Research advances in early screening for colorectal cancer (Review)

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Abstract. Early detection and intervention for colorectal cancer (CRC) play crucial roles in reducing the disease burden. However, existing screening methods remain limited in terms of sensitivity, specificity, and compliance. The present review systematically examines and compares cutting-edge research in the field of early screening for CRC performed in recent years, evaluates mainstream screening technologies from multiple dimensions, and provides a theoretical reference basis for the construction of efficient, accurate and sustainable early CRC screening strategies.

Contents

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second-leading cause of cancer-related deaths, resulting in a major burden on global healthcare systems (1). Early screening can reduce the incidence of CRC through the identification and removal of precancerous lesions; by promoting the early diagnosis and timely treatment of potential CRC lesions, early screening has decreased mortality rates by 52.4% and incidence rate by 25.5% (2). Currently, numerous countries and regions worldwide implement CRC screening programs. However, due to differences in national circumstances, globally unified CRC screening guidelines are lacking. For example, the United Kingdom, Canada, and the European Union recommend initiating screening at age 50, while the United States recommends starting CRC screening at age 45 (3). China employs risk stratification for individuals ≥40 years: High-risk groups begin screening at age 40, while low-risk groups start screening at age 50 (4). Research has indicated that the global CRC screening participation rate is ~54%; among surveyed regions, South America has the highest rate (90.19%), while North America has the lowest rate (45.57%) (5). The current methods for screening for CRC can be divided into two main categories: Invasive procedures and noninvasive tests. Invasive methods, including colonoscopy (CS) and flexible sigmoidoscopy (FS), serve as the diagnostic gold standard, with their high sensitivity and specificity. However, their invasive nature, high costs, and low patient compliance limit their implementation in resource-constrained settings (6). Noninvasive methods, such as stool tests, blood tests, and imaging studies, are easy to perform and well tolerated by patients, but the sensitivity or cost-effectiveness of some approaches are relatively low (7). Therefore, a comprehensive review of research progress in both categories of CRC screening would not only help clarify their respective advantages and limitations but also provide better options in settings with differences in resources.

2. Study selection methods

Digital databases including PubMed and Google Scholar were searched for studies published from 2015 to 2025. Key terms such as 'CRC screening' and 'colonoscopy' were used, and the search strategies were tailored for each database. All studies were required to focus on screening individuals for CRC. The studies also had to be original research, such as trials or reports of official guidelines, covering topics such as how well a screening method works. Studies that did not address CRC screening, duplicate publications and studies with missing data were removed. Unfinished research, such as conference summaries, as well as studies for which the full text could not be obtained were also excluded. The program Zotero 7.0 [Center for History and New Media (CHNM); Corporation for Digital Scholarship] was used to manage the studies. First, after removal of duplicate records, the titles and abstracts of

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the remaining studies were reviewed. Studies that did not fit the inclusion criteria were excluded, after which the full texts of the remaining studies were assessed. The list of studies included based on the predefined criteria was then finalized.

3. Screening methods

Feacal occult blood test (FOBT). FOBT is a common tool for screening for CRC that is noninvasive, inexpensive, and easy to use. Two main types of FOBT are currently in use: The guaiac-based faecal occult blood test (gFOBT) and the faecal immunochemical test (FIT). The gFOBT works by detecting the peroxidase activity of haem, a component of haemoglobin. This peroxidase activity changes the colour of the colourless guaiacol molecule, indicating the presence of hidden blood in the stool (8). Research has shown that the gFOBT has a sensitivity between 12.9 and 79.4% for detecting CRC, while its specificity ranges from 86.7 to 97.7% (9). A large meta-analysis reviewing four major clinical trials, including >320,000 participants from several countries, revealed that gFOBT screening decreased the incidence of CRC by 20% and mortality by 16% (10). However, the gFOBT has several limitations. Its chemical-based method has low sensitivity, and is affected by the diet and medications of the individual, which often cause false-positive and false-negative results. Therefore, patients must follow dietary and medication restrictions before the test. They also usually need to provide stool samples from three separate days for accuracy. For these reasons, the gFOBT is now being replaced by the FIT (11).

The FIT utilizes specific monoclonal or polyclonal antibodies that react with haemoglobin in human faeces. The detection of antibody-haemoglobin complexes in the stool indicates the presence of faecal occult blood, thereby suggesting potential colorectal lesions (12). The FIT has better sensitivity and specificity than the gFOBT in identifying CRC. A meta-analysis used a common cut-off point of 10 μg Hb/g and found that the sensitivity and specificity of the FIT in identifying CRC were 91% (95% CI, 84-95%) and 90% (95% CI, 86-93%), respectively. However, the FIT has low sensitivity for detecting precancerous lesions of CRC, failing to detect 60 to 75% of advanced adenomas (13). Currently, most countries use the FIT for CRC screening; in China, the population participation rate for FIT-based CRC screening programs is typically higher than 45%, with initial screening compliance rates as high as 94.0% (14). A European cross-sectional study showed that regions using the FIT for CRC screening had population participation rates ranging from 22.8 to 71.3%, which were significantly higher than those in regions using gFOBT screening (4.5 to 66.6%) (15). Continuous FIT screening can significantly reduce CRC-related mortality rates in the population and is cost effective (16,17). Research has indicated that multiple rounds of FIT show the most significant efficacy in population-based CRC screening, detecting more CRCs and adenomas while requiring the fewest number of colonoscopies (18). However, the costs of FIT reagents and testing equipment are higher than those of the gFOBT, limiting its adoption in low-income areas.

