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REVIEW

Disparities in Recommendations for Colorectal Cancer Screening Among Average-Risk Individuals: An Ecobiosocial Approach

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Abstract: Regardless of the high global burden of colorectal cancer (CRC), the uptake of CRC screening varies across countries. This systematic review aimed to provide a picture of the disparities in recommendations for CRC screening in average-risk individuals using an ecobiosocial approach. It was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was conducted through Scopus, Web of Science, PubMed, and EBSCOHost. Full-text guidelines which were published between 2011 and 2021, along with guidelines which provided recommendations on CRC screening in average-risk individuals, were included in the review. However, guidelines focusing only on a single screening modality were excluded. Fourteen guidelines fulfilling the eligibility criteria were retained for the final review and analysis. Quality assessment of each guideline was performed using the AGREE II instrument. Disparities in guidelines identified in this review were classified into ecological (screening modalities and strategies), biological (recommended age, gender and ethnicities), and social (smoking history, socioeconomic status, and behavior) factors. In general, unstandardized practices in CRC screening for average-risk individuals are likely attributable to the inconsistent and non-specific recommendations in the literature. This review calls on stakeholders and policymakers to review the existing colorectal cancer screening practices and pursue standardization.

Keywords: colorectal cancer, screening, guidelines, ecology, biology, social, disparities

Introduction

Colorectal cancer (CRC) is the second leading cause of death in the cancer population worldwide. The age-standardized incidence rate of CRC in high-income countries is 29.0 per 100,000 population, four times higher compared with low- and middle-income countries with 7.4 per 100,000 population.[1] Nevertheless, the reported CRC mortality rates in high-income countries were 45%, which is generally lower than in low- and middle-income countries with 64%, possibly due to the availability of advanced treatment and screening services.[1–3] CRC also increasingly becomes a public health concern in countries with a middle to high human development index (HDI) following the adoption of a westernized lifestyle as the consequence of economic growth.[4,5]

While the CRC incidence of the elderly population shows a gradual decrease, the burden of CRC in the younger age groups is conversely on the rise.[5–7] Previous studies consistently demonstrated an uptrend in young-onset CRC over the past 20 years, particularly in high-HDI countries from North America and Oceania.[6,8–10] In the US alone, at least seven population-based studies based on different data sources ranging from surveillance to patient registries confirmed the increasing trend in the incidence of young-onset CRC between 2017 and 2021.[9,11–16] A recent multinational cohort study in Asia also identified a similar increasing trend in young-onset CRC, in line with the trend shown in other regions.[6] The alarming increase of young-onset CRC can be partly explained by the exemption from recommended screening besides

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the influence of sedentary lifestyle changes and westernized dietary patterns as traditionally studied by many among the older generation. Thus, future studies that explore the underlying factors related to young-onset CRC are recommended to better understand the progress of disease and preventive strategies.

However, the current uptake of CRC screening widely varies across countries, even among those with strong support from their health systems. The US reported that 67.3% of the adults aged between 50 and 75 turned up for CRC screening yearly.[17] On the other hand, the screening uptake in average-risk individuals was 39% lower among those living in rural areas and with a lower socioeconomic status, as reported in Australia.[18] Since the introduction of the national CRC screening program in 1992, Japan only achieved a screening uptake of 41.4% in men and 34.5% in women.[19] Similarly, approximately one-third of the average-risk individuals in Korea took up CRC screening despite the availability of national guidelines.[20] At the same time, other countries without a nationwide CRC screening program in the Asia Pacific region reported a much lower CRC screening uptake, generally below 10%.[21] Overall, the global CRC screening uptake in average-risk individuals is only approximately 65%,[26] much lower than the 80% targeted by the US Preventive Task Force.[27]

In fact, screening has long been recognized as an effective primary preventive strategy to lower the incidence and mortality of CRC.[17,28,29] Whereas CRC screening is mainly recommended only for average-risk individuals, who are above 50 years of age,[22–24] the younger population has been relatively neglected. The health policy, capacity of the health system and public awareness are all likely to have a great impact on the uptake of CRC screening, particularly of the older age group.[23,25,28,30] These seem to arise as cross-cutting issues throughout the high-, middle-, and low-income countries.

Current literature has broadly classified the individual-level risk factors associated with CRC into modifiable and non-modifiable.[31,32] The expansion of studies on the ecological influence against carcinogenesis illustrates the extent to which the availability of a healthy environment, accessibility to healthcare facilities, and the existence of effective screening programs contributed to the CRC incidence.[28,33,34] Spatial studies demonstrated a possible link between neighborhood influence and geographic pattern of CRC distribution across different socioeconomic backgrounds.[35,36] The epidemiological characteristics of CRC incidence were leveraged in those aged above 50 years, family history of CRC, male preponderance, higher among Whites, and presence of comorbidities such as inflammatory bowel disease and type 2 diabetes, hence the priority for screening.[37] Notwithstanding that, social factors as determined by sedentary lifestyles, cigarette smoking, unhealthy dietary pattern, and poor health-seeking behavior, in the long term have an indirect contribution to the occurrence of CRC. The overlap between the ecological, biological and social factors emphasizes the complex interaction and equal need for intervention.

