CME

ACG Clinical Guidelines: Colorectal Cancer Screening 2021

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Colorectal cancer (CRC) is the third most common cancer in men and women in the United States. CRC screening efforts are directed toward removal of adenomas and sessile serrated lesions and detection of early-stage CRC. The purpose of this article is to update the 2009 American College of Gastroenterology CRC screening guidelines. The guideline is framed around several key questions. We conducted a comprehensive literature search to include studies through October 2020. The inclusion criteria were studies of any design with men and women age 40 years and older. Detailed recommendations for CRC screening in average-risk individuals and those with a family history of CRC are discussed. We also provide recommendations on the role of aspirin for chemoprevention, quality indicators for colonoscopy, approaches to organized CRC screening and improving adherence to CRC screening. CRC screening must be optimized to allow effective and sustained reduction of CRC incidence and mortality. This can be accomplished by achieving high rates of adherence, quality monitoring and improvement, following evidence-based guidelines, and removing barriers through the spectrum of care from noninvasive screening tests to screening and diagnostic colonoscopy. The development of cost-effective, highly accurate, noninvasive modalities associated with improved overall adherence to the screening process is also a desirable goal.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B890 and http://links.lww.com/AJG/B891

Am J Gastroenterol 2021;116:458–479. https://doi.org/10.14309/ajg.0000000000001122

INTRODUCTION

In the United States, colorectal cancer (CRC) ranks second to lung cancer as a cause of cancer mortality and is the third most commonly occurring cancer in both men and women. A study estimated that in 2020 approximately 147,950 new CRC cases would have been diagnosed and 53,200 individuals would have died of the disease (1). Between 2011 and 2015, the average annual incidence rates per 100,000 population were 45.9 and 34.6 for men and women respectively (2). CRC incidence and mortality rates have shown a steady decline of approximately 1.7% and 3.2%, respectively per year. The decline began in the mid 1980s and has accelerated since the early 2000s. It is believed to be driven by changes in risk factors, early detection of cancer through CRC screening, and removal of precancerous polyps with colonoscopy, in addition to advances in surgical and treatment approaches.

Most CRCs develop through the adenoma-carcinoma sequence, presenting opportunities to prevent cancer by removing its precursor lesions, in addition to identifying CRC in its earliest, curable stages (3). Approximately 70% of sporadic CRCs develop from adenomatous polyps and 25%–30% arise from sessile serrated lesions (SSLs) through the SSL-to-carcinoma pathway (4). CRC screening efforts are directed toward removal of adenomas, SSLs and detection of early-stage CRC. Certain screening modalities such as colonoscopy, sigmoidoscopy, CT colonography and to a lesser extent stool-based testing, will detect advanced adenomatous polyps, whereas colonoscopy is optimal for the detection of SSLs. Endoscopic removal of polyps reduces CRC incidence and CRC mortality (5,6). Given new evidence regarding enhancing screening adherence, newer methods for CRC screening, and evidence to support the efficacy of screening, the purpose of this article is to update the 2009 American College of Gastroenterology (ACG) CRC screening guideline (7).

METHODS

The guideline is framed around several key questions which are outlined below. The key questions were developed by the authors and vetted through the ACG leadership. We placed emphasis on having practical recommendations that would be helpful for practicing providers in the United States. We conducted a focused literature search and used existing guidelines and technical reviews on CRC screening by key organizations. We used a modified Grading of Recommendations, Assessment, Development and Evaluation methodology (8) to evaluate the quality of the evidence and strength of recommendation. We used "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Two Grading of Recommendations, Assessment, Development

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Received March 17, 2020; accepted December 2, 2020

and Evaluation–trained methodologists assisted in evidence synthesis and grading of the evidence.

Literature search

We conducted a comprehensive literature search with the help of a librarian from the University of Minnesota on the key questions using Ovid (MEDLINE), EMBASE, and the Cochrane databases from 1980 to October 2020. Emphasis was placed on studies from 2008 onward, since publication of the last guideline. The references for review articles were also searched. A detailed search strategy is provided in Supplementary Appendix 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B890). The inclusion criteria were observational studies and randomized controlled trials (RCTs) with men and women age 40 years and older. Exclusion criteria were patients/populations with familial cancer syndromes (hereditary nonpolyposis colorectal cancer and polyposis syndromes) and special populations such as patients with human immunodeficiency virus or previous transplant. Outcomes included were CRC incidence, CRC mortality, incidence of colorectal advanced neoplasia defined as adenomas or SSL ≥10 mm, ≥3 adenomas/SSL, any villous histology, high-grade dysplasia or submucosal cancer in a colonic polyp or a traditional serrated adenoma, and harms of screening (complications, anesthesia-related complications, deaths, and overdiagnosis through additional testing).

Key questions

KQ1a. In average-risk individuals, what are the effectiveness and harms of CRC screening in reducing the incidence of advanced neoplasia and CRC, and CRC mortality?

KQ1b. How does the effectiveness vary by modality, age, and race?

KQ2. In average-risk individuals, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?

KQ3. In individuals with a family history of CRC or adenomatous polyps, what is the effectiveness of CRC screening in reducing CRC incidence and CRC mortality?

KQ4. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?

KQ5. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening modality in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?

KQ6. What are the quality indicators for different modalities of CRC screening associated with diagnostic performance of the screening test and incidence of postcolonoscopy colorectal cancer?

KQ7. What are the effectiveness and harms of aspirin chemoprevention for the endpoints of reduction in the incidence of CRC or mortality of CRC?

KQ8. What interventions improve adherence to CRC screening and to each modality of screening?

KQ9. What interventions improve adherence to follow-up of a positive CRC screening test, such as fecal immunochemical testing (FIT)?

RESULTS

See Table 1 for summary and Supplementary Appendix 2 (see Supplementary Digital Content 2, http://links.lww.com/AJG/B891) for updates from the 2009 guideline. Results for individual questions are provided below.

KQ1a. In average-risk individuals, what are the effectiveness and harms of CRC screening in reducing incidence of advanced neoplasia and CRC, and CRC mortality?

KQ1b. How does the effectiveness vary by screening modality, age, and race?

Recommendations

1. We recommend CRC screening in average-risk individuals between ages 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC.

Strong recommendation; moderate-quality evidence

2. We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC.

Conditional recommendation; very low-quality evidence

3. We suggest that a decision to continue screening beyond age 75 years be individualized.

Conditional recommendation; very low-quality evidence

4. We recommend colonoscopy and FIT as the primary screening modalities for CRC screening.

Strong recommendation; low-quality evidence

5. We suggest consideration of the following screening tests for individuals unable or unwilling to undergo colonoscopy or FIT: flexible sigmoidoscopy, multitarget stool DNA test, CT colonography or colon capsule.

Conditional recommendation; very low-quality evidence

6. We suggest against Septin 9 for CRC screening.

Conditional recommendation, very low-quality of evidence

DISCUSSION

The "ideal" screening test should be noninvasive, have high sensitivity and specificity, be safe, readily available, convenient, and inexpensive. For CRC screening, there are multiple approved tests and strategies, each with its strengths and weaknesses. In some instances the "best" screening test can be considered the one that is acceptable to the patient and gets completed. One approach to CRC screening tests is to divide them as 1-step (direct) tests (i.e., colonoscopy, which is diagnostic and therapeutic) or 2-step tests that require colonoscopy if positive, to complete the screening process. All screening tests other than colonoscopy are 2-step tests. A major limitation of non–colonoscopy-based CRC screening tests (eg, stool-based, flexible sigmoidoscopy, CT colonography [CTC], or colon capsule [CC]) is that a positive test requires a follow-up colonoscopy. This 2-step testing approach represents a continuum of screening, requires strong systems-based support to complete the screening cascade, and is more effectively applied in organized screening (9). In the United States, there are few select health care systems with organized, programmatic screening, and most screening is accomplished with a 1-step opportunistic approach. Because the focus of the guideline is on providers practicing in the United States, the review highlights options for CRC screening currently in use, which mainly include colonoscopy, and in an

Table 1. Summary and strength of GRADE recommendations

	Summary	Recommendation strength	GRADE quality of evidence
1	We recommend colorectal cancer (CRC) screening in average-risk individuals between ages 50 and 75 yr to reduce incidence of advanced adenoma, CRC, and mortality from CRC	Strong	Moderate
2	We suggest CRC screening in average-risk individuals between ages 45 and 49 yr to reduce incidence of advanced adenoma, CRC, and mortality from CRC	Conditional	Very low
3	We suggest that a decision to continue screening beyond age 75 yr be individualized	Conditional	Very low
4	We recommend colonoscopy and fecal immunochemical testing (FIT) as the primary screening modalities for CRC screening	Strong	Low
5	We suggest consideration of the following screening tests for individuals unable or unwilling to undergo a colonoscopy or FIT: flexible sigmoidoscopy, multitarget stool DNA test, CT colonography, or colon capsule	Conditional	Very low
6	We suggest against Septin 9 for CRC screening	Conditional	Very low
7	We recommend that the following intervals should be followed for screening modalities: FIT every 1 yr; colonoscopy every 10 yr	Strong	Low
8	We suggest that the following intervals should be followed for screening modalities: multitarget stool DNA test every 3 yr; flexible sigmoidoscopy every 5–10 yr; CT colonography every 5 yr; colon capsule every 5 yr	Conditional	Very low
9	We suggest initiating CRC screening with a colonoscopy at age 40 or 10 yr before the youngest affected relative, whichever is earlier, for individuals with CRC or advanced polyp in 1 first-degree relative (FDR) at age <60 yr, or CRC or advanced polyp in ≥2 FDR at any age. We suggest interval colonoscopy every 5 yr	Conditional	Very low
10	We suggest consideration of genetic evaluation with higher familial CRC burden (higher number and/or younger age of affected relatives)	Conditional	Very low
11	We suggest initiating CRC screening at age 40 or 10 yr before the youngest affected relative and then resuming average-risk screening recommendations for individuals with CRC or advanced polyp in 1 FDR at age ≥60 yr.	Conditional	Very low
12	In individuals with 1 second-degree relative (SDR) with CRC or advanced polyp, we suggest following average-risk CRC screening recommendations	Conditional	Low
13	We recommend that all endoscopists performing screening colonoscopy should measure their individual cecal intubation rates (CIRs), adenoma detection rates (ADRs), and withdrawal times (WTs)	Strong	Moderate-quality evidence for ADR; low-quality evidence for WT, CIR
14	We suggest that colonoscopists with ADRs below the recommended minimum thresholds (<25%) should undertake remedial training	Conditional	Very low
15	We recommend that colonoscopists spend at least 6 min inspecting the mucosa during withdrawal	Strong	Low
16	We recommend that colonoscopists achieve a CIR of at least 95% in screening subjects	Strong	Low
17	We suggest low-dose aspirin in individuals between ages 50–69 yr with a cardiovascular disease risk of ≥10% over the next 10 yr, who are not at an increased risk for bleeding and willing to take aspirin for at least 10 yr to reduce the risk of CRC	Conditional	Low
18	We recommend against the use of aspirin as a substitute for CRC screening	Strong	Low

Table 1. (*continued*)

	Summary	Recommendation strength	GRADE quality of evidence
19	We recommend organized screening programs to improve adherence to CRC screening compared with opportunistic screening	Strong	Low
20	We suggest the following strategies to improve adherence to screening: patient navigation, patient reminders, clinician interventions, provider recommendations and clinical decision support tools	Conditional	Very low
21	We suggest the following strategies to improve adherence to follow-up of a positive screening test: mail and phone reminders, patient navigation, and provider interventions	Conditional	Very low

organized setting, fecal immunochemical test (FIT). Other 2-step tests such as flexible sigmoidoscopy, multitarget stool DNA test, CTC, and CC are reserved for individuals unwilling or unable to undergo colonoscopy or FIT, or those with incomplete colonoscopy (CTC or CC). Comparative effectiveness studies are lacking. The options for screening are discussed below and summarized in Table 2.

