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Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations

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Abstract

AIM

To summarize and compare worldwide colorectal cancer (CRC) screening recommendations in order to identify similarities and disparities.

METHODS

A systematic literature search was performed using MEDLINE, EMBASE, Scopus, CENTRAL and ISI Web of knowledge identifying all average-risk CRC screening guideline publications within the last ten years and/or position statements published in the last 2 years. In addition, a hand-search of the webpages of National Gastroenterology Society websites, the National Guideline Clearinghouse, the BMJ Clinical Evidence website,

Google and Google Scholar was performed.

RESULTS

Fifteen guidelines were identified. Six guidelines were published in North America, four in Europe, four in Asia and one from the World Gastroenterology Organization. The majority of guidelines recommend screening average-risk individuals between ages 50 and 75 using colonoscopy (every 10 years), or flexible sigmoidoscopy (FS, every 5 years) or fecal occult blood test (FOBT, mainly the Fecal Immunochemical Test, annually or biennially). Disparities throughout the different guidelines are found relating to the use of colonoscopy, rank order between test, screening intervals and optimal age ranges for screening.

CONCLUSION

Average risk individuals between 50 and 75 years should undergo CRC screening. Recommendations for optimal surveillance intervals, preferred tests/test cascade as well as the optimal timing when to start and stop screening differ regionally and should be considered for clinical decision making. Furthermore, local resource availability and patient preferences are important to increase CRC screening uptake, as any screening is better than none.

Key words: Guidelines; Systematic review; Fecal occult blood test; Fecal immunochemical test; Colonoscopy; Colorectal cancer; Screening; Flexible sigmoidoscopy

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Core tip: To our knowledge, this is the first systematic review comparing global colorectal cancer (CRC) screening guidelines for average risk individuals, aiming to highlight similarities and discuss areas of controversy. It is well established that screening reduces CRC incidence and mortality, however there are regional differences when it comes to implementing such screening. Moreover, several guidelines have been published or updated recently. Our review showed that average-risk individuals should undergo CRC screening from age 50 to 75, using guaiac-based fecal occult blood test, fecal immunochemical test, flexible sigmoidoscopy or colonoscopy.

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INTRODUCTION

According to the World Health Organization, colorectal cancer (CRC) is the third most common cancer diagnosed among men, and the second most common in

women^[1]. CRC screening of average-risk individuals decreases CRC incidence and mortality. Available CRC screening modalities include fecal occult blood testing (FOBT) that can either be guaiac-based (gFOBT) or immunochemical (FIT). Research including randomized controlled trials has shown that annual FOBT reduces CRC mortality by approximately 30%^[2-8], whilst both annual and biennial FOBT screenings reduce CRC incidence^[9]. However, those reductions can be obtained only if a positive FOBT is followed by more invasive investigations such as colonoscopy. Flexible sigmoidoscopy (FS) has shown to decrease CRC incidence by 30% and CRC-related mortality by 50%^[10]. Colonoscopy is often referred to as the CRC screening gold standard because it allows an examination of the complete colon and it can remove pre-cancerous polyps immediately. However, whilst randomized controlled trials (RCTs) demonstrated that FS screening reduces CRC incidence and mortality^[10,11], similar high-quality evidence is lacking for screening colonoscopy. Other potential screening methods include double contrast barium enema (DCBE), CT colonography, video capsule colonoscopy and stool DNA (sDNA) testing. However, their exact respective roles in CRC screening remain even less well recognized. Several guidelines on CRC screening have recently been updated^[12-15]. This systematic review provides an overview over the current guidelines and discusses areas of uncertainty and controversy amongst them.

MATERIALS AND METHODS

Search strategy

Computerized medical literature searches were initiated from January 2007 to September 2017 using MEDLINE, EMBASE, Scopus, CENTRAL and ISI Web of knowledge. The selection of articles utilized a combination of MeSH headings and controlled vocabulary adapted to each databases related to (1) colorectal cancer; and (2) guideline (or recommendations, or position statement or consensus). Recursive searches and cross-referencing were also carried out using a "similar articles" function; hand searches of articles were identified after an initial search. We included all fully published adult human studies in English. In addition, we performed a hand-search of the webpages of National Gastroenterology Society websites (the complete list of screened societies is available in Appendix 1), the National Guideline Clearinghouse, the BMJ Clinical Evidence website, and Google and Google Scholar to identify relevant publications. Two authors independently performed searches, with a third available to resolve disagreements in citation selection.

Trial selection and study population

Selection criteria included guidelines, consensus recommendations or position statements that include specific recommendations for CRC screening in average-risk (asymptomatic, with no personal nor

family history) individuals. Exclusion criteria were: Guidelines (or consensus) publications older than ten years, position statements older than 2 years, articles reporting only on national colorectal screening programs [*i.e.*, Association of Coloproctology of Great Britain and Ireland (ACPGBI)] without issues actual guideline or consensus recommendations, and articles that were only reviewing existing guidelines or current screening practice, guidelines addressing only screening for moderate and/or high-risk population, older versions of an existing guideline, society guidelines that issue identical recommendations to multi-society or national guidelines or guidelines that were only published incomplete [*i.e.*, Australian Government NHMRC guidelines]. In case of an existing national guideline, more regional guidelines for that given country were excluded, as were guidelines or position papers addressing only one screening modality, guidelines or position papers providing only combined recommendations for average-risk and moderate/high-risk populations [*i.e.*, such as the Gastroenterological Society of Australia's (GESA) guidelines^[16]], and publications in languages other than English. The British^[17] and the New Zealand^[18] guidelines were both excluded because they only issued recommendations for moderate to high-risk individuals and no specific guidelines for average risk individuals.

RESULTS

Included recommendations

The systematic database search yielded 1360 records and nine additional records were identified by hand searching. Overall, 1369 records were screened. From these, forty-six full texts were identified and screened further. Fifteen guidelines corresponding to the selection criteria were included in this systematic review (Figure 1).