The introduction of the ecobiosocial concept in CRC research to address the interdependency between ecological, biological, and social factors can potentially produce strong evidence to guide future preventive and control management strategies.[38] While such a concept has long been adopted in the management of vector-borne diseases such as dengue,[39,40] its use in chronic non-communicable diseases is limited. In the context of CRC screening, the ecobiosocial concept could be valuable to help identify disparities in ecological factors, including screening modalities and strategies; biological factors, including in the recommended age, gender and ethnicity; and social factors, including smoking history, socioeconomic status, and health-seeking behaviors. As all these factors are important, equal attention must be given to them to ensure the success of a CRC screening program. Therefore, this review was performed to provide a picture of the ecological, biological, and social disparities in recommendations for CRC screening in average-risk individuals.

Materials and Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Adopting the PRISMA guidelines enabled the systematic retrieval of literature and synthesis of evidence.[41] A specific research question was formulated, followed by a systematic search, identification, screening, quality appraisal, and data extraction of the literature obtained from databases (Figure 1).

Formulation of the Research Question

The research question was built on the PICo concept that identifies the average-risk individuals (population), CRC screening guidelines (interest), and screening strategies (context). The PICo concept has been extensively used in the evidence-based medical research area for developing clinical questions.[42,43] The application of the PICo process

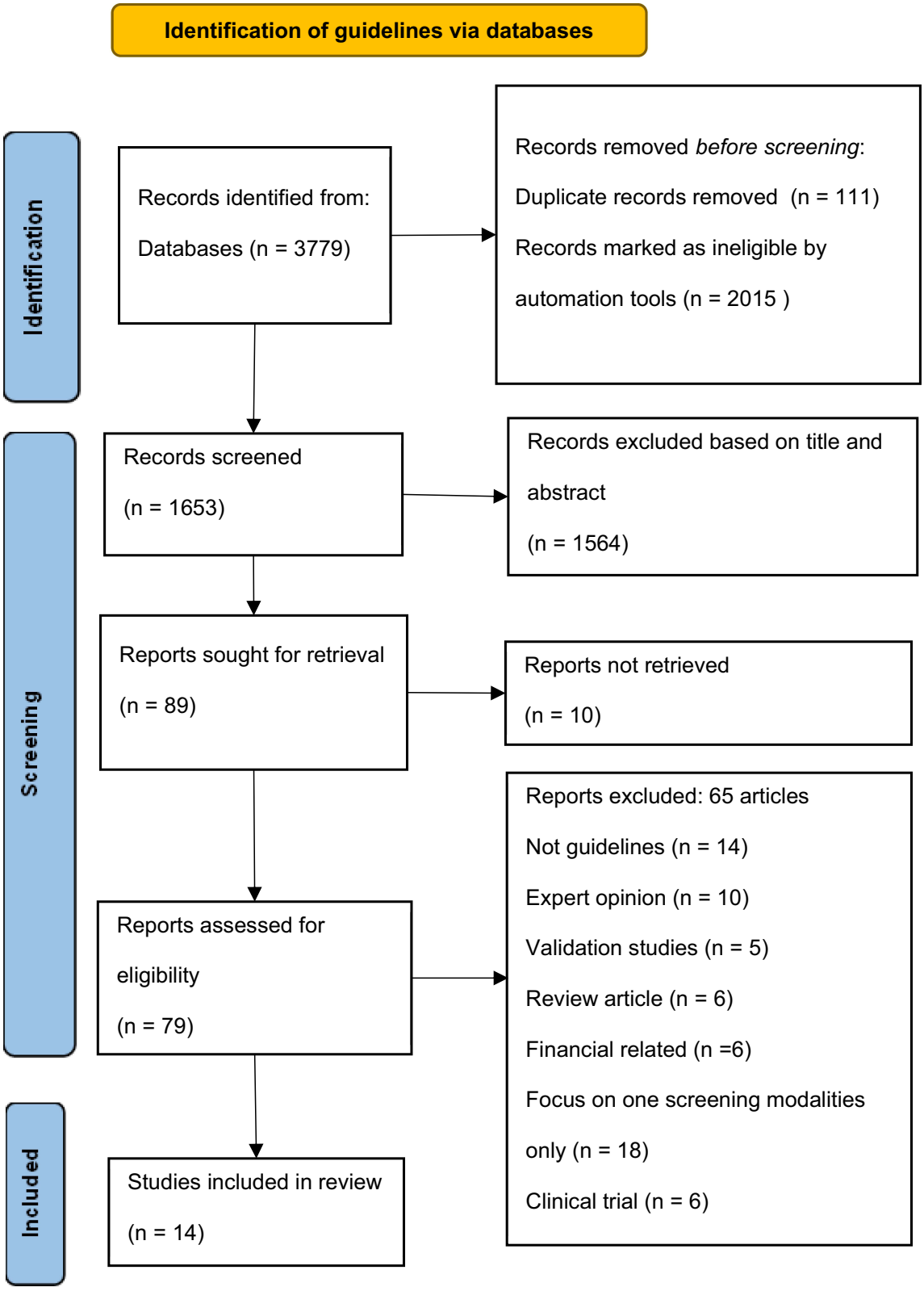

Figure 1 PRISMA flow diagram.
Notes: Adapted from: Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi:10.1136/bmj.n71.[41] Creative Commons Attribution (CC BY 4.0) license (http://creativecommons.org/licenses/by/4.0/).

facilitates well-built questions, a fundamental need in a thorough search of the scientific literature.[42] Based on the systematic process, the research question was framed as "How do disparities in guidelines affect CRC screening strategies for the average-risk individuals?".

Literature Search and Identification

The literature search started with deciding on the keywords. The search strings were created for each database, combined with the Boolean operators (Table 1). The literature search was performed between November 1–4, 2021 through four databases (Scopus, Web of Science, PubMed, and EBSCOHost) accessible to the authors, yielding 3779 records. A total of 111 duplicate records were found and removed. The records were then exported from the databases and organized using a Microsoft Excel sheet.

