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Colorectal cancer screening and prevention: A brief review of the current guidelines and modalities

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Abstract

Colorectal cancer (CRC) remains a frequently addressed topic in primary care. Recent studies have been published detailing modifiable risk factors for CRC, as well as preventative measures. Providers must be up to date on screening recommendations and modalities. Colonoscopy is the preferred method of screening for CRC, and the screening recommendations in the United States were recently updated in 2020. It is also common for the practitioner to encounter patients who refuse colonoscopy but are willing to undergo alternative methods of testing. The COVID pandemic has also placed a burden on hospital resources, and colonoscopy may not be logistically feasible in some healthcare settings. Therefore, awareness of the guidelines for the various alternative modalities, along with their respective guidelines for frequency of screening is critical. This article provides a brief review of the risk factors associated with colon cancer, the screening modalities (including colonoscopy, sigmoidoscopy, CT colonography, fecal immunohistochemical testing (FIT), guaiac-based fecal occult blood testing (gFOBT), multi target stool DNA testing (MTs-DNA), and others) and the most recent screening recommendations for the general population.

Keywords: Colorectal cancer; Screening; Methods; Modalities; Guidelines

1. Introduction

Colorectal cancer (CRC) screening is a mainstay of primary care in the United States. The implementation of routine diagnostic screening has led to a decrease in the number of deaths from colon cancer especially in older populations due to early detection [1, 2]. CRC is the fourth largest cause of cancer-related deaths in the United States, behind lung, breast, and prostate cancers [3]. The incidence worldwide is similar across gender, however females above the age of 65 have higher mortality rates compared to aged-matched men [4]. Most cases are isolated in nature with no prior family history, however the hereditary component has been estimated to be as high as 30%, and some studies are showing an alarming increase in the rate of early-onset CRC (before years of age 50) [1,5]. The screening guidelines for colorectal cancer have also been updated most recently in 2020 by the United States Preventive Services Task Force (USPSTF) with a "draft recommendation" for initiating CRC screening at age 45 rather than the previously advised age 50 [6]. Although colonoscopy has become a much more convenient procedure to perform and to undergo, with many colonoscopies being performed as outpatient, it is common for the practitioner to encounter patients who refuse colonoscopy but are willing to undergo alternative methods of testing. Recent studies have been published detailing modifiable risk factors for CRC, as well as preventative measures other than colonoscopy. Therefore, it is of utmost importance to be up to date on both the guidelines for screening colonoscopy and the various alternative modalities,

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along with their respective guidelines for frequency of screening. This article discusses the risk factors associated with colon cancer, the screening modalities, and the most recent screening recommendations for both the general population and high-risk populations.

2. Risk Factors and Prevention

There are several lifetime risk-factors for CRC that range from demographic, genetic, behavioral, and environmental factors. The non-modifiable risk factors showing a positive association include age 50 and older, male gender, black race, first-degree relative or personal history of colonic adenomatous polyps or colon cancer, familial adenomatous polyposis, Lynch syndrome, Peutz- Jeghers syndrome, MUTYH-associated polyposis, abdominopelvic radiation, cystic fibrosis, diabetes and presence of ulcerative pan colitis or Crohn's disease for more than eight years or left sided ulcerative colitis for fifteen years. Modifiable risk factors associated with higher CRC risk include diet (high red and processed meat, low fruit and vegetable intake), alcohol and tobacco use, obesity and sedentary lifestyle [7].

Low-dose aspirin (81 mg) has been shown to reduce CRC risk in patients without previously diagnosed CRC in multiple studies and is thought to do so by preventing micro-metastases [8-10]. Aspirin at a higher dosage of 600 mg daily, has also been found to reduce the risk of CRC in patients with Lynch syndrome [11]. The American College of Gastroenterology and the USPSTF both advise that patients aged 50-69 years old with a 10% or higher 10-year risk of cardiovascular disease take daily low dose aspirin as a preventive measure for CRC [12, 13].

Vitamin D has also been shown to reduce the risk of CRC. Several studies have supported this phenomenon, and vitamin D is thought to provide reduction via the prevention and regulation of cell proliferation in the intestinal epithelium [14,15]. One study found the optimal 25-hydroxy vitamin D level to be 75-100 nmol/L, however there are no current society recommendations with regards to vitamin D supplementation for the prevention of colon cancer [16].

Of note, whole grains, weight loss, and regular physical exercise have also been shown to decrease the risk for CRC.