Current guidelines follow as:

North America

Six guidelines were published in North America. A summary and their respective ratings of evidence are shown in Table 1.

American College of Gastroenterology (ACG, 2009): The ACG guidelines distinguishes prevention tests from detection tests^[19]. Prevention tests, such as FS, colonoscopy and CT colonography, allow physicians to identify cancer and precursor lesions, whereas detection tests (fecal tests) have low sensitivity for adenomatous polyp detection and lower sensitivity than prevention tests for cancer. The preferred screening test recommended by ACG is colonoscopy, repeated every 10 years, starting at age 50 (strong recommendation, moderate-quality evidence) except for African Americans in whom screening should start

at age 45 instead of age 50 (weak recommendation, low or very low-quality evidence). No upper age limit is recommended. However, if colonoscopy is not an option because of unavailability or individual preference, another prevention test, such as FS, repeated every 5-10 years (weak recommendation, moderate-quality evidence) or CT colonography, repeated every 5 years (strong recommendation, low or very low-quality evidence) is suggested. If the individual declines prevention tests, a detection test should be offered. The preferred detection test is annual FIT (strong recommendation, moderate-quality evidence), but alternatives are annual Hemoccult Sensa (gFOBT) (strong recommendation, moderate-quality evidence) or sDNA testing every 3 years (weak recommendation, moderate-quality evidence).

American College of Physicians (ACP, 2015): The ACP recommends screening for individuals between 50 to 75 years^[20], using one of four suggested modalities: "high-sensitivity FOBT" or FIT (annually), FS every 5 years, colonoscopy every 10 years, or a combination of "high-sensitivity" FOBT/FIT (every 3 years) and FS (every 5 years). The ACP does not favor any one of these tests over another. According to this position statement, individuals 75 years or older and people with a life expectancy less than ten years should not undergo screening.

US Preventive Services Task Force (USPSTF, 2016): The USPSTF, an independent panel of experts, recommends screening average-risk individuals from age 50 to 75 (grade A recommendation)^[13]. It is estimated that the benefit risk ratio decreases after age 75, especially in individuals with prior screening history. However, a healthy individual aged 76 to 85 without previous screening will likely benefit from screening^[13]. For individuals between 76 to 85 years, screening is defined as a personal decision (grade C recommendation). No ranking was established among screening tests, since the USPSTF's goal is to maximize overall screening uptake, no matter which test is employed. It is mentioned that all screening tests have certain advantages and limitations and no one screening test has been identified to be superior to all others. Therefore, individuals undergoing screening should be allowed to choose their preferred screening option amongst the following options: annual high-sensitivity gFOBT, annual FIT, sDNA test every 1 to 3 years, FS every 5 years, colonoscopy every 10 years, CT colonography every 5 years, or a combination of FS every 10 years with annual FIT.

Canadian Task Force on Preventive Health Care (CTFPHC, 2016): The CTFPHC, comprised of an independent group of experts, recommends screening individuals aged 60 to 74, using gFOBT or FIT every two years, or FS every 10 years (strong recommendation,

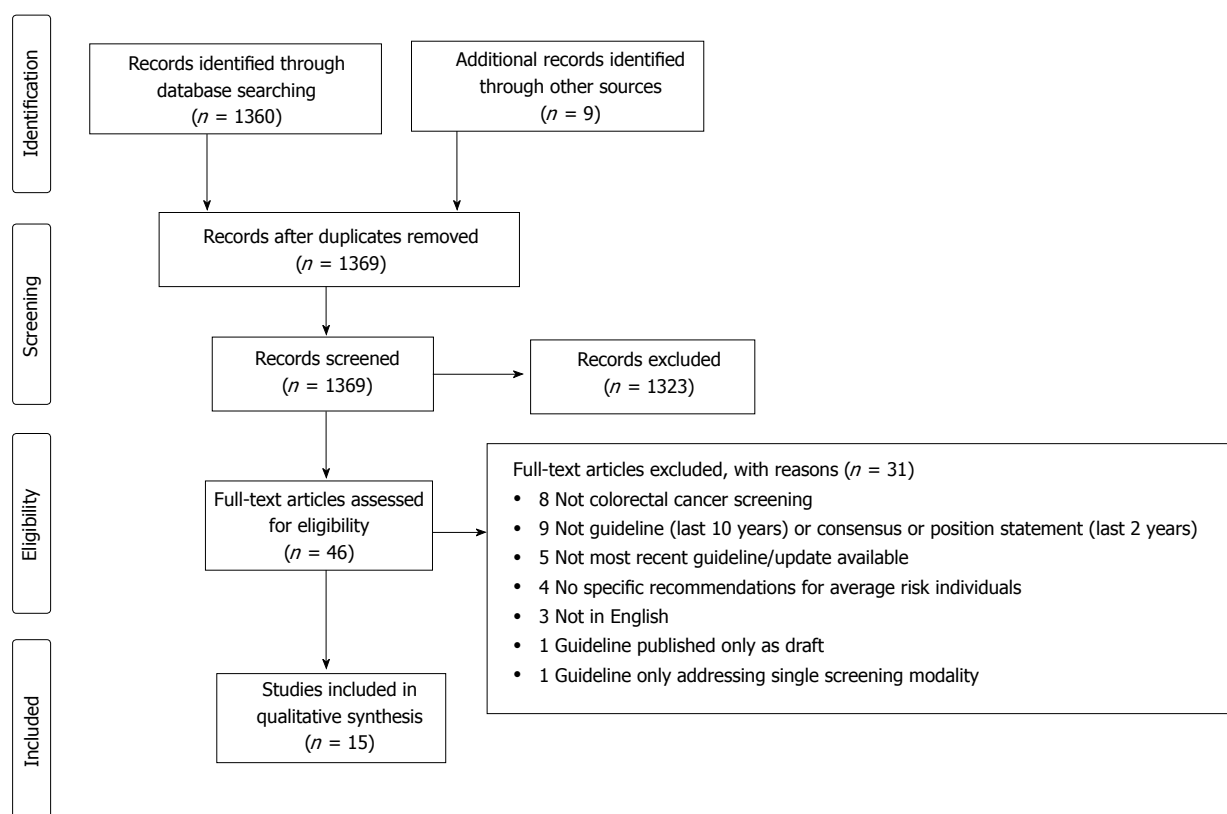


Figure 1 Prisma diagram.