Screening

The title and abstract of each article were examined to evaluate their relevance. To be selected for the review, the articles must be (1) published between 2011 and 2021, (2) full original text, and (3) guidelines, recommendations by consensus, or position statements providing recommendations for CRC screening in average-risk individuals. Articles reporting on national CRC screening programs, focused only on single CRC screening modalities, and expert opinions were excluded from the review.

Eligibility

A total of 79 articles were retrieved for eligibility confirmation. All of them were thoroughly examined and the reason to exclude any of them was recorded. Sixty-five articles were excluded at this stage as they were either not in the form of guidelines (n = 14), expert opinions (n = 10), focusing only on a single screening modality (n = 18), review articles (n = 6), focusing on financial issues related to CRC screening (n = 6), community trials (n = 6), or studies on instrument validation (n = 5).

Quality Appraisal

The selected 14 guidelines went through the risk of bias assessment. The degrees of methodological rigor and transparency of the guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. AGREE II is a validated tool, which has been widely used to assess the methodological quality of guidelines.[44] It consists of 23 items, which are further categorized into six domains: scope and purpose, stakeholder involvement, the rigor of development, clarity of presentation, applicability, and editorial independence.

Table 1 Keyword Search Used in the Identification Process

Database	Search String
Scopus	TITLE-ABS-KEY ((“healthcare polic*” OR “health polic*” OR “health care polic*” OR “health guidelines” OR “guidelin*”) AND (“colorectal cancer*” OR “colorectal tumo*r*” OR “colorectal malignanc*” OR “colorectal neoplasia”) AND (“screening” OR “primary prevention” OR “early detection”))
Web of Science	TS= ((“healthcare polic*” OR “health polic*” OR “health care polic*” OR “health guidelines” OR “guidelin*”) AND (“colorectal cancer*” OR “colorectal tumo*r*” OR “colorectal malignanc*” OR “colorectal neoplasia”) AND (“screening” OR “primary prevention” OR “early detection”))
PubMed	((“healthcare policy” OR “health policy” OR “health care policy” OR “health guidelines” OR “guidelines”) AND (“colorectal cancer*” OR “colorectal tumor*” OR “colorectal malignancy” OR “colorectal neoplasia”) AND (“screening” OR “primary prevention” OR “early detection”))
EBSCOHost	((“healthcare policy” OR “health policy” OR “health care policy” OR “health guidelines” OR “guidelines”) AND (“colorectal cancer*” OR “colorectal tumor*” OR “colorectal malignancy” OR “colorectal neoplasia”) AND (“screening” OR “primary prevention” OR “early detection”))

The authors rated each item on a seven-point scale between 1 (strongly disagree) and 7 (strongly agree) for each set of guidelines. One point was given if the information was poorly reported or unavailable for an item, while seven points were given if the information provided was sufficient. The domain scores were then converted to percentages using the following formula: (Obtained score – Minimum possible score)/(Maximum possible score – Minimum possible score) x 100%. The results of the quality appraisal are presented in Table 2. The authors also independently recommended the inclusion of each set of guidelines for the review.

The selected guidelines encompassed CRC screening using both stool-based tests and visualization techniques. The variations in quality across the guidelines were mostly due to the stakeholder involvement, rigor of development, and applicability. Nine[22,24–26,45–49] out of 14 guidelines scored more than 6 points out of 7; whereas another five guidelines scored between 3 and 5 points. Of the six domains assessed, both the clarity of presentation and editorial independence had mean domain scores as high as 98% on average. This indicated a high clarity of recommendations and the absence of potential influences or conflicts of interest. The domain with the lowest mean score was applicability (77%), which implies insufficient consideration of the practicality of recommendations.

Data Abstraction and Analysis

The two authors independently extracted information from each selected guideline, including the authors, year of publication, organization, country of origin, recommended age range for CRC screening, screening modality, screening interval, screening strategy, and other relevant information (Table 3). Subsequently, they independently suggested the categorization of findings under three themes: ecology, biology, and social factors. Any disagreements in the data extraction analysis were resolved by consensus between the authors.

Results

The systematic searching strategy has finalized 14 guidelines to be analyzed in the review. Descriptive summary of included guidelines concerning organization and countries or regions involved is shown in Figure 2. The CRC screening guidelines published spanned six countries with two regions that include the United States (6),[22,24–26,49,50] Canada (1),[51] China (1),[52] Saudi Arabia (1),[53] Korea (1),[47] Spain (1),[54] the European Union member state countries (2)[48,55] and the Asia Pacific region (1).[45] Comparing the location of selected guidelines based on the WHO regions, seven guidelines accounted for the Region of the Americas (AMR), three guidelines from the European Region (EUR), three guidelines from the Western Pacific Region (WPR), and one from the Eastern Mediterranean Region (EMR). The guidelines were published between 2012 and 2021.

Screening Modalities

Three guidelines by the United States Preventive Services Task Force (USPSTF), Saudi Arabia, and the National Comprehensive Cancer Network (NCCN)[49,50,53] recommended colonoscopy as the primary CRC screening modalities. The USPSTF guideline specifically indicates that individuals who underwent colonoscopy screening are not required to perform additional iFOBT screening. This demonstrates the strong system-based support held in the US that is able to cope with the colonoscopy demand for the population. Similarly in Saudi Arabia where the population at large prefers colonoscopy compared with the stool-based test for CRC screening. Besides the 1-tier approach of using colonoscopy as the screening basis, other guidelines recommended for 2-tier approach whereby FIT is performed first then followed by colonoscopy if a positive result.

