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Update on Colorectal Cancer Prevention and Screening

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Abstract

Colorectal cancer (CRC), the 3rd most common cancer type worldwide, results in almost 700,000 deaths from cancer annually. In the United States, there are an estimated 134,490 new cases of CRC diagnosed in 2016, and approximately 49,190 Americans will die from CRC. Risk factors include: advancing age; male gender; Ashkenazi Jewish descent; African-American race; low socioeconomic status; inflammatory bowel disease; diabetes; personal or family history of adenomatous polyps, advanced serrated polyps, CRC, or hereditary syndromes; and certain lifestyle behaviors (obesity, eating red or processed meats, sedentary lifestyle, smoking, excessive alcohol intake). Adhering to a healthy lifestyle, dietary modifications, such as a high fiber or Mediterranean diet, and chemopreventive agents, such as aspirin, have potential for CRC prevention, but the currently best preventive method is through screening and removal of precancerous tubular, tubulovillous, and villous adenomas. Several CRC screening tests exist, categorized as CRC prevention tests, those that can detect advanced adenomas as well as cancer (colonoscopy, flexible sigmoidoscopy, computed tomography colonography, double contrast barium enema), and CRC detection tests, ones that primarily detect cancer (guaiac fecal occult blood test, fecal immunochemical test, stool DNA test). CRC screening guidelines differ in the age for screening, tests recommended, and testing intervals. Expanding federal funding for CRC screening, newer modalities to improve bowel preparation tolerability, and continued research for new non-invasive screening strategies, such as the methylated septin 9 DNA blood test and colon capsule endoscopy, may increase CRC screening compliance and help meet the US target goal of 80% screened by 2018.

Keywords

Colorectal cancer, Cancer screening tests, Colonoscopy, Adenoma, Primary prevention

Introduction

Colorectal cancer (CRC) is the 3rd most common cause of cancer worldwide, with an estimated 1.4 million cases diagnosed in 2012 [1], and an estimated 694,000 deaths annually [2]. In the United States, there are an estimated 134,490 cases of CRC diagnosed annually, and each year approximately 49,190 Americans die from CRC [3]. Medicare dollars spent on CRC treatment are expected to increase to $14.02 billion in 2020 from $7.49 billion in 2000[4]. In addition to Medicare dollars, the personal out-of-pocket financial burden of CRC treatment can be significant, especially when there are treatment complications after surgery [5].

The five-year CRC survival rate is 90% for localized disease, but decreases to 13% for distant disease [3]. However, only 40% of CRCs in the US are diagnosed at an early stage; therefore, it is paramount to improve detection of CRC at an early or precancerous stage. CRC may develop from distinct pathways emerging from defects in the intestinal mucosa that evolve into adenomas and serrated polyps [6]. Colon polyps may be flat (sessile) or may grow small stalks (pedunculated). Not all polyps are precancerous, and the majority do not develop into cancer. An adenoma is the specific type of polyp that has the ability to evolve into a cancerous lesion. The majority of adenomas are tubular adenomas, while less common tubulovillous and villous adenomas have more potential for malignancy. Serrated polyps, which are usually identified in the proximal colon, may be the precursors of up to 30% of cases of CRC [7,8]. It generally takes about 10 years for a small adenoma to evolve into CRC [9]. This 10-year interval makes CRC an ideal cancer to target at the precancerous stage and provides the foundation for CRC screening intervals. While the majority of cases of CRC develop from an adenoma over a 10 year-period, hereditary forms of CRC and inflammatory bowel diseases involve distinct pathogenic mechanisms that necessitate shorter screening intervals [9].

Colorectal Cancer Risk Factors

Non-modifiable CRC risk factors

Several demographic characteristics such as age, gender, race, and ethnicity, are associated with higher risk of CRC (Table 1). Over 94% of new cases of CRC are diagnosed after 50 years of age [10], and the likelihood of CRC increases in each decade after 50 years of age. In addition to advanced age, the incidence of CRC is slightly higher in men. At age 60 years, a man has a 1.26% chance of developing CRC over the next 10 years, while the chance of a woman developing CRC for the same 10-year interval after 60 years of age is 0.89% [11].