The FOBT essentially tests for gastrointestinal bleeding, and thus it requires that the tumour be accompanied by bleeding at the time of testing, which inevitably leads to missed diagnoses for tumours with intermittent bleeding and low sensitivity for colon polyps that bleed infrequently. Additionally, it may also result in misdiagnoses of other common benign conditions that cause gastrointestinal bleeding. A persistently positive FOBT should raise a strong suspicion of a colonic tumour, and CS should subsequently be performed to determine the nature of the lesion.

Hematological tests. Haematological testing is a noninvasive screening method. It detects specific cancer signs in the blood to help identify CRC or growths that may develop into cancer. Common blood markers for this cancer are carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, and CA242. A study by Gao *et al* (19) reported the performance of several markers and found that, in detecting CRC, CEA had a sensitivity of 46.59%, CA199 had a sensitivity of 14.39%, CA724 had a sensitivity of 44.80%, and CA125 had a sensitivity of 10.04%, while their specificities were 80, 89, 97, and 99%, respectively (19). Attempts have been made to combine multiple markers, such as CEA and CA19-9 (20,21). This method can improve accuracy to some extent. However, it is still not sufficient for early cancer screening in the clinic. These tumour markers have some limitations, however; their sensitivity and specificity are insufficient, they cannot reliably identify early-stage CRC, and they can yield false-positive results. For these reasons, tumour markers are not recommended for screening for CRC.

Haematological tests can also be used to assess patient outcomes. Studies have indicated that low levels of prealbumin, albumin (ALB), and transferrin are independent risk factors for postoperative anastomotic leakage (AL) [odds ratios (ORs) of 2.621, 3.982, and 2.109, respectively] (22,23). When combined with tumour location and intraoperative bleeding in a predictive model, the area under the curve (AUC) reached 0.942, with a sensitivity of 0.844 and specificity of 0.922 (24). Another study demonstrated that the combined use of three preoperative serum biomarkers, Onodera prognostic nutritional index, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio, achieved an AUC of 0.910 (95% CI, 0.900-0.929) for predicting AL, with a sensitivity of 89.8% and specificity of 82.6% (22). Wang *et al* (25) demonstrated that an elevated preoperative cancer inflammation prognostic index (CIPI) and platelet-to-albumin ratio (PAR) are correlated with a poor CRC prognosis, with the preoperative CIPI and PAR serving as independent risk factors for the overall survival (OR) of patients with CRC [hazard ratio (HR)=5.69 and 2.63, respectively].

Radiological examinations

Computed tomographic colonography (CT-C). CT-C uses spiral CT to acquire volumetric data and computerized image postprocessing techniques to reconstruct two-dimensional and three-dimensional images of the colon, thereby enabling the diagnosis of colonic diseases (26). In 2005, the American Cancer Society (ACS) recommended the CT-C reporting and data system as the standard for evaluating primary CRC (27). Recent research by the ESGAR committee has indicated that CT-C outperforms barium enema (28). The effectiveness of the CT-C examination primarily depends on the size of the target lesion. A study was conducted at a single centre and included

480 patients. The study compared CT-C to endoscopy. For detecting cancerous lesions, CT-C had a sensitivity of 93.3%. Endoscopy performed slightly better, with a sensitivity of 96.7%. The study also assessed the detection of polyps that were 5 mm or larger. Here, the sensitivity of CT-C relative to endoscopy was 77.7%. However, CT-C showed markedly high specificity for this task, at 98.9% (29).

CT-C is primarily used as a supplementary approach to identify proximal concurrent polyps or tumours in patients with obstructive CRC when endoscopy cannot be fully completed due to the intestinal stricture, obstruction, or poor patient cooperation; for symptomatic individuals at high risk for endoscopy and sedation, particularly elderly patients, frail patients, or those receiving anticoagulant therapy (30); for symptomatic patients who refuse conventional CS; for follow-up evaluations of patients with known colorectal polyps/CRC; for localizing primary tumours in patients with metastatic cancer; and for assessing chronic inflammatory bowel disease (26). The contraindications for this procedure can be divided into two groups. The first group is absolute contraindications, which include acute medical conditions such as acute diverticulitis, active ulcerative colitis, active Crohn's disease, and recent abdominal or pelvic surgery. The second group is relative contraindications, for which caution is needed; these include the presence of a colostomy, general contraindications for CT scans, pregnancy, severe claustrophobia, and a past history of a poor reaction to iodine-based contrast dye (31).

The advantages of CT-C include the following: i) Minimal trauma with a low incidence of complications such as intestinal perforation and splenic rupture (32); ii) improved patient tolerance because it is unaffected by intestinal morphology and enables complete colon imaging even in patients with intestinal stricture; and iii) the capability to diagnose extracolonic lesions (33). A meta-analysis by Pickhardt *et al* (34) of 44 studies involving 49,676 patients revealed that among asymptomatic screened populations, 4% of extracolonic diseases detected by CT-C required medical intervention, while 8% warranted follow-up. iv) CT-C also provides morphological information for tumour staging by visualizing the tumour location, invasion depth, involvement of adjacent organs, lymph node status, and distant metastases. Consequently, CT-C holds promise as an alternative method to CS for CRC follow-up. CT-C strategies include monitoring small colorectal polyps for three years and referring patients with large polyps for CS, achieving an optimal balance between cost and clinical efficacy (34). v) Participation rates exceed those of CS, and the costs are more favourable (35). Disadvantages include the following: a) higher bowel preparation requirements; b) low sensitivity for lesions <6 mm in diameter and flat lesions, increasing the risk of missed diagnoses (36); c) potential exposure to ionizing radiation (although a recent study has confirmed that using iterative reconstruction techniques enables a feasible radiation dose reduction while maintaining image quality); d) potential production of extraintestinal findings requiring further investigation and potential overtreatment; and e) inability to match the therapeutic and biopsy capabilities of CS (37).