ONE-STEP SCREENING

Colonoscopy

Colonoscopy is the most commonly performed gastrointestinal procedure in the United States. It allows for not only the detection of early-stage cancers but also the detection and removal of polyps and confers a long-term protection from CRC incidence and mortality (5,10,11). A systematic review of 6 observational studies reported a pooled reduction of 69% (95% confidence interval [CI] 13%–78%) in overall CRC incidence and reduction of 68% (95% CI 57%–77%) in CRC mortality associated with screening colonoscopy (12). In the Nurses' Health Study and Health Professionals Follow-up Study, Nishihara et al. (13) reported a reduced mortality from CRC after screening colonoscopy (hazard ratio [HR] 0.32; 95% CI 0.24–0.45) overall, and a reduction in death from proximal colon cancer (HR 0.47; 95% CI 0.29–0.76). In a case-control study among US veterans, Kahi and Pohl et al. (14) reported reduction in CRC mortality of 70% with screening colonoscopy (odds ratio [OR] 0.30; 95% CI 0.24–0.38) including a 52% reduction in proximal CRC mortality (OR 0.48; 95% CI 0.35–0.66) in veterans exposed to screening colonoscopy. A nested case-control study of members of Kaiser Permanente reported a 67% reduction in the risk of death from CRC (OR 0.33; 95% CI 0.21–0.52), with a 65% reduction in proximal CRC (OR 0.35, 95% CI 0.18–0.65) (15). Brenner et al. (16) reported a reduction of 91% (95% CI 87%–93%) in CRC incidence, including a 78% reduction in proximal CRC incidence (95% CI 67%–86%) in a German population-based study of screening colonoscopy. These and other select studies are summarized in Table 3 (17–20).

TWO-STEP APPROACH SCREENING TESTS

Stool-based tests

Three large RCTs with 11–30 years of follow-up were conducted in Europe and the United States (21–23). These trials randomized average-risk individuals between ages 45 and 80 years to annual or biennial screening using guaiac fecal occult blood testing (gFOBT) compared with usual care. With biennial screening, after 13, 20, and 30 years of follow-up, there was a corresponding 18% reduction in CRC mortality (21,24–30). With annual FOBT screening, there was a sustained 33% reduction in CRC mortality over 30 years (23). The Minnesota FOBT trial also reported a reduction in CRC incidence of 20% after 18 years of follow-up (31).

There have been many advances in stool-based tests for CRC screening. gFOBT has been largely replaced by FIT, which has higher sensitivity for CRC (32–34). The FIT sampling technique is easier as many tests require a single fecal sample and it has higher adherence than gFOBT because no dietary modifications or medication restrictions are required. Both quantitative and qualitative FITs are commercially available, with the option to set thresholds for the detection for quantitative tests based on population risk. However, in the United States, the Food and Drug Administration (FDA) requires that FIT be reported as positive or negative and does not allow reporting of the actual amount of hemoglobin per gram of stool. Studies have shown that FIT has greater sensitivity for detecting CRC and advanced adenomas than both standard and high sensitivity FOBT with comparable specificity (35,36). In a meta-analysis of 19 studies of asymptomatic average-risk adults, the pooled sensitivity of a 1-time FIT was 79% (95% CI 0.69–0.86), and pooled specificity was 94% (95% CI 0.92–0.95) for CRC at a cutoff of 20 μg of hemoglobin/gm of stool, the most commonly used cutoff in the United States (37). A more recent systematic review and meta-analysis including 19 studies reported 91% sensitivity and 90% specificity for FIT for detection of CRC at a quantitative cutoff of 10 μg/g (38). The sensitivity of a 1-time FIT for detection of advanced adenoma ranges from 6% to 56% (34) and between 5% and 16% for SSLs (39–41), based on the underlying population and FIT cutoff used. Although there are no randomized clinical trials on long-term outcomes such as reduction in CRC mortality with FIT, the programmatic effectiveness of annual FIT over multiple rounds of screening showed an overall CRC detection of 80% (42). In a cost-effectiveness modeling study, Knudsen et al. (43) found that a comparable number of life-years was gained with a screening strategy of the annual fecal-based test (such as FIT) and colonoscopy every 10 years. It must be emphasized that a positive FIT requires a follow-up colonoscopy, and quality assurance programs to ensure that colonoscopy is performed. Rates of diagnostic colonoscopy for the evaluation of a positive stool test are suboptimal (44) and require improvement in both programmatic and particularly opportunistic screening (45) (See KQ8 and KQ9 below). Implementation of an organized CRC screening program by Kaiser Permanente in Northern California based on primarily FIT outreach reported an increase in CRC screening rates from 38% to 82% among members, with a corresponding decrease in CRC incidence of 25% and CRC mortality of 52% over the same period (46). Biennial FIT is a strategy comparable to annual FIT, with similar

Table 2. Summary of performance characteristics for CRC screening tests

	Performance characteristics	Pros	Cons
Stool- and blood-based tests			
FIT[a]	79% sensitivity and 94% specificity for CRC	Noninvasive No risk of complications Can be done at home Programmatic screening possible	Positive results require colonoscopy Needs to be repeated annually Low sensitivity for advanced adenomas Does not detect serrated lesions
mtsDNA stool test	92% sensitivity and 87% specificity for CRC Long-term reduction in CRC incidence and mortality is unknown	Noninvasive No risk of complications Can be done at home Better sensitivity for advanced adenomas and large serrated lesions than FIT alone	Positive results require colonoscopy Repeat interval unknown but 3 years proposed More expensive than FIT alone Concern for overtesting and harms from a positive test and negative colonoscopy
Septin 9	48% sensitivity and 91% specificity for CRC Long-term reduction in CRC incidence and mortality is unknown	Minimally invasive No risk of complications Can be added to routine blood draw	Low sensitivity for CRC Repeat interval unknown Positive results require colonoscopy
Direct visualization tests			
Colonoscopy	100% detection rate for CRC. Reported incidence of PCCRC 3%–9% Long-term reduction in CRC incidence 31%–71% and CRC mortality 65%–88% from observational studies	Diagnostic and therapeutic Can detect cancers and precursor polyps Infrequent repeat interval (q10 years) possible	Operator dependent Requires bowel preparation and sedation Risk of complications 4–8 in 10,000
Flexible sigmoidoscopy	90%–100% sensitivity for distal colon CRC Long-term reduction in CRC incidence 21%; reduction in CRC mortality 26%	Less invasive than colonoscopy Low risk of complications	Positive results require colonoscopy Needs to be repeated every 5–10 years Requires enema preparation
CT colonography	90%–100% for CRC Variable sensitivity for polyps, poor sensitivity for flat lesions and sessile serrated lesions	Less invasive than colonoscopy Does not require sedation Lower risk of complications than colonoscopy	Positive results require colonoscopy Requires bowel preparation Followup may be required for extracolonic findings Limited availability of trained radiologists across the United States
colon capsule	81% sensitivity and 93% specificity for polyps ≥6 mm	Minimally invasive Does not require sedation Newer generation tests can be done at home	Requires bowel preparation Positive examinations require colonoscopy Repeat interval unknown

CRC, colorectal cancer; FIT, fecal immunochemical test; RCT, randomized controlled trial.
[a]At FIT cutoff of 20 μg/g of stool.

yield of colorectal neoplasia (47) and lower burden of screening (48). Recent systematic reviews and meta-analyses have reported a relative reduction in CRC mortality of 12% over 15 years with biennial fecal-based testing (highly sensitive gFOBT or FIT) compared with no screening (49,50). In a recent guidance, the American College of Physicians also suggested biennial fecal-based stool testing as an option comparable to colonoscopy every 10 years (51). However, given the larger effect estimate of annual FOBT in clinical trials, and the effectiveness of annual FIT CRC screening programs, annual testing is the preferred interval.