3. Screening Methods

Colonoscopy is the most preferred method of CRC screening due to the high sensitivity and detection rate. Evidence has also shown it is associated with reduced mortality (up to 68%) and CRC incidence [17]. It is also the most invasive method of screening and must be performed by a trained endoscopist. An overwhelming majority of colonoscopies are performed in the outpatient setting which can be convenient to both the endoscopist and the patient [18]. The main risk is perforation which has multiple causes including direct trauma from the endoscope, barotrauma from insufflation, perforation via tissue biopsy or removal of the tissue itself through cold or hot snare [19]. The most common site of perforation is the sigmoid followed by the cecum [20, 21]. Perforation is a serious complication and carries a morbidity rate of 40-50% and a mortality rate that ranges from 5-8% [22-24]. The rate of perforation is relatively low, with one study finding an incidence rate of 0.57 per 1000 procedures [19, 25, 26]. A recently published study found perforation from colonoscopy in hospitalized patients to be highest in patients who were above the age of 65, Caucasians, those with underlying inflammatory bowel disease or who underwent polypectomy, and end-stage renal disease [24]. Screening colonoscopy is often the topic of much anxiety for patients, with many patients refusing colonoscopy out right. Patient apprehension is typically due to the negative stigma of undergoing an invasive procedure, fear of pain, and the requirement to undergo bowel preparation with a clear liquid diet and a laxative such as polyethylene glycol. Poor bowel preparation and subsequent inadequate visualization of the colon can result in a lower detection rate, and/or create the need for a repeat colonoscopy. Split- dose preparation has been shown to increase the detection rate for sessile polyps and possibly adenomas. It involves taking half of the preparation the evening before and half of the preparation on the day of colonoscopy starting 4-5 hours before the procedure and finishing 3 hours before the procedure starts. The clinician-led discussion regarding the importance of screening has proven to be of favorable influence on a patient's decision to undergo screening, and patients with a history of polyps or family history of CRC are more likely to perceive colonoscopy positively [27,28].

Flexible sigmoidoscopy is the other endoscopic option for CRC screening and has been shown to decrease the mortality from CRC by 27%. It is particularly useful in patients with a palpable rectal mass, rectal bleeding, or without the stigmata of proximal CRC (such as anemia) [29]. The main disadvantage of this modality is the potential to miss proximal lesions due to its limited anatomical focus, and flexible sigmoidoscopy has, as mentioned, a lower reduction in mortality for CRC when compared to colonoscopy [30]. Although colonoscopy is the optimal screening method, flexible

sigmoidoscopy still has a demonstrated reduction in mortality and incidence of CRC when compared to no screening and there is limited preparation compared to colonoscopy [31].

Computed tomographic (CT) colonography, also known as "virtual colonoscopy" is a radiologic method of screening in which 2D and 3D images of the colon are produced and assessed for the presence of polyps by a radiologist. As with colonoscopy, it requires the patient undergo bowel preparation beforehand, and the colon is insufflated thus carrying a risk of perforation (although this risk is low when compared to colonoscopy) [32]. CT colonography of course does expose the patient to radiation, and other concerns include limited detection of sub centimeter polyps, and it only providing imaging rather than removal or biopsy of lesions. Extra-colonic findings are common however, recent studies have found it to be more cost effective and a reasonable alternative to colonoscopy in asymptomatic and average risk patients [32-34].

Guaiac-based fecal occult blood testing (gFOBT) is a simple screening method that can be performed easily in the office setting or at home. gFOBT works by detecting fecal presence of hemoglobin because of occult bleeding from CRC. The card contains a reagent paper that will yield a positive result (i.e., color change) through a peroxidase reaction [35]. gFOBT is limited by high false positive rate and lower sensitivity for pre-cancerous polyps [36,37]. High sensitivity gFOBT has superior performance than older tests. It does require dietary restriction forty-eight hours beforehand which includes foods such as beets, broccoli, and red meat. The test may be more favorable to patients as it does not require bowel preparation or anesthesia.

Fecal immunohistochemical testing (FIT) is another non-invasive method of screening for CRC. It works primarily by detecting the presence of blood in the stool via immunoassay. Unlike gFOBT, it is capable of quantifying presence of stool in hemoglobin. FIT testing performed annually has been associated with a reduction in mortality for CRC and is a better option than gFOBT for detection [36, 38]. A previous study also found FIT testing in combination with colonoscopy to be an optimal screening strategy in terms of cost effectiveness and resource allocation [39].