Previous studies showed the sensitivity and specificity of FIT superseded gFOBT, thus it was chosen as the primary screening test by many.[26,46] Apart from that, only the ACS guideline acknowledged high-sensitivity gFOBT and multi-targeted DNA stool blood test for baseline CRC screening for the average-risk group which can be repeated every year for the former and three yearly for the latter.[25] The expansion of screening modalities suggested by the ACS that includes FIT, HSgFOBT, mt-sDNA, colonoscopy, CT colonography, and flexible sigmoidoscopy may underscore the importance of patient preferences and choices for particular testing to encourage screening uptake.

Table 2 Scaled AGREE II Domain Scores for Each Guideline and Overall Assessment

	ACG[26]	ACS 2018[25]	ACP 2019[22]	APWG 2015[45]	CTF 2016[46]	ESMO 2013[55]	Eu G 2013[48]	China 2014[52]	Saudi 2015[53]	Korea 2012[47]	NCCN 2020[50]	SEOM 2014[54]	USMSTF 2017[24]	USPSTF 2021[49]	Average Score (%)
Scope and Purpose (%)	100	100	100	89	100	89	100	94	83	100	100	67	100	100	94
Stakeholder Involvement (%)	72	94	100	89	100	39	72	50	100	94	89	61	94	100	83
Rigor of Development (%)	90	98	96	92	96	52	100	48	92	100	90	58	94	100	86
Clarity of Presentation (%)	94	100	100	100	100	94	94	89	100	100	100	94	100	100	98
Applicability (%)	83	75	79	88	88	50	100	63	67	83	79	50	92	83	77
Editorial Independence (%)	100	100	100	100	100	100	100	100	100	100	100	83	83	100	98
Overall (out of 7)	6	6	6	6	7	4	7	4	5	7	5	4	6	7	

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Table 3 Characteristics of Included Guidelines

Author, Year	Organization	Countries/ Regions	Earliest Age at Screening	Age to Stop Screening	Primary Screening Modalities	Screening Interval	Screening Strategy	Additional Considerations
Shaukat et al., 2021[26]	American College of Gastroenterology (ACG)	United States	50–75 years (strong recommendation) 45–49 years (conditional recommendation)	Individualized screening beyond 75 years	Colonoscopy and FIT (strong recommendation)	FIT annually Colonoscopy every 10 years (strong recommendation)	Organized screening program (strong recommendation)	Outreach programs to boost screening among African Americans.
Wolf et al., 2018[25]	American Cancer Society (ACS)	United States	50–75 years (strong recommendation) 45–50 years (qualified recommendation)	Discourage individuals over age 85 years from continuing screening	FIT HSgFOBT mt-sDNA Colonoscopy CTC FS	Annually Annually Every 3 years Every 10 years Every 5 years Every 5 years	NA	Emphasizes the importance of patient preferences and choice of screening options.
Qaseem et al., 2019[22]	American College of Physicians (ACP)	United States	50–75 years	Discontinue CRC screening for those older than 75 years or adults with a life expectancy of 10 years or less	FIT or HSgFOBT Colonoscopy Or FS Plus FIT	Every 2 years Every 10 years Every 10 years Every 2 years	NA	gFOBT benefit to reduce CRC mortality; harm of stool-based test is associated with subsequent colonoscopy.
Sung et al. 2015[45]	Asia Pacific Working Group	Asia Pacific region (14 Asia Pacific countries)	50–75 years (grade B recommendation)	Discontinue screening at the age of more than 75 years	FIT (grade A recommendation) Colonoscopy (grade B recommendation) - following a positive FIT test FS	Every 1–2 years Every 10 years Every 5 years	NA	Various ethnicity with different CRC risk. Identification of at-risk individuals by age, male gender, family history of CRC, smoking and obesity. The Asia Pacific Risk Score as risk stratification for screening program.
Canadian Task Force on Preventive Health Care, 2016[46]	Canadian Task Force on Preventive Health Care	Canada	50–59 years (weak recommendation) 60–74 years (strong recommendation)	Discourage screening for those age 75 years and above	FOBT (gFOBT or FIT) Or FS FOBT (gFOBT or FIT) Or FS	Every 2 years Every 10 years Every 2 years Every 10 years	NA	Colonoscopy is not recommended as the primary screening test for CRC.

(*Continued*)

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Table 3 (Continued).

Author, Year	Organization	Countries/ Regions	Earliest Age at Screening	Age to Stop Screening	Primary Screening Modalities	Screening Interval	Screening Strategy	Additional Considerations
Labianca et al. 2013[55]	European Society for Medical Oncology (ESMO)	European Union member states	50–74 years 55–64 years (grade C recommendation) 50–74 years (grade D recommendation)	Discontinue screening at 75 years and above	gFOBT FIT FS Colonoscopy	Annually or should not exceed 2 years Should not exceed 3 years Between 10–20 years Between 10–20 years	Organized screening	Clinical management and long-term implication of cancer survivorship.
Karsa et al. 2013[48]	European Colorectal Cancer Screening Guidelines Working Group	European Union member states	60–64 years (grade B recommendation) 55–64 years (grade C recommendation) 50–74 years (grade D recommendation)	Discourage screening at 75 years and above	FOBT gFOBT FS Colonoscopy	Should not exceed 3 years Should not exceed 2 years Between 10–20 years Between 10–20 years	Organized screening	Average risk colonoscopy screening should not be performed before age 50 years.
Fang et al. 2014[52]	Chinese Society of Gastroenterology	China	50–74 years	75 years and above not included in the screening program	FOBT (at least two FOBT immunoassays) Questionnaire on high-risk factors Colonoscopy Sigmoidoscopy	Every 3 years	Opportunistic screening (direct colonoscopy or positive FOBT + colonoscopy)	Preliminary screening should be performed for risk stratification, followed by colonoscopy.
Lin JS et al. 2021[49]	US Preventive Services Task Force	United States	50 years and above (strong consensus)	Individualized screening for age 76 to 85 years according to the overall health and screening history	Colonoscopy Sigmoidoscopy (offered to those refuse colonoscopy) FOBT	Every 10 years Annually	NA	Individuals underwent colonoscopy screening do not necessary perform additional FOBT screening.