In developed countries, individuals with low socioeconomic

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Table 1: Risk Factors for Colorectal Cancer.

Age over 50 years
Male Sex
African-American Race
Ashkenazi Jewish Descent
Low Socioeconomic Status
Personal history or first-degree relative with Adenomatous Polyps
Personal history or first-degree relative with Colorectal Cancer
Type 2 Diabetes Mellitus
Inflammatory Bowel Disease Crohn's Disease Ulcerative Colitis
Hereditary Conditions Familial Adenomatous Polyposis Hereditary Non-Polyposis Colorectal Cancer (Lynch Syndrome) Turcot Syndrome Peutz-Jeghers Syndrome MUTYH-Associated Polyposis
Lifestyle Behaviors Obesity Eating red or processed meat Sedentary lifestyle Tobacco smoking Excessive alcohol

status (SES) are at higher risk for developing CRC. Analysis of data from an ongoing National Institute of Health study demonstrates that low education level and residence in a low SES neighborhood confers a significant risk of developing CRC [12]. While low SES is an independent risk factor for CRC, other modifiable health risks such as obesity may contribute to higher CRC risk in low SES populations [13]. In this ongoing NIH study, the combination of health behaviors with BMI measurement explained about 36% of the association of low socioeconomic status and risk for CRC (95% CI = 28.0% to 51.2%) [13].

Globally, Ashkenazi Jews from Eastern Europe have a higher risk of CRC than any other ethnic groups, most commonly due to a specific mutation in the I1307K APC gene [14]. In the United States, African Americans have the highest incidence and mortality from CRC [10]. Reasons for this are not completely understood because CRC incidence remains high in African Americans even when adjusted for known and suspected risk factors [15]. Additionally, African American and other minority populations in the U.S. may be especially vulnerable to developing CRC at an earlier age. Analysis of the Surveillance, Epidemiology, and End Results data from 1973 to 2009 showed that a higher proportion of U.S. minorities are diagnosed with CRC prior to age 50 years when compared to non-Hispanic Whites [16].

Having a personal history of adenomatous colorectal polyps or colorectal cancer (even if it was completely removed) also increases the risk of CRC [17]. Additionally, having a first-degree relative with a history of an adenomatous polyp or CRC increases the risk of CRC. Outside of specific genetic diseases that increase risk of CRC, a family history of CRC is identified in approximately 20% of new CRC cases [18].

Certain diseases increase the likelihood of developing CRC. Inflammatory bowel disease (IBD), including both Crohn's disease and ulcerative colitis, increase the risk of CRC due to prolonged bowel inflammation that leads to dysplasia [19]. Once considered primarily a disease of Westernized regions, IBD incidence and prevalence in developing countries is on the rise [20]. In the next decade, a global increase in IBD may lead to a higher incidence of CRC worldwide. Additionally, inherited syndromes such as Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colon Cancer (HNPCC, also known as Lynch Syndrome) increase the risk of CRC with FAP accounting for about 1% of cases of CRC, and HNPCC accounting for 2-4% of colorectal cancers [17]. Other more rare inherited conditions associated with increased risk of CRC at a younger age include Turcot Syndrome, Peutz-Jeghers Syndrome and MUTYH-associated polyposis [21]. Also, people with Type 2 diabetes have a 1.3-fold increased risk of developing CRC [22], and a recent meta-analysis reveals that diabetics have poorer disease-free survival rates compared to non-diabetics [23].

Modifiable CRC risk factors

Epidemiological evidence suggests that diet and lifestyle habits are risk factors for CRC [24]. Diets high in red meat, including beef, lamb, veal and sheep, have been linked with increased risk of CRC, with beef conferring the greatest risk (RR = 1.11, 95% CI = 1.01 to 1.11) [25]. A meta-analysis of 19 case-control studies and 7 prospective studies showed that consumption of processed meats (hot dogs, sausage, bacon, and some cold-cut meats) was also associated with increased risk of CRC (RR = 1.11, 95% CI = 1.01 to 1.11) [26]. Conversely, pork and poultry have not been shown be related to higher CRC risk [25].

