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EDITORIAL

Screening of colorectal cancer: Methods and strategies

Zhen Liao, Jin-Tao Guo, Fan Yang, Shu-Peng Wang, Si-Yu Sun

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Abstract

Colorectal cancer (CRC) has high incidence and mortality rates, and the emergence and application of CRC screening have helped us effectively control the occurrence and development of CRC. Currently, common international screening methods include tests based on feces and blood, and examination methods that allow for visualization, such as sigmoidoscopy and colonoscopy. Some methods have been widely used, whereas others such as multi-target stool RNA test are still being explored and developed, and are expected to become front-line screening methods for CRC in the future. The choice of screening method is affected by external conditions and the patients' situation, and the clinician must choose an appropriate strategy according to the actual situation and the patient's wishes. This article introduces various CRC screening methods and analyzes the factors relevant to the screening strategy.

Key Words: Colorectal cancer; Screening; Stool-based test; Endoscopic examination; Computed tomography colonography; Blood-based test

Core Tip: Screening for colorectal cancer have helped us effectively control its occurrence and development. This article presents various colorectal cancer screening methods and analyzes pertinent factors in screening strategies.

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INTRODUCTION

Colorectal cancer (CRC) ranks third globally in terms of cancer incidence (10.0%), and second in terms of mortality (9.4%) [1]. Advanced CRC readily metastasizes to the liver, lungs, bones, brain, and even pancreas[2] and spleen[3], significantly impacting patient prognosis. Hence, early screening for CRC and even intercepting it in the precancerous state are crucial for reducing the incidence and mortality rates of CRC.

In the early 1990s, the American Cancer Society, National Cancer Institute, and American College of Physicians advocated sigmoidoscopy or fecal occult blood tests for CRC screening based on clinical practice, despite the absence of reported randomized controlled trials (RCTs) supporting the safety, efficacy, and practicality of these methods at that time. With medical advancements, colonoscopy, fecal immunochemical tests (FIT), computed tomography colonography (CTC), and FIT-DNA tests have gradually emerged as new screening modalities[4]. Screening plays a pivotal role in reducing mortality by identifying asymptomatic early-stage cancers and preventing diseases by detecting and removing precancerous lesions (adenomas and serrated polyps). Recent data also demonstrate that widespread CRC screening has decreased CRC mortality rates globally[5].

In addition to the benefits of screening methods, judicious application of screening strategies aids in diminishing disease occurrence and progression. Each screening method has its own set of advantages and disadvantages, and is suitable for different demographic groups. Correspondingly, each method has a recommended screening frequency, and the recommended onset and cessation ages for screening are continuously adjusted based on the evolving clinical reality. Therefore, this article presents various CRC screening methods and analyzes pertinent factors in screening strategies.

METHODS OF SCREENING

Stool-based test

Guaiac-based fecal occult blood test: The guaiac-based fecal occult blood test (gFOBT) method leverages the peroxidase activity of hemoglobin in stool to decompose hydrogen peroxide in the reagent, reacting with a guaiac developer to indicate the presence of hemoglobin. This approach is simple to perform, can be conveniently conducted at home, and poses no harm to the patient's body, making it an ideal screening method for early-stage detection. Numerous studies have demonstrated that annual or biennial gFOBT effectively reduced CRC morality rate. Lin *et al*[6] synthesized findings from five RCTs in a comprehensive study. Over a follow-up period ranging from 11-30 years, the study compared CRC mortality rates between the screening and non-screening groups after 2-9 rounds of screening, revealing a lower mortality rate in the screening group [at 19.5 years, risk ratio (RR) = 0.91, 95% confidence interval (CI): 0.84-0.98; at 30 years, RR = 0.78, 95%CI: 0.65-0.93]. Another meta-analysis of 10 RCTs and 47 model studies indicated that gFOBT screening reduced the CRC-specific mortality rate by 21% [RR = 0.79, (95%CI: 0.68-0.91), P =0.001][7]. However, the gFOBT detection method lacks specificity for blood. Dietary substances with peroxidase activity (such as plant peroxidase and red meat) can also yield positive test results, whereas antioxidants (such as ascorbic acid) may inhibit hemoglobin peroxidase activity, leading to false-negative results[8]. Consequently, dietary restrictions are necessary before the gFOBT examination. The sensitivity of gFOBT is notably lower than that of other screening methods and may require multiple samples. The effect of gFOBT on the incidence risk of CRC is limited because the early manifestations of CRC often involves polyps without bleeding symptoms, and only colonoscopy can reliably detect the lesions. The USPSTF recommends annual gFOBT screening.