Additional modalities of screening through stool include tests for mutations and molecular abnormalities in RNA and DNA, particularly those associated with the development of colon polyps or CRC. A popular test that is approved for screening in the United States is Cologuard™ which is a multi-target stool DNA (MTs-DNA) test that detects DNA mutation, methylation, and employs FIT. The test is approved for asymptomatic patients with average risk of CRC. This test is another convenient option for patients as it is non-invasive and can be done in the patient's home, and in light of the COVID-pandemic there have been recommendations to use this method in the appropriate patient population (as opposed to colonoscopy) so as to avoid unnecessary exposure and consumption of hospital resources [36,40]. Epi proColon™ is another less invasive test which detects methylated septin 9, a biomarker associated with CRC, and is approved in the United States [41]. Despite their utility, each of these tests have disadvantages including reliance on patient collection of stool samples (for MTs-DNA), and lower specificity than FIT resulting in more false-positive results. Most current literature supports FIT as the most cost-effective non-invasive method of screening [39, 42, and 43].

Other less invasive tests that are currently being studied involve evaluation of the gut microbiota, microRNA biomarker analysis of stool and serum, tumor-derived circulating endothelial cell clusters, metabolite biomarkers such as volatile organic compounds, and other DNA and RNA biomarkers [42-45]. Currently there are no approved tests in the United States that employ these techniques, although there is potential for this to change with further research.

4. Screening Recommendations in the United States

The recommendations for colorectal cancer screening in the United States were recently updated by the USPSTF in 2020 (as a draft recommendation), the American College of Gastroenterology (ACG) in 2021, and the American Cancer Society (ACS) in 2018 [6,12,46]. The most notable change in their guidelines was to start screening at age 45 in all average risk adults. The USPSTF categorized their recommendation as "level B" which states, "there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial" [47]. The ACG also noted their guideline as "conditional" and very low-quality evidence [12]. The American College of Physicians (ACP) most recently updated their guidelines in 2019, however they recommend that screening start at age 50 [48,49]. Screening is generally advised to be discontinued in patients above age 75 or if life expectancy is less than 10 years, however the ACG notes that the decision to continue screening in patients above this age threshold should be an individualized decision [12]. The USPSTF recommends colonoscopy to be discontinued in patients older than 85 [6]. The guidelines for all three bodies with respect to age is summarized in Table 1.

Table 1 Screening age range recommendations across major US medical societies.

	USPSTF	ACG	ACP	ACS
Age 45-50	Yes	Yes	No	Yes
Age 50-75	Yes	Yes	Yes	Yes
Age > 75	No*	Individualized**	No*	Individualized**

*In addition, the recommendation is to stop screening if life expectancy is less than 10 years [6, 48, and 49].
**The ACG and ACS recommend screening for patients above 75 years of age be individualized and discussed with the patient [12, 46].

The screening frequency and intervals for the different screening modalities can be variable depending on the medical society, however all societies recommend colonoscopy every 10 years if choosing this intervention. There are several major discrepancies which should be noted, as the ACP does not provide guidelines for CT colonography or MT-sDNA due to limited evidence, and only advises doing flexible sigmoidoscopy every 10 years on the condition it is combined with FIT every 2 years [48, 49]. The USPSTF recommends the option of either performing flexible sigmoidoscopy alone every 5 years or performing it every 10 years in combination with FIT annually [6]. Unlike the other societies, the ACG does not provide a recommendation for gFOBT [12]. The recommendations for all currently approved modalities in the United States are summarized in Table 2.

Table 2 Screening frequency recommendations for currently approved modalities across major US societies.

	USPSTF	ACG	ACP	ACS
Colonoscopy	10 years	10 years	10 years	10 years
Flexible Sigmoidoscopy	5 years	5-10 years	N/A**	5 years
CT Colonography	5 years	5 years	N/A**	5 years
gFOBT	1 year	N/A**	2 years	1 year
FIT	1 year	1 year	2 years	1 year
MTs-DNA	1-3 years	3 years	N/A**	3 years
Flexible Sigmoidoscopy + FIT	10 years + 1 year*	N/A**	10 years + 2 years*	N/A**

*The USPSTF recommends flexible sigmoidoscopy every 10 years if combined with FIT every year [6]. The ACP recommends flexible Sigmoidoscopy every 10 years if combined with FIT every 2 years [48,49]. **No recommendation is given.

5. Conclusion

The implementation of screening has certainly led to an overall improvement in the efforts to detect precancerous lesions and prevent progression to colorectal cancer. Although colonoscopy remains the optimal method of screening, this may change as new modalities develop supporting evidence. Ultimately the decision of which screening method to use is one that should be made by the physician and the patient, and it is the duty of the physician to remain cognizant of these frequently changing guidelines. The COVID 19 epidemic may also change the screening modalities relying more on home-based screening test like FIT, gFOBT or MTs-DNA testing.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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