CRC screening in this population is not considered to be cost-effective.

The incidence and mortality due to CRC has declined over the past several decades due to screening examinations used to detect and remove premalignant colon polyps, as well as modification of risk factors and improvements in the treatment of CRC.[4] This review will address current CRC screening guidelines, as well as the various available methods available for screening, and the risks and benefits associated with these methods.

Screening Guidelines for Average-Risk Individuals

Multiple organizations have issued guidelines for CRC screening in average-risk individuals. The **Table** shows definitions for average-, moderate-, and high-risk groups. A joint statement from the American Cancer Society (ACS), US Multi-Society Task Force (MSTF) on Colorectal Cancer, and the American College of Radiology (ACR) recommends several options for CRC screening, beginning at age 50 years in average-risk individuals, and ending when an individual's life expectancy is less than 10 years.[5] Their recommendations focus on prevention of CRC through structural examinations that detect and remove premalignant adenomas in addition to CRC. Structural exams include flexible sigmoidoscopy, colonoscopy, double-contrast barium enema (DCBE), and computed tomographic colonography (CTC) at varying intervals. Stool-based tests, which are used primarily to detect CRC and not polyps, are also recommended if individuals are unwilling or unable to undergo structural exams. Stool-based tests include annual guaiac fecal occult blood test (FOBT), annual fecal immunohistochemical test (FIT), and stool DNA at varying intervals.

A second set of guidelines, published by The US Preventive Services Task Force (USPSTF) recommend CRC screening in individuals ages 50-75 years, and do not recommend barium enema, CTC, or fecal DNA testing.[3] They also do not express a preference for structural exams over stool-based tests.

Various Modalities for CRC Screening

Stool-Based Exams

There are multiple methods of CRC screening to detect either precancerous lesions or early-stage cancers. Stool-based tests such as guaiac-based FOBT, FIT, and fecal DNA tests identify CRCs but not adenomas.

Fecal Occult Blood Testing

The two types of FOBT currently used for CRC screening are guaiac-based testing and FIT. The traditional guaiac-based stool testing identifies hemoglobin in the stool by the presence of a peroxidase reaction, which turns the testing paper blue. False-positive test results can occur due to certain foods in a patient's diet, such as red meat (blood in meat can turn the test positive) or certain vegetables (those containing peroxidase properties can turn the test positive). On the other hand, false-negatives can be

the result of excess vitamin C (which inhibits the peroxidase reaction). These foods must be avoided in the days leading up to the test. The second type of FOBT, FIT, reacts with antibodies that are specific for the globulin component of hemoglobin. There are no dietary restrictions necessary for FIT.

In general, FOBTs have the benefits of being inexpensive, noninvasive, and very convenient, as they are performed at home. Individuals are required to submit one to three consecutive stool samples, depending on the test, by mail to a processing facility. If results are negative for blood, the test should be repeated annually. If positive, a colonoscopy is recommended for follow-up. The FOBT has varied sensitivity based on the number of stool tests performed. The sensitivity of a single test has been reported as less than 30% for men and women of all age groups.[6] If three tests are performed, the sensitivity does improve from 80% to 92%.[7] Specificity is generally less than 50%.

The FOBT using guaiac-based testing has been shown in randomized controlled trials to reduce CRC incidence and mortality.[8-14] Reductions in mortality are between approximately 15% to 33%, with the variation in mortality reduction due to annual versus biennial screening, and whether specimens were rehydrated or not. Rehydration improves the detection of heme, which may increase both the true-positive and false-positive rate. There are no randomized controlled trials looking at the effect of FIT on CRC incidence and mortality, but it is assumed to be equally or more effective based on the improved performance characteristics.

Fecal DNA Testing

Evaluation of fecal DNA can also be used for CRC screening, as CRCs shed DNA in the stool, which then can be tested for mutations involved in the adenoma-to-carcinoma sequence. Cologuard is the mult-target fecal DNA screening test that was recently approved by the Food and Drug Administration (FDA), and targets two highly discriminant methylated genes (*BMP3* and *NDRG4)* and multiple informative point mutations on *KRAS,* as well as a marker for total human DNA (ß-actin) and fecal hemoglobin. Individuals must submit an entire bowel movement and ship it to the processing facility on ice. Benefits of fecal DNA testing include the fact that it is noninvasive, does not require a bowel preparation or sedation, and does not require any dietary restrictions like the guaiac-based FOBT does.

