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Review

Colorectal Cancer Screening

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Abstract

Colorectal cancer (CRC) is a common health problem with a high incidence and mortality rate, but it is also highly preventable. The development of most CRC is a multistep process that includes a series of histological, morphological, and genetic changes. screening for CRC can be of great help in reducing its incidence. Here, we review the history of CRC development, risk factors, characteristics of various screening modalities, and quality indicators of colonoscopy. In addition, we discuss the use of artificial intelligence in CRC screening and interventions to improve screening adherence. However there are many patients eligible for screening who still do not receive screening. Therefore, it is important for primary care physicians to understand the characteristics of various screening modalities to recommend appropriate screening strategies for patients to maximize patient participation, adherence, and quality of screening with the aim of reducing CRC morbidity and mortality.

Key words: Colorectal Cancer; Screening; Colonoscopy; Fecal Occult Blood Test; Fecal Immunochemical Test.

1. Introduction

Colorectal cancer (CRC) is a global health burden, the third most common cancer, and the second leading cause of death after lung cancer (1). Global colorectal cancer incidence and mortality rates are significantly higher in men than in women. By 2030, the global burden of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths (2).

Most CRC occurs through the adenoma-carcinoma sequence (3), and its slow progression from precancerous lesions to cancer gives the opportunity to reduce the burden of disease through early screening. The significance of screening is to reduce the morbidity and mortality of CRC as well as to save the cost of CRC treatment (4). However, the effectiveness of screening is influenced by a number of factors, which may be related to various factors such as

limitations in test performance and low patient compliance (5). As a result, this has led to significant differences in global CRC morbidity and mortality (6). This article will focus on discussing the advantages, disadvantages of various screening modalities including emerging screening modalities such as blood-based tests, urine-based metabolomic tests and stool-based microbiological tests to provide background and guidance for primary care physicians.

2. History of colorectal cancer

CRC is a general term for malignant neoplasms associated with various histology of the colon and rectum, and more than 90% of colorectal cancers are adenocarcinomas originating in the mucosal epithelium of the large intestine (7). Colorectal cancer is a multistep developmental process from normal epithelium to precancerous lesions (so-called adenomas), to malignant lesions (cancer), to invasion of surrounding tissues and eventually can spread systemically (metastasis) (8)(Figure 1). As a pathogenesis of CRC, adenoma-carcinoma sequence has been widely studied.

Most colorectal neoplasms originate from precancerous polyps, and there are two main types of polyps with malignant potential: adenomatous polyps and sessile serrated polyps (SSPs), each of which is associated with a different risk of developing CRC (9). Precancerous polyps usually have distinctive features and can be identified by colonoscopy. Adenomatous polyps are usually well-defined with an elevated appearance and may have a stalk or a tip, whereas sessile serrated polyps are flat (no tip) and usually have a "mucus cap" with faint polyp margins (10). These different polyp subtypes lead to the development of cancer through different tumor pathways. The adenoma-carcinoma pathway accounts for 60-70% of all CRCs, whereas the serrated tumor pathway accounts for 15-30% of CRCs (11, 12).

The adenoma-carcinoma sequence describes the evolution of histological changes from adenoma to carcinoma due to various mutations (13). Adenomas occur when the normal mechanisms regulating DNA repair and cell proliferation are altered (14). Many adenomas start as small polyps that enlarge and become dysplastic and eventually cancerous (15). The adenoma-carcinoma pathway occurs through alterations in the APC and RAS genes (4), firstly inactivating mutations in the APC gene are thought to be the initiating step in the adenoma-carcinoma sequence, which affects chromosome segregation during cytokinesis. Subsequently, mutations in the KRAS oncogene occur, with downstream effects on cell growth, differentiation, motility and survival. Over time, these mutations may lead to loss of function of the P53 gene, a major regulator of transcription and apoptosis, thereby affecting a wide range of cellular functions and eventually leading to carcinogenesis (16, 17).