Alsanea et al. 2015[53]	Tripartite Task Force from Saudi Society of Colon & Rectal Surgery, Saudi Gastroenterology Association and Saudi Oncology Society	Saudi	45–70 years (strong recommendation)	Discourage screening for those age more than 70 years; consider individualized comorbidities and life expectancy	Colonoscopy FIT FS	Every 10 years Annually Every 5 years (when combined with annual FIT) Every 3 years (without annual FIT)	NA	Colonoscopy alone every 10 years is the recommended modality.
Lee et al., 2012[47]	Korean Multi-Society Task Force	Korea	50 years and older (strong recommendation)	Discontinue screening after age 80 years	FOBT Colonoscopy CT colonography	Annual Every 5 years or earlier if high risk of interval cancer	NA	Screening modalities recommended by the Korean guideline includes FOBT, CT colonography, double-contrast barium enema, and colonoscopy.
Provenzale et al. 2020[50]	National Comprehensive Cancer Network (NCCN)	United States	50–75 years	Screening should be individualized for those aged 76–85 years based on comorbidity and life expectancy	Colonoscopy Stool based: HsgFOBT or FIT FIT-DNA based testing FS CTC	Every 10 years Annually Every 3 years 5–10 years 3–5 years	NA	Factors such as age, first-degree relatives with CRC, high BMI, cigarette smoking, diet, use of aspirin and adherence are important to consider for effective screening.
Segura PP et al 2014[54]	Spanish Society of Medical Oncology (SEOM)	Spain	50–74 years	Individualized screening for those 75 years above	FIT FS Colonoscopy	Every 1–2 years Every 5 years Every 10 years	Opportunistic screening	Combination strategy using stool test and flexible sigmoidoscopy should not be considered in CRC screening.
Rex et al 2017[24]	US Multi-Society Task Force on Colorectal Cancer (USMTF)	United States	50–74 years 45 years (in African Americans)	Discontinue screening at 75 years or having less than 10 years of life expectancy	Colonoscopy FIT	Every 10 years Annually	Organized screening	Sequential offers of screening test, multiple screening options and risk stratified screening are recommended.

Abbreviations: FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; HSgFOBT, High-sensitivity guaiac-based fecal occult blood test; FOBT, fecal occult blood test; mt-sDNA, multitarget stool DNA; CTC, CT colonography; FS, flexible sigmoidoscopy.

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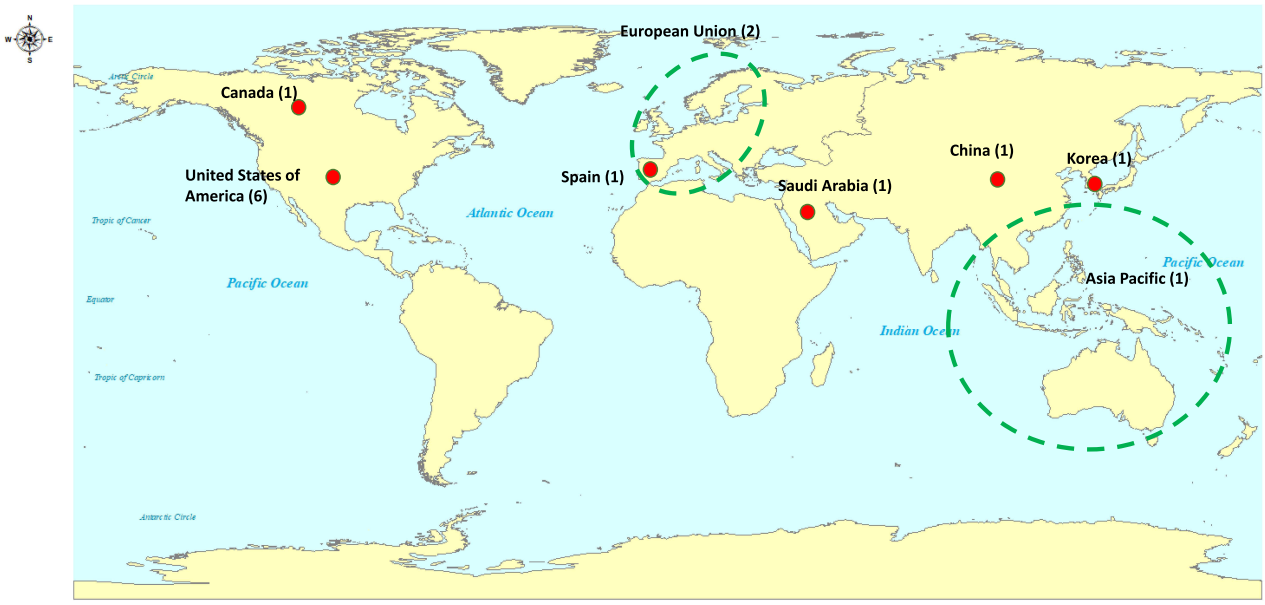

Figure 2 Summary of guidelines included based on countries and regions.
Notes: () number of guidelines included, ● countries of origin, - - - regions.