Magnetic resonance colonography (MRC). MRC uses contrast agents to distend the colon, allowing the detailed soft-tissue imaging of MRI to visualize the bowel wall and any internal abnormalities. As a screening method that does not use radiation, MRC is specifically indicated for patients who are unsuitable for CS, for individuals who must avoid radiation exposure, and for the further evaluation of suspicious findings initially detected by CT-C (38).

The primary advantage of MRC lies in its absence of ionizing radiation, effectively eliminating the radiation exposure risk associated with CT scans. This property makes it particularly suitable for younger screening populations and individuals requiring long-term follow-up. Additionally, due to its high soft tissue resolution, MRC outperforms CT in visualizing lesions such as intestinal wall thickening and early submucosal carcinomas. Combining functional sequences such as diffusion-weighted imaging (DWI) further increases its ability to detect small lesions. Furthermore, this technology enables a multiparametric assessment. The combined use of dynamic contrast-enhanced scanning and DWI sequences effectively differentiates neoplastic lesions from inflammatory lesions, providing multidimensional information for a clinical diagnosis (38). A meta-analysis revealed that the sensitivity of MRC for diagnosing CRC ranges from 48 to 100%, whereas its specificity ranges from 60 to 100% (39). Regarding safety, MRC does not require iodine contrast agents, eliminating associated allergic reactions. While gadolinium agents may be used in some cases, the risk of nephrogenic systemic fibrosis associated with newer macrocyclic gadolinium agents has been significantly reduced. However, the clinical adoption of MRC faces clear challenges: The examination duration is lengthy, with a single scan taking 20-30 min, which is significantly longer than 5-10 min for CT-C, and it is susceptible to artefacts from respiratory motion and bowel peristalsis; costs are higher, with equipment and examination expenses significantly exceeding those of CT-C or the FOBT; bowel preparation demands are stringent, and inadequate bowel filling or residual stool may lead to missed lesions, placing high demands on patient compliance; and MRC exhibits lower sensitivity and specificity, particularly for lesions smaller than 5 cm. Typically, such lesions are unlikely to possess malignant potential; therefore, compared with conventional CS, this property does not preclude its use for screening (40). Furthermore, its widespread adoption is constrained by the need for high-field MRI equipment (≥1.5T), posing significant challenges for implementation in primary healthcare settings. These limitations substantially restrict the broad application prospects of MRC in CRC screening (41).

Although MRC is not the first-line choice for CRC screening, its radiation-free nature and high soft tissue resolution make it a valuable and complementary tool for specific populations. With future technological advancements, rapid scanning sequences such as compressed sensing and parallel imaging can shorten examination times and reduce motion artefacts; AI-assisted tools can automatically identify polyps and analyse imaging features through deep learning, increasing diagnostic efficiency. Concurrently, novel targeted molecular probes used as contrast agents, such as nanoparticle-labelled CEA, can specifically accumulate in tumour tissues to improve early lesion detection rates (41). While MRC holds promise for greater roles in early screening, its short-term integration with methods such as CS and CT-C is still needed to develop personalized screening strategies.

Visual endoscopic examinations

Colon capsule endoscopy (CCE). Capsule CS is a noninvasive, convenient intestinal imaging technology that captures real-time images of the entire colonic mucosa by having patients swallow a swallowable capsule containing a miniature camera. The first-generation capsule colonoscope (CCE-1) was introduced in 2006 (42). A European multicenter study demonstrated that the examination completion rate of CCE-1 reached 92.8% compared with that of CS, with a sensitivity of 68 to 85% for diagnosing polyps, adenomas, and CRC (43). Second-generation colon capsule endoscopes, featuring increased performance with a high imaging frequency and a wide field of view, were introduced in 2009. For screening colonic polypoid lesions ≥6 mm, CCE-2 demonstrates high accuracy. A meta-analysis reported that the sensitivity and specificity of CCE-2 for detecting ≥6 mm colonic polyps were 86.0 and 88.1%, respectively (44). A systematic review encompassing 582 studies revealed that CCE detection rates for CRC ranged from 64 to 100%, with a detection rate of 93% for completed CCE procedures. Furthermore, the diagnostic accuracy of CCE-2 is comparable to that of CS, and its diagnostic efficacy surpasses that of CT-C, making it a viable alternative to CS (45).

CCE is indicated for patients who experience difficulty with or cannot tolerate CS or in whom the CS procedure cannot be completed. Common contraindications for CCE include dysphagia or swallowing disorders, recent abdominal gastrointestinal surgery, known or suspected intestinal obstruction, the presence of a cardiac pacemaker or other implanted electronic medical devices, and pregnancy (46).

The European Society of Gastrointestinal Endoscopy proposes CCE as a screening tool for average-risk patients, those with an incomplete CS, patients who refuse a conventional CS, and patients with contraindications to conventional CS (47). The U.S. Food and Drug Administration (FDA) has approved CCE II for patients with previously incomplete CS (48). The recommended screening frequency is once every 5 years (49). Capsule CS is a fundamentally noninvasive and painless procedure that requires only the swallowing of a small capsule without any need for intubation or anaesthesia. This approach minimizes patient discomfort and directly leads to higher levels of acceptance and satisfaction. However, its clinical application has clear limitations, primarily the stringent bowel preparation requirements. Compared with CS or CT-C, CCE demands more extensive bowel preparation. In addition to laxatives such as polyethylene glycol for cleansing, a 'propellant' is required to facilitate capsule advancement and expulsion (50). Studies confirm that the sensitivity of lesion detection using CCE is significantly higher in patients whose bowel cleansing is 'good' or better than in those whose cleansing is inadequate (51,52). Furthermore, colon capsule endoscopy cannot replace the diagnostic and therapeutic functions of CS; further examination or treatment remains necessary for suspicious lesions.