Adenomas have different histologic classifications and have different malignant potential. Adenomas may be further characterized as tubular or villous adenomas according to the criteria established by the World Health Organization. Tubular and villous adenomas, especially those exhibiting villous histology (i.e., at least 25% villous), or those exhibiting highly atypical hyperplasia are referred to as 'progressive colon tumors' or 'progressive pathological adenomas' and they carry the greatest risk of malignancy (18). The risk of adenoma developing into colorectal cancer increases with the increase of polyp size (19, 20). If polyps were larger than 1cm at initial examination, the relative risk of metachronous tumors was 2.7 times the expected risk. Adenomas smaller than 1cm have about a 1% risk of developing cancer. For adenomas of 1-2cm, the risk is about 10%, and for those over 2cm, the risk is 50% (21).

2. Influence factors

A variety of modifiable and non-modifiable risk factors are known to influence the progression of CRC, and mitigation of these risk

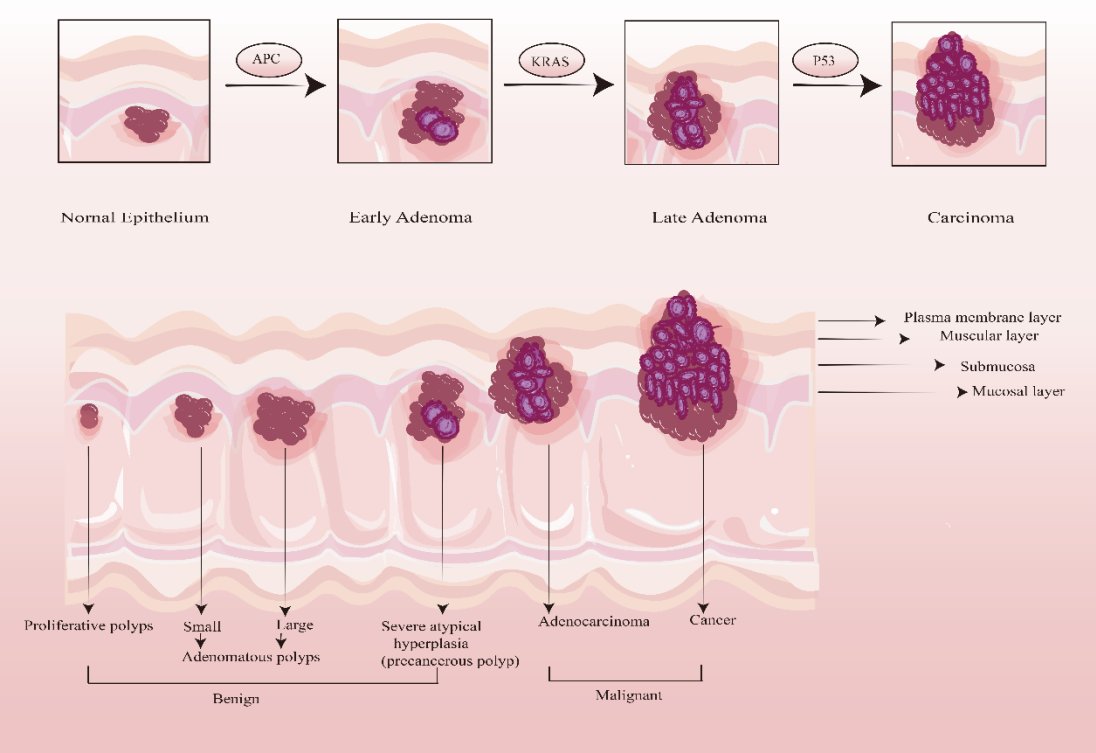

Figure 1. Histological and genetic changes during colon cancer carcinogenesis.