The multitarget stool DNA (mtsDNA) test is an FDA-approved stool test that comprises an assay for mutant *KRAS*, methylated *BMP3*, methylated *NDRG4*, and a FIT for hemoglobin (39). Cutoff values are calculated by an analytic regression algorithm. In a study with 9,989 average-risk individuals undergoing colonoscopy comparing the diagnostic accuracy of the mtsDNA test with FIT alone, there was higher sensitivity for detection of CRC (92% vs 74%), advanced adenoma (42% vs 24%), and SSLs ≥10 mm (42% vs 5%) but lower specificity for detection of CRC or advanced lesions (87% vs 95%). The specificity of the mtsDNA test decreases with advancing patient age. In 2 recent modeling studies, annual FIT and colonoscopy every 10 years were found be more effective and less costly than mtsDNA testing every 3 years (52,53). There is active interest from patients and providers in the optimal follow-up of individuals with a positive mtsDNA test and a negative colonoscopy. This is discussed in the section on special considerations below. Based on the current available data (54,55) we recommend that asymptomatic individuals with a positive mtsDNA test and a negative high-quality colonoscopy not undergo additional testing, such as upper endoscopy, CT of the abdomen, or repeat colonoscopy at an interval shorter than the recommended repeat screening interval (unless indicated by other symptoms or laboratory testing). If the mtsDNA test is negative, the interval for a repeat mtsDNA test or transition to another screening test is 3 years as per manufacturer

Table 3. Select studies summarizing effectiveness of screening colonoscopy in reducing CRC incidence and mortality

	US 2009	Canada 2005	Germany 2014	Switzerland 2012	US (NHS) 2013	US 2013[b]	US (VHA) 2018	US (Kaiser Permanente) 2018
Design	Cohort	Case control	Case control	Cohort	Cohort	Case control	Case control	Case Control
N[a]	715	2,915[a]	6,332[a]	22,686	88,902[a]	980	24,820[a]	5,207
CRC incidence	0.52 (0.22–0.82)	0.69 (0.44–1.07)	0.09 (0.07–0.13)	0.31 (0.16–0.59)	NR	0.29 (0.15–0.58)	NR	NR
Relative risk reduction in CRC incidence	48%	31%	91%	69%	NR	71%	NR	NR
Proximal CRC incidence	NR	1.02 (0.72–1.45)	0.22 (0.14–0.33)	NR	NR	0.36 (0.16–0.80)	NR	NR
Relative risk reduction in proximal CRC incidence	NR	2% increase	78%	NR	NR	64%	NR	NR
CRC mortality	0.35 (0.0–1.06)	NR	NR	0.12 (0.01–0.93)	0.32 (0.24–0.45)	NR	0.30 (0.24–0.38)	0.33 (0.21–0.52)
Relative risk reduction in CRC mortality	65%	NR	NR	88%	68%	NR	70%	67%
Proximal CRC mortality	NR	NR	NR	NR	0.47 (0.29– 0.76)	NR	0.48 (0.35–0.66)	0.35 (0.18–0.65)
Relative risk reduction in proximal CRC mortality	NR	NR	NR	NR	53%	NR	52%	65%

CRC, colorectal cancer; NHS, Nurses Health study; NR, not reported; VHA, Veterans Health Administration.
[a]N is total for study and the screening colonoscopy cohort was a subgroup.
[b]Included late stage cancers (stage IIB and higher only).

recommendations. Longitudinal studies on outcomes after the mtsDNA test and optimal repeat interval are awaited.

Flexible sigmoidoscopy

Flexible sigmoidoscopy allows direct evaluation of the left side of the colon and if adenomas are found, referral for a colonoscopy is required. Four large randomized trials of flexible sigmoidoscopy screening with comparable 10–13 years of follow-up have been published (56–59). Two trials, from the United Kingdom (Flexi Scope trial) and Italy (SCORE), offered once-only flexible sigmoidoscopy examination to participants age 55–64 years and reported a reduction in CRC incidence by 23% and 18% and CRC mortality by 31% and 22%, respectively (56,57). The US trial (Prostate, Lung, Colorectal and Ovarian [PLCO]), which included participants age 55–74 years and offered flexible sigmoidoscopy screening every 3–5 years, reported that CRC incidence was reduced by 21% and CRC mortality by 26% (59). One trial from Norway compared once-only flexible sigmoidoscopy plus FOBT or once-only flexible sigmoidoscopy with no screening and found comparable reduction in CRC incidence and mortality with the 2 strategies (60). In this study, flexible sigmoidoscopy screening reduced CRC incidence by 20% and CRC mortality by 27% after 11 years of follow-up (60). A systematic review reported that the largest reduction in CRC mortality from flexible sigmoidoscopy screening was seen for distal CRC, of about 37% (61). A recent study of pooled flexible sigmoidoscopy trials reported no reduction in CRC incidence or mortality in women 60 or older (58). In an updated follow-up of the Norwegian NORCCAP trial, authors also reported no reduction in CRC incidence or mortality with flexible sigmoidoscopy screening in women (62). Rates of screening flexible sigmoidoscopy have declined in the United States for the following reasons: the infrastructure needed is similar to that of colonoscopy, it does not examine the entire colon it requires colonoscopy for those with adenoma findings and the lack of sedation makes the procedure uncomfortable. Given recent evidence of lower effectiveness in women and practical issues with scheduling and availability, flexible sigmoidoscopy should be considered a screening test for individuals unwilling to undergo colonoscopy or FIT.

Alternate imaging tests for individuals who refuse colonoscopy or FIT or are not candidates for colonoscopy

CTC and CC are 2 nonendoscopic screening tests in this category. The diagnostic accuracy of CTC in average-risk screenees has been assessed in multiple studies. The sensitivity ranges between 68% and 98% for lesions ≥6 mm and 67%–94% for lesions ≥10 mm, whereas specificity ranges from 80% to 93% for lesions ≥6 mm and 86%–98% for lesions ≥10 mm (63,64). However, the diagnostic accuracy of CTC for SSLs is significantly lower than that of colonoscopy (3.1% vs 0.8% for colonoscopy and CTC, respectively) (65). There also remain concerns for detection of right-sided and flat polyps and operator dependence (66). The CC is FDA approved for imaging the colon in patients with previously incomplete colonoscopy or in patients with lower gastrointestinal bleeding who are at too high risk to undergo a colonoscopy. The test characteristics of CC have been improving because of enhancements to software and hardware. In a prospective study of 884 average-risk individuals due for screening, 79% of CCs could be completed, and sensitivity to detect adenomas ≥6 mm was 81% and specificity was 93%. For polyps ≥10 mm, the sensitivity and specificity were 80% and 97%,

respectively (67). Another recent study with 253 participants who underwent back-to-back colonoscopy and CC reported a per-patient sensitivity for >9 mm polyps of 87% (68). A recent comparative efficacy study of CTC and CC enrolled 321 individuals at 14 medical centers and reported that the sensitivity of CTC and CC for polyps ≥6 mm was 32% and 84%, respectively, and that for polyps ≥10 mm was 53% and 84%, respectively (69). The reasons why CTC had low diagnostic yield are unknown, and further analyses are awaited. At this time, CTC and CC are options for individuals unable to undergo colonoscopy or FIT, provided that the tests are locally available and reimbursed for the indication of screening. It is important to note that both tests require a follow-up diagnostic colonoscopy if the result is positive.

Blood-based tests

A blood-based test assessing methylated Septin 9 is FDA approved for CRC screening in average-risk individuals age 50 years or older who refuse other CRC screening methods. A screening study reported a sensitivity of 48% for CRC detection and 11% for advanced adenoma detection (70). With enhancements in the test assay, a small case-control study reported a sensitivity of 90% and a specificity of 88% for CRC (71). A recent systematic review aggregated 39 eligible studies and reported a pooled sensitivity for CRC of 62% and specificity of 90% (72). Given the low sensitivity and the lack of longitudinal and comparative data on test performance, the test is not considered an optimal screening modality at this time.

CRC screening in average-risk individuals starting at age 45 years

Recent studies have highlighted a rising incidence of CRC in individuals younger than 50 years in the United States. Although CRC incidence has continued to decline in those age 50 years and older, the incidence rates have doubled in 20- to 49-year-olds (73–75). In 2018, the American Cancer Society published guidelines with a qualified recommendation to lower the starting age for CRC screening from 50 to 45 years of age in the average-risk adult population (76), even though current recommendations of the US Preventive Services Task Force (USPSTF) and the Multi-Specialty Task Force (MSTF) are to begin screening at age 50 years (77–79). These qualified recommendations were based on predictive modeling analyses and age-cohort epidemiological evidence of a relative increase of 51% in CRC incidence among individuals younger than 50 years between 1974 and 2013 (75,80). Modeling studies using 2 of the 3 Cancer Intervention and Surveillance Network models found that initiating screening at age 45 years was on the efficiency spectrum (76) and that initiating screening at age 45 years instead of age 50 years would result in approximately 25 more life-years gained per 1,000 individuals screened.

Recent epidemiological data show alarming trend reversals for CRC incidence in the United States. Notably, CRC incidence among individuals age 50–64 years, which had historically declined by 2%–3% per year, has increased by 1% annually between 2011 and 2016 (1, 81). A similar increase in the incidence rate is observed in individuals younger than 50 years and has been partly ascribed to a birth cohort effect, in which increased CRC risk in individuals born after 1950 is carried forward as they age. It has been estimated that persons born around 1990 have twice the risk of colon cancer and 4 times the risk of rectal cancer compared with those born around 1950 (80). Although the reasons for these observations are complex and multifactorial, the fact that other developed countries are reporting similar increases in early-onset CRC and birth-cohort effects suggests that the Western lifestyle (especially exemplified by the obesity epidemic) is a significant contributor (82).

An advantage of initiating screening at age 45 years instead of 50 years includes reduced CRC risk due to early detection of CRC in this age group. Over time, detection and removal of polyps in individuals age 45–49 years would reduce the incidence of CRC in those age 50 years and older. In addition, preventing young CRC is a desirable goal because the societal impact of CRC death at an early age is particularly devastating.

The disadvantages of such an approach are the resources required to screen an additional 21 million individuals between ages 45 and 49 years and detracting from efforts to screen individuals age 50 years and older to reach the target goal of 80% set by the National Colorectal Cancer Roundtable. Given that current rates of screening uptake are close to 60% (57.9% ages 50–64 and 62.4% ages 50–75) (83), expanding the population to be screened may reduce these rates as emphasis shifts to screening 45- to 49-year-olds at the expense of efforts to screen the unscreened 50- to 75-year-olds. A recent Markov analysis evaluated the population-level impact of lowering the screening age to 45 years and found that although it may be cost-effective to begin younger, elevating the screening rate in persons 50–75 to the target of 80% would prevent 3 times as many deaths attributed to CRC for approximately 66% less cost (84).

There are few empirical data regarding the effectiveness of screening in younger average-risk individuals, and the most appropriate screening modality in this age group is not known.