Increased consumption of alcohol confers increased risk of colon cancer. A meta-analysis examining 27 cohort and 34 case-control studies found a 21% increase in relative risk of CRC for individuals, particularly men, who consumed 1 to 4 alcoholic beverages daily [27]. There seemed to be a dose-response for alcohol consumption and CRC risk. For individuals drinking greater than 4 alcoholic beverages daily, there was a 52% increased relative risk of CRC (RR = 1.11, 95% CI = 1.01 to 1.11) [27].

Smoking tobacco of any type is associated with increased CRC risk [28]. The amount of tobacco and the length of time spent smoking correlates linearly with CRC risk. A meta-analysis of 26 studies showed that the relationship of smoking with CRC follows a dose-dependent curve, with a pooled risk estimate of 1.25 (95% CI 1.14 to 1.37) for ever vs. never smokers [29].

Obesity and physical inactivity may increase the risk of CRC for some individuals. It was previously thought that increased body mass index (BMI) and waist circumference conferred an increased risk of CRC in both men and women irrespective of cancer genotype [20]. New evidence suggests that increased weight and sedentary lifestyle may be risk factors only for individuals testing negative for the specific genetic mutation CTNNB1 (multivariate HR = 1.34, 95% CI 1.13 to 1.28) [30]. The CTNNB1 biomarker is negative in about 50% of colorectal cancers. For the other half of individuals with a positive CTNNB1 marker, physical inactivity and obesity did not contribute to increased CRC risk (multivariate HR = 1.07, 95% CI 0.92 to 1.25) [30].

Prevention of Colorectal Cancer

Diet and Lifestyle

Diets high in fiber seem to be protective against CRC [31]. High fiber foods, such as vegetables, fruits, and whole grains, may confer protection against CRC by increasing carcinogen transit time through the intestines, and by exerting an anti-inflammatory effect on the intestines [32,33]. The recommended intake of fiber for adults over 19 years of age ranges from 21-38 grams daily [34].

A Mediterranean diet may also help to prevent CRC [35]. A 2014 meta-analysis of 21 cohort and 12 case-control studies found a 14% decreased relative risk of CRC when participants strictly adhered to a Mediterranean diet [36]. A prototypic Mediterranean diet is high in olive oil, vegetables, fruits, legumes, cereals and fish, and includes a moderate intake of red wine during meals [36].

Adhering to a healthy lifestyle, including maintaining a healthy weight (BMI < 25), eating a healthy diet (high in fiber, fish, nuts, fruits and vegetables), being physically active(> 57 METs for men and > 82 METs for women), not smoking, and limiting alcohol consumption (< 24 g/day for men and < 12 g/day for women), has been associated with a lower incidence of CRC [37]. In this large European prospective cohort study, with a median follow up of 12 years, the hazard ratio for CRC decreased with each additional healthy lifestyle factor, from 0.87 (95% confidence interval (CI) 0.44 - 0.77) for two factors, to 0.63 (95% CI 0.54 - 0.74) for five factors; *P*-trend < 0.0001.

Chemoprevention

There are several agents that may potentially play a role in CRC chemoprevention, with aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) being the most promising agents. A large case-control study examined 2279 cases and 2907 controls to ascertain a link between aspirin use and CRC incidence [38]. The study concluded that daily use of 75 mg of aspirin was associated with lower CRC incidence, with reduction in CRC becoming statistically evident after 5 years of aspirin therapy [38]. Similarly, a recent population-based case control study found a 27% relative decrease in CRC risk with 5 or more years of continuous low-dose aspirin (75-150 mg), and 30-45% reduction with long-term NSAID use, particularly NSAIDs with the highest cyclooxygenase-2 selectivity [39]. Moreover, a randomized double-blinded study showed that carriers of the gene for HNPCC (CAPP2 gene) incurred a decreased incidence of CRC if treated with 600 mg of aspirin daily for a period of 2 years [40]. While the 2007 USPSTF guidelines recommended against routine chemoprevention of CRC with aspirin or NSAIDs in average risk individuals [41], people who routinely take aspirin for prevention of heart disease, or chronic NSAIDs for treatment of arthritis, might see this potential added benefit of CRC prevention. The USPSTF is currently updating its recommendations on this topic, and the draft recommendation summary recommends low-dose aspirin to prevent CRC in adults 50 to 59 years of age who have a life expectancy of 10 years or greater and do not have increased bleeding risks [42].