Unfortunately, false-negatives do occur, as all genetic abnormalities associated with CRC cannot be incorporated in the stool test. In addition, false-positives also can occur, which may be due to upper gastrointestinal (GI) tract neoplasms or a "true" false-positive with no abnormalities in the GI tract. One study showed that almost 10% of average-risk patients with a negative colonoscopy had a positive fecal DNA test.[15] All positive fecal DNA tests must be followed up with a diagnostic colonoscopy. Moreover, when comparing fecal DNA testing to FIT testing, the sensitivity of fecal DNA for the detection of CRC and advanced adenomas (92.3% and 42.4%, respectively) exceeded that of FIT testing by an absolute difference of almost 20 percentage points. Fecal immunohistochemical testing, however, was more specific for the detection of both CRC and advanced adenomas, with an absolute percentage point difference of 6.6% and 8.3%, respectively. Typically, sensitivity is a more important test characteristic for screening exams, as it is important for the test to rule out diseases such as cancer.[15]

TABLE. Colorectal Cancer Risk Stratification

Risk Category	Definition
Average	Age ≥50 years; no personal history of adenomas, SSA/P, or CRC No family history of CRC No personal history of inflammatory bowel disease
Moderate	Personal history of adenomas, SSA/P, or CRC Family history of advanced adenomas or CRC
High	Hereditary CRC syndromes Personal history of inflammatory bowel disease

CRC, colorectal cancer; SSA/P, sessile serrated adenoma/polyp.

Because fecal DNA testing is able to identify the majority of CRC cases, an expert consensus includes this modality as an acceptable option for CRC screening in average-risk adults. However, fecal DNA tests still require careful evaluation in future studies because the limited sensitivity for adenomas in comparison with colonoscopy and CTC and the substantial increased cost compared with other fecal tests remain important barriers to widespread use. As previously discussed, fecal DNA testing proves to be a reasonable alternative to colonoscopy, and does have certain advantages, as it is noninvasive, conveniently performed at home, and no work is missed. Although the current application of fecal DNA testing is currently reserved for CRC screening in average-risk individuals, additional expanded indications may continue to arise, such as surveillance in patients with inflammatory bowel disease (IBD) or detection of upper GI cancers. Further study into these potential applications is necessary at this time.[16]

Despite FDA approval in August 2014, fecal DNA testing is not currently recommended by the USPSTF as an approved screening modality, and the appropriate interval between screening fecal DNA tests is unknown. As practice patterns evolve, and more data are collected, clinical algorithms for fecal DNA testing will be developed and will help guide clinical practice. Similarly, in 2014, the Centers for Medicare and Medicaid Services (CMS) ruled that fecal DNA testing would be covered once every three years for average-risk, asymptomatic Medicare beneficiaries be-

tween the ages of 50 to 84 years.[17] However, coverage by third-party payors varies.

Structural Exams

Flexible Sigmoidoscopy

There are two common structural exams used for CRC screening. The first is flexible sigmoidoscopy, which is able to evaluate the colonic mucosa for CRC and polyps, typically up to the splenic flexure. As compared with colonoscopy, flexible sigmoidoscopy requires only a simple bowel preparation of enemas prior to the procedure, as opposed to a large-volume oral solution; has typically less patient discomfort during the procedure; and generally has fewer complications. In addition, flexible sigmoidoscopy can be performed in an office setting; sedation is optional, allowing patients to return to work or other duties after the procedure; and can be performed by a wide range of providers, including primary care physicians and nurse practitioners who have had proper training.[18]

The specificity and sensitivity of flexible sigmoidoscopy is high, with adequate visualization of the colonic mucosa to the splenic flexure. If flexible sigmoidoscopy is used for screening purposes, it should be performed every 5 years if no polyps or CRC are found. If polyps or CRC is found, a full colonoscopy should be performed.

Several randomized controlled trials have shown both a reduction in CRC incidence and mortality from flexible sigmoidoscopy.[19,20,21] The reduction of incidence and mortality when using flexible sigmoidoscopy is reported to be 23% to 31%.[21] The most recent study to evaluate the impact of flexible sigmoidoscopy on CRC incidence and mortality examined over 100,000 average-risk patients over age 50 years who were randomized to screening, which required once-only flexible sigmoidoscopy or once-only flexible sigmoidoscopy and FOBT, or to the control group, who received no screening. Patients with a positive result on flexible sigmoidoscopy, such as a cancer, adenoma, polyp of 10 mm or larger, or who had a positive FOBT, were offered colonoscopy. After a median of 11 years of follow-up, CRC incidence was reduced by 20% and mortality by 27% in the intervention group, as compared with the control group.[22,23]

Colonoscopy

Colonoscopy is the other structural exam commonly used for CRC screening. Unlike flexible sigmoidoscopy, colonoscopy is able to evaluate the entire colonic mucosa for both CRC and polyps; however, the effectiveness of colonoscopy in detecting CRC and polyps depends on adequate visualization of the mucosa.[24] Therefore, prior to the procedure, patients are required to take a bowel preparation. In addition, the majority of patients will receive sedation during the procedure, which minimizes patient discomfort and allows for a complete examination.[25] Sedation, however, does delay patient recovery and discharge, adds cost to the overall procedure, increases the risk of cardiopulmonary complications, requires that an escort accompany the patient home, and may prevent the patient's return to work or other significant activities that same day. However, colonoscopy has the ability to detect and remove polyps during the same examination.