CRC screening in elderly individuals

With gains in life expectancy, and increases in the geriatric population, CRC screening in the elderly has substantial public health consequences. Because few detailed subgroup analyses of screening trials have been reported, few empirical data exist on when best to stop offering screening (85). There are several reasons why the elderly may not derive the same benefit or may even be harmed by screening. The first reason is diminished life expectancy. The benefits of polypectomy are delayed by 7–10 years after screening has occurred (86), and, thus, screening is of limited benefit for those not expected to live for at least a further 7–10 years. Second, there is an increase in competing causes of death in the elderly. The value of screening decreases as the risk of dying of other causes increases; hence, for the elderly, the benefit may become small enough to be negligible or even negatively impact their life expectancy. Third, elderly individuals may be more susceptible to risks associated with undergoing screening compared with their younger counterparts (87). These risks vary from anxiety, false-positive results, and unnecessary treatments to complications from procedures related to screening, such as dehydration, electrolyte disturbance, impact on renal function with the preparation, alteration of anticoagulation or antiplatelet agents, risk of perforation and hemorrhage during colonoscopy, and cardiovascular events periprocedure. In older patients, the benefits of early detection and prevention of CRC may be offset by higher risk of procedure-related harm and diminished health and life expectancy. Several authors have addressed this issue using different approaches (88). Lin et al. (89) reported that elderly individuals undergoing screening derive 15% or less benefit from screening compared with their younger counterparts in terms of gains in life expectancy. In their analysis of elderly individuals age between 70 and 94 years, Ko et al. (90) found that the risk of screening-related complications was higher than the estimated benefit from screening in some subgroups. A more recent simulation study found that the optimal age

to forego FIT-based screening varied considerably based on sex, comorbidity status, and screening history, ranging from 66 years old for individuals with poor health and adequate previous screening to 90 years in case of individuals in good health and no previous screening (91). Therefore, the point where benefits of screening become negligible or are outweighed by potential harm likely varies significantly between individuals. The decision to continue or discontinue screening in the elderly should not be solely based on chronological age but should also take into account health status, screening history, benefits and harms of screening, and values and preferences of the patient (92–94). The most recent guideline on CRC screening from the USPSTF concluded that in adults age 76–85 years, the decision to screen for CRC should be an individualized, taking into account the patient's overall health and screening history. The guideline specifies that screening would be most appropriate for those not previously screened, those healthy enough to undergo treatment if CRC is detected, and those without substantially limited life expectancy. In adults age 86 years and above, screening is not recommended because of competing causes of mortality. The guideline identified when to stop screening as an important area of future research (85). Although further studies are awaited, providers should consider life expectancy, patient risk, values, and preferences and participate in shared decision making for screening individuals older than 75 years.

Boosting CRC screening rates in African Americans

African Americans have among the highest rates of CRC of any racial/ethnic group in the United States (1). Compared with whites, incidence rates are 24% higher in African American men and 19% higher in African American women (95). Stage-adjusted CRC mortality is also disproportionately higher in African Americans, with rates being 47% higher in African American men and 34% higher in African American women compared with whites (96). The reasons for these differences are not entirely clear but disparities in care, such as lower rates of screening, diagnostic follow-up, and treatment are postulated. One study estimates that 19% of the racial disparity in CRC mortality rates can be attributed to lower screening rates and 36% to lower stage-specific survival among African Americans (97). Health systems with equal access to the screening-diagnosis-treatment care continuum do not show such disparities (98,99). Nationally, screening rates in blacks are lower than in whites, suggesting an unmet need for efforts to improve screening in this group. Recent trends from Surveillance Epidemiology and End Results (SEER) show a decline in CRC incidence and mortality for black men and women (74). Based on recent SEER data, modeling studies (70) show similar benefit of CRC screening in African Americans and whites starting at age 45 years. Special efforts and outreach programs are needed to boost screening in African Americans to reduce the disparities in screening rates and reduce incidence rates.

Harms of screening

Harms of stool-based tests include anxiety about false-positive results and harms related to colonoscopy. The main harms of colonoscopy are bleeding (pooled event rate of 8 per 10,000) and perforation (pooled event rate of 4 in 10,000) (61). The risk of complications is greater with polypectomy and in older age groups (100). Other harms include the risk of electrolyte imbalance and nephropathy from bowel preparations or cardiopulmonary events from moderate or deep sedation and splenic injury (101,102). With colonoscopy, there is also concern for post-colonoscopy CRC (PCCRC), defined as CRC diagnosed after a colonoscopy which did not detect cancer (103). The rate of PCCRC is estimated at 1 per 3,174 colonoscopies (95% CI 1 per 2,710 to 1 per 3,875) (103,104). A strong quality monitoring and improvement program is key to reducing PCCRC. This is discussed further in KQ6.

The harms of CTC include concerns for radiation exposure and extracolonic findings. With improved protocols requiring less radiation (1–5 mSv), the risk of radiation exposure may not be an issue. Extracolonic findings are reported in 27%–69% of studies with a wide range of work-up (105). The downstream sequelae of these incidental findings have not been adequately quantified.

The harms of CC come from the potential side effects of the preparation required before the examination (e.g., electrolyte imbalances) and the possibility of capsule retention in the small bowel. However, in the trial evaluating screening CC, no serious harms were reported (67).

KQ2. In average-risk individuals, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?

Recommendations

7. We recommend that the following intervals should be followed for screening modalities:

FIT every 1 year

Colonoscopy every 10 years

Strong recommendation; low-quality evidence

8. We suggest that the following intervals should be followed for screening modalities:

Multitarget stool DNA test every 3 years

Flexible sigmoidoscopy every 5–10 years

CTC every 5 years

CC every 5 years

Conditional recommendation; very low-quality evidence

DISCUSSION

There are no RCTs comparing various screening intervals. The optimal interval to repeat FOBT/FIT is not known. In the long-term follow-up of the Minnesota FOBT trial, CRC mortality was reduced by 33% with annual screening and by 18% with biennial screening (23). The European RCTs found biennial FOBT to be effective in reducing CRC mortality. One modeling study (106) favored annual FIT. In a cost-effectiveness analysis, annual FIT and colonoscopy performed every 10 years yielded similar life years gained. Ongoing RCTs that compare annual FIT and biennial FIT with colonoscopy for CRC incidence and mortality reduction will further address the question. For now, annual FIT screening is recommended. Several population-based studies have reported a low risk of CRC after a negative screening colonoscopy for at least 10 years and up to 20 years (107–109). Lee et al. reported a 46% and 88% reduced risk of CRC and CRC related deaths, respectively, up to 12 years after a negative colonoscopy (HR 0.54; 95% CI 0.31–0.94 and 0.12; 95% CI 0.02–0.82, respectively). Pilonis et al. reported the effect of colonoscopy in the Polish population compared with the general population and found the standardized incidence and mortality ratios to be reduced 10 years or 15 years after a negative

colonoscopy, compared with the general population (standardized mortality ratio of 0.13; 95% CI 0.0–0.17 and 0.15; 95% CI 0.06–0.31 for the 10- and 15-year interval, respectively). There are no longitudinal studies of repeat testing or interval on the mtsDNA test or Septin 9. Modeling studies performed by the Cancer Intervention and Surveillance Network have compared various screening strategies and found comparable life-years gained with the following intervals: annual FIT, colonoscopy every 10 years, flexible sigmoidoscopy every 10 years with annual FIT, CTC every 5 years, and mtsDNA test every 3 years (61). In another modeling study, rescreening 10 years after a negative screening colonoscopy at age 50 years reduced CRC compared with no further screening, and using high sensitivity FOBT or FIT annually or CTC every 5 years was less costly than continued colonoscopy (110).

KQ3. In individuals with a family history of CRC or adenomatous polyps, what is the effectiveness of CRC screening in reducing CRC incidence and CRC mortality?

KQ4. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence and CRC mortality?

KQ5. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening modality in reducing colorectal advanced neoplasia incidence, CRC incidence and CRC mortality?

Recommendations

9. We suggest initiating CRC screening with a colonoscopy at age 40 or 10 years before the youngest affected relative, whichever is earlier, for individuals with CRC or advanced polyp in 1 first-degree relative (FDR) at age <60 years or CRC or advanced polyp in ≥2 FDR at any age. We suggest interval colonoscopy every 5 years.

Conditional recommendation; very low-quality evidence

10. We suggest consideration of genetic evaluation with higher familial CRC burden (higher number and/or younger age of affected relatives).

Conditional recommendation; very low-quality evidence

11. We suggest initiating CRC screening at age 40 or 10 years before the youngest affected relative and then resuming average-risk screening recommendations for individuals with CRC or advanced polyp in 1 FDR at age ≥60 years.

Conditional recommendation; very low-quality evidence

12. In individuals with 1 second-degree relative (SDR) with CRC or advanced polyp, we suggest following average-risk CRC screening recommendations.

Conditional recommendation; low-quality evidence

DISCUSSION

It is estimated that between 3% and 10% of US adults have an FDR with CRC, and higher proportions have either an FDR or SDR with CRC (111,112). On average, a family history of CRC is believed to be associated with a 2-fold increase in CRC risk, but the magnitude depends on the age of the individual at risk, age at diagnosis of the relative(s), degree of familial relation between the individual and relative(s), and number of affected relative(s). Professional organizations (7,113) have published CRC screening recommendations, which primarily take into account the age and number of affected relatives. In all situations, it is critical for clinicians to obtain a 3-generation family history and remain alert for features suggestive of an inherited CRC syndrome, such as clustering of cancer cases within one side of a family, younger age at diagnosis, or the presence of synchronous and metachronous cancers. Maintaining a high index of suspicion for an inherited CRC syndrome and using appropriate screening tools (114) is critical because a family history of CRC or advanced adenomas can guide clinicians to appropriately modify the starting age for screening and the interval of subsequent surveillance.

Studies assessing CRC risk based on family history have varied considerably with regard to setting, patient population, degree of CRC risk, study design, and methodology. One important issue has been inconsistent distinction between the increased risk for the individual based on their family history vs risk to family members of an individual with cancer (115,116). The former scenario is the focus of the following sections because most patients present or are referred for screening because of concerns about their family history of CRC or advanced polyps.

Age of the individual at risk

Several studies and meta-analyses (115,117–119) have reported that the risk of CRC decreases with increasing age of the individual at risk. An analysis (119) of the Nurses' Health Study and Health Professionals Follow-up Study reported that the relative risk of subjects with an FDR with CRC decreased from 5.37 at ages 30–44 years to nearly 1 after the age of 65 years. A recent systematic review and meta-analysis (120) analyzed nearly 9.3 million subjects from 63 studies, and found that, overall, a family history of CRC in an FDR was associated with a higher risk of CRC (risk ratio [RR] 1.76; 95% CI 1.57–1.97). The increased risk was more pronounced in younger individuals (RR 3.29 [95% CI 1.67–6.49] for <40 years vs 1.42 [95% CI 1.24–1.62] for ≥40 years). Compelling information can also be derived from a secondary analysis (121) of the PLCO randomized CRC screening trial, which included nearly 145,000 individuals. Overall, a family history of CRC was associated with modestly increased CRC incidence (HR 1.30; 95% CI 1.10–1.50) and CRC mortality (HR 1.31; 95% CI 1.02–1.69). The HR for incident CRC in subjects with only 1 FDR with CRC was 1.23 (95% CI 1.07–1.42). The study supports the notion that the relevance of a family history of CRC wanes as the individual at risk ages (121,122). A cost-effectiveness analysis by Naber et al. (123) estimated that the risk of developing CRC in a person with 1 affected FDR decreased with age, from 5 fold for ages 30–44 years to no difference at ≥70 years.