Another potential chemopreventive agent against CRC is lipid-lowering statin medications. However, results from studies examining the association of statins with CRC risk have been mixed. A meta-analysis of 40 studies, including 8 randomized clinical trials (RTCs), 13 cohort, and 19 case-control studies, found an overall slight decrease in CRC risk with use of statins (fixed RR 0.94, 95% CI 0.92-0.96; random RR 0.91, 95% CI 0.92- 0.96) [43]. The lower CRC risk found was statistically significant for the observational studies, but did not reach statistical significance in the clinical trials (RR 0.89, 95%CI 0.74-1.07). This lack of statistical significance was possibly due to the short follow-up time in the clinical studies, the few cases of CRC found, and the outcome of CRC as a secondary measure in those RCTs [43]. Similar to aspirin, individuals on statins for prevention of heart disease may see a secondary benefit of lower CRC risk.

The use of bisphosphonates in the treatment of osteoporosis, particularly long-term use, may also protect against CRC. A meta-analysis of eight population-based observational studies found that use of bisphosphonates was associated with 15% decrease in the relative risk of CRC (RR 0.85, 95% CI 0.80-0.90). This seemingly protective effect was greater with long-term use of 3 or more years (RR 0.78, 95% CI 0.66-0.91) [44].

Hormone replacement therapy (HRT) has been associated with lower CRC risk in post-menopausal women [45], possibly due to estrogen's anti-proliferation effect, among other protective mechanisms [45]. However, HRT is associated with an increased risk of breast cancer and heart disease [45]. Analysis of the Women's Health Initiative clinical trials does not support a statistically significant benefit in using HRT for CRC prevention, and thus doing so is not recommended [46,47].

Lastly, probiotics may theoretically play a role in preventing CRC. Normal intestinal flora exhibit protective mechanisms on gut health. Decreases and alterations in normal flora have been shown to contribute to the development of adenomas and CRC [48]. Taking probiotics may replace damaged or depleted micro-organisms, but more studies are needed to elucidate particular probiotic strains and doses, as well as the overall usefulness of probiotic supplementation for CRC prevention [48]. In summary, while a growing body of evidence supports the potential use of aspirin, statins, bisphosphonates and probiotics as chemopreventive agents against CRC, larger and longer RCTs are needed to ascertain the benefits and risks of using these agents to prevent CRC in the high-risk or general population. Until then, CRC screening and polypectomy remain the best options for prevention.

Colorectal Cancer Screening Tests

Numerous methods are available to screen for CRC. CRC screening tests can be categorized as CRC prevention tests- those that can detect advanced adenomas as well as cancer (colonoscopy, flexible sigmoidoscopy, computed tomography colonography, double contrast barium enema), and CRC detection tests- ones that primarily detect cancer (guaiac fecal occult blood test, fecal immunochemical test, stool DNA test).

Stool tests

The high-sensitivity guaiac fecal occult blood test (gFOBT), such as Hemoccult SENSA (Beckman Coulter, Inc) detects peroxidase activity of hemoglobin in stool, which may be indicative of bleeding from an occult neoplasm in the gastrointestinal tract. Two samples, collected on a card from 3 bowel movements on 3 different days, are required for adequate testing. It is not recommended that stool collected during a digital rectal exam at a physician's office be used for CRC screening, and repeat gFOBT after a positive screen is not recommended [49]. Because the gFOBT is not specific for human hemoglobin, foods such as red meat, fruits or vegetables containing plant peroxidases (e.g., radishes, turnips, horseradish, cantaloupe), may produce false positive results. These foods should therefore be discontinued at least 3 days prior to testing. Medications, such as NSAIDs or aspirin may also cause false positive results, while large doses of vitamin C, which can oxidize guaiac, may produce a false negative result. These medications and vitamin C should be discontinued for 7 days prior to testing. Annual or biennial gFOBT screening has been shown in RCTs to reduce CRC mortality by 16% [50].