No randomized controlled trials have evaluated the effectiveness of colonoscopy. Observational cohort studies, however, do show that colonoscopy decreases the risk of CRC. The National Polyp Study included approximately 2000 patients who underwent colonoscopy with polypectomy, and showed a 76% to 90% decrease in the incidence of CRC as compared with patients in other studies who did not have polypectomy.[26] In addition, another study examined this same cohort to determine the effect of endoscopic detection and removal of adenomatous polyps on mortality from CRC during a surveillance period of up to 23 years after polypectomy. The study found a 53% reduction in CRC mortality in these patients as compared with the expected mortality rate for the general population.[27]

Colonoscopy has also been shown to detect proximal lesions that may be missed by sigmoidoscopy.[28] A meta-analysis of 16 studies showed a 40 to 60% lower risk of developing an incident CRC and death after screening colonoscopy as compared with screening flexible sigmoisocopy.[29]

Even though colonoscopy is considered the most sensitive screening exam and the "gold standard," colonoscopy may be less effective in detecting proximal adenomas or cancers.[30-32] One study by Singh et al[30] examined the mortality benefit from colonoscopy in 50,000 patients between ages 50 and 80 years undergoing average-risk screening. The study found a 29% overall reduction in CRC mortality and a 47% reduction in mortality from distal CRCs; however, there was no reduction in mortality from proximal CRCs.

The effectiveness of colonoscopy may be related to technical issues or the cleanliness of the bowel preparation, or may be related to inherent biologic features of these proximal polyps and masses, such as higher rates of microsatellite instability or the fact that they proceed through the CpG island methylator phenotype (CIMP) molecular pathway.[33,34] In addition, quality indicators that may affect the effectiveness of colonoscopy include the adenoma detection rate of the colonsocopist, withdrawal time greater than 6 minutes, cecal intubation rate, and adequate colon cleanliness.[35,36] Adenoma detection rate is often considered the most important quality indicator.

Colonoscopy is generally a safe procedure, and procedural risks have been quoted in a review of the literature to be 2.8 per 1000 colonoscopies, with most of these complications associated with polypectomy.[37] Post-polypectomy bleeding can be immediate or delayed (5-7 days, but up to 29 days has been reported), and the rates vary from .3% to 6.1%.[38] The risk of bleeding is related to the size and location of the polyp, technique of polypectomy, and the coagulation status of the patient.

Nonprocedure-related complications also occur, and are typically related to sedation or the bowel preparation. Sedation-related complications include hypoxia, aspiration, or cardiac arrhythmias, and risk factors for complications include older age, underlying pulmonary disease, increasing American Society of Anesthesiologists (ASA) score, dementia, anemia, obesity, and emergency procedures.[39] Bowel preparation complications include shifts in fluid and electrolytes, abdominal discomfort, nausea, and vomiting.[40] Inadequate bowel preparations also occur in up to 25% of colonoscopies, and poor preparation leads to increased procedure time, increased complications, and possible missed lesions such as small adenomas or even CRCs.[41,42]

Radiologic Exams

Double-Contrast Barium Enema

Double-contrast barium enema uses rectal instillation of barium to coat the distal colonic mucosa, inserts air in the rectum to distend the colon, and then takes multiple x-ray images to evaluate the colonic mucosa. The test is relatively safe and has the benefit that it does not require sedation; however, it does require an oral preparation. A DCBE is less effective than colonoscopy because it detects only about 50% of adenomas larger than 1.0 cm and 39% of all polyps.[43] In addition, false-positives do occur with excess stool, air, or other mucosal irregularities. If the results of DCBE are abnormal, a colonoscopy must be performed for further evaluation. The use of DCBE has significantly declined over the past decades, partially due to newer radiologic techniques such as CTC and the use of endoscopic procedures.