FIT: The FIT utilizes the high sensitivity of the antigen-antibody response of human hemoglobin to quantitatively detect the level of hemoglobin in feces, measuring the content of human hemoglobin per gram of formed feces. Compared with gFOBT, FIT not only has the advantages of non-invasive and ease of performance but also exhibits high specificity for CRC screening. The FIT remains unaffected by diet or medication, and its sample collection is simpler, thereby increasing population compliance. Automated test reading and quantitative measurement of fecal hemoglobin concentration with FIT enable the adjustment of positively threshold and sensitivity for CRC detection[9]. Findings from an RCT suggests that FIT is significantly more sensitive than gFOBT (sensitivity difference = 18.9%, 95%CI: 10.2-32.6)[10]. Grobbee *et al*[11] analyzed data from 63 studies, revealing sensitivities of 59% for gFOBT and 89% for FIT for CRC detection. In recent years, FIT has progressively supplanted gFOBT as the preferred stool screening method for CRC owing to its relative advantages[12]. However, to date, no randomized trial has assessed the long-term effectiveness of FIT on CRC mortality. Although data modeling has predicted a significant reduction in the CRC-specific mortality rate with FIT compared to no screening[7], actual prospective data as reference and evidence are lacking. The USPSTF recommends annual FIT screening.

Stool DNA test: Currently, the only stool DNA test approved by the US Food and Drug Administration is the multi-target stool DNA (mt-sDNA) test, which integrates a FIT component known as the FIT-DNA test. This test detects cells containing tumor-altered DNA shed from colon cancer by sensitively identifying specific genetic and epigenetic biomarkers, allowing for differentiation between tumor and non-tumor tissues. Leveraging this principle, the stool DNA test identifies DNA biomarkers from cancer cells sloughed off the inner membrane of the colon and rectum in the fecal matter. As a standalone screening test, the stool DNA test surpasses the FIT in terms of sensitivity. The mt-sDNA test boasts a 92% sensitivity for CRC detection, significantly higher than that of FIT (74%)[13]. Nonetheless, the mt-sDNA test exhibits low specificity, leading to false-positive results. Consequently, patients with positive stool screening results are advised to undertake sigmoid colonoscopy or colonoscopy to ascertain the presence of lesions. An increase in false-positive outcomes necessitate more follow-up colonoscopy examinations and associated adverse events. Similar to FIT,

there is no direct evidence evaluating the impact of stool DNA testing on CRC mortality[14]. The USPSTF recommends stool DNA screening every 1-3 years.

Multi-target stool RNA test: The multi-target stool RNA (mt-sRNA) test is not yet available in the market and is still undergoing phase III clinical trials. In a blinded, prospective, cross-sectional study conducted by Barnell *et al*[15] from June 2021 to June 2022, 8920 participants aged > 45 years from 49 states in the United States completed the mt-sRNA test. Stool samples were collected form participants before undergoing colonoscopy at a local endoscopy center. After the study, the results of the mt-sRNA test (positive or negative) were compared with the data obtained from other tests. The findings revealed that, compared to FIT, the mt-sRNA test exhibited significantly improved sensitivity for detecting CRC (94% *vs* 78%, respectively, McNemar $P = 0.01$). We anticipate further reports on the experimental results from the Erica K team to enhance our understanding of the mt-sRNA test. Once this method becomes commercially available, it is imperative to conduct additional research to ascertain the specificity of mt-sRNA testing for CRC screening and its impact on CRC incidence and mortality. Such studies will aid in the informed selection and application of this method in the future.