The immunochemical fecal occult blood test (iFOBT), also known as fecal immunochemical test (FIT), uses antibodies directed against human hemoglobin to detect trace amounts of blood in the stool [51]. Therefore, this test is not affected by ingestion of specific food or drugs. Since globin is rapidly degraded through the gastrointestinal tract, the FIT detects blood specifically from the lower gastrointestinal tract. Samples are taken from 1, 2, or 3 bowel movements, depending on the manufacturer. A recent meta-analysis showed that most commercially available FIT screening tests are moderately sensitive and highly specific for CRC detection [52] (Table 2).

A third stool-based test approved for CRC screening in the US is

Table 2: Colorectal Cancer Screening Tests.

Screening modality	Sensitivity		Specificity	Cost per test US dollars	Serious Complications
	Advanced Adenoma	Cancer			
FOBT	17.7%-49.4%	50.0-87.0%	90.0-95.0%	$8-$23	NS
FIT	16.0-48.0%	71.0-87.0%	92.5-98.0%	$13-$40	NS
sDNA	42.4-44.6%	92.3-92.6%	83.8-89.8%	$400-$800	NS
CT Colonography	83.3%-93.0%	93.3%-96.5%	89.0%-96.5%	$400-$800	0-6/10,000
Sigmoidoscopy	71.3%-85.6%	58.3%-75.0%	89.0-95.0%	$169-$507	3.4/10,000
Colonoscopy	85.0%-95.0%	92.0%-97.0%	90.0-100%	$645-$1013	25/10,000

FOBT: high sensitivity guiac fecal occult blood test (HemoccultSensa); FIT: fecal immunochemical test; sDNA: multi-target stool DNA test (Cologuard); DCBE: double-contrast barium enema; CT: computed tomography; Advanced adenoma: adenomas ≥ 10 mm.
Serious complications: deaths or hospitalizations from perforation, major bleeding, diverticulitis, severe abdominal pain, and cardiovascular events.
NS: estimated to be non-significant although evidence lacking

the Cologuard™ multi-target stool DNA test (sDNA), which identifies cells from 2 sources [53]. First, the test uses an immunochemical assay to identify human hemoglobin in the stool. Second, the test identifies methylation and mutations of 3 DNA markers (NDRG4, BMP3, K-ras) associated with CRC in abnormal cells from precancerous and/or cancerous colonic lesions that have shed into the stool. Similar to the FIT, the sDNA test does not require any medication or diet restrictions. However, it does require the collection of an entire bowel movement in a collection bucket, as well as a second sample by using a probe to scrape the stool. In a recent study of 9989 participants, fecal DNA screening was shown to be associated with significantly higher sensitivity but less specificity (92% sensitive, 87% specific) as compared to FIT screening (74% sensitive, 95% specific) [53]. While high sensitivity is a desirable quality in CRC screening, sDNA testing, with a cost of about $400-800 per screen, may be cost-prohibitive for some patients. Medicare recently approved coverage for the Cologuard™ multi-target sDNA test once every 3 years for asymptomatic average risk adults age 50-85 years [54]. A positive result on any of the stool tests needs to be followed by full visualization of the entire colon via diagnostic colonoscopy.

Radiological Tests

Computed tomography (CT) colonography (also known as virtual colonoscopy) and double contrast barium enema (DCBE) are radiographic tests that can be used for CRC screening. Both tests require the same bowel preparation as for traditional colonoscopy. CT colonography uses x-ray and specialized computer software to generate both 2 and 3-dimensional images of the colon and rectum. To distend the colon for better visualization, a flexible tube is placed in the rectum to pump air or carbon dioxide gas into the colon. With a DCBE exam, a patient's colon is coated with barium contrast inserted through an enema rectal tube, and air or carbon dioxide gas is insufflated to distend the colon. Multiple x-ray images are taken of the entire colon. A randomized controlled study comparing CT Colonography with DCBE found CT Colonography to be the more sensitive screening modality, and CT Colonography was preferred over DCBE in symptomatic patients [55]. CT Colonography has been shown to be comparable to standard optic colonoscopy for the detection of CRC [56], and its sensitivity and specificity is far superior compared to DCBE [57].