factors plays an integral role in colorectal cancer prevention (22). And protective factors can reduce the risk of colorectal cancer (Table 1). Age, race, history of inflammatory bowel disease, potential susceptibility mutations, and family history of advanced colorectal polyps or cancer are unmodifiable risk factors (10). For most people, age is the most important risk factor for developing colorectal cancer (13). Because cancer is an age-related disease, the development and mortality of colorectal cancer increases rapidly after the age of 50 years, with an estimated 90% of cases and deaths worldwide occurring after this age (23). Inflammatory bowel disease has been shown to increase the risk of colorectal cancer. This is most evident in ulcerative colitis (UC) (13). A meta-analysis of 81 studies yielded a colorectal cancer incidence rate of 1.58/1000 person-years in patients with UC (24). Among the common malignancies, colorectal cancer (CRC) accounts for the largest proportion of familial cases. Approximately 30% of colorectal cancer cases are hereditary (25, 26). Hereditary colorectal syndromes include many specific genetic disorders associated with the development of colorectal cancer; hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome and familial adenomatous polyposis (FAP) are the most common familial syndromes associated with the development of colorectal cancer and have been reported in only 2%-5% of colorectal cancer cases (27, 28). Patients with a personal history of colorectal cancer or adenoma have a higher risk of colorectal cancer (29). Individuals with two first-degree relatives with colorectal cancer have an increased risk of developing advanced tumors compared to the average risk of colorectal cancer (30). According to a meta-analysis of 17 studies including 924,932 men and women, men had a higher risk of developing advanced colorectal neoplasms than women (31).

Epidemiological studies have shown that lifestyle and dietary habits are the most common environmental factors for colorectal adenoma and colorectal cancer (32). These modifiable risk factors can be reduced by modest changes in dietary and physical activity habits. A sedentary lifestyle increases the risk of colorectal cancer (33). A large case-control study noted that high physical activity was associated with a reduced risk of colon cancer and that promoting physical activity, especially outdoor activity, may be a promising strategy for colon cancer prevention (34). In addition, smoking and alcohol consumption have been shown to increase the risk of colorectal cancer (35, 36). A meta-analysis of prospective studies indicated that high intake of red meat and processed meat significantly increased the risk of colorectal cancer (37). Modifiable risk factors should be discussed at the time of colorectal cancer screening to further reduce the risk of colorectal cancer.

In a cross-sectional study involving 2548 patients, Eileen Shaw et al. found that increased dietary fiber intake and the use of nonsteroidal anti-inflammatory drugs (NSAIDS) were generally associated with a reduced risk of colorectal cancer (38). Enrico et al. studied the effects of aspirin in two large randomized trials with more than 20 years of post-trial follow-up and found that regular use of aspirin or NSAIDS was associated with a reduced risk of colorectal cancer, especially after 10 or more years of use (39). Other studies have shown that taking aspirin for 5 years or longer can reduce the risk of proximal colon cancer by about 70%, and also reduce the risk of rectal cancer (40). Folic acid supplementation is believed to reduce the incidence of colorectal cancer, but more effective evidence is needed for verification (41, 42).

Table 1. Risk factors and protective factors for colorectal cancer

Risk factors		Protective factors
Modifiable	Unmodifiable	
Sedentary	Age	Sports activities
Smoking	Race	dietary fiber
Drinking	IBD	vitamin
Red meat or processed meat	Susceptibility gene mutation	aspirin
	Late polyps of the colonic	folic acid
	Family history of cancer	

4. Screening method

Various screening modalities have been studied to reduce colorectal cancer morbidity and mortality in average-risk individuals. There are several different screening modalities for CRC, each with advantages and limitations（Table 2）

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4.1 Fecal occult blood test

The fecal occult blood test (FOBT) for clinical diagnosis of CRC and as a screening tool for CRC is based on the fact that CRC releases tiny, invisible traces of blood (occult blood) into the intestinal lumen. FOBT is designed to detect hemoglobin in the stool (43). Currently, there are two main types of FOBT screening modalities: guaiac-based tests (gFOBT) and immunochemical tests (iFOBT).