moderate-quality evidence)^[12]. Individuals aged 50 to 59 can get screened, using the same modalities (weak recommendation, moderate-quality evidence), however the benefit-harm ratio might be less favorable in this age group. According to CTFPHC, individuals between ages 50 and 59 can decide to defer screening until 60. Hence personal concerns and preferences should be discussed. Screening individuals beyond 75 is not recommended (weak recommendation, low-quality evidence), based on the absence of randomized controlled trials (RCTs) showing a reduction in CRC mortality and morbidity in this age group. The CTFPHC recommends against colonoscopy for screening (weak recommendation; low-quality evidence), based on the lack of high-quality evidence proving its efficacy when compared to other screening tests. Indeed, even if colonoscopy might provide benefits that are equivalent or greater to those obtained with FS, it requires a greater amount of resources and carries an increased risk of complications. However, if an individual prefers undergoing a colonoscopy, it can be considered^[12].

National Comprehensive Cancer Network - (NCCN Guidelines, 2017): The working group suggests screening average-risk individuals starting at age 50. For individuals aged 76 to 85, screening is recommended as an individual decision, depending on overall health status and comorbidities in these individuals. Subjects in this age category who most

likely benefit from screening are those who have not had a prior screening test. No preferred screening test is recommended, but different options are suggested, all are recognized as appropriate, however, some are based on high-level evidence, and identified as category 1, while others are recommended based on low-level evidence (category 2A; Table 1). Screening recommendations include colonoscopy every 10 years (category 2A), annual high sensitivity gFOBT (category 1) or FIT (category 2A), sDNA test every 3 years (category 2A), FS every 5 to 10 years (category 1), FS every 5 to 10 years combined with gFOBT/FIT at year 3 (category 2A), and CT colonography every 5 years (category 2A)^[15]. These guidelines also mention that FIT is more sensitive than gFOBT.

United States Multi-Society Task Force of Colorectal Cancer Guidelines (2017): The working group of experts, representing the American College of Gastroenterology, the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy, recommends screening average-risk individuals starting at age 50 (strong recommendation; high-quality evidence), except for African Americans, in which screening should start at age 45 (weak recommendation; very-low-quality evidence)^[21]. Screening should be interrupted at age 75 in individuals with negative prior screening or when life expectancy does not exceed 10 years (weak recommendation; low-

Table 1 Summarized recommendations for colorectal cancer screening in average-risk individuals, published in North America between 2007 and 2017

Continent	Country/association	Publication year	Age	Screening tests recommended	Recommendation	Note
North America	United States: ACG	2009	≥ 50	Preferred prevention test: Colonoscopy (10 yr). If not possible or refused by individual: FS (5-10 yr) - OR CTC (5 yr) OR detection test	Grade 1B except for FS (2B) and CTC (1C)	Screening starting at age 45 for African American population
				Preferred detection test: FIT (1 yr). If not possible: Annual gFOBT (Hemoccult Sensa) OR- Fecal DNA testing (3 yr) High sensitivity FOBT/FIT (1 year) OR FS (5 years) OR FOBT/FIT (3 yr) + FS (5 yr) OR colonoscopy (10 yr)	FIT : Grade 1B	
	United States: ACP	2015	50-75	Screening not recommended	-	
				≥ 75 and individuals whose life expectancy is estimated to less than 10 years	-	
	United States: USFSTF	2016	50-75	gFOBT/FIT (1 yr) OR FIT-DNA (1-3 yr) OR FS (10 yr) + FIT (1year) OR FS (5 yr) OR colonoscopy (10 yr) OR CT-colonoscopy (5 yr)	Grade A recommendation	
				Screening is considered an individual decision,	Grade C recommendation	
	Canada: CTFPHC	2016	50-59	gFOBT/FIT (2 yr) OR FS (10 yr) OR defer until age 60	Weak recommendation; moderate-quality evidence	Colonoscopy not recommended for screening (weak recommendation; low-quality evidence), but could be discussed
				gFOBT/FIT (2 years) OR FS (10 yr)	Strong recommendation; moderate-quality evidence	
	United States: NCCN	2017	≥ 75	Screening not recommended, but can be discussed	Weak recommendation; low-quality evidence	FIT is identified as more sensitive than gFOBT
				Colonoscopy (10 years) OR gFOBT/FIT (1 yr) OR Fecal DNA test (3 yr) OR FS (5-10 yr) (+/- gFOBT/FIT at year 3) OR CTC (5 yr)	Category 2A except for annual gFOBT and FS every 5-10 years (which are category 1)	
United States: US Multi-Society Task Force of Colorectal Cancer	2017	76-85	50-75	Screening should be an individual decision, can be discussed	Strong recommendation; moderate-quality evidence	Screening for African American starting at age 45 (weak recommendation; very-low-quality evidence)
				First-tier (preferred tests): Annual FIT OR colonoscopy (10 yr)	CTC and FIT-DNA : Strong recommendation; low-quality evidence	
				Second-tier: CTC (5 yr) OR FIT-fecal DNA testing (3 yr) OR FS (5-10 yr)	FS: Strong recommendation; high-quality evidence	
				Third-tier: Capsule colonoscopy (5 yr)	Weak recommendation; low-quality evidence	
			76-85	Screening should be considered for individuals without prior screening	Weak recommendation; low-quality evidence	

CRC: Colorectal cancer; FS: Flexible sigmoidoscopy; DCBE: Double contrast barium enema; CTC: CT colonography, FOBT: Fecal occult blood test; gFOBT: Guaiac-based fecal occult blood test; FIT: Fecal immunochemical test.