Endoscopic Tests

Flexible sigmoidoscopy and colonoscopy are invasive endoscopic methods available for detection of precancerous polyps and CRC. Both procedures involve inserting a flexible fiberoptic lighted tube into the rectum and colon to inspect for suspicious lesions. Flexible sigmoidoscopy uses a shorter instrument that reaches the sigmoid and descending colon, while colonoscopy examines the rectum and entire colon. The advantage of flexible sigmoidoscopy and colonoscopy compared to other screening tests is that adenomatous polyps or other suspicious lesions identified during examination can be removed, potentially preventing CRC. However, these tests may not be available in low resource areas. Colonoscopy requires thorough bowel preparation, and sedation is usually administered, especially in the U.S., prior to examination. Flexible sigmoidoscopy usually does not require pre-procedure sedation, but completion of the exam may be limited due to patient discomfort [58]. In a study of 1020 people undergoing screening sigmoidoscopy in the United Kingdom, patients reported no major adverse health effects [59]. Flexible sigmoidoscopy has been shown in RCTs to significantly decrease both the incidence of CRC and mortality from distal colon cancers with an overall 18% relative decrease in CRC incidence (RR 0.82, 95% CI 0.73-0.91), 33% relative decrease in left-sided CRC incidence (RR 0.67, 95% CI 0.59-0.76), and 28% decrease in CRC mortality (RR 0.72, 95% CI, 0.65-0.80) [60-62]. A large cohort study, involving 88,902 participants that were tracked for 22 years, found that both sigmoidoscopy and colonoscopy were associated with decreased risk of distal rectum CRC and decreased CRC mortality, however only colonoscopy was associated with decreased risk of proximal colon cancer [30]. Three large-scale RCTs of colonoscopy as a primary screening method to decrease CRC incidence and mortality are currently ongoing in the US and Europe, with results not expected until after 2021 [63-65]. Risks of screening for CRC with colonoscopy include a 1.3% chance of a major adverse event such as bowel perforation or bleeding, and about a 33% chance of a minor adverse event, such as abdominal discomfort or changes in bowel habits after screening colonoscopy [66].

A comparison of diagnostic accuracy, costs, and complications of currently recommended CRC screening tests are summarized in Table 2 [52-54,57,67-69]. Newer CRC screening options under investigation include the methylated septin 9 DNA Test (mSEPT9) and the colon capsule endoscopy. In the mSEPT9 test, a blood sample is screened for the biomarker mSEPT9 that may be evident in both precancerous lesions and overt CRC. Sensitivity for the second-generation mSEPT9 test has been shown to be 75% to 90%, with a specificity of 87% to 88% [70,71]. Colon capsule endoscopy is a minimally invasive diagnostic study that does not require sedation and can potentially be done in the privacy of one's home [72]. In this procedure, a capsule containing cameras is swallowed and images detailing the bowel are transmitted to the ordering physician. The FDA has approved capsule endoscopy as an alternative to CRC screening when currently available CRC screening modalities are contraindicated [72]. These promising new CRC screening tests may be attractive, painless and non-invasive/minimally invasive future options for individuals who are reluctant to undergo currently recommended screening tests.

Guidelines for Colorectal Cancer Screening

There are several CRC screening guidelines recommended for average-risk individuals, issued by the United States Preventive Services Task Force (USPSTF), the American Cancer Society (developed by a joint committee with the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology), and the American College of Gastroenterology (Table 3) [49,73]. An update of the 2008 USPSTF CRC screening guidelines is currently under progress [74], and an update of the 2008 ACS CRC screening guideline is anticipated in 2018.