FS. FS is an endoscopic procedure that involves a visual examination of the sigmoid colon and rectal lining. It facilitates the detection of abnormalities such as polyps and tumours and permits immediate biopsy or removal. This technique is limited to the lower third of the colon and is therefore not a complete screening solution for the entire bowel. Research has demonstrated that FS reduces the incidence of CRC by 24% (HR, 0.76; 95% CI, 0.72-0.81) and mortality by 25% (HR, 0.75; 95% CI, 0.67-0.83). With respect to distal CRC, the incidence and mortality rates decrease by 41 and 45%, respectively (53). Another meta-analysis involving 702,275 individuals showed that FS reduced the incidence of CRC by 26% [relative risk (RR), 0.74; 95% CI, 0.66-0.84] and mortality by 30% (RR, 0.70; 95% CI, 0.58-0.85) (54). Bretthauer and Pilonis (55) found that a single FS reduces the incidence of CRC by 24% and the mortality rate by 25%, providing sustained protection against CRC for >20 years.

FS has clear clinical value in CRC screening, with its core advantages coexisting alongside limitations. In terms of advantages, the primary benefit lies in its minimally invasive and safe nature: No general anaesthesia is needed, and the procedure can be completed with only local lubrication, resulting in minimal patient discomfort and a significantly lower complication rate than CS (56); its secondary benefits are that it is highly efficient and cost effective, with a short examination time averaging 10-15 min and simplified bowel preparation, making it suitable for large-scale population screening. Additionally, its ability for immediate intervention further increases screening efficiency, as detected polyps can be directly biopsied or resected, avoiding the need for a second examination. However, its application is constrained by several major limitations, including limited coverage, as it can only visualize areas within 60 cm of the anus, making it unable to assess the transverse colon, ascending colon, and caecum, thereby carrying a risk of missed diagnoses (57); and operator dependence, with frequent obstruction at the intestinal tortuosity requiring skilled techniques to prevent false tract formation.

Despite its limited coverage, FS serves as an effective supplement or alternative to CS when CS is unsuitable for large-scale population screening, increasing accessibility. Future optimization through technologies such as high-definition imaging and narrow-band imaging, combined with screening methods such as multitarget stool DNA (mt-sDNA), will further expand its value in CRC screening.

CS. CS involves the insertion of a tube equipped with a camera and light source to directly observe structural changes in the intestinal mucosa. It enables direct tissue sampling for pathological diagnosis and serves as the gold standard for CRC screening. A study revealed that CS has a sensitivity of 95-97% for detecting CRC (58). The advantage of CS lies in its ability to directly visualize the intestinal mucosa, enabling the detection of minute lesions such as polyps and tumours with exceptionally high diagnostic accuracy. The integration of artificial intelligence (AI) systems can further improve detection rates during the examination (59). Polyps can be removed directly during the CS procedure, thereby avoiding the risk of secondary surgery for some patients. Regular CSs can promptly identify and address precancerous lesions, effectively reducing the incidence of CRC. A clinical study demonstrated that CS reduced the incidence of CRC by 31% [RR, 0.70 (95% CI, 0.66-0.75)] and mortality by 50% [RR, 0.68 (95% CI, 0.61-0.76)] (60). However, CS has inherent limitations. The administration of laxatives is needed prior to

the procedure to clear the bowel, making bowel preparation cumbersome. Although it is an invasive procedure with an extremely low complication rate, risks such as bowel perforation and bleeding objectively exist (61). Furthermore, the high cost of CS makes it unsuitable for large-scale screening programs.

4. Progress in screening methodologies

mt-sDNA testing. CRC typically originates in the epithelial tissue of the colon and rectum and initially grows towards the intestinal lumen. During progression, tumour cells continuously shed into the intestinal cavity and are expelled with faeces. The measurement of mt-sDNA enables the early detection of CRC and advanced adenomas through the analysis of Kirsten rat sarcoma viral oncogene homolog (KRAS) gene mutations, methylation of the bone morphogenetic protein 3 (BMP3) and N-Myc downstream-regulated gene 4 protein (NDRG4) genes, and haemoglobin levels in abnormal faecal cells. Mt-sDNA is a noninvasive CRC screening tool approved by the U.S. FDA. Its sensitivity and specificity for CRC are 93.9 and 90.6%, respectively. Its sensitivity and specificity for advanced precancerous lesions were reported to be 43.4 and 92.7%, respectively. The negative predictive values for CRC and advanced precancerous lesions are 99.97 and 93.0%, respectively (62-64). Mt-sDNA has been recommended by multiple authoritative academic organizations, including the U.S. National Preventive Services Task Force, the American Cancer Society, and the National Cancer Collaboration Group, for use in early colorectal tumour screening among asymptomatic individuals. The recommended screening interval is once every three years or once annually. China has incorporated it as a noninvasive screening option for individuals unwilling to undergo CS or FIT (65).

Although mt-sDNA offers higher sensitivity than the FIT in screening for CRC and larger adenomas, and requires no dietary restrictions or bowel preparation, its clinical application still faces multiple challenges. First, its specificity falls short of expectations. The specificity of mt-sDNA for CRC (86.6%) is significantly lower than that of the FIT (94.8%), increasing the risk of false positives (62). Second, its detection rate for precancerous lesions remains inadequate at ~42%, limiting its value for early intervention. Third, the high testing cost directly reduces patient compliance. The reliance of faecal DNA testing on bacterial genetic material necessitates more efficient methods for human DNA isolation and purification. Its technical complexity, along with specialized equipment and personnel requirements, further limits its accessibility within primary healthcare settings (66).