Age at Screening

Generally, the recommended starting age for screening is at 50 years and above. However, the ACG guideline[26] recommended the earliest age for screening to begin at 45–49 years (conditional recommendation) specifically for African Americans in view of the highest mortality rates recorded among the ethnicities. On the other hand, the ACS guideline[25] allowed for early CRC screening at 45–50 years (qualified recommendation) while emphasizing the importance of patient preferences for timing and screening options. The guidelines published in Saudi Arabia[53] preferred early screening as early as 45 years with strong recommendations, owing to the epidemiologic trend of CRC incidence recorded in the country.

There has been no clear consensus on the age to stop screening.[25,45,54] Most of the guidelines recommends the healthcare provider to proceed for individualized risk assessment for those beyond age 75, considering the comorbidities and ten years life expectancy. However, few guidelines allowed for continuous screening as long as the potential complications following screening procedures are clearly explained to the patient. In resource-limited settings, average-risk individuals of more than 75 years were excluded from the CRC screening program to prevent unnecessary harm following the invasive procedures of colonoscopy.

Screening Strategy

Six[24,26,48,52,54,55] of the 14 guidelines studied mentioned the preferable screening program strategies for implementation at country level. Four guidelines[24,26,48,55] supported the organized screening as a way to achieve higher screening uptake, hence significant reduction of CRC incidence and mortality. However, it requires a high-resource setting for an affordable population-based screening. On the other hand, opportunistic screening offers a great window for early detection by utilizing the optimal resources via recommendation by the healthcare providers. This strategy is more suitable in countries with limited resources for colonoscopy services and experts. In fact, two guidelines in the Asian region[45,52] had adapted the risk stratification approach to selectively perform preliminary screening to gauge the targeted group for intervention.

Compared with organized screening, opportunistic screening depends highly on regular physician visits.[56] Thus, a key advantage of opportunistic screening is the integration with other existing health services offered at primary care

facilities. It also helps to minimize the chance of over screening to reduce unnecessary harmful risks following positive stool testing. Besides, other preventive measures such as a quit smoking program and weight reduction activities readily available at the primary care settings provide additional value to the primary prevention of CRC.

Discussion

All the 14 CRC screening guidelines included in this review were of good quality. The need for well-structured organized screening programs at the national and regional level was highlighted to boost screening adherence.[57] Even with the varying range of age recommendations for starting screening, the benefits and harm of screening were justified in many of the guidelines.[26,52,53,55] However, low screening participation remains a concern in many countries and requires a holistic approach by the stakeholders. Much attention has been given to investigate factors influencing CRC screening participation in average-risk individuals. Literature explored the reasons for the lack of screening uptake including limited access to screening, patient preferences, and lack of physician knowledge on screening guidelines.[58–60]

Based on the ecobiosocial approach, the disparities in ecology discussed in the review refer to the healthcare system, screening program strategy, and institution involved in offering CRC screening to the average-risk population. The biological factors explain the diversity of age, sex, and ethnicity preference within the screening guidelines. Meanwhile, the social factors focus more on the patient-level background that includes the socioeconomic status, smoking status, and screening behavior which are of no less importance to be considered in planning effective intervention strategies.

Ecological Disparities

The expansion of screening modalities has been considered in many CRC screening guidelines. In addition to the usual practice of stool test (gFOBT, FIT, FIT-fecal DNA) some guidelines endorsed CRC screening via structural visualized methods (colonoscopy, sigmoidoscopy), imaging technique (CT colonography, barium enema), and the Septin9 serum assay.[24] Considering the cost-effectiveness and reliability of the testing, the most common primary screening modality recommended is the stool-based test.[61–63] With a sensitivity of 93.9% and specificity of 100% for CRC detection, iFOBT outperformed other types of fecal occult blood tests.[64] In high-resource countries, colonoscopy is regarded as the first-tier screening[24,53] following the population preference. Thus, understanding the pattern of utilization of primary screening modalities within certain culture-specific populations or level of socioeconomic status is critical to inform the effectiveness of the screening program.

Comparison studies on CRC screening have concluded that implementation of a population-based screening program provides more benefits and is more cost-effective when compared with no screening, even in countries with limited financial resources.[65–67] Notwithstanding that, the availability of treatment for CRC must be prioritized to ensure successful screening.[23] Concerted efforts by multidisciplinary teams are needed to identify the most effective strategies that suit the country's background, considering the life-years gained relative to the cost of the screening strategy.

Even though organized screening offers higher screening outcomes compared with opportunistic screening, the prerequisites demand conscientious components as outlined by the IARC.[26] One of the crucial elements is to have an appropriate quality assurance structure for each of the process flows.[65,68,69] In regions where considerable CRC screening guidelines are published, the approach to screening is largely opportunistic. It is generally understood that countries with an opportunistic program face huge challenges of low screening uptake.[21,70,71] However, the involvement of multiple professional organizations in quality assurance of the CRC opportunistic screening program in the US highlighted the significant impact on the high uptake of the screening.[72,73] Therefore, the review highly recommends the formation of a National Colorectal Cancer Roundtable consisting of multidisciplinary representatives and experts to specifically monitor the quality of the CRC screening program throughout each stage.