The USPSTF guidelines recommend screening all adults starting at age 50 years until age 75 years with FIT or high-sensitivity gFOBT, flexible sigmoidoscopy, or colonoscopy. The updated draft recommendations changed the timing of flexible sigmoidoscopy, from every 5 years combined with either FIT or gFOBT every 3 years, to flexible sigmoidoscopy with annual FIT every 10 years [74]. The American Cancer Society (ACS) recommendation adds the sDNA test, DCBE, and CT colonography to its recommended acceptable options, but places greater priority in prevention of CRC. Meanwhile, the American College of Gastroenterology's separately updated guideline recommends a preferred strategy with colonoscopy every 10 years or FIT annually as the preferred cancer prevention and cancer detection test, respectively. It also recommends initiating screening at age 45 years in black persons, who have higher CRC incidence and mortality rates compared to whites. While the USPSTF recommends individualized screening decisions after age 75 and against screening in persons over age 85, neither the ACS nor the American College of Gastroenterology recommend an upper age to stop screening. The current USPSTF guidelines do not offer recommendations for screening elderly persons without a previous CRC screening test. A recent observational study suggests that CRC screening is warranted in previously unscreened elderly persons up to 86 years old who are at average risk for CRC and who do not have significant comorbidities [75].

A family history of CRC or advanced adenoma diagnosed prior to age 60, and hereditary conditions that increase the risk of CRC require more aggressive screening (Table 4) [76,77]. Patients with Crohn's disease and ulcerative colitis are also at higher risk for CRC, and although there is controversy about when to start screening in these individuals, it is generally recommended that screening with colonoscopy begin 8-10 years after the diagnosis of inflammatory bowel disease [78].

In the United States, only 59% of people over age 50 years who

Table 3: Comparison of U.S. Colorectal Cancer Screening Guidelines for Average Risk Individuals.

Recommendations	Joint Guideline:[1] ACS US Multi-Society Task Force[2] American College of Radiology March 2008	American College of Gastroenterology[3] December 2008	USPSTF[4] 2016 Draft Recommendation
Age to Start Screening	50 years	50 years (45 years for black persons)	50 years
Age to Stop Screening	Stop when curative therapy is not an option	Not addressed	Individualize decision between age 76 and 85 and stop screening after age 85
Colorectal Cancer Detection Tests			
gFOBT or FIT	Annually	Annual FIT is preferred CRC detection test for those who decline colonoscopy or other CRC prevention test. Annual Hemoccult SENSA is an alternative CRC detection test.	Annually
Multi-target Stool DNA test	Every 3 years	Every 3 years as alternative to FIT for CRC detection	Insufficient evidence to recommend
Colorectal Cancer Prevention Tests			
DCBE	Every 5 years	Replaced by CT colonography	Not Addressed
CT Colonography	Every 5 years	Every 5 years as alternative to colonoscopy for CRC prevention	Insufficient evidence to recommend
Flexible Sigmoidoscopy	Every 5 years with or without annual gFOBT or FIT	Every 5 to 10 years as alternative to colonoscopy for CRC prevention	Every 10 years together with annual FIT
Colonoscopy	Every 10 years	Preferred test every 10 years for CRC prevention	Every 10 years

[1]Any one of the recommended tests is acceptable, but prevention of colorectal cancer is the greater priority
[2]US Multi-Society Task Force includes the American College of Gastroenterology, American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy
[3]Preferred strategy of CRC preventive tests over CRC detection tests, with colonoscopy as preferred test
[4]Any one of the recommended tests is adequate
ACS: American Cancer Society; USPSTF: United States Preventive Services Task Force; gFOBT: high sensitivity guaiac fecal occult blood test; FIT: fecal immunochemical test; CRC: colorectal cancer; DNA: deoxyribonucleic acid; DCBE: double-contrast barium enema; CT: computed tomography

Table 4: Recommendations for Colorectal Cancer Screening in High-Risk Individuals.