Liquid biopsy. Liquid biopsy, first proposed by Pantel and Alix-Panabières in 2010 (67), can be used to detect cancer-related cellular products such as circulating tumour cells (CTCs), circulating tumour DNA (ctDNA), cell-free circulating nucleic acids, microRNAs (miRNAs or miRs), long noncoding RNAs (lncRNAs), exosomes, and proteins in bodily fluid samples such as peripheral blood (68). As a noninvasive detection method, liquid biopsy allows the analysis of CTCs or ctDNA in peripheral blood through dynamic repeated sampling. With breakthroughs in single-cell sequencing and microfluidic technology, liquid biopsy has evolved from a theoretical concept to a critical tool for clinical staging, recurrence prediction, and assessments of the targeted therapy response. It enables real-time tracking of tumour recurrence and metastatic processes while dynamically evaluating treatment responses, providing immediate molecular evidence for personalized therapy (69).

ctDNA. ctDNA comprises fragmented DNA that enters the bloodstream following tumour cell death via apoptosis or necrosis. These circulating fragments harbour tumour-specific genomic alterations, including mutations in the adenomatous polyposis coli, KRAS, and TP53 genes and promoter methylation events, such as the methylation of Septin 9 (SEPT9), NDRG4, and BMP3 (70). DNA methylation is a biochemical process in which DNA methyltransferases catalyse the addition of a methyl group to the fifth carbon of a cytosine residue within a CpG dinucleotide, resulting in 5-methylcytosine. In oncology, DNA methylation biomarkers represent specific, aberrant methylation alterations observed in tumour cells. These epigenetic changes are not merely incidental but are dynamically maintained across the continuum of tumorigenesis, from initiation through progression (71). As a cytoskeletal GTPase belonging to the conserved septin family, SEPT9 is a cell cycle-associated protein that participates in multiple biological processes, such as cellular proliferation and autophagy (72). In patients with CRC, cytosine methylation occurs within the V2 region of the SEPT9 gene. Methylated SEPT9 (mSEPT9) serves as a specific molecular biomarker of the early stages of CRC development. Moreover, the degree of SEPT9 methylation progressively increases with the progression of CRC pathological CRC (73). The mSEPT9 gene is released into peripheral blood and can be detected through specific DNA amplification, enabling its application in CRC screening and diagnosis. The fundamental principle involves extracting patient blood samples, isolating ctDNA, and analysing this ctDNA using highly sensitive molecular biology techniques (74).

mSEPT9 is currently the only blood-based tumour marker test approved by the U.S. FDA for CRC screening (75). In accordance with the 2020 National Comprehensive Cancer Network (NCCN) guidelines for CRC screening, for individuals who decline other recommended screening methods, plasma SEPT9 gene methylation testing is recommended. A positive mSEPT9 result still requires follow-up CS (76). A meta-analysis revealed that the diagnostic sensitivity and specificity for CRC ranged from 62-71 and 91-92%, respectively (77). The mSEPT9 detection rates for stage I CRC and adenomas are only 45 and 15%, respectively. Therefore, mSEPT9 has limited value for screening early-stage CRC and adenomas. mSEPT9 is expressed at low levels in healthy tissues but is expressed at significantly high levels in pathological tissues such as CRC, making it a potential biomarker for CRC diagnosis (78,79). Its sensitivity and specificity for detecting CRC are 90 and 88%, respectively (80). However, mSEPT9 exhibits relatively low sensitivity for early-stage CRC and advanced adenomas. Studies indicate that the positive detection rate in the CRC group increases with increasing malignancy, and elevated mSEPT9 levels correlate significantly with higher TNM and Dukes stages (81). These findings suggest that SEPT9 may aid

in clarifying the pathological diagnosis and staging of CRC. A meta-analysis suggested that variations in sensitivity may also be related to the detection methods. Previous studies using the Epi proColon test 1.0 and PCR showed that switching to the Epi proColon test 2.0 improved sensitivity (71.1-95.6%) while maintaining high specificity (81.5-99%) (82).

ctDNA testing requires only a small blood sample, making it convenient and rapid with a minimal physical burden on patients, thereby improving testing compliance. ctDNA overcomes tumour heterogeneity. ctDNA in the blood can originate from cells in different tumour sites, thus providing a more comprehensive reflection of the genetic profile of the tumour (83). A prospective, multicentre, observational study involving 27,010 participants revealed that ctDNA had a sensitivity of 79.2% (95% CI, 68.4-86.9%) for CRC, a specificity of 91.5% for advanced CRC, a negative predictive value of 90.8%, and a positive predictive value of 15.5% (84). A previous meta-analysis revealed that ctDNA serves as an early biomarker for the long-term prognosis of patients with unresectable CRC (85). Lygre *et al* (86) reported that postoperative detection of ctDNA serves as a prognostic factor in patients with nonmetastatic right-sided CRC, with a positive predictive value for recurrence as high as 100%. Cassinotti *et al* (87) reported sensitivities of 55 and 84% when three-gene and six-gene methylation panels, respectively, were used to distinguish patients with adenomas and CRC from healthy controls. Therefore, multiple differentially methylated genes can be identified in CRC tissues, precancerous lesions, and normal tissues. These genes can be combined into multiple gene panels for joint detection to enhance sensitivity (88,89). The detection of ctDNA requires ultrasensitive methods for identifying low-frequency mutations, which are costly and lack standardization due to significant variations in sensitivity and specificity across different testing platforms. Novel multimodal ctDNA blood testing technology integrates genomics, epigenomics, fragmentomics, and proteomics for early CRC diagnosis, achieving detection sensitivities and specificities of 93 and 90%, respectively (90). The half-life of ctDNA is only 2 h (91), and rapid sample processing is needed to avoid an increased risk of false negatives.