In general, utilization of any CRC screening test (USD 2428 per person) was proven to be more cost-effective compared with no screening (USD 3580 per person) per lifetime.[74] Based on cost-evaluation studies, the fecal immunochemical test (FIT) was more effective when performed annually rather than 2-yearly with reported incremental cost-effectiveness ratio (ICER) below the acceptance threshold, among the average-risk population.[75] Regarded as the gold standard for CRC screening methods, colonoscopy every 10years appears to be cost-effective when compared with annual FOBT despite the requirement for highly skilled personnel, instruments, and designated infrastructure.[74] The sensitivity for colonoscopy is the highest with 91% and 94% specificity (Table 4) and outweighs alternatives due to the ability to detect and remove

Table 4 Comparison of CRC Screening Methods

CRC Screening Test	Advantages	Disadvantages	Mechanism of Action	Target Population	Risk During Application	Specificity	Sensitivity
Stool test Guaiac fecal occult blood test (FOBT/gFOBT)	Noninvasive	False positives may be due to peroxidase activity from high consumption of meat, fruit, vegetables and NSAIDs use. Stool samples should be taken three times for reliable outcome. Compliance to diet restriction at least 3 days is necessary before taking the test; such as avoid eating red meat and vegetables such as broccoli and cauliflower. Discontinuation of NSAIDs and vitamin C prior to testing. Inability to distinguish between upper and lower gastrointestinal bleeding. It does not detect Hb at concentration below 600 microgram/g of feces, hence limits the ability to detect small polyps with less bleeding	It detects the peroxidase activity of hemoglobin in erythrocytes	Asymptomatic individuals	False positive when consumed high amount of red meat and vegetables containing heme iron	95.2%	52%
Stool test: Fecal immunochemical test (FIT/iFOBT)	Noninvasive Does not require dietary restriction Single testing sample is sufficient Able to determine Hb level at lower concentration (as low as 25 ng/mL of the buffer) compared with the guaiac methods	Limited to detection of bleeding from the colon and rectum. Relatively more expensive than the guaiac methods	Utilizes specific monoclonal antibodies to Directly detects human globin within hemoglobin in the stool	Asymptomatic individuals	NA	94%	79%
Colonoscopy	Gold standard	High cost Invasive Requires skilled experts Discomfort Potential complications Bowel preparation required	Direct visualization during procedure enables removal of polyps or tumor cells identified in colon	If positive iFOBT result, colonoscopy is mandatory to enhance the screening effectiveness; symptomatic individuals	Bowel perforation, bleeding, deaths secondary to perforation	94%	91%

Flexible Sigmoidoscopy	Simpler bowel preparation compared to colonoscopy No dietary restriction	Operator-dependent	Examine the distal 40 cm to 60 cm of the lower GI tract	Sigmoidoscopy can be performed once or 5-yearly in combination with iFOBT among the average risk individuals	Discomfort during procedure	94%	75%
CT colonography	Noninvasive assessment Sedation-free Extra colonic organs can be assessed simultaneously Able to detect asymptomatic polyps	Bowel preparation Radiation risk Biopsy is not possible, thus patient may need to undergo repeated procedure with another bowel preparation Additional cost to patient	Visualizes the structural assessment of colon and allows for identification of extracolonic findings	Asymptomatic individuals	Discomfort during procedure	NA	NA
Colon capsule endoscopy		Strict bowel preparation Diet restriction Use of suppositories and prokinetics to ensure smooth capsule through the bowel	Double-headed capsule is used to visualize the colon beyond the haustral folds	Patient is unwilling or unable to undergo colonoscopy	Capsule impaction and retention (1.4%), requiring surgical removal	59%	77%

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precursor cancer lesions as well as tumor cells upon examination.[76] Comparison studies made between FOBT yearly and sigmoidoscopy once showed that FOBT method was consistently less costly and more effective.[67,75,77] Thus, the feasibility of a selected screening test must take into account the availability of resources, acceptance by the population, and effectiveness of the screening program.

Biological Disparities

The incidence and mortality of young-onset CRC have been rising in many countries across all continents,[9,83,84] indicating an alarming epidemiological shift towards the younger age group of less than 50 years. The low effectiveness of CRC screening in the young has partly been driven by the screening policy that recommends the earliest age to screen at 50 years and above of the average-risk individuals,[45,52] thus missing out on the younger group. The impending health complications of the working-age group population require an upscale of screening efforts and the need to consider lowering the recommended age for CRC screening in the future.

While the CRC occurrence in men was predominantly higher than in women,[30,85,86] less is seen in the screening policy that stratifies sex as the eligible individuals. Only two guidelines proposed the risk score consisting of age, sex, family history, and smoking as an effort to prioritize screening among average-risk individuals.[45,52] Even though the approach is only relevant to resource-limited countries, targeted awareness activities and health promotion may benefit the population in the long term, considering the relatively lower screening participation among men.[30]

Screening provides an opportunity for an earlier stage at diagnosis across all ethnicities. Although notable differences by ethnicity have been reported in the CRC incidence and prognostic values, the screening eligibility has failed to underscore the racial inequalities. Of the 14 guidelines included, only the ACG guidelines confer screening to African Americans at 45 years,[26] while the Asia Pacific Consensus recommended individual countries in Asia to devise respective screening policies accounting for the ethnic difference.[45] Previous studies linked the high CRC incidence in black individuals with a lower rate of screening participation, largely influenced by access to screening.[14,87] In a more diverse screening population, CRC screening uptake was highest among whites and Hispanics compared with blacks by more than 10-fold.[29] Although CRC mortality was recorded as highest in black individuals, the current screening guidelines do not align similarly for black and white individuals. Thus, it is time for the stakeholders to revise the quality screening program to reduce the overall burden.