The gFOBT is an early form of FOBT currently available, which is a simple test with proven benefits (44). And gFOBt is inexpensive and a non-invasive screening modality. gFOBt primarily detects the presence of heme (hemoglobin in blood) in stool samples, which chemically reacts with a developer (hydrogen peroxide) to oxidize guaiacol and turn blue (45). However, to obtain a significant color change, a moderate amount of heme is required and therefore the sensitivity of gFOBt is relatively low

(46). gFOBT relies on a pure oxidation reaction and therefore peroxidase in food can influence the assay results. Hemoglobin is present in red meat and peroxidase is present in fresh fruits and vegetables. Therefore, these foods have the potential to produce false positive results (47). In contrast, the administration of antioxidants such as vitamin C can lead to false negatives (48). There are other drawbacks, such as the lack of automated tools that make the results unquantifiable and the significant variation in the assessment of gFOBT results by laboratory staff (49). In addition, this test is unable to detect polyps and has a relatively low sensitivity for advanced adenomas (50).

The fecal immunochemical test (FIT) identifies hemoglobin in stool specimens by detecting the formation of monoclonal antibodies or polyclonal antibody-hemoglobin complexes (51). Therefore, FIT is independent of food and operator and requires a smaller volume of stool specimens. In addition, the sensitivity and specificity of FIT for cancer and adenoma has been shown to be superior to gFOBt (47, 52). One comparative study found that FIT had a similar positive predictive value for cancer (5.9% vs. 5.2%) and a higher positive predictive value for advanced adenomas (27.2% vs. 17.5%) as gFOBt. A large controlled trial found significantly higher detection rates of advanced adenomas and cancers with FIT (53). A cohort study found that participation in a FIT screening program reduced colorectal cancer incidence by 33% in men, 21% in women, and 65% and 54%, respectively, in colorectal cancer mortality (54). An intention-to-screen study from Italy demonstrated a causal relationship between the introduction of FIT screening and a steady 28% reduction in the annual incidence of CRC after 8 years (55). Therefore, the main choice of non-invasive screening is currently FIT, which has the advantage of reduced invasiveness and significantly lower costs (56).In conclusion, stool tests are a non-invasive and inexpensive method that can detect occult bleeding. However, they cannot detect polyps, as the latter usually do not bleed, and they are less sensitive to adenomas (50, 57). In addition, annual examinations are required to improve sensitivity.

Table 2. advantages and disadvantages of CRC screening

Methods	Advantages	Disadvantages
gFOBT	• the operation is simple • the cost is low • non-invasive	• It's influenced by food, what you eat • Low sensitivity • Failure to detect polyps
FIT	• non-invasive • Not affected by food, operator • High sensitivity and specificity • Mortality benefits	• It is less sensitive to adenoma • Failure to detect polyps • A positive result requires a colonoscopy
Fecal DNA testing	• High sensitivity • It can improve the detection rate of CRC	• The high cost • Low specificity • Positive results require colonoscopy
CTC	• Once every three years • No need to calm down • Lower risk of complications • Assessable extraintestinal lesions	• Contrast agent allergy • Radiation exposure • Positive results require colonoscopy

Flexible Sigmoidoscopy		• Intestinal preparation is required • No data suggest mortality benefit
Colonoscopy	• Little or no sedation is required • Can prevent distal CRC death • Visualize the entire colon	• Missed proximal colon lesions • Complications such as intestinal perforation and bleeding • Change diet and clear intestines
Colon capsule endoscopy	• Biopsy or resection of lesions • Incidence rate and mortality benefits of CRC	• Bleeding, perforation, abdominal pain and other complications
Blood Screening Test		• Need sedation or anesthesia • Invasive examination • Higher cost • Intestinal cleaning
Urine-based tests	• The patient has good tolerance • No need to calm down • Less invasive	• Easy to miss diagnosis • Higher cost • No biopsy and no treatment
Stool-based Microbiome tests	• Noninvasive • High participation and compliance • Convenient inspection • Specimens are easy to collect • Abundant metabolites • Noninvasive • Adenomatous polyps can be diagnosed • Combined with tumor markers can improve the diagnostic rate • Noninvasive • The combination of tumor markers can improve the diagnostic rate	• There is no evidence for first-line screening • Abnormal results require colonoscopy • Abnormal results require colonoscopy • FDA not approved for CRC screening • Abnormal results require colonoscopy • FDA not approved for CRC screening