CTCs. CTCs are tumour cells that detach from the primary focus of the tumour and are transported in the peripheral circulation or invade blood vessels through epithelial-mesenchymal transition (92). In 2010, the U.S. Joint Commission on Cancer (AJCC) included CTCs in the TNM staging system for a more accurate evaluation of tumour distal metastasis (93). Baek *et al* (94) used a CTC concentration ≥5/7.5 ml as the cut-off value and reported that the sensitivity and specificity for distinguishing between patients with CRC and healthy individuals can reach 75 and 100%, respectively. Research has shown that the sensitivity of preoperative CTC detection for CRC can reach 95.2% (95). The presence of CTCs in peripheral blood is significantly related to the OS and progression-free survival (PFS) of patients. As an index for detecting metastatic CRC, CTCs are currently mainly used to evaluate the prognosis of patients with CRC. A previous study by Lu *et al* (96) showed that the PFS of patients with increased total numbers of epithelial CTCs, interstitial CTCs and CTCs was significantly reduced ($P<0.05$).

Clinically, a CTC analysis supports the multifaceted management of CRC, including an auxiliary diagnosis, efficacy evaluation, minimal residual disease detection, therapeutic guidance, and recurrence surveillance. However, CTC detection is not sufficiently sensitive for diagnosing early-stage CRC. Second, CTC detection in CRC varies greatly across different technology platforms. At present, the mainstream technology platforms include the CellSearch platform (http://cellsearchctc.com), microflow control chip technology, and nanotechnology-based capture (97). The CellSearch platform is currently the only CTC detection platform approved by the U.S. FDA for metastatic CRC. It is based mainly on EpCAM antibody-conjugated magnetic beads that can enrich CTCs and identify them through cell keratin staining. The operation is standardized, and the results are reliable. The results of CTCs from patients with CRC obtained using the CellSearch platform revealed that the sensitivities for detecting stage I, II, III and IV disease were 4.9, 10.5-20.7, 8.3-24.1 and 18.8-60.7%, respectively (92), whereas the sensitivities of the CTC-biopsy membrane filtration method were 12.5, 31, 74 and 91.7%, respectively (98). Improving the CTC detection rate of early CRC and precancerous lesions depends on sensitive detection technology. Finally, the cost of CTC testing is relatively high, which limits its popular application.

Exosome detection. Exosomes have become an important liquid biopsy marker in recent years. These membranous vesicles have a diameter of 30-150 nm and a density of 1.13-1.19 g/ml and are released from the cell after multiple intracellular vesicles fuse with the cell membrane (99). Studies have shown that exosomes contain a variety of nucleic acids, such as miRNAs, lncRNAs, circular RNAs, transfer RNAs and small nuclear RNAs, which mediate intercellular communication, cell proliferation, immunomodulation, angiogenesis and other processes and participate in the development of tumours (100,101). Exosomes are common in all types of body fluids, such as cerebrospinal fluid, plasma, urine, ascites, breast milk and saliva, and have unique detection advantages, such as high abundance, rich information load, stable content and easy access (102).

miRNAs are small noncoding RNAs that participate in regulating gene expression by binding to mRNAs with high conservation and high stability (103). In CRC, the expression of specific miRNAs undergoes characteristic changes and can be used as potential biomarkers for early diagnosis, outcome assessment and risk stratification. A meta-analysis revealed that the sensitivity of miR-21 for CRC was 77%, and the specificity was 83% (104). The upregulation of miR-21 has been shown to be affected by genetic and epigenetic changes, as well as tumour progression, and to be related to TNM stage, poor prognosis and OS (105,106). In addition, its overexpression was shown to significantly increase the resistance of CRC tumours to 5-FU and radiation, highlighting its potential as a tool for identifying diagnostic biomarkers and evaluating therapeutic responses (107). In a cohort of 207 patients, the sensitivity of miR-139-3p was 96.60%, the specificity was 97.80%, and the AUC value was 0.994 (108). Numerous types of miRNAs have been identified, but different indicators present substantial differences in their diagnostic specificity and sensitivity for CRC. A number of studies have shown that the combination

of multiple miRNAs is advantageous for the early diagnosis of CRC (109,110). Quadra-FEVOR, a biomarker combination composed of four miRNAs, namely, miR-16-2-3p, miR-375-3p, miR-378a-3p and miR-7-5p, was significantly upregulated in patients with CRC; in the diagnosis of CRC, the specificity was 93.5%, the sensitivity was 100%, and the AUC was 0.9405 (111). However, exosome heterogeneity is significant, and more advanced detection technologies need to be established.

Imaging-based innovations. CS is a highly sensitive method for detecting CRC and various precancerous lesions and is the gold standard for screening for CRC. The missed diagnosis rate of polyps or adenomas in traditional two-dimensional (2D) colonoscopy is 9-28% (112). Three-dimensional (3D) imaging technology can be used to improve the sensitivity of CS for lesions, and highlight their morphological characteristics that can serve as evidence for a diagnosis. A multicentre, randomized controlled trial revealed that the polyp detection rate of the second-stage 3D group was significantly higher than that of the 2D group (27.7% vs. 19.9%; P=0.002), and the polyp miss rate was significantly lower (28.8% vs. 39.1%; P=0.002) (113).