Age of the affected relative(s)

The age of the affected relative is inversely associated with an individual's CRC risk. Guidelines have traditionally used a dichotomous categorization with age 60 years as the threshold to designate the risk category (based on a 2-fold CRC risk cutoff), with more intensive surveillance recommended for those with an FDR <60 years old at the time of their CRC diagnosis (7,113). The recommendation to start screening at age 40 years or 10 years

before the youngest affected relative is based on the seminal study by Fuchs et al. (119), showing that cumulative incidence of CRC was similar between those age 40 years with a family history and those age 50 years without a family history. A population-based study from Utah (124) reported that the risk of colorectal neoplasia among FDRs of patients diagnosed with CRC was greater when the index case was diagnosed at age <60 years (HR 2.11; 95% CI 1.70–2.63 vs 1.77; 95% CI 1.58–1.99 for ≥60 years old). Another study from Utah (125) found that the risk of CRC was increased among FDRs of index cases with CRC regardless of the age of diagnosis but was highest when both index case and FDR were younger. The HR ranged from 1.6 to 7.0 for FDR <50 years old (overall HR 2.28, 95% CI 1.86–2.80) and 1.7 to 2.3 for FDR ≥50 years old (overall HR 1.81, 95% CI 1.71–1.92). A systematic review and meta-analysis (117) estimated that the pooled risk of CRC was 3.55 (95% CI 1.84–6.83) with ≥1 FDR <50 years old compared with 2.18 (95% CI 1.56–3.04) with ≥1 FDR ≥50 years old, although the difference did not reach statistical significance. The meta-analysis by Taylor et al. (126) reported RRs of 3.31 (95% CI 2.79–3.89), 2.53 (95% CI 2.24–2.85), 2.22 (95% CI 2.04–2.40), and 1.97 (95% CI 1.83–2.12) with ≥1 FDR diagnosed at <50 years, between 50 and 59 years, between 60 and 69 years, and between 70 and 79 years, respectively. Conversely, the secondary analysis of the PLCO trial (121) reported that individuals (who were all at least 55 years old) with 1 FDR with CRC had a comparable risk of CRC regardless of age at diagnosis in the affected FDR: The HRs were 1.27 (95% CI 0.97–1.63), 1.33 (95% CI 1.06–1.62), and 1.14 (95% CI 0.93–1.45) if the FDR was <60, 60–70, and >70 years old, respectively (P trend = 0.59) (121).

Degree of familial relation

The closer the familial relation between a person and an affected relative with CRC, the higher the risk for that person. This is illustrated in an analysis of the Nordic Twin Study of Cancer (127), which showed that monozygotic twins of affected cotwins had a 3-fold increased risk of CRC compared with the general population, whereas dizygotic twins had a 2-fold increased risk. In assessing different CRC family history scenarios, the most common situation is that of 1 FDR with CRC (>90%) (126). Recent evidence suggests that the risk of CRC in an individual with an affected FDR does not depend on the identity of the relative. In a large colonoscopy study involving 16 Asia-Pacific regions (128), the risk of CRC (adjusted OR [AOR] 0.90, 95% CI 0.34–2.35, P = 0.830), advanced colorectal neoplasia (AOR 1.07, 95% CI 0.75–1.52, P = 0.714), and colorectal adenoma (AOR 0.96, 95% CI 0.78–1.19, P = 0.718) in subjects with either parent affected was similar to that of subjects with affected siblings.

The Utah population-based study (124) found that all relatives of an index person with CRC were at increased risk, including FDR, SDRs, and first cousins. However, the magnitude of the risk associated with an affected SDR is generally more modest than observed for FDR. In an analysis by Taylor et al. (126), the RRs associated with SDR alone (without concomitant FDR) ranged from 1.05 (95% CI 0.99–1.11) to 1.48 (1.11–1.93) with increasing numbers of SDRs affected, whereas the RRs associated with concomitant 1 FDR and at least 1 SDR ranged from 2.12 (95% CI 1.90–2.35) to 3.37 (95% CI 2.20–4.93).

Number of affected FDRs

The literature consistently shows that the higher the number of affected relatives with CRC, the greater the relative and absolute risks for an individual to develop CRC (112,117,118,126). The cost-effectiveness analysis by Naber et al. (123) used the Microsimulation Screening Analysis (MISCAN) model to estimate costs and effects of colonoscopy screening strategies with different age ranges and intervals, based on lifetime CRC risk estimate inputs derived from the studies by Taylor et al (126) and Fuchs et al (119). It is important to note that the study did not take into account the age of the affected relative with CRC, and that high numbers of FDRs or FDRs and SDRs (≥2) with CRC or Lynch syndrome-related cancers should trigger suspicion and workup for an underlying inherited CRC syndrome. Nevertheless, the findings show that increasing numbers of FDRs are associated with increased lifetime CRC risk in all age groups. In the secondary analysis of the PLCO trial by Schoen et al. (121), subjects with ≥2 FDRs had significantly higher adjusted HR for CRC incidence than those with 1 FDR (2.04; 95% CI 1.44–2.86 vs 1.23; 95% CI 1.07–1.42).

Family history of polyps

Many of the limitations observed in studies assessing familial CRC risk apply to those assessing the effect of the family history of adenomas. In fact, most studies assessed the risk of adenomas in persons with an FDR with CRC, rather than CRC risk in persons with a FDR with adenoma (129). In a prospective study from Hong-Kong, Ng et al. (130) reported that the prevalence of advanced adenomas was 11.5% among siblings of patients with advanced adenomas, compared with 2.5% among siblings of individuals without advanced adenomas (OR 6.05; 95% CI 2.74–13.36). In addition, the prevalence of all colorectal adenomas was significantly higher (39.0% vs 19.0%; OR 3.29; 95% CI 2.16–5.03). A recent study from the same group of investigators shows that a family history of nonadvanced adenomas is less relevant than that of advanced adenomas: the prevalence of advanced adenomas was 3.9% among FDR of individuals with nonadvanced adenomas, compared with 2.4% among FDR of individuals with normal colonoscopies (OR 1.67; 95% CI 0.72 to 3.91). A multicenter multinational prospective study (128) of nearly 12,000 asymptomatic subjects in the Asia-Pacific region found that subjects with at least 1 FDR affected with CRC were significantly more likely to have CRC (AOR range 2.02–7.89), advanced colorectal neoplasia (AOR range 1.55–2.06), and colorectal adenoma (AOR range 1.31–1.92) than those without a family history.

Although conventional adenomas have historically been the major relevant CRC precursor lesion, accumulating evidence has shown that the serrated pathway is a major contributor to CRC. Although there is a paucity of data regarding familial risk associated with serrated polyps (outside the serrated polyposis syndrome), it is logical to include advanced serrated polyps (SSL ≥10 mm, SSL with dysplasia and traditional serrated adenoma) under the broader category of "advanced polyps," which also encompasses advanced adenomas, until more data are available.

Alternatives to colonoscopy in patients with a family history of CRC

There are no RCTs comparing the yield and effectiveness of colonoscopy compared with other CRC screening modalities specifically for individuals with a family history of CRC, except for FIT. In 1 RCT (131), investigators randomized nearly 1,900 FDRs of patients with CRC to a single colonoscopy examination or 3 consecutive annual FITs. Advanced neoplasia was detected in

4.2% and 5.6% FDRs in the FIT and colonoscopy groups, respectively (OR 1.41; 95% CI 0.88–2.26), and no CRCs were missed with the FIT strategy. A recent meta-analysis (132) assessed the performance characteristics of FIT in patients at increased CRC risk due to a personal or family history of CRC. Subgroup analysis for patients with a family history of CRC revealed FIT sensitivity of 86% (95% CI 31%–99%) and specificity of 91% (95% CI 89%–93%) for CRC; for advanced neoplasia, sensitivity was 46% (95% CI 37%–56%) and specificity was 93% (95% CI 90%–95%).

KQ6. What are the quality indicators for different modalities of CRC screening associated with diagnostic performance of the screening test and incidence of postcolonoscopy colorectal cancers?

Recommendations

13. We recommend that all endoscopists performing screening colonoscopy should measure their individual cecal intubation rates (CIRs), adenoma detection rates (ADRs), and withdrawal times (WTs).

Strong recommendation, moderate-quality evidence for ADR, low-quality of evidence for WT, and CIR.

14. We suggest that colonoscopists with ADRs below the recommended minimum thresholds (<25%) should undertake remedial training.

Conditional recommendation, very low-quality evidence

15. We recommend that colonoscopists spend at least 6 minutes inspecting the mucosa during withdrawal.

Strong recommendation, low-quality evidence

16. We recommend that colonoscopists achieve CIRs of at least 95% in screening subjects.

Strong recommendation, low-quality evidence

DISCUSSION

For optimal performance of a diagnostic test, it is imperative that quality control programs and monitoring be in place. For stool- and blood-based tests, this responsibility falls on the laboratory clinic directors or the manufacturer. The discussion in this section is limited to quality assurance in colonoscopy because it is a highly operator-dependent test. Although the National Polyp Study suggested that colonoscopy may reduce the incidence of CRC by 76%–90% (6), subsequent studies reported that the reduction in incidence and mortality is lower at about 60% and is more pronounced in the distal colon (133). PCCRCs which are cancers that appear after a colonoscopy in which no cancer is diagnosed and classified as interval and noninterval, are partly explained by missed lesions during the index colonoscopy (134–137). PCCRCs account for about 3%–9% of CRC (137–140) and have a predilection for the proximal colon. A comprehensive review on the terminology and recommended reporting for PCCRCs (103) outlines the importance of having a robust quality colonoscopy program in place that includes tracking and reporting of these cancers.

Although it is proposed that some PCCRCs may arise from neoplastic lesions that harbor genetic features that are associated with a more rapid progression to cancer, as well as lesions that are not visualized or may have been incompletely resected, multiple studies have reported the association between quality of the colonoscopy and the rate of PCCRC (135,136,141–143). The ADR, which is the proportion of average-risk patients undergoing screening colonoscopy in whom an adenoma is found, is regarded as a robust measure of colonoscopy performance quality that correlates with subsequent cancer risk (144–146). Over the past 2 decades, assessments of detection performance have repeatedly and consistently demonstrated that colonoscopy is highly operator dependent with regard to detection (146–152). Adenoma detection typically varies between colonoscopists in the same group by ≥3-fold on a per patient basis and up to 10-fold on a per adenoma basis (146–152). In response to evidence of variable detection, recommendations were made in 2002 by the US Multi-Society Task Force on Colorectal Cancer for quality measurements related to detection at colonoscopy (153). The MSTF proposed ADR to be the fraction of persons age ≥50 years who have one or more adenomas detected and removed and that the minimum acceptable minimal thresholds be 25% in men and 15% in women (153). Subsequently, revisions to the US recommendations on ADR measurement have been made by a joint quality task force of the ACG and American Society for Gastrointestinal Endoscopy. In 2006, the joint task force recommended that ADR measurement be confined to first-time screening colonoscopies (154). In 2015, the specified minimum recommended minimal thresholds for detection were increased to 25% overall, 30% in males and 20% in females (155), for any screening colonoscopy, not limited to first time screening. Furthermore, in 2015, the task force specified that adenomas counted toward the ADR be only conventional adenomas so that SSL were excluded from the definition (155).