Endoscopic examination

Sigmoidoscopy: Sigmoidoscopy involves the use of a flexible endoscope to visually assess the internal condition of the rectum and distal colon after intestinal cleansing. This method accurately screens for CRC and identifies and treats precancerous lesions (such as adenomas and serrated polyps) to prevent CRC occurrence. Typically, sedation or anesthesia is unnecessary during sigmoidoscopy. As the earliest endoscopic method employed for CRC screening, sigmoidoscopy, along with gFOBT, is the sole CRC screening method supported by evidence from RCTs. Sigmoidoscopy screening contributes to a reduction in the CRC mortality rate. In an RCT with a median follow-up of 16.8 years, the CRC mortality rate with sigmoidoscopy screening (417 deaths, 3.37 per 10000 people per year) was lower than that of the unscreened group (549 deaths, 4.48 per 10000 people per year, RR = 0.75, 95%CI: 0.66-0.85). Flexible sigmoidoscopy screening continues to exhibit long-term efficacy in reducing CRC mortality rates[16]. A meta-analysis encompassing four large-scale randomized trials of sigmoidoscopy screening conducted in Norway, the United States, the United Kingdom, and Italy, with a 15-year follow-up of the screened population, revealed a difference in CRC mortality of 0.13 deaths per 100 individuals (95%CI: 0.07-0.19) and a mortality ratio of 0.80 (95%CI: 0.72-0.88) between the sigmoidoscopy screening and non-screening groups[17]. In a meta-analysis comprising solely RCTs, patients undergoing sigmoidoscopy, colonoscopy, and gFOBT were followed up and compared with those receiving standard care, revealing that the sole screening test that significantly extended life was sigmoidoscopy (110 d, 95%CI: 0-274). Current evidence does not support the notion that common CRC screening tests prolong life, except for sigmoidoscopy[18]. Nevertheless, sigmoidoscopy has largely been supplanted by colonoscopy, which can examine the entire large intestine and is more effective than sigmoidoscopy[14]. The USPSTF recommends sigmoidoscopy every 5 years, or every 10 years if combined with annual FIT.

Colonoscopy: Before undergoing a colonoscopy examination, patients must adhere to specific standards to ensure that their entire intestines are thoroughly cleansed. Similar to sigmoidoscopy, endoscopists can address precancerous lesions during examination. However, colonoscopy offers the advantage of visualizing the entire colon and rectum, covering a broader area than sigmoidoscopy. Additionally, patients have the option to choose sedation or anesthesia during the examination, which improves the comfort during examination. In an RCT, after a 10-year follow-up, the risk of CRC decreased from 1.22% to 0.84%, and the risk of CRC-related death decreased from 0.30% to 0.15% compared to the conventional care group. Participants invited for colonoscopy in this trial had a lower risk of CRC at the 10-year follow-up than those who were not screened[19]. One possible explanation is that colonoscopy not only screens for CRC but also prevents its occurrence by detecting precancerous lesions. Hence, colonoscopy screening can reduce both the mortality and incidence rates[20]. Further, rectal endoscopic ultrasonography can be used to identify locoregional tumor stage in the rectum with shear wave elastography[21]. Nonetheless, colonoscopy is more invasive and burdensome than stool-based tests or sigmoidoscopies. Colonoscopy examinations necessitate more clinical resources and lack RCT data. Despite being considered the gold standard for CRC screening, colonoscopy is not the most popular screening method for the general population. Therefore, colonoscopy has not replaced sigmoidoscopy in certain regions. Considering these factors, it is crucial to strike a balance between the benefits, harms, and cost-effectiveness of various CRC screening tests[19]. The USPSTF recommends colonoscopy screening every 10 years.

Colon capsule endoscopy: Colon capsule endoscopy (CCE) entails participants swallowing a capsule-sized wireless camera, which captures images of the colorectal mucosa and transmits them to the examiner for evaluation. If the images reveal colorectal polyps or cancer, a colonoscopy is necessary for definitive screening. CCE does not involve radiation exposure, sedation, or gas inhalation during examination[22,23]. The sensitivity of the latest CCE-2 (second generation) for detecting advanced tumors of 10 mm or larger is 76.7% (95%CI: 63.7-86.2), with a specificity of 90.7% (95%CI: 83.6-95.0). The sensitivity of this screening method depends on the percentage of colon surface area displayed in the images and the capsule excretion time. The sensitivity for detecting advanced tumors (> 6 mm) reaches 100% when the transmission time is 3-5 h. Although the USPSTF has not yet approved CCE for average-risk CRC screening, the US Food and Drug Administration has sanctioned its use for CRC screening in individuals with an incomplete history of colonoscopy or a high risk of complications during colonoscopy. Among individuals with incomplete colonoscopy, CCE outperforms CT colonography in detecting tumors > 6 mm and carries a lower risk of serious adverse events than traditional colonoscopy[24].