Table 2 Summarized recommendations for colorectal cancer screening in average-risk individuals, published in Europe between 2007 and 2017

Continent	Country/Association	Year	Age	Screening tests recommended	Recommendation	Note
Europe	Scotland: TIS	2011 (revised in 2016)	Age not mentioned	FIT (quantitative) (interval not mentioned)	Grade A recommendation	Performance of FS unsure in the Scottish population. Colonoscopy and CT colonography are not recommended
	Germany: GGPO	2014	≥ 50	Preferred test: Colonoscopy (10 yr) If refused by individual: FS (5 yr) + annual FOBT OR Annual FOBT	Colonoscopy: Grade B recommendation; 3b level of evidence. FS: Grade B recommendation; 2b level of evidence. Adding FOBT to FS: Grade B recommendation; 3b level of evidence. FOBT as a screening test: Good clinical practice	General use of FIT is not recommended, but FIT can be used instead of gFOBT if it has a proven high specificity (> 90%) and sensitivity. Genetic stool tests, CT colonography, MR-colonography and capsule endoscopy are not recommended.
	Spain: SEOM	2014	50-74	FIT every 2 yr OR, depending on available resources, annual or biennial gFOBT OR FS (5 yr) OR colonoscopy (every 10 yr)	Grade B (moderate) quality of evidence, except for FOBT every 2 yr (grade A quality of evidence)	Combination of gFOBT and FS, and CT colonography are not recommended
	European Guidelines	2013	50-74	Recommended test: gFOBT/FIT (1-2 yr) Other options include colonoscopy (10-20 yr) OR FS (10-20 yr)	Recommendation based on good evidence for gFOBT, reasonable evidence for FIT and FS, and limited evidence for colonoscopy	Evidence supports FIT superiority compared to gFOBT

CRC: Colorectal cancer; FS: Flexible sigmoidoscopy; FOBT: Fecal occult blood test; gFOBT: Guaiac-based fecal occult blood test; FIT: Fecal immunochemical test.

quality evidence). However, individuals without prior screening could still benefit from screening and therefore could undergo screening until age 85, depending on their age and comorbidities (weak recommendation; low-quality evidence). The panel ranked screening tests in 3 tiers based on performance, costs and practical considerations. Colonoscopy every 10 years and annual FIT are ranked as first-tier and therefore are recommended as preferred tests (strong recommendation; moderate-quality evidence). CT colonography every 5 years, FIT-DNA test every 3 years (both strong recommendation; low-quality evidence) and FS every 5 to 10 years (strong recommendation; high-quality evidence) are ranked as second-tier tests. Capsule colonoscopy every 5 years, however, is ranked as a third-tier test (weak recommendation; low-quality evidence)^[21].

Europe

Four different European guidelines were included in this review. A summary of recommendations and adopted methodology for rating of evidence are shown in Table 2.

European Colorectal Cancer Screening Guidelines Working Group (2013): The European Colorectal Cancer Screening Guidelines Working Group (working group of experts) recommends screening individuals between ages 50 and 74^[22,23]. FOBT is mentioned as the only screening method approved throughout the European Union (EU). The guideline mainly provides information on how to set up screening programs of great quality, using the most commonly used modalities in Europe, which are FOBT, FS and colonoscopy^[22,23]. As for stool-based tests, gFOBT and FIT are recognized as effective, but it is suggested that quantitative FIT is superior in terms of specificity and sensitivity and is recommended over gFOBT. FOBTs should be repeated on an annual or biennial basis or, at the very least every three years if FIT is used^[22]. The guidelines highlight the lack of high quality evidence assessing colonoscopy. However, according to the authors, current evidence support 10 year surveillance if colonoscopy is used, suggesting that interval extension to 20 years might be appropriate^[22]. FS is discussed as potential screening test, but no screening interval is clearly defined; the authors suggest using the same interval as for colonoscopy screening^[22]. FOBT with FS, CT colonography, stool DNA testing and capsule endoscopy are not recommended^[22].

German Guideline Program in Oncology (2014): The German Guideline Program in Oncology (GGPO), a working group of experts, recommends screening starting at age 50^[24]. The GGPO does not establish an upper age screening limit, citing a lack of studies concerning benefit to risk ratio in older individuals. The decision

should be based on a subject's health with associated comorbidities. Here too, the guideline distinguishes cancer prevention (colonoscopy, sigmoidoscopy, CT-colonography, capsule endoscopy) from cancer detection (FOBT, genetic stool tests) tests. Colonoscopy is recommended as gold standard, and should be repeated every 10 years (grade B recommendation; 3b level of evidence). Based on indirect evidence, colonoscopy is recommended as the most specific and sensitive screening test for the detection of cancer and adenomas. If an individual refuses colonoscopy, FS should be offered every 5 years (grade B recommendation; 2b level of evidence), combined to an annual FOBT for assessment of the proximal colon (grade B recommendation; 3b level of evidence). Because a positive FOBT needs to be followed up with a complete colonoscopy, any annual FOBT should be completed before the associated FS in order to avoid unnecessary FS. FOBT alone is recognized as an effective screening test, and should be repeated annually rather than once every two years (1b level of evidence) in individuals refusing colonoscopy (this recommendation is identified as good clinical practice). There exist a variety of FIT modalities offered in Germany with greatly varying specificities and sensitivities, making it difficult to favor FIT as a blanket statement over gFOBT. However, a given FIT test could replace gFOBT if its given specificity has been shown to be greater than 90%, while also exhibiting a high sensitivity (grade 0 recommendation; 3a level of evidence). Genetic stool tests were not recommended for CRC screening, because of insufficient data (grade B recommendation; respectively 3b and 4 levels of evidence). Radiologic screening modalities such as CT- and MR-colonography were not recommended, but could be used in case of an incomplete colonoscopy in an individual requesting a complete colon examination (grade B recommendation; 3b level of evidence)^[24].