Abbreviations: FIT: fecal immunochemical test; CTC: Computed tomographic colonography; FDA: Food and Drug Administration

4.2 Fecal DNA testing

Stool DNA testing is a screening method that utilizes the molecular properties of cancer. Based on the fact that cancerous tissues and larger polyps shed cells containing altered DNA into the colon, it is these molecular fragments that are targeted by stool DNA testing (58), such as mutated KRAS and β-actin, and these genetic mutations can be detected in stool specimens analyzed by DNA testing (59, 60). Compared to colonoscopy, fecal DNA testing for CRC has a sensitivity of 92%, much higher than the 74% sensitivity of another non-invasive screening method, fecal immunochemical testing (FIT). Stool DNA testing has a higher detection rate for advanced adenomas and non-tipped serrated polyps than FIT (42% vs. 24% and 42% vs. 5%, respectively) (61). Thus, fecal DNA testing is more accurate than FIT testing. And the high sensitivity of fecal DNA testing can improve the detection rate of colorectal cancer (62). However, it is costly, has relatively low specificity and still requires colonoscopy. However one study using a Markov cohort simulation model to compare the effectiveness of FIT and multi-target fecal DNA testing (Mt-sDNA) for screening CRC found that annual FIT appeared to be more effective as a first non-invasive screening test for CRC compared to triennial Mt-sDNA (63).

4.3 Computed tomographic colonography

CTC (Computed tomographic colonography) is a rapid non-invasive imaging of the colon structure that uses CT and special software to create 3D images of the colon to identify colon lesions, also known as "virtual colonoscopy". It does not require sedation and has a lower risk of complications compared to colonoscopy (64-66). In addition, it allows the assessment of extracolonic lesions (67-69). However, CTC also has many disadvantages compared to colonoscopy, such as contrast allergy in some patients, risk of perforation, potential radiation exposure, and the need for further colonoscopy if lesions are detected, thus requiring a second bowel preparation (70, 71). In addition, this test requires an adequate bowel preparation, which is performed without sedation and requires the injection of air and contrast agents, which may cause discomfort in many patients. A meta-analysis of 33 studies involving 6393 patients showed that CTC had a sensitivity of 70% and specificity of 93% for polyps between 6 and 9 mm in diameter and a sensitivity of 85% and specificity of 97% for polyps larger than 9 mm in diameter (72). In the overall detection of colorectal cancer, the sensitivity of CTC examination (96%) was not statistically significant compared to colonoscopy (91%) (73). However, in terms of participation alone, two tissue screening studies conducted in Europe have shown that CTC has a better participation rate than colonoscopy (74, 75). Of note, no studies have evaluated CTC as a reduction in colorectal cancer incidence or associated mortality.

4.4 Flexible sigmoidoscopy

Flexible sigmoidoscopy is a screening modality that involves endoscopic examination of the distal colon, including endoscopy of the rectum, sigmoid colon, and descending colon, and therefore tends to miss proximal colon lesions, so this modality has been largely replaced by colonoscopy (76). Bowel preparation is primarily a cleansing enema and usually requires little or no sedation (77).

However, there is evidence from randomized controlled trials and observational studies that sigmoidoscopic screening prevents most distal colorectal cancer deaths as well as colonoscopy screening (78). A randomized controlled trial evaluating the difference in mortality and CRC incidence between a flexible sigmoidoscopic screening group and a control group (no sigmoidoscopic screening specified) found a 22% reduction in overall CRC incidence and a 31% reduction in distal CRC incidence; overall CRC mortality was reduced by 43% (79). It

was also found that the benefits of sigmoidoscopic screening were different in men and women and in different age groups. A meta-analysis showed that sigmoidoscopic screening reduced the incidence of CRC in men and women, with no difference in the effect of screening in different age groups of men, but no significant reduction in CRC incidence in women aged 60 years or older (80).Therefore this screening modality may be more beneficial for men. Potential complications of sigmoidoscopy include colitis, bowel perforation, bleeding, and infection.