CTC

Before undergoing CTC, the patients were required to undergo intestinal preparation using laxatives, followed by oral administration of contrast medium and insufflation of gas *via* the rectum to expand the colon and rectum. Subsequently, an abdominal CT examination was conducted. The obtained images were then reconstructed using specialized computer software to generate two-dimensional or three-dimensional images of the large intestine[25], enabling the evaluation of polyps and cancer. In a meta-analysis involving 11151 patients, CTC demonstrated a sensitivity of 96.1% (95%CI: 93.8-97.7) in detecting CRC, which is comparable to that of colonoscopy[26]. However, a guidance statement indicated a sensitivity range of 0.86 to 1 for CTC, with no evidence from feasible studies evaluating its effectiveness in CRC screening [27]. The accuracy of CTC detection is contingent on the experience of the radiologist. Radiologists must undergo specific preliminary training to effectively perform and interpret test results[28]. The USPSTF recommends CTC screening every 5 years.

Blood-based test

Serum methylated septin 9 test: The blood-based SEPT9 methylation test is an inaugural FDA-approved blood test for CRC screening. This method targets the detection of abnormal methylation in the *SEPT9* gene promoter region of substances (circulating tumor DNA or ctDNA) released from CRC cells into the peripheral blood. A meta-analysis comprising 25 independent studies, predominantly case-control or cohort studies, with only one randomized multi-center screening study and two opportunistic screening studies included, demonstrated a sensitivity ranging from 48.2% to 95.6% and specificity ranging from 79.1% to 99.1%[29]. Another study compared the serum methylated septin 9 test (mSEPT9) in peripheral blood to gFOBT in 650 participants, revealing a positive result for mSEPT9 in 73% of patients with CRC, with a specificity of 94.5%. These data suggest that mSEPT9 outperforms gFOBT in CRC screening[30]. However, a positive result for mSEPT9 does not definitively indicate the presence of lesions akin to stool-based tests, necessitating confirmation *via* colonoscopy. A single-tube methylation-specific quantitative polymerase chain reaction assay (mqMSP) was developed, utilizing 10 different methylation markers to quantitatively analyze plasma samples containing tumor DNA at concentrations as low as 0.05%. In a cohort study, mqMSP detection demonstrated a sensitivity of 84.9% and specificity of 83.3%. Multichannel detection entails the simultaneous use of multiple circulating tumor DNA (ctDNA) markers, which may enhance the capability of liquid biopsies[31]. This approach could potentially represent a future development trend for serum mSEPT9 testing.

Cell-free DNA blood-based test: Cell-free DNA (cfDNA) is released by dying and decomposed cancer cells, containing tumor-specific genetic information. Analyzing specific mutations and methylation patterns in these DNA fragments enables the detection of cancer through cfDNA blood-based tests. A recent large-scale study evaluated the performance of cfDNA blood-based tests in asymptomatic and early-stage CRC within a screening-relevant population. The results demonstrated an 83% (95%CI: 72.2-90.3) sensitivity for CRC and 90% (95%CI: 88.8-90.3) specificity for advanced neoplasia, comparable to those of other screening methods. There was no apparent differences among subgroups and no reported serious adverse events. Additionally, blood-based tests are seamlessly integrated into routine healthcare encounters and are relatively simple to complete, making them easier to administer and enhancing patient adherence. The study reported a 3.7% rate of invalid cfDNA blood-based test results, well within the recommended target range (< 5%) for programmatic FIT offering[32]. Thus, cfDNA blood-based tests represent a promising alternative for CRC screening.