ADR has been validated as a predictor of cancer occurring after colonoscopy in 3 landmark studies (146,152,156). In a provocative study by Kaminski et al. (146), in which 45,026 patients involved in a Polish nationwide colorectal cancer screening program were followed over time, endoscopists with ADRs less than 20% (categorized as less than 11.0%, 11.0%–14.9%, 15.0%–19.9%, and 20.0% or more) had a more than 10-fold higher rate of PCCRC than those with higher ADRs. Another more recent study reported a decreased risk of PCCRC for physicians with ADR >33.5% compared with those with ADR of <19.06%. In this study, each 1% increase in ADR was associated with a 3% reduction in the incidence of CRC and a 5% reduction in fatal CRC (152). Further, endoscopists have been shown to increase their ADRs with training, and such improvements in ADR have been linked to subsequent reductions in CRC in the patients of colonoscopists who achieve higher ADRs (157). Thus, ADR has been shown to be highly variable between endoscopists, strongly linked to the risk of PCCRC, subject to improvement with training, and associated with improved cancer outcomes when that improvement is achieved. ADR measurement requires resource investment primarily because many endoscopy and pathology databases are not yet linked, necessitating manual entry of pathology data. The use of endoscopy software programs, natural language processing, and national registries such as GiQUiC may be used to automate ADR reports. Nevertheless, the powerful association of ADR with cancer outcomes is generally considered to constitute an essential mandate to make the measurements. Recent screening recommendations from the MSTF encourage patients to ask colonoscopists for their ADR (158). For reporting purposes, ADR from screening colonoscopy of average-

risk individuals age 50 years and older should be reported. Practices may consider breakdown by patient sex and first time vs repeat screening colonoscopy, but this is often logistically difficult.

Recent data suggest that the recommended thresholds of ADR of 30% for men and 20% for women should be considered minimum targets and that colonoscopists with ADRs above the thresholds should strive for aspirational ADRs in the range of 45–50% for a mixed-gender patient population (156). Thus, in the largest PCCRC the highest quintile of ADR was above 33.5% (152). Furthermore, in a large practice in Minnesota, evidence of improving cancer protection was found as ADR approached 50% (156). Gains in ADR can be achieved by education regarding the spectrum of endoscopic appearances of precancerous lesions and optimal withdrawal technique (159). Split-dose bowel preparations improved ADR in retrospective trials (160) and RCTs (161). Technical measures that have been associated with increased detection include rotating the patient during withdrawal (162,163) so that the segment under examination is nondependent and better distended (162) and by examination of the colon twice (164). Double examination has frequently been focused on the cecum and ascending colon (165) because several studies indicate that colonoscopy is less effective in preventing right-sided compared with left-sided CRC (11,13,16,133). Double examination is often considered by colonoscopists to refer to a first examination in the forward view, followed by reintubation of the cecum and a second examination in retroflexion (165). However, 2 randomized trials found that a second forward-viewing examination of the entire right colon is equally effective (166,167). All of the abovementioned measures have the advantage of not requiring special colonoscope equipment. However, in addition to the above measures, several specialized devices in the colonoscope or attached to the colonoscope facilitate detection. These include certain mucosal exposure devices added to the colonoscope tip (168–170), highlighting technologies including high definition colonoscopes (171), chromoendoscopy (172–174), and newer and brighter forms of electronic chromoendoscopy including narrow band imaging (175) and linked color imaging (176). Finally, artificial intelligence and emerging computer-aided detection technology are additional tools to improve ADR in the near future (177,178). Thus, an array of options is available to colonoscopists to improve ADR.

Several aspects of detection quality measurement remain under investigation and may lead to future changes in recommendations regarding measurement. For example, it is clear that measuring adenomas per colonoscopy or a similar measure such as adenomas per positive colonoscopy provides greater separation between the highest and lowest detectors in a group of colonoscopists and logically better reflects the quality of examination over the entire colon (179). Although these measures could reasonably replace ADR, obstacles to immediate implementation include some uncertainty regarding optimal minimum acceptable and aspirational thresholds, lack of validation in PCCRC studies, and concerns that APC use might incentivize resected lesions from the same colon segment to be submitted to pathology separately (155). The latter practice would seem to unnecessarily increase costs. A second issue is whether ADR measurement should be confined to first-time screening colonoscopies or should include patients undergoing surveillance and diagnostic examinations (180) and second screening examinations 10 or more years after a first examination (181). Surveillance colonoscopy ADRs run 7%–10% above screening ADRs, and diagnostic colonoscopy ADRs run below screening ADRs (180). This results in the mean ADR for colonoscopies performed for all 3 groups of indications often being similar to the screening ADR. Although a formal change awaits results of additional studies, it may be reasonable to incorporate other indications when the numbers of available screening colonoscopies for a given colonoscopist is low. Colonoscopies for an indication of a positive FIT should be excluded from the ADR calculation because this indication is associated with considerably higher ADR relative to screening (34). For centers that rely heavily on primary FIT screening, it is possible to measure ADR for colonoscopy in the FIT-positive population alone (34). The MSTF recommends minimum acceptable thresholds for ADR in FIT-positive populations of 45% for men and 35% for women (34). Aspirational thresholds for ADR in the FIT population may reach $\geq$75% in males. By extension, it is appropriate to exclude positive mtsDNA colonoscopies from the routine ADR calculation because the test includes a FIT (182). A third issue that remains under investigation is whether to create a separate target for detection of SSLs. SSLs are precursors of 25–30% of CRCs (183). This pathway is characterized by mutations in the BRAF oncogene, gene promoter hypermethylation (i.e., CpG island methylator phenotype), and a presumed more rapid progression to CRC; these lesions are also more prevalent in the proximal colon, a location where we recognize colonoscopy to be less protective for CRC compared with the distal colon (150,184,185). Detection and complete resection of SSLs is undeniably important for cancer prevention, and serrated detection seems to vary more among endoscopists than detection of conventional adenomas (150,186). However, the risk of cancer in SSLs is substantially lower compared with conventional adenomas of comparable size (187). This finding raised concerns that the risk of cancer arising from individual SSLs that are missed at colonoscopy has been overestimated. There are also no studies on the association of the detection rate of SSLs and PCCRC. The obstacles to incorporation of serrated lesions into a detection target are first the large interobserver variation between pathologists in differentiation of SSLs from hyperplastic polyps (155). Thus, development of a separate target for SSLs could easily become a measure of pathologist performance as much as endoscopist performance. Targets that include a summation of SSLs and hyperplastic polyps generally have excluded the rectosigmoid to avoid incentivizing the resection of diminutive hyperplastic rectosigmoid polyps, which are generally considered harmless. However, the unreliability of endoscopic markers of the sigmoid-descending colon junction would complicate implementation of a summated serrated target. Fortunately, recent studies have reported that detection rates of adenoma, SSL, and advanced adenoma are tightly correlated such that a high detector of one type of polyp is likely to be a high detector of the other 2 (150,188). Currently, there are no indicators that can assess the completeness of polyp resection, and this remains an area of future need.

Withdrawal time, the time measured from when the colonoscope reaches the cecum to the time the scope is withdrawn from the anus in the absence of polyp removal, has also been studied as a quality metric in colonoscopy. Withdrawal time has been recommended as a surrogate detection target also since

2002 (153). The initial recommendation for withdrawal time to average at least 6–10 minutes in normal colonoscopies without biopsy or polypectomy was modified in 2006 to a recommendation that normal colonoscopies average at least 6 minutes (154). This modification followed from a study showing that ≥6 minutes of withdrawal time produced excellent separation of colonoscopists with relatively high from low ADR (147). Studies have demonstrated that a withdrawal time of ≥6 minutes (excluding the time to perform polypectomy or other maneuvers) increased the detection of neoplastic lesions during colonoscopy in patients with intact colons (134) and reduces the risk of PCCRC (156). Furthermore, this study and another that focused on serrated lesions (189) suggested that very high-level detection is associated with minimum average withdrawal times in normal colonoscopies of 9 minutes rather than 6 minutes. These findings may be expected to alter recommendations for minimum average withdrawal time in future quality recommendations.

It is important to note that the withdrawal time should be spent washing and suctioning, looking behind folds and performing segmental inspection. However, similar to the limitations of ADR measurement, withdrawal time measurement can be gamed, in that an endoscopist may spend the entire withdrawal time in 1 segment. Because an effective technique requires time for application, an increasingly effective technique is strongly associated with longer average withdrawal times, at least up to 9 minutes (156,189). Stated differently, adequate withdrawal times are a consequence of effective technique, and longer times that are not spent applying effective technique do not increase detection (190). Recent evidence indicates that mucosal exposure devices on the colonoscope tip can significantly reduce withdrawal time without loss of or with actual increases in detection (191,192), but this finding warrants additional study. Successful ADR improvement programs focus primarily on lesion recognition skills and the withdrawal technique (159). We recommend that the withdrawal time be recorded in the endoscopic record of every examination by noting the time the cecum is intubated. However, the main value of the measurement is to investigate low ADR performance because low ADR accompanied by low withdrawal time can be reasonably assumed to reflect an inadequate withdrawal technique, indicating the need for immediate remediation of the technique.

Another important measure of colonoscopy quality that affects the risk of PCCRC is the cecal intubation rate (CIR). CIR is defined as passage of the colonoscope tip into the cecal caput, permitting full evaluation of the mucosa between the ileocecal valve and appendiceal orifice and should be accompanied by photography of the appendiceal orifice, the ileocecal valve, and the terminal ileum if intubated (134). This quality indicator has been proposed because of the well-known findings that large portions of colorectal neoplasms are located in the proximal colon, including the cecum (134). In a Canadian study, low CIR was associated with increased rates of PCCRC (137). Current US recommendations are that CIR should be ≥90% overall and ≥95% in screening patients (155). Measuring success by notation of landmarks and by inclusion of photography is often instructive (155).