Risk Factor	Recommendation
One first-degree relative with advanced adenoma or CRC at < 60 years of age or two first-degree relative with advanced adenoma or CRC at any age	Colonoscopy every 5 years starting at age 40 years or 10 years younger than youngest affected relative's age at diagnosis, whichever is earlier
Familial Adenomatous Polyposis (FAP) or family history of FAP	Colonoscopy or flexible sigmoidoscopy annually as appropriate starting at puberty until patient and physician determine appropriate time for colectomy
Hereditary Non-Polyposis Colorectal Cancer(HNPCC or Lynch Syndrome) or family history of HNPCC	Colonoscopy every 2 years starting at age 20-25 years until age 40; then annually after age 40
Crohn's Disease & Ulcerative Colitis	Generally recommend screening colonoscopy 8-10 years after initial diagnosis

Advanced adenoma: adenoma 10 mm or greater, has villous elements, or high grade dysplasia
CRC: colorectal cancer

meet criteria for CRC screening have been adequately screened [79]. Colonoscopy is the most common CRC screening test used in the U.S., increasing significantly from 19% in 2000 to 55% in 2010 [80]. Recent declines in CRC incidence of at least 3% per year from 2003-2012 are likely attributable to increased CRC screening, especially with colonoscopy [3]. Despite an increase in CRC screening, the U.S. has a formidable challenge to achieve the 80% CRC screening rate by 2018 set by the National Colorectal Cancer Screening Roundtable [17]. Well-established barriers to CRC screening in the United States include lack of awareness of the importance of screening [81], lack of physician recommendation [82], fear of embarrassment, avoidance of bowel preparation, and/or pain and discomfort with colonoscopy [83]. A recent study found that patients overdue for screening and reluctant to undergo colonoscopy, are often amenable to screening if a provider mails a FIT screening kit to their home [84]. Furthermore, compliance with the home-based FIT screening program is significantly enhanced by making introductory phone calls and reminder phone calls if the test was not returned [84].

Discussion

Colorectal cancer is an ideal cancer for prevention and screening because it is slow growing; thus there is an opportunity to intervene at the precancerous or localized stage. There are several methods available to screen for CRC that range from home-based stool tests (FOBT, FIT, or sDNA) to radiological (DCBE and CT colonography) and endoscopic procedures (flexible sigmoidoscopy or colonoscopy). CRC screening should be considered a public health priority in the United States, however, less than 60% of people are up-to-date with recommended CRC screening.

It is promising that there has been an uptrend in CRC screening in the United States, which has likely contributed to an overall decrease in CRC incidence. Having public funds directed toward CRC screening and mandating private insurance companies to pay for CRC screening will likely increase rates of CRC screening. In a study that examined mandated coverage for CRC screening versus non-mandated coverage, it was shown that men age 51 to 64 years were more likely to have CRC screening if their state mandated their private insurance to pay it, though there was no significant difference in screening behavior among women [85]. On the federal level, provisions in the Affordable Care Act specifically mandated private insurance coverage for CRC screening and allocated funds for CRC screening to federally qualified community centers [86]. In the United States, having more visits to a primary care physician is associated with lower CRC incidence, CRC mortality, and overall mortality [87]. This association is mostly due to previous receipt of CRC screening or polypectomy. It has been shown that using the patient-centered medical home model within federally funded centers increases CRC screening by enhancing access, maintaining screening registries and facilitating overall better population management [86]. Additionally, expanding federally-qualified health centers to the most underserved regions of the country may increase CRC screening among racially and socioeconomically underserved populations [88].

In additional to government mandates and expanding federal funding for CRC screening, modalities to improve bowel preparation tolerability [89] and more vigorous research to improve and further validate the colon capsule endoscopy and mSEPT9 blood test or other biomarkers may increase overall CRC screening rates. Continued research for new screening strategies that are effective, affordable, available, and non-invasive is needed. Pursuant to this goal, the National Cancer Institute has funded the Early Detection Research Network's collaborative ongoing clinical trial that is validating promising biomarkers, including blood-based biomarkers, for CRC

screening in at least 6000 patients [72]. In the meantime, in low resource areas and in patients unwilling to undergo colonoscopy, perhaps shifting to more widely available home-based gFOBT, FIT, or multi-target sDNA tests, may increase CRC screening compliance and forge a path toward achieving the National Colorectal Cancer Screening Roundtable's target goal of 80% screened by 2018.

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