STRATEGIES OF SCREENING

Repeated testing

For stool-based screening methods, such as FIT, the CRC detection rate from a single test is low but significantly improves with repeated testing, surpassing the detection rates of other methods. A randomized trial indicated similar CRC detection rates between one-round FIT every two years and once sigmoidoscopy, with even higher rates observed with three-round FIT. Moreover, in detecting advanced adenomas, the detection rate in the one-round FIT group was lower than that in the once-sigmoidoscopy group, while the three-round FIT group exhibited a higher detection rate than the one-round FIT group. The incidence of complications was similar between the repeat FIT and sigmoidoscopy groups [9]. However, repeated testing is contingent on obtaining negative results. If the fecal test result is positive, a colonoscopy should be performed to confirm the presence of lesions rather than repeating the fecal test.

Age

In the past, experts recommended initiating CRC screening in the general population at the age of 50 years, with CRC diagnosed before this age categorized as early onset CRC (eoCRC), which was relatively uncommon. However, studies have found that certain populations, such as black individuals, possess genes predisposing them to a higher risk of CRC, warranting a lower screening age threshold (*e.g.*, 45 years) for more effective early disease detection. Nevertheless, this recommendation did not accurately reflect the situation for the majority of the population and lacked support from realistic data, thus failing to gain widespread acceptance[4]. Before 2018, most international guidelines recommended CRC screening for average-risk individuals aged between 50 and 75[33]. However, with shifting demographic trends, the incidence and mortality rates of eoCRC have increased.

To address the growing burden of eoCRC, the American Cancer Society revised its screening guidelines in 2018, lowering the starting age of average-risk individuals from 50 years to 45 years. Subsequently, in October 2020, the USPSTF issued a draft recommendation statement supporting this adjustment. Notably, in 2020, over 140000 people in the United States were diagnosed with CRC, with one-seventh of these cases occurring in individuals under the age of 50 years[34].

In 2021, the USPSTF released updated CRC screening guidelines, recommending screening for all adults aged 50 years to 75 years (level A recommendation). Additionally, it advised CRC screening for adults aged 45-49 years (level B recommendation). For individuals aged 76 years to 85 years, the USPSTF suggested that clinicians selectively consider CRC screening (level C recommendation), as evidence indicates minimal net benefit from screening in this age group. When determining the appropriateness of CRC screening for individuals, patients and clinicians should consider factors such as overall health status, screening history, and personal preferences[14].

Adjustment of the screening age marks the beginning of a new era, bringing forth both opportunities and challenges for population screening[35].

Compliance

The compliance of participants in various screening methods significantly impacts the experimental results. For instance, in an RCT comparing colonoscopy, gFOBT, and FIT, researchers observed relatively low compliance in the colonoscopy group compared to that in the gFOBT and FIT groups. This discrepancy may be attributed to the invasiveness of colonoscopy, the need for intestinal preparation, and the participants' limited knowledge of CRC screening[36]. In another randomized trial, the compliance rate was 83.6% in the colonoscopy group and 73.1% in the gFOBT group after the first screening round (RR = 1.14, 95%CI: 1.10-1.19, $P \leq 0.001$). However, compliance decreased to 38.3% after four consecutive rounds of gFOBT, indicating unsatisfactory compliance with multiple rounds of gFOBT compared to colonoscopy screening[37]. Approximately 33% of adults aged 50-75 years did not undergo screening as recommended, further highlighting low compliance rates[38]. Such low compliance rates can lead to experimental results failing to meet expectations, resulting in a lower CRC detection rate and impacting the overall judgment of the study.

CONCLUSION

As CRC screening becomes more widespread, numerous studies have consistently demonstrated its crucial role in reducing CRC mortality, although its impact on CRC morbidity varies. Recent data reveal significant declines in the age-standardized incidence of CRC in certain countries, such as the United States, Japan, and France, while other countries, such as Baltic countries, Russia, China, and Brazil, experience an increase in CRC incidence. In high-incidence countries, the decline in CRC incidence is attributed to population-level changes driven by healthier lifestyle choices, such as reduced smoking rates and increased acceptance of screening.

Despite the availability of numerous screening methods, determining the most effective strategy remains challenging owing to limited evidence. The International Agency for Research on Cancer asserts that insufficient evidence exists to rank the effectiveness of screening tests, with no face-to-face studies demonstrating the superiority of one method in reducing CRC mortality or morbidity. However, evidence suggests that in some emerging economies, utilizing more affordable and less invasive methods, such as gFOBT and FIT, for CRC screening may be cost-effective. This approach provides viable options for managing escalating disease burden.

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