Extensive recommendations addressing an array of colonoscopy quality indicators are available (155). In 2015, the joint task force recommended priority quality indicators consisting of the ADR, the CIR, and the use of appropriate screening and surveillance intervals. Achieving the priority indicator targets established by the joint quality task force ensures colonoscopy that is complete to the cecum, provides effective detection and cancer prevention, and is cost-effective through avoidance of overuse.

KQ7. What are the effectiveness and harms of aspirin chemoprevention for the endpoints of reduction in incidence of CRC or mortality of CRC?

Recommendations

17. We suggest low-dose aspirin in individuals between the ages of 50–69 years with a cardiovascular disease risk of ≥10% over the next 10 years, who are not an increased risk for bleeding and willing to take aspirin for at least 10 years to reduce the risk of CRC.

Conditional recommendation; low-quality evidence

18. We recommend against the use of aspirin as a substitute for CRC screening.

Strong recommendation, low-quality evidence

DISCUSSION

Multiple, long-term studies demonstrate the benefit of aspirin in reducing both CRC incidence and mortality. In 2016, the USPSTF performed a systematic review and analysis of primary and secondary prevention trials of cardiovascular disease to evaluate the effect of aspirin on CRC incidence and mortality (193). They found no effect on CRC risk within 10 years of aspirin therapy in 69,535 subjects (RR 0.99, 0.85–1.15) although analyses in 47,464 subjects after 10–19 years of initiating aspirin demonstrated a 40% reduced risk for CRC (RR 0.60, 0.47–0.76). However, it is important to note that the included studies generally did not report or break down results by the CRC screening history of the included individuals. Although we have strong evidence that CRC screening reduces CRC incidence and mortality, it is not clear whether long-term aspirin use provides further incremental benefit and whether the benefit is outweighed by harms. Although most of the large chemoprevention trials included in the review were conducted before screening was widespread, Women's Health study reported screening rates of nearly 50% and a reduction in CRC incidence with aspirin use. This study randomized 39,876 women in the United States to aspirin 100 mg every other day or placebo (194). The mean age of participants was 55 years. After follow-up of an average of 10.1 years, no effect of aspirin was observed on CRC incidence (RR 0.97, 0.77–1.24). During the 18-year follow-up of this cohort (195), a reduced incidence of CRC was observed in the aspirin group (HR 0.80, 0.67–0.97), driven particularly by a decrease in proximal colon cancer (HR 0.73, 0.55–0.95). When the analysis was restricted to the posttrial events, the delayed effect of aspirin was magnified (HR 0.58, 0.42–0.80). Therefore, it is reasonable to assume that aspirin is beneficial in reducing the risk of colon cancer in the screened and unscreened. Another caveat to consider is that the real-world benefit of aspirin and screening depends on adherence, and individuals adherent to screening may also be the ones who likely take aspirin for at least 10 years or longer.

Other studies of the role of aspirin in reducing CRC incidence have shown mixed results. In the Physicians Health Study, 22,071 healthy male physicians age 40–84 years were randomized to aspirin 325 mg every other day vs placebo for 5 years (196). The study found no association between aspirin and CRC (RR 1.15, 0.80–1.65).

The Iowa Women's Health Study is a prospective cohort study of 41,836 postmenopausal women age 55–69 years at study entry (197). Compared with those who never used aspirin, ever use of aspirin was associated with a lower risk of colon cancer in women reporting the use of aspirin 2–5 times (HR 0.79, 0.59–1.04) and >6 times per week (HR 0.76, 0.58–1.00), respectively. The effect was driven by a decrease in proximal colon cancer (HR 0.67, 0.51–0.87) in those who reported use of aspirin >2 per week vs nonusers. No association was found between distal colon or rectal cancer and aspirin.

A 32-year follow-up of the Nurses' Health Study and Health Professionals Follow-up Study included 135,965 health care professionals (88,084 women and 47,881 men, respectively) who reported on aspirin use biennially (198). Compared with nonregular use, regular aspirin use (defined as reported aspirin use at least 2 times per week, including standard and low-dose aspirin) was associated with a lower risk for CRC (RR 0.81, 0.75–0.88), including in women (RR 0.84, 0.76–0.93) and men (RR 0.77, 0.68–0.87). The minimum duration of regular use associated with a lower risk was 6 years, and the strength of the association increased with the duration of use RR 0.86 (0.78–0.94) for 6–10 years and RR 0.76 (0.69–0.84) for >16 years.

The 20-year follow-up of 5 randomized cardiovascular disease prevention trials confirmed that aspirin was associated with a decrease in CRC mortality (HR 0.61, 0.43–0.87) (199). The risk of CRC decreased with longer, scheduled use of aspirin from ≥2.5 years (HR 0.54, 0.36–0.80) to ≥5 years (HR 0.48, 0.30–0.77). Similar benefit was seen in aspirin doses greater than 75 mg daily. The risk of CRC death was increased in subjects allocated to 30 vs 283 mg daily in the Dutch TIA trial (OR 2.02, 0.70–6.05) (200).

In a case-control study from the United Kingdom, aspirin users had a lower risk of fatal CRC (RR 0.68,0.56–0.82), which was associated with a less-advanced CRC cancer stage at the time of diagnosis: Dukes B (RR 0.54, 0.42–0.68), Dukes C (RR 0.71,0.56–0.91), and Dukes D (RR 0.60, 0.48–0.74) (201).

Any benefit of aspirin use must be weighed carefully against the risk of aspirin use. The USPSTF systematic review of bleeding events from 10 cardiovascular disease primary prevention trials in adults (mean age, 53.2–70.1 years) addressed the risk of major GI or intracranial bleeding (202). Major GI bleeding included cases leading to death, those requiring hospitalization, transfusion, or those described by the trial investigator as serious. Intracranial bleeding included hemorrhagic stroke and intracerebral, subdural, and subarachnoid hemorrhage. An increased risk for major GI bleeding (0.29 more cases per 1,000 person-years) and hemorrhagic stroke or other intracranial bleeding (0.11 more cases per 1,000 person-years) were observed.

KQ8. What interventions improve adherence to CRC screening and to each modality of screening?

Recommendations

19. We recommend organized screening programs to improve adherence to CRC screening compared with opportunistic screening.

Strong recommendation; low-quality evidence

20. We suggest the following strategies to improve adherence to screening: patient navigation, patient reminders, clinician interventions, provider recommendations, and clinical decision support tools.

Conditional recommendation; very low-quality evidence

DISCUSSION

Organized CRC screening

CRC screening is a process that occurs in a multilevel health care environment. The International Agency for Research on Cancer defines an organized screening program as one that has the following features: (i) an explicit policy with specified age categories, method, and interval for screening; (ii) a defined target population; (iii) a management team responsible for implementation; (iv) a health care team for decisions and care; (v) a quality assurance structure; and (vi) a method for identifying cancer occurrence in the population (203,204). In contrast, opportunistic screening is done outside an organized screening program, often delivered through fee-for-service reimbursement of physicians. Compared with opportunistic screening, organized screening focuses much greater attention on the quality of the screening process, including follow-up of participants. In the United States, screening is mainly opportunistic, and among those up to date on screening in the 2010 National Health Interview Survey data, colonoscopy was the most commonly reported test (54.6%), followed by flexible sigmoidoscopy and FOBT (8.8%) (205). Insurance status is the most important determinant of CRC screening (206). In the National Health Interview Survey study 2000–2005, Trivers et al. (207) found that among adults age 50–64 years, the reported rate (proportion [95% CI]) for FOBT or endoscopy in the past years was 41.5% (39.3%–43.7%) among patients with private insurance, 31.2% (24.2%–39.1%) among people with public insurance, and 16.1% (11.9%–21.4%) among people with no insurance. Higher screening rates are reported with organized screening compared with opportunistic screening. In the PASSI study in Italy, Carrozzi et al. (208) found that of the total 38% of people reported screening, 31% of people were in the organized screening program compared with 7% with opportunistic screening. A winning example of organized CRC screening in the United States is the Kaiser Permanente Northern California integrated health system (46). In that system, which serves approximately 4 million members, before 2006, CRC screening was opportunistic, predominantly using sigmoidoscopy and gFOBT. Starting in 2007, screening transitioned to mailed FIT outreach in individuals who were not up to date. Screening outreach included mail, secure e-mail, and phone reminders. In addition, reminders for providers were added to the electronic medical record. A recent study reported that the CRC screening rate rose from 38.9% in 2000 to 82.7% in 2015. Another successful example of organized CRC screening in the United States with screening rates approximately 80% is the Veterans health care system, with novel use of provider alerts and other electronic health care reminders and processes to follow through on inviting individuals due for screening (209).

Interventions to boost screening adherence

At the screening organization level, small media interventions to raise awareness (e.g., brochures) and invitations/reminders are associated with increased participation, as is support for scheduling and appointments (210). A recent systematic review and meta-analysis of interventions intended to increase CRC screening by any recommended modality in the United States reported that FOBT/FIT outreach (i.e., active distribution of fecal blood tests), patient navigation, patient reminders,

clinician interventions of academic detailing, and clinician reminders were associated with increased CRC screening rates (211). Combinations of interventions were associated with greater increases than single components. In a randomized trial in Scotland, Libby et al. (212) compared the rate of FOBT uptake in 3 groups: invitation letter alone, invitation letter plus a prenotification letter, and the last two plus a booklet of information on CRC and screening. FOBT uptake was highest in the group that received all 3 mailings (uptake rate: prenotification letter + invitation: 59%, prenotification letter + booklet + invitation: 58.5%, and only-invitation group: 53.9%, $P < 0.001$). Furthermore, adding a FIT in the mailing kit compared with letters or invitation alone increases the screening rate but leads to an increase in cost (213).

At the provider level, the involvement of the primary care provider or general practitioner (GP) is associated with increased participation in both organized and opportunistic screening settings. A recommendation to be screened from a primary care provider—who is known and trusted by the person—is clearly effective in raising participation. A cluster RCT conducted in France within the context of organized screening showed that providing GPs with a list of their patients who were not up to date with CRC screening resulted in a small increase in FIT screening at 1 year. The between-group difference was 4.2% (95% CI 2.3%–6.2%) for the patient-specific reminder group compared with the usual care group (214). A cluster RCT conducted at federally qualified health centers in the United States showed that clinics with electronic health record-embedded tools (introductory letter, mailed FIT, reminder letter) had higher screening participation (18.3% vs 14.5%, difference 3.8% points, 95% CI 0.6%–7.0%) compared with usual care (215).