Spanish Society of Medical Oncology (SEOM, 2014): The Spanish Society of Medical Oncology recommends screening for average-risk individuals between ages 50 and 74. Biennial FOBT is recommended based on high-quality evidence (grade A) with FIT considered as the preferred test. As alternative to FIT, annual or biennial high-sensitivity gFOBT, FS repeated every 5 years or colonoscopy repeated every 10 years can be used (grade B quality of evidence). Based on moderate-quality evidence (grade B), the SEOM recommends against using a combination of FS and gFOBT. It also recommends against the use of CT colonography until sufficient data become available (grade B quality of evidence)^[25].

Scottish Intercollegiate Guidelines Network (Healthcare Improvement Scotland, 2016): According to the Scottish Intercollegiate Guidelines Network the most appropriate tool for population

screening is a quantitative FIT (grade A recommendation). Although no specific fecal hemoglobin concentration cut-off is identified, the working group suggests using a cut-off value that is higher than the sensitivity of gFOBT. The guidelines state FS has been proven to be an efficacious screening test, perhaps more so than FIT, but its effectiveness is unproven if offered to the Scottish population and it is therefore not recommended; neither are colonoscopy nor CT colonography^[14]. The guideline does not specify an age range nor surveillance intervals following a negative FIT.

Asia

Four different Asian guidelines were included in this systematic review. Guideline recommendations from Asia and methodology for rating of evidence are summarized in Table 3.

Korean Guidelines for Colorectal Cancer Screening and Polyp Detection (2012):

The Korean Multi-Society Task Force recommends screening for average-risk individuals starting at age 50 (strong recommendation; low-quality evidence)^[26]. No upper age limit is identified. Colonoscopy is the preferred screening test (strong recommendation; low-quality evidence), and should be repeated every 5 years (weak recommendation; very low-quality evidence). FOBT is another recommended option (strong recommendation; moderate-quality evidence), but FIT should be used rather than gFOBT because of higher specificity, convenience and compliance (strong recommendation; low-quality evidence). Other screening tests such as CT colonography (strong recommendation; low-quality evidence) and DCBE (weak recommendation; low-quality evidence) are also identified as possible options. The efficacy of FS is recognized, and FS is listed as a potential screening test, but the consensus document states this modality is not commonly employed in Korea since it does not investigate the entire colon, and must be followed by a colonoscopy if positive; the guideline also states that, in Korea, individuals and physicians often prefer colonoscopy^[26].

Chinese Society of Gastroenterology (2014):

Given its large national population and attendant resources utilization issues, the Chinese Society of Gastroenterology consensus does not recommend colonoscopy or FS as first line screening test for average-risk individuals. The guidelines suggest that individuals between ages 50 and 74 undergo FOBT and that a questionnaire be used to identify high-risk factors. The immunoassay FOBT should be preferred over a chemical FOBT, however, the guidelines also suggest gFOBT followed by FIT can be used. Individuals should undergo colonoscopy if they meet any one of the five following conditions: (1) positive FOBT; (2) history of CRC in first-degree relatives; (3) personal history of intestinal adenomas; (4) personal history

Table 3 Summarized recommendations for colorectal cancer screening in average risk individuals, published in Asia between 2007 and 2017

Continent	Country/region	Year	Age	Screening tests recommended	Recommendation	Note
Asia	South Korea	2012	≥ 50	Colonoscopy (at least 5 years) is the priority OR FOBT (FIT) OR CTC OR DCBE	Colonoscopy (strong recommendation; low-quality evidence) with 5-year interval (weak recommendation; very low-quality evidence). FOBT (strong recommendation; moderate-quality evidence). CTC (strong recommendation; low-quality evidence). DCBE (weak recommendation; low-quality evidence)	FS efficacy is recognized, but FS not widely used because it doesn't explore entire colon, might need a colonoscopy after, and FS less preferred by individuals and physicians
	China	2014	50-74	FOBT (chemical FOBT or FIT) + Questionnaire every 3 yr	A for FIT; A for FS; B for colonoscopy	FIT is preferred over gFOBT
	Asia Pacific	2015	50-75	FIT (preferred choice) OR FS OR colonoscopy (intervals not mentioned)		
	Saudi Arabia	2015	45-69	Colonoscopy (10 yr) is the recommended modality; if not possible: FS (5 yr) + FIT / gFOBT (1 yr) OR FS (3 yr)	Colonoscopy: Strong recommendation; low-quality evidence. FS: Strong recommendation; moderate-quality evidence.	FIT is preferred over gFOBT. FOBT used alone is not recommended, but could be used depending on availability of other modalities.
			≥ 70	Screening not recommended	Conditional recommendation; low-quality evidence	Screening for people over 70 could be beneficial in certain cases (depending on health status)

CRC: Colorectal cancer; FS: Flexible sigmoidoscopy; DCBE: Double contrast barium enema; CTC: CT colonography; FOBT: Fecal occult blood test; gFOBT: Guaiac-based fecal occult blood test; FIT: Fecal immunochemical test.

of cancer; and (5) or if meeting two of the six following criteria: history of chronic diarrhea, chronic constipation, bloody mucus, chronic appendicitis or appendectomy, chronic cholecystitis or cholecystectomy, or a long-term mental depression. If colonoscopy is not available FS is recommended. Screening should be repeated every 3 years^[27].