Additionally, biological factors found to relate with CRC also include genetic predisposition in the family and comorbidities such as inflammatory bowel disease, Lynch syndrome, and type 2 diabetes.[7,78] Studies showed that young-onset CRC is linked with high degree of familial history.[7] While patients with chronic diseases had regular follow-up with health clinics, this provides a great window of opportunity for CRC screening of those at risk.

Despite the extensive discussion on the promoting factors for CRC, several studies highlighted protective factors likely to reduce the rate of cancer. The ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) has been linked with reduction of risk for CRC via inhibition mechanism against cyclooxygenase-2 (COX 2) activity known to trigger the tumorigenesis.[79] In addition, some evidence supported the protective role of high fiber dietary intake and high consumption of fruits and vegetables which relate to a healthy gut environment.[80] Therefore, further review on the need of a standardized dietary guideline pertaining to CRC is highly desirable to advise on the primary prevention strategy.

Social Disparities

In a large population-based case control study, a strong association were recorded between smoking and pre-cancerous lesions for CRC.[78,87] The inflammatory pathway found was mediated through a series of gene-environment interactions initiated by the cigarette smoking.[88,89] An overall increase of more than 20% in CRC risk among smokers[87,90] highlighted the importance of risk stratification for screening of the total average-risk population. Nonetheless, only the WPRO region published guidelines[45,52] truly consider smoking in the risk score for screening selection purposes. Smoking cessation programs coupled with CRC screening may benefit to reduce further the CRC incidence as well as mortality.

The social disparities identified within the guidelines also involved the issue of low socioeconomic status group whereby studies had associated this with a lower CRC screening participation rate.[91] This is hampered by the low awareness and lack of health-seeking behavior that collectively contributed to the low screening uptake, both of which were likely influenced by the level of socioeconomic status.[92–94] Substantial studies demonstrated the great impact of patient-level barriers towards CRC screening uptake,[95–97] indicating extensive efforts are needed to educate the public on CRC and the importance of early detection.

The use of the ecobiosocial approach helps to elucidate the disparities in a systematic manner. The ecological, biological, and social factors are equally important to ensure continuous effective preventive measures within a population. The interdependent relationship between these factors should be emphasized in bridging the gap in the cancer continuum.[38] In addition, a diversified ethnicity population compounded with culturally specific lifestyles may impede a universal CRC screening strategy when there is a lack of planning, as there is no one screening structure that can fit all settings.

Against the background of industrialization and drastic economic development, the shift towards a westernized lifestyle is inevitable. The proliferation of the food retailing industry likely exposes people to easy access of fast-food outlets, which already known for energy-dense and nutrient-poor foods.[81] Neighborhoods with a high proportion of fast-food outlets may be significantly influential as they are perceived as an easier choice, thus frequently consumed more than other, healthier food. Studies showed that people living in the vicinity of greater access to fast-food outlets opted for an unhealthy diet, which has been linked to excessive weight gain and obesity over time.[68,81] Compounded with lack of access to healthcare facilities offering CRC screening services, this not only dilutes the preventive strategies focus, but limits the opportunity for screening among those at risk and who eventually presented late for treatment. A well-organized CRC screening program as practiced in Canada and the US witnessed the success of increased screening uptake by nearly half, from 38.9% in 2000 to 82.7% in 2015 and this was reflected in the reduction of yearly CRC incidence by 25% and 52.4% of CRC mortality.[82] Readily available and responsive CRC screening services within community reach, support the best practice of early detection and intervention. Besides, being receptive to the consumer preference on the options of screening modalities may provide additional value to encourage participation. The ecobiosocial approach serves to review the disparities in a holistic manner whereby it incorporates the influence of surrounding environments reflecting the real situation within a living community and not just merely the individual-level determinants.[38]

The approach helps to explain the role of each component towards an efficient and effective CRC screening program. In order to overcome the issue of lack of adherence to CRC screening, multiple measures must be taken including the healthcare screening services with either opportunistic or organized systems, availability of facilities offering CRC screening, coverage of the targeted population to screen, incorporation of risk stratification scoring, and patient preference for screening methods.[38,71]

Examining the recent updated international CRC screening guidelines, the review identified the need to develop a specific CRC screening policy at the national or regional level tailored to the respective population to improve the screening uptake. This is particularly concerning in Asian regions where the incidence of CRC is the highest but there is a limited number of established guidelines, supported by low CRC screening uptake. Concerted efforts must be given to increase awareness and there is the need to be equipped with experts and up-to-date facilities. Furthermore, the translation of the ecobiosocial approach as proposed in the review provides insights to the stakeholders in planning and evaluation of a comprehensive accredited screening program of the country.

Countries that do not publish their guidelines were not included, leading to publication bias. Certain guidelines such as the European Guidelines consist of more than one volume to explain each component of the screening program in detail, limiting the extent of clarification on the disparities addressed. With wide arrays of screening options and approaches, the current guidelines on average-risk individuals are broad and non-specific, leading to dilution of organizational focus. Revision to the screening policy should consider the overall level of risk underlying the average-risk individuals to yield better screening outcomes.

Conclusion

Considering the identification of ecobiosocial disparities in CRC screening guidelines and the epidemiological shift towards young-onset CRC, further reviews of the status quo recommendations are warranted on the matter. The disparities addressed call for a need to revise the current guidelines to reach consensual recommendations for a standardized universal CRC screening program.

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Disclosure

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