Despite these advances, existing optical diagnostic techniques [such as narrow-band imaging (NBI) and blue-light imaging (BLI)] face clinical constraints: Their accuracy relies heavily on operator experience, leading to poor consistency among novices (114). While AI has been explored for polyp detection (86), its adoption is hindered by limited specificity, poor model interpretability, and high heterogeneity in training data. The FDA approved the SCALE EYE system, a measurement-enabled imaging technology comprising a laser-equipped colonoscope (model EC-760S-A/L) and endoscopic support software (EW10-VM01) (https://www.fujifilm.com/us/en/news/fujifilm-receives-510k-clearance-for-scale-eye) to overcome these challenges. This system displays linear or circular virtual measurements/scales of the region of interest on the monitor, enabling endoscopists to estimate the lesion size *in vivo* accurately and objectively with a single button press, eliminating the reliance on visual estimation, consumables, or additional instruments.

5. Conclusions

The early symptoms of CRC are atypical, and numerous patients have progressed to middle and late stages or even distant metastasis by the time of diagnosis. Therefore, early detection is key to preventing and treating CRC early. For every 1% increase in the detection rate of adenoma, the risk of cancer is reduced by 3% (115); thus, CRC screening is a key strategy for reducing the disease burden. The present review systematically examined the principles, effectiveness and latest progress in a variety of CRC screening methods. Current screening methods include faecal detection, haematological examinations, imaging examinations, endoscopic technology and the emerging liquid biopsy, each with its own advantages and limitations. A table presenting the comparison, clinical applicability, challenges and future directions of CRC screening methods on the basis of data from literature is provided (Table I).

Different screening methods have unique characteristics in terms of sensitivity, cost and applicability (Table I). FOBT is a basic screening method, among which the immune method FIT has gradually replaced the chemical method due to its high sensitivity and specificity, but the detection rate of precancerous lesions is limited. The use of tumour markers such as CEA and CA199 in haematological examinations is not recommended for the initial screen due to insufficient sensitivity and specificity, but nutritional and inflammatory markers such as ALB and the NLR are valuable for a prognostic evaluation. In the field of imaging, CT-C is an important supplement due to its noninvasive nature and ability to detect extracolonic lesions, whereas MRC is suitable for special groups and has the advantage of no radiation. In terms of endoscopic technology, CS, the gold standard, has both diagnostic and therapeutic functions, but its invasiveness limits its popularity; CCE improves compliance through its noninvasive design but is limited by the requirements of intestinal preparation; and FS is limited by the scope of the examination. Emerging molecular diagnostic technology has made breakthroughs. mt-sDNA achieves high-sensitivity screening for CRC and advanced adenomas by detecting KRAS mutations and methylation markers, however, the cost and false-positive rate rquire optimization; the detection of ctDNA methylation, such as mSEPT9, in liquid biopsy and CT-C analysis, is noninvasive. Novel monitoring approaches have been developed. The diagnostic specificity of exosomal miRNA combinations such as quadra-FEVOR reaches 93.5%; innovations in imaging technology include 3D imaging assisted by AI; 3D colonoscopy reduces the polyp missed diagnosis rate by 28.8%, and the AI algorithm improves the effectiveness of early lesion identification.

In the evaluation of CRC screening strategies, economic benefits, such as the direct costs as associated with the examination, and indirect benefits, such as reduced treatment expenditure due to early detection, need to be comprehensively considered. A literature analysis revealed that different screening methods result in significant differences in cost and benefits (116). From the perspective of a low-cost strategy, the cost of the FIT is low because it is easy to operate and low in price, which is suitable for large-scale population censuses (117). However, its high false-positive rate may lead to unnecessary CS, thus increasing the overall cost to a certain extent. By contrast, the single cost of CS is relatively high, but it has the advantage of completing diagnosis and treatment at one time, which can significantly reduce the medical burden of disease progression in long-term follow-up; thus, the cost-effectiveness in high-risk groups is particularly prominent. In addition, although mt-sDNA is more sensitive, it is expensive. At present, it is suitable mainly for high-risk patients or those with specific needs. Promoting CS screening among high-risk groups can achieve improved cost-effectiveness. Considering the aforementioned factors, in areas with relatively limited resource allocation, prioritizing FIT for initial screening and referring positive patients for a CS for diagnosis and treatment are appropriate measures (118). In areas with higher socioeconomic status, high-end strategies that combine mt-sDNA with an imaging examination can be explored to improve screening efficiency and meet individualized needs.

Research has shown that formulating differentiated screening strategies according to the individual risk can not

Table I. Comparison of colorectal cancer screening methods.

A, FOBT

Screening methods	Sensitivity (%)	Specificity (%)	Advantages	Limitations
gFOBT	12.9-79.4	86.7-97.7	Noninvasive, low-cost, easy to operate	Low sensitivity, affected by diet and medication, requires continuous monitoring.
FIT	91	95	Higher sensitivity than gFOBT, no dietary restrictions required	Low sensitivity for detecting precancerous lesions, with costs higher than gFOBT.
mt-sDNA	93.9	90.6	High sensitivity, noninvasive	High cost, with only 43.4% sensitivity for adenomas and a risk of false positives.

B, Haematological tests

Screening methods	Sensitivity (%)	Specificity (%)	Advantages	Limitations
CEA	46.59	80	Easy to operate, widely applicable	Low sensitivity; not recommended for screening purposes.
CA19-9	14.39	89		
CA724	44.80	97		
CA125	10.04	99		

C, Radiological examinations

Screening methods	Sensitivity (%)	Specificity (%)	Advantages	Limitations
CT-C	27-100	88-100	Whole colon imaging with a low complication rate	Radiation exposure, low sensitivity for minor lesions, high requirements for bowel preparation
MRC	48-100	60-100	Radiation-free, high soft tissue resolution	Long inspection times, high costs, and limited sensitivity

D, Visual endoscopic examinations

Screening methods	Sensitivity (%)	Specificity (%)	Advantages	Limitations
CCE	86.0	88.1	Noninvasive and painless, with high patient acceptance	Intestinal preparation is rigorous; biopsy is not a viable x requirements for bowel preparation
FS	N/A	N/A	Minimally invasive and safe, with short examination times	Only the left half of the colon is examined, posing a risk of a missed diagnosis.
CS	95-97%	>99%	Gold standard, capable of simultaneous diagnosis and treatment	Invasive, risk of complications, high cost

Table I. Continued.