The updated Asia Pacific Consensus Recommendations on colorectal cancer screening (2015): The Asia Pacific Working Group recommends screening average-risk individuals between 50 and 75 (grade B recommendation; II-2 quality of evidence)^[28]. Utilization of a stool-based test is recommended (grade A recommendation; I quality of evidence). Quantitative FIT should be used over gFOBT (grade A recommendation; I quality of evidence), because of its higher sensitivity, specificity and individual adherence. FS is considered appropriate for screening (grade A recommendation; I quality of evidence), as is colonoscopy (grade B recommendation; II-2 quality of evidence). Colonoscopy is considered the gold standard among endoscopic modalities. However, considering resource-limitations for population based screening, the consensus recommendations state that using FIT is the preferred choice for average risk screening and colonoscopy resources should be used for screening of high risk individuals. With regards to surveillance intervals, the guidelines review the literature supporting 1-2 years for FIT, and 10 years for colonoscopy based on previous studies or other guidelines, however, the guideline itself does not provide specific recommendations. CT colonography and capsule endoscopy are not recommended but mentioned as appropriate for individuals in whom colonoscopy is not possible (grade B recommendation; II-1 and II-2 quality of evidence, respectively)^[28].

National Guidelines for Colorectal Cancer Screening in Saudi Arabia (2015): The national Saudi guidelines published by a working group of experts recommend screening for CRC in average-risk individuals starting at age 45, based on a median national age of CRC diagnosis of 55 for women and 60 for men^[29]. Screening individuals aged 70 or more is not recommended (conditional recommendation; low-quality evidence) because of the risks of complications. However, it is mentioned that certain individuals could benefit from screening after age 70, if they have no comorbidities and an expected life expectancy of 10 years or more. The preferred modality in this guideline is colonoscopy, repeated every 10 years (strong recommendation; low-quality evidence). Use of colonoscopy is preferred over FS (conditional recommendation; low-quality evidence), since it examines the full colon, and has to be less frequently repeated. However, the guidelines also recommend FS, repeated

Table 4 Recommended test in terms of available resources according to World Gastroenterology Organization's colorectal cancer screening cascade

Level of recommendation	Recommended screening test
1	Colonoscopy every 10 yr
2	Colonoscopy, once in a lifetime
3	FS every 5 yr, followed by a colonoscopy if FS was positive
4	FS, once in a lifetime, followed by a colonoscopy if FS was positive
5	FS, once in a lifetime, followed by a colonoscopy only if advanced neoplasia is detected
6	Fecal blood test annually, followed, if positive, by a colonoscopy or barium enema (depending on colonoscopy's availability)

FS: Flexible sigmoidoscopy.

every 3 years, as alternative (strong recommendation; moderate-quality evidence). This test is considered more feasible than colonoscopy, but less favored in Saudi Arabia. FS is preferred over gFOBT for screening average-risk individuals (conditional recommendation; very low-quality evidence). This guideline does not recommend stool-based tests if used alone, but these can be offered depending on the availability of other modalities. Nonetheless, the possibility of combining an annual stool-based test with FS, repeated every 5 years, is recommended to maximize screening benefits. The superiority of FIT over gFOBT is also mentioned^[29].

World Gastroenterology Organization (WGO, 2007)

The WGO issued a CRC screening cascade with recommendations based on resource availability. Six different levels, ranging from 1 (best resource availability) to 6 (minimal resource availability), are detailed. All recommendations apply to average-risk individuals 50 years or older (Table 4). No upper age limit is identified. CT colonography and DNA testing are not included in the cascade, but they are mentioned as alternate modalities if an individual refuses to undergo other recommended tests^[30].

DISCUSSION

The vast majority of guidelines recommend starting CRC screening for average-risk individuals at age 50. This is based on the steep increase of CRC beginning around age 50. In 2009, 90% of worldwide CRC were diagnosed in individuals aged 50 or more^[31]. A comparative effectiveness modeling completed by the USPSTF showed that starting screening at age 45 instead of 50 in average-risk population could result in a modest increase of life-years gained, but also in an increase in the lifetime number of colonoscopies, worsening the burden of screening for individuals^[13]. The CTFPHC guidelines (Canada) suggest starting screening at age 50, while allowing to defer screening until age 60^[12]. Several European programs start screening around age 60, which is justified by the higher prevalence of CRC after this age^[32,33]. In fact, the majority of CRC cases in United States are diagnosed between 65 to 74 years^[34]. However, African Americans

have a higher prevalence of CRC and consequently the ACG recommends screening for African American individuals to start at age 45^[35]. Interestingly, Saudi Arabia, also recommends starting to screen at age 45 because the median age at time of CRC diagnosis is 55 in Saudi women and 60 in Saudi men^[29], as compared to 70 in Canada^[36] and 68 in United States^[34].

Ten of fifteen guidelines identified recommend an upper age screening threshold varying from age 70 to 75, based on associated harms potentially exceeding benefits if screening is continued after that point^[37]. Nonetheless, as screening might still be beneficial in selected elderly individuals, the decision to stop screening should be individualized^[12,13,29]. The pertinence of setting 75 as the maximal screening age, instead of a higher threshold fixed at 85 years old, has been demonstrated by Zauber *et al.*^[38] in 2008. The study showed that reducing the upper age limit from 85 to 75 leads to small decreases in life-years gained, but also results in a great reduction of colonoscopy use, making age 75 likely to be more beneficial in a population based screening environment.