CT Colonography

Computed tomographic colonography is a noninvasive test that takes multiple thin-slice images of the colon, and creates two- and three-dimensional images of the colon surface.[44] **Figures 1** and **2** provide examples of images from CTC. While the test typically does require a bowel preparation, newer techniques are being used that do not require a preparation, including an oral iodinated contrast that tags stool, which is then subtracted from the final images. As with colonoscopy, patients may experience abdominal cramping due to air or carbon dioxide introduced into the colon via a rectal catheter for distension. A CTC test does require specialized radiologists for image interpretation, and any abnormal results require a colonoscopy for further evaluation, ideally on the same day when possible in order to avoid a second bowel preparation.

The sensitivity and specificity of CTC were 90% and 86% respectively in a study of 2600 average-risk patients who underwent a traditional bowel preparation with images interpreted by an experienced reader.[45] For preparation-free CTC (using stool tagging), the sensitivity and specificity for adenomas 10 mm or larger were 91% and 85%, respectively, which was very similar to that of CTC with a traditional bowel preparation.[46,47]

FIGURE 1. A Sessile Polyp Found on a Screening CT Colonography

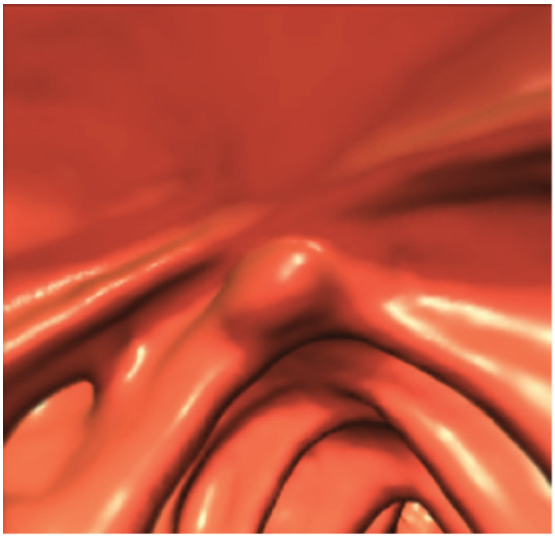

Image courtesy of Raquel Alencar, MD, PhD; Brigham and Women's Hospital, Boston, MA.

FIGURE 2. A Large Polyp Found on CT Colonography; This Polyp was Later Found to Have High-Grade Dysplasia After Removal

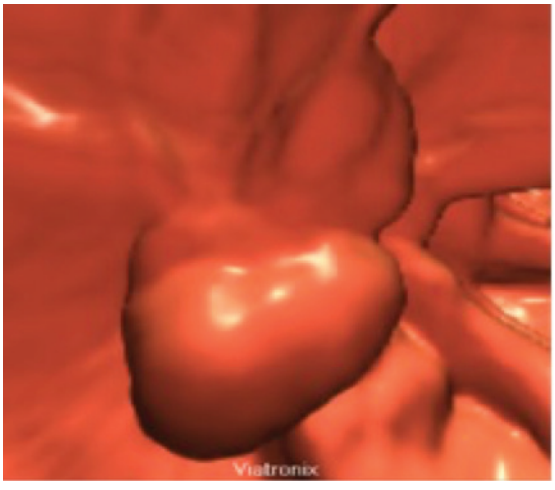

Image courtesy of Raquel Alencar, MD, PhD; Brigham and Women's Hospital, Boston, MA.

CTC has several benefits, as it is a noninvasive test with little or no risk of complications, including bleeding, perforation, or cardiovascular complications.[29] In addition, no sedation is necessary, and patients are able to return to work or other duties the same day. When only left-sided polyps are found with CTC, flexible sigmoidoscopy can be performed for polypectomy, instead of

full colonoscopy, which is often safer and more cost-effective.[48]

Despite this, there are several disadvantages of CTC, including the fact that flat adenomas may be missed on CTC, and these flat adenomas are often the ones that have greater malignant potential. Sigmoid diverticular disease often presents a challenge for CTC interpretation because of the resulting luminal narrowing.[48] Chronic diverticular disease may be difficult to distinguish from a left-sided mass lesion. In addition, CTC may identify extracolonic findings, such as masses of unclear clinical significance and/or abdominal aortic aneurysms, which may create significant and unnecessary anxiety for the patient, as well as increased cost due to further evaluation.[49] One study of 2869 women found an adnexal mass in approximately 4% of patients, which led to further testing, but no women had ovarian cancers identified.[49,50] Lastly, there is uncertainty regarding the long-term harms of the radiation exposure related to CTC.51 This topic requires further study.

Conclusions

Colon cancer is a common malignancy in both women and men, but it is preventable with screening. Professional societies have published guidelines for screening and surveillance, and there are risks and benefits to each type of screening modality. With a focus on improving CRC screening rates, as well as improving risk factors associated with CRC and CRC treatments, CRC incidence and mortality rates will continue to decline in the future.

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