Screening methods	Sensitivity (%)	Specificity (%)	Advantages	Limitations
E, Liquid biopsy				
mSEPT9	62-71	91-92	Noninvasive, blood samples are easily obtained	Low sensitivity for early-stage lesions and high costs.
ctDNA	79.2	91.5	Noninvasive, capable of dynamic monitoring	Limited sensitivity for early detection, posing challenges for standardization
CTCs	75	100	High prognostic value	Early diagnosis suffers from insufficient sensitivity and significant variations in technical platforms
miRNAs	77-100	83-93.5	High Sensitivity	Insufficient standardization, and heterogeneity issues

FOBT, faecal occult blood test gFOBT, guaiac-based faecal occult blood test; FIT, faecal immunochemical test, mt-sDNA, multitarget stool DNA; CEA, carcinoembryonic antigen; CA-, carbohydrate antigen; CT-C, computed tomographic colonography; MRC, magnetic resonance colonography; CCE, colon capsule endoscopy; FS, flexible sigmoidoscopy; CS, colonoscopy; mSEPT9, methylated SEPT9; ctDNA, circulating tumour DNA; CTCs, circulating tumour cells; miRNAs, microRNAs; N/A, not available.

only increase the early detection rate but also effectively prevent the excessive inspection of low-risk groups and missed inspection of high-risk groups (119). The Asia-Pacific CRC Working Group has developed a scoring system, namely, the Asia-Pacific CRC Screening Score (APCS), which includes four risk factors: Age, sex, family history of first-degree relatives with CRC, and smoking. The system can be used clinically to evaluate the risk of CRC through the comprehensive score of risk factors. The score is 0-1 for low risk, 2-3 for medium risk, and 4-8 for high risk (120). Specifically, for high-risk groups with strong risk factors, direct use of CS as a first-line method is recommended, and the screening frequency is usually once every 1-2 years to ensure the high-sensitivity monitoring of precancerous lesions and early tumours. By contrast, individuals at medium risk can be assessed with noninvasive or minimally invasive initial screening schemes, such as the FIT or mt-sDNA once a year, with a timely referral for CS for diagnosis and treatment after positive results. For low-risk individuals without clear risk factors, the screening interval can be appropriately extended based on the premise of ensuring basic coverage, such as using the FIT every 2 years or CT-C every 5 years, to maintain a reasonable detection level while controlling costs (3).

In the process of screening for CRC, insufficient screening compliance and poor follow-up management often restrict the overall prevention and control effect. Therefore, formulating targeted intervention measures and optimizing management paths are particularly important. Compliance can be improved in three ways to enhance the participation of the patients: First, the screening process can be simplified by developing convenient home testing kits, such as faecal self-picking boxes; second, health education can be strengthened to increase the willingness of patients to actively participate in the examination by explaining the clear benefits of screening in early detection and reducing the death rate; and third, policy support can be improved by promoting coverage of screening costs through medical insurance, and providing targeted subsidies for vulnerable groups with low participation rates to reduce the economic burden and create positive incentives. However, even if the initial screening can be performed smoothly, the lack of follow-up management may still affect the overall value of screening. Therefore, optimization of the tracking and long-term follow-up mechanism of positive results at the same time is necessary. On the one hand, an electronic health record system covering screening, diagnosis and treatment should be established to automatically identify and review reminders of positive patients and ensure that diagnostic steps such as CS are not delayed; on the other hand, in long-term management, patients need to be reviewed every 3-5 years after adenoma removal, and liquid biopsy technology can be introduced for dynamic recurrence monitoring to improve the timeliness and accuracy of risk detection while reducing the frequency of repeated endoscopy.

In the future, CRC screening systems need to be improved through the dimensions of technological innovation and system optimization to overcome existing bottlenecks and improve the overall prevention and control effectiveness. At the technical level, the rapid development of liquid biopsy has provided new opportunities for early detection. However, currently, the sensitivity of single markers such as mSEPT9 for stage I cancer is

only 45%, suggesting that technical problems such as tumour heterogeneity and weak signals still need to be overcome. Moreover, the application of AI-assisted endoscopy systems also has considerable prospects, but the standardization and cross-centre verification of relevant algorithms are still necessary prerequisites before they can be widely implemented in clinical practice. In terms of access, the research and development of portable testing equipment, such as miniaturized CT colon imaging or MRC devices, can help reduce equipment and operation costs, thus benefiting areas with scarce medical resources. However, technological progress must be supplemented by standardized construction and policy support to be transformed into sustainable public health benefits. The formulation of unified screening guidelines and paths based on national epidemiological characteristics and health economic evidence is urgently needed to avoid the waste of resources and decrease in efficiency caused by the use of different strategies. In addition, attention should be paid to the construction of a multidisciplinary collaboration mechanism, systematically integrating professionals in the fields of digestive medicine, medical imaging and public health, and forming a full-chain service network covering screening, diagnosis, treatment and follow-up. In summary, future improvements should be made simultaneously in advancing cutting-edge technology, improving costs and accessibility, and establishing standards and cross-field collaboration to promote CRC screening in a more accurate, efficient and equitable direction.

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Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The author declares that she has no competing interests.

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