As for screening modalities, all guidelines have considered gFOBT, FIT, FS and colonoscopy as mainstays of CRC screening. However, there exist discrepancies with regards to which test(s) should be preferred. FOBTs are widely used, being recommended either as preferred test or not based on whether the context is that of population-based screening or an area with limited endoscopy resources. Even though RCTs have clearly demonstrated the efficacy of gFOBT with such evidence lacking for FIT, several guidelines suggest FIT is superior to gFOBT because of its greater specificity and sensitivity^[39]. FIT is also associated with improved adherence^[40], and does not require dietary restrictions. Stool-based tests are recommended on an annual or biennial basis^[9]. As annual FOBT has been shown to decrease CRC-related mortality^[8] and increase the number of life-years gained compared to biennial FOBT^[38], the majority of guidelines suggest 1-2 year intervals for FOBT screening. Optimal diagnostic FIT threshold levels of positivity remain an area of uncertainty that has not been directly discussed with guideline recommendations.

Major disparities throughout the different guidelines

can be found relating to the use of endoscopy. While colonoscopy is often referred to as the gold standard, and is suggested as preferred screening test by many guidelines, others recommend FS based on available higher quality evidence. This area of controversy is best illustrated by the CTFPHC recommendations (Canada) on CRC screening. Authors conclude that the available evidence supports using guaiac fecal occult blood testing (gFOBT) and flexible sigmoidoscopy for CRC screening because these modalities have been shown to reduce mortality while such evidence does not exist for colonoscopy, and therefore recommend against using colonoscopy as a screening test. This recommendation is graded as a weak one, which means that a majority of people would not want colonoscopy, but many would^[12]. It is interesting to notice that current literature was interpreted differently by other guidelines, such as USPSTF's, which strongly recommended colonoscopy, based on moderate-quality evidence^[21]. What is even more interesting is that both CTFPHC and USPSTF used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, but ended up drawing different conclusions^[12,21]. This might be explained by USPSTF's more flexible approach: the working group used a modified qualitative approach based on a review of the literature, but did not include a meta-analysis (which is usually included in GRADE system)^[21]. In CTFPHC's case, using a rigid approach led to recommending FS over colonoscopy, but it is unlikely that such a recommendation would change current screening practice, which include colonoscopies on a regular basis, even if high-quality evidence is not currently available. Appropriate colonoscopy studies addressing this lack have been initiated and should be completed between 2021 and 2036^[41-46]. In the meantime, other guidelines recommend colonoscopy based on case-control and prospective cohort studies that suggest it results in a reduction in CRC-related mortality ranging from 65% to 88%^[7,47-49]. The screening interval following a negative colonoscopy is usually set at 10 years, based on the natural history of progression of adenomas into carcinomas^[50,51]. In the case of FS, suggested screening intervals vary from 3 to 10 years; more evidence is required to determine optimal screening intervals, especially after colonoscopy and RCTs addressing this important area of uncertainty are underway^[52]. Guidelines published by the ACP, NCCN, USPSTF, Saudi Arabia and GGPO all suggest the possibility of combining FOBT and FS^[13,15,20,24,29]. Adding FIT to FS increases sensitivity for detecting proximal invasive cancer, while also providing a 10% increase in higher sensitivity for advanced distal neoplasia. Combining both tests generates better results than using either test alone^[53]. Screening intervals for such combination have not been established, but combining the intervals used for FS (5 years) with an additional FIT every 1-2 years seems reasonable.

Individual's adherence to a screening modality is an important factor when it comes to efficient CRC screening, hence the importance to select a test that makes it easy for a patient to adhere. Less invasive procedures are usually more accepted by individuals than more invasive procedures, and therefore, higher participation rates can be noted. Studies have shown that higher adherence rates were obtained with gFOBT, FIT^[54] and FS when compared to colonoscopy^[55] and CT colonography^[56] (see Table 5). There is evidence that FIT is more accepted than gFOBT because it only requires one stool sample and no dietary restrictions^[40,57]. Participation rates for FS were equal to participation rates for FIT in a study^[55], while they were lower than the latter according to another^[56]. An article published in 2012 documented that the most frequently cited reason to decline colonoscopy was unpleasantness of the examination, whilst the most frequent reasons to decline CT colonoscopy were "no time/too much effort" and lack of symptoms^[58]. Less invasive and less time-consuming procedures such as gFOBT and FIT could therefore be more easily accepted by individuals.

When it comes to cost-effectiveness, gFOBT, FIT, FS, colonoscopy, sDNA and CT colonography are all cost-effective in comparison to no screening^[59]. Prices differ between tests, gFOBT and FIT being the two most affordable ones, with costs ranging from 5 to 23 USD and 23 to 25 USD, respectively^[60,61] (see Table 5). However, a lower cost per test is not necessarily associated with higher cost-effectiveness. Even though colonoscopy is currently one of the most expensive screening test available, Patel and Kilgore showed that colonoscopy every 10 years was cost-effective when compared to annual FOBT or FS every 5 years. A combination of FS every 5 years and annual FOBT was also better than either test alone^[59].

All recommendations considered, there appears to be no single "best" CRC screening test for an average risk individual. The preferred modalities include FOBT, FS or colonoscopy and the appropriate choice should be based on local resource availability and individual willingness to undergo and adhere to the chosen test and surveillance requirements. The WGO created a screening cascade with six levels of recommendations, graded according to available resources (Table 4)^[30]. The first level constitutes the "best-case scenario" (if all resources are available), while the last one would be the "worst-case scenario" (with very limited resources). The USPSTF also ranked screening methods in three tiers, depending on performance, costs and practical considerations^[21]. Such ranking is useful in clinical practice compared to a menu of options where no clear indication is given about which test should be prioritized. A screening cascade or ranking can therefore guide the physician while allowing a certain flexibility when it comes to choosing a screening test. Guidelines from USPSTF and CTFPHC^[12,13], emphasize