Recommendations to undergo CRC screening via a mailed letter from physicians consistently are associated with increased adherence to CRC screening (216–219). A systematic review reported that in organized programs, letters of invitation—especially if signed by the GP—and reminder letters to nonparticipants increased uptake (9). In addition, patient-physician communication also influences the screening uptake rate. In an RCT, Boguradzka et al. (220) found a higher participation rate for patients who received primary care physician's counseling on CRC screening than people who received an information leaflet (47% vs 13.7%). In an observational study in Kaiser Permanente Northwest, Mosen et al. (221) found that more comprehensive discussion of CRC screening was associated with increased screening (OR 1.51, 95% CI 1.03–2.21). In a cross-sectional telephone survey among Latino patients, Nápoles et al. (222) found that physician explanations (OR 1.27; 95% CI 1.03–1.58) and greater physician encouragement (OR 6.74; 95% CI 3.57–12.72) were associated with taking endoscopy. In this study, they also found that patients reporting quite a bit/a lot of physician encouragement had 6 times higher odds of obtaining the FOBT as those reporting none/a little encouragement (OR 6.54; 95% CI 2.76–15.48).

Patient navigator and reducing structural barriers also enhance screening uptake. Muliira et al. (223) reviewed 15 studies and found that a patient navigator will improve uptake of CRC screening with rates ranging from 11% to 91%. Patient navigators were most effective in patients who belong to minority groups. However, in a randomized trial, Lairson et al. (224) found that the navigator comes at an increased cost (patient navigator intervention: $289 vs standard intervention: $167). Reducing structural barriers such as offering extended or nonstandard clinic hours (225) and direct mailing FOBT kits (216) have also been demonstrated to be effective strategies. For colonoscopy uptake, peer coaching (encouragement from a volunteer patient who had previously undergone colonoscopy) was associated with increased uptake compared with a mailed brochure in a US study (226).

Finally, clinician and patient reminder systems also influence uptake of CRC screening. In an RCT, Hirst et al. (227) found a higher uptake of gFOBT among patients who received text reminders than patients receiving usual care. In an RCT with 8 primary care clinics in Florida, Roetzheim et al. (228) reported an increased odds of completing gFOBT (OR 2.5; 95% 1.65–4) with the intervention of screening and flagging medical charts due for screening and having an office responsible for arranging screening tests for patients.

KQ9. What interventions improve adherence to follow-up colonoscopy after a positive noncolonoscopy CRC screening test?

Recommendations

21. We suggest the following strategies to improve adherence to follow-up of a positive screening test: Mail and phone reminders, patient navigation, and provider interventions.

Conditional recommendation; very low-quality evidence

DISCUSSION

In a retrospective cross-sectional study, May et al. (229) found that among the 347 veterans (37.9%) who did not undergo follow-up colonoscopy, the reasons were patient related (49.3%), provider related (16.4%), system related (12.1%), or multifactorial (22.2%). Interventions including health education leaflets, patient reminders, holding seminars, and helplines have been found to increase the completion rate for patients with a positive screening result. In the Bureau of Health Promotion project in Taiwan, Chang et al. (230) found that after making health education leaflets, sending return visit reminder to patients, holding seminars, and opening a consultation helpline, the completion rate for colonoscopy for evaluation of positive screening patients increased from 53.63% to 66.08%. Mail or telephone reminders have been shown to increase the follow-up of screen-positive patients (231). In the Promoting Adherence to Referral for Colonoscopy study, Zorzi et al. (232) reported that the participation rate after an initial invitation by mail and by phone was similar (86.0% vs 84.0%, RR: 1.02; 95% CI 0.97–1.08); among nonresponders to the initial invitation, the compliance rate with a recall by appointment with a specialist practitioner was 50.4%, significantly higher than with a mail recall (38.1%; RR:1.33; 95% CI 1.01–1.76) or with face-to-face counseling with the GP (30.8%; RR:1.45; 95% CI 1.14–1.87).

SPECIAL CONSIDERATIONS

False-positive stool test

A common dilemma faced by endoscopists is the scenario in which a stool test is positive but the subsequent colonoscopy is negative.

In this situation, there is a tendency for overtesting or early repeat screening. This is a bigger concern from patients and providers for the mtsDNA test, which has a FIT plus methylated DNA markers. Evidence from 2 studies are reassuring in this regard. In a follow-up study with 1,050 participants with a positive mtsDNA test, only 8 aerodigestive cancers were detected at 4 years of follow-up, and the incidence rate was not different from that of the general population or the mtsDNA-negative group (233). In a second prospective study, Cooper et al. (234) invited 30 individuals with a false-positive mtsDNA test for repeat testing and upper endoscopy and colonoscopy. Over a follow-up of up to 29 months, of 12 patients who were restudied, 7 had a negative second mtsDNA test and normal upper and lower endoscopy. Of the 5 with persistent positive test, 3 had positive findings including advanced adenoma. No cancers or deaths were detected in a chart review of the 30 subjects. In an updated retrospective review of 1,216 individuals who underwent an mtsDNA test followed by colonoscopy, the incidence of aerodigestive cancers in the group with negative mtsDNA and negative colonoscopy was not different from the rate in the mtsDNA-positive and colonoscopy-negative group (RR 2.2; 95% CI 0.8–6.2) or the rate in the general population based on SEER (RR 0.8; 95% CI 0.3–1.9) (54). In the presence of high-quality colonoscopy, defined as complete, with adequate preparation and performed by an endoscopist with adequate ADR, routine follow-up screening intervals should be followed for repeat screening.

Tailoring screening based on the risk score for advanced adenoma and CRC

There are important differences in the incidence and mortality rates for CRC among men and women. Women reach comparable cumulative incidence rates at higher ages than men. Brenner et al. (235) used age- and sex-specific data from SEER registry data for years 2000–2003 to calculate 10-year cumulative CRC incidence rates for men and women at every year of age between 50 and 70 years. They found that women achieve comparable 10-year cumulative incidence rates 4–6 years later compared with men at ages 50, 55, and 60 years. This is believed to be due to the protective effect of estrogen and healthier lifestyle in women. However, women have longer life expectancies than men; thus, the lifetime risk of developing CRC for women is comparable to that of men. In an update of the Minnesota FOBT trial (23), the authors reported that men benefitted more than women (RR of CRC deaths 0.62 (95% CI 0.50–0.78) in men vs 0.83 (95% CI 0.67–1.04) in women in the combined screening groups vs unscreened groups. Furthermore, tailoring screening to individualized risk scores, which incorporates not only age and sex but also race, body mass index, use of aspirin, smoking history, and other dietary and lifestyle risk factors, would be highly desirable to stratify individuals into risk of harboring advanced neoplasia and tailor screening recommendations. Although many such models have been developed and validated (236–240), large-scale trials testing the strategies and validating the risk scores across different populations are needed. Peng et al. (241) compared the performance of 17 risk models for predicting the presence of advanced neoplasm in CRC screening and concluded that the models yielded modest discriminatory power, and further validation in diverse populations was needed. Imperiale et al. (242) reported a 13-variable predictive model for advanced neoplasia with good discrimination. Guo et al. (243) developed a polygenic risk score for CRC based on 90 single-nucleotide polymorphisms that could be used to lengthen the repeat colonoscopy interval beyond 10 years for individuals with low or intermediate scores. External validation of these models and development of other models specific to the US population are awaited.

Future studies on CRC screening

To provide evidence for comparative effectiveness of CRC screening tests, there are several ongoing RCTs. The Colonoscopy vs Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer trial (244) (ClinicalTrials.gov number NCT01239082) is a randomized comparison of 1-time colonoscopy with annual FIT plus colonoscopy as follow-up to a positive test, to examine CRC incidence and mortality over 10 years. A randomized trial comparing colonoscopy with biennial FIT is being conducted in Spain (ClinicalTrials.gov number, NCT00906997). Two additional European studies are comparing screening colonoscopy with no screening (the Nordic-European Initiative on Colorectal Cancer) trial (ClinicalTrials.gov number NCT00883792) or with FIT or no screening (Screening of Swedish Colons, NCT02078804) with respect to mortality from CRC.

Further studies are needed to develop validated risk stratification tools particularly in those 45–49 years. Development of one or more highly accurate blood-based CRC screening tests is an important research priority. Interventions to improve CRC screening should focus on underlying racial ethnic and socioeconomic disparities. Studies are needed to evaluate the utility of colonoscopy at 5-year intervals in individuals with 1 FDR with CRC <50 and whose own colonoscopy is negative every 5 years for up to age 65 years.

CONCLUSIONS

Despite the availability of multiple screening modalities and various public health initiatives to boost CRC screening, nearly one-third of the eligible US population is unscreened. CRC screening rates must be optimized to reach the aspirational target of >80%. Substantial reductions can be made by achieving high rates of adherence and providing fail safe systems to decrease barriers through the spectrum of care from a positive non-colonoscopy test to colonoscopy to complete the screening process. Acknowledging the available screening tools for use in the correct settings of each population will increase the compliance of different populations. Consistent with this goal, adoption of cost-effective, highly accurate, noninvasive methodologies associated with reduced complications and barriers than more invasive methods may improve overall acceptance of the screening process. FIT is a widely accepted and cost-effective noninvasive 2-step CRC test and is optimal for programmatic screening and when systems are in place to navigate patients into colonoscopy. Colonoscopy is a 1-step CRC screening test, the final common pathway for a positive noncolonoscopy screening test, and most appropriate screening test for individuals with a family history of CRC. The quality of provision of CRC screening, by any method, must be monitored and improved to achieve the reductions in CRC incidence and mortality.

ACKNOWLEDGMENTS

This guideline was produced in collaboration with the Practice Parameters Committee of the American College of Gastroenterology. The committee expresses special thanks to Douglas J. Robertson, MD, MPH, who served as guideline monitor for this document, and

Millie Long MD, MPH, FACG, who assisted with the GRADE methodologic process.

CONFLICTS OF INTEREST

Guarantor of the article: Aasma Shaukat, MD, MPH, FACG.
Specific author contributions: All authors contributed to researching, writing, and editing this article.
Financial support: None to report.
Potential competing interests: A. Shaukat: scientific consultant for Iterative Scopes and Freenome. C.A. Burke: research support—Ferring, Janssen, and Cancer Prevention Pharmaceuticals; consultant—Freenome and SLA pharmaceuticals. D.K. Rex: consultant—Olympus Corporation, Boston Scientific, Medtronic, Aries Pharmaceutical, Braintree Laboratories, Lumendi, Norgine, Endokey, GI Supply, and Covidian/Medtronic; research support—EndoAid, Olympus Corporation, Medivators, and Erbe USA; ownership—Satisfai Health. C. Kahi, L. Rabeneck, and B.G. Sauer: none to report.

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