Table 5 Screening tests characteristics

Screening test	Specificity/sensitivity for advanced adenoma detection (%)	Specificity/sensitivity for CRC detection (%)	Price (USD)	Participation rates after first-time invitation (%) ^[56]	Decreased mortality for CRC (%)	Risk of complications (%) ^[63]
gFOBT	95.4/8.6 ^[64]	97.7/23.8 ^[9]	5 ^[61] , 23 ^[61]	47	14 ^[65] , 32 ^[7]	0
FIT	96.8-97.4/20.3-25.7 ^[64]	94.0/79.0 ^[66]	23 ^[60] , 25 ^[61]	42	59 ^[65]	0
FS	87.0/95.0 ^[67]		169 ^[60] , 238 ^[61]	35	33 ^[65] - 50 ^[10]	Perforation: 0.01 Major bleeds: 0.02
Colonoscopy	91.3/92.9 (for adenomas > 10 mm) ^[68]	100.0/91.2 ^[68]	645 ^[60] , 803 ^[61]	28	61 ^[65] - 65 ^[48]	Perforation: 0.04 Major bleeds: 0.08
sDNA test	89.8 [†] /42.4 ^[69]	89.8 [†] /92.3 ^[69]	150 ^[61]	NR	NR	0
CTC	87.3/91.2 (for adenomas > 10 mm) ^[68]	99.0/96.8 ^[68]	570 ^[60]	22	NR	Perforation: Less than 0.02

[†]Specificity was not defined separately for advanced adenoma detection and colorectal cancer detection. CRC: Colorectal cancer; gFOBT: Guaiac fecal occult blood test; FIT: Fecal immunochemical test; FS: Flexible sigmoidoscopy; sDNA test: Stool DNA test; CTC: CT colonography; NR: Not reported.

that individual screening preferences should be considered to optimize screening uptake^[62] - i.e.: any screening test is better than none.

Only guidelines published in English were included, resulting in an over-representation of North American recommendations compared to other continents, and potentially limiting the generalizability for any true global overview. Interestingly, there are also a number of English speaking countries that are not represented in this review because their guidelines did not include recommendations for average-risk individuals (such as the British^[17] and the New Zealand^[18] guidelines) or issued only combined recommendations for average and moderate-risk individuals (such as the Gastroenterological Society of Australia's guidelines^[16]) or are at an incomplete publication stage. i.e., with the Australian Government NHMRC guidelines being currently under revision and not published as final version, no Australian guideline has been included in our review. It is also important to note that many of the reviewed guidelines adopted their own system to grade the strength of recommendation/evidence, limiting a more direct comparison.

In conclusion, average-risk individuals aged 50 to 75 should undergo CRC screening. Screening for individuals below 50 and above 75 should be individualized, but it is important to consider stopping screening at a certain age. Colonoscopy (every 10 years), FS (every 5 years) and annual or biennial FOBT are the most common recommended modalities for CRC screening. The superiority of FIT when compared to gFOBT has been established with regards to test performance characteristics, while a combination of FIT and FS has been associated with better results than either test alone. Despite the current absence of RCT data, colonoscopy is considered the preferred screening modality in many CRC guidelines. Ideal screening intervals remain an area of uncertainty and is currently under investigation in RCTs. Finally, resource availability and individual preferences should be considered when choosing the most appropriate screening intervention to improve the uptake of and optimize the real-life effectiveness of CRC screening.

ARTICLE HIGHLIGHTS

Research background

Screening has shown to decrease colorectal cancer (CRC) incidence and mortality. Different screening guidelines for average-risk individuals have been issued worldwide, and several guidelines were published or updated recently. To our knowledge, this is the first systematic review aiming to summarize and compare worldwide CRC screening recommendations.

Research motivation

CRC screening recommendations for average-risk individuals differ greatly from one guideline to another, especially when it comes to choosing a preferred screening test. We aimed to compare those recommendations in order to highlight areas of uncertainty, and therefore orient future research by underlining areas where evidence is still lacking.

Research objectives

The main objectives were to compare screening recommendations in order to highlight common ground between guidelines, but also point out discrepancies caused by lack of high-quality evidence, making it easier to orient future research.

Knowing which recommendations should clearly be perpetuated and which ones need further investigation can be helpful when it comes to updating guidelines or publishing new ones.

Research methods

A systematic review of the literature was completed to identify all CRC screening guidelines for average-risk individuals published in English in the last ten years and/or position statements published in the last two years. Articles describing an established screening program without issuing recommendations, or articles only reviewing existing guidelines were excluded. Guidelines providing combined recommendations for average-risk and moderate/high-risk individuals, addressing only screening for moderate/high-risk individuals or older versions of existing guidelines were also excluded.

Research results

Fifteen guidelines were included, six of which were published in North America, four in Europe, four in Asia and one by the World Gastroenterology Organization (WGO). A majority of guidelines recommend screening average-risk individuals between ages 50 and 75. Preferred screening methods include colonoscopy (every 10 years), flexible sigmoidoscopy (FS - every 5 years), guaiac-based fecal occult blood test (gFOBT) or fecal immunochemical test (FIT), both repeated annually or biennially. FIT is often recommended over gFOBT, and combining FS with a stool based test is an option that should be considered. The role of colonoscopy varies greatly from one guideline to another, as some identify it as the screening gold standard whilst others highlight the lack of high-quality evidence supporting its use. Screening intervals as well as rank order between tests are also areas of uncertainty.

Research conclusions

Average-risk individuals should undergo CRC screening between ages 50 and 75. Colonoscopy, FS, gFOBT and FIT are recognized as cost-efficient and currently recommended in a majority of guidelines, however their respective role and rank are not clearly established. Local resources availability and patient preferences should be considered when implementing a screening program, in order to maximize screening uptake, as any screening is better than none.

Research perspectives

Establishing a clear ranking of screening methods rather than simply offering a menu of options could be useful in clinical practice. Future research should aim to provide high-quality evidence demonstrating screening tests efficiency, especially colonoscopy, in order to facilitate comparison between tests and help establishing such ranking. Screening intervals should be further investigated.

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