4.5 Colonoscopy

Compared with other types of screening, such as fecal occult blood test, sigmoidoscopy, and CTC, colonoscopy is considered the gold standard for colorectal cancer screening because of its high sensitivity and specificity for detecting precancerous lesions and cancers (81-83) and is the primary modality for CRC screening (84). Adequate and effective bowel cleansing prior to colonoscopy is a necessity as it requires dietary changes and laxative preparations prior to colonoscopy. Moreover, most people need to be sedated for the examination (85, 86).

Colonoscopy has several advantages; first, this examination allows visualization of the entire rectum, colon, and terminal small intestine (87) It is not only diagnostic, identifying lesions and biopsies, but also therapeutic, removing polyps and early cancers and treating bleeding in a single examination (88, 89). In addition it has been demonstrated that colonoscopy can detect cancerous and precancerous lesions by direct visualization (90). Secondly colonoscopy can be effective in preventing the development of CRC. Several retrospective cohort studies and network meta-analyses have examined the effect of colonoscopy on CRC morbidity and mortality. Studies have shown that patients who underwent colonoscopy screening had 61% to 88% lower cancer mortality than those who did not undergo screening; the relative reduction in CRC incidence was 48%. Network meta-analyses have shown that colonoscopy is the most effective screening modality to prevent CRC deaths(91-93). Colonoscopy significantly reduces CRC mortality, but its clinical benefit varies by cancer site. One study showed a 29% reduction in overall CRC mortality and a 47% reduction in distal CRC mortality, but no reduction in proximal CRC mortality (84, 94, 95). In addition, although it is an expensive test, the procedure is usually performed under sedation, thus maximizing patient comfort, satisfaction, and acceptance of colonoscopy (96, 97).

Of course, there are disadvantages to colonoscopy. For example, there is a risk of perforation, bleeding, and death. One study showed a pooled prevalence of 0.5/1,000, 2.6/1,000, and 2.9/100,000 for perforation, bleeding after colonoscopy, and death, respectively (98). Of these, bleeding was a more common adverse event than perforation (99, 100). Other adverse events include dehydration or electrolyte disturbances due to bowel preparation, respiratory distress due to sedation, or cardiovascular events (101). To ensure careful and accurate examination of the intestinal mucosa, air needs to be injected into the intestinal lumen in order to adequately dilate it, and this has been associated with adverse effects such as abdominal pain and bloating after colonoscopy (102). A meta-analysis has shown that the injection of carbon dioxide during colonoscopy resulted in less postoperative abdominal pain and bloating compared to the injection of air, and there was no difference in the rate of cecum intubation or examination time (103, 104). Poor bowel cleansing may be the cause of incomplete colonoscopy, prolonged examination time or even failed examinations. Some studies have shown that the rate of missed adenoma detection is about 20% to 49% when there is no adequate bowel cleansing (105, 106). Despite adequate bowel preparation, some lesions can be missed even by experienced endoscopists. Miss rates of 16.8%,

17%, and 5.4% have been reported for polyps, adenomas, and advanced adenomas, respectively (107). The rate of missed adenomas can be reduced with adequate observation time during the examination.

4.6 Colon capsule endoscopy

Colon capsule endoscopy (CCE) is a gelatinous pill-shaped device with a camera function that, when swallowed, allows it to take pictures of the intestinal mucosa as it passes through the gastrointestinal tract (108, 109).The second generation of CCE, introduced in 2009, has been approved by the FDA and is increasingly recognized for its role in colonoscopy and is rapidly becoming a suitable alternative to conventional colonoscopy in specific patient populations (110). Prospective, multicenter pilot studies have found that CCE-2 has a sensitivity of 84% and 88% and a specificity of 64% and 95% for ≥6 mm and ≥10 mm polyps, respectively (111). CCE appears to assess colon disease activity in inflammatory bowel disease (IBD) As well as for the assessment of suspected lower gastrointestinal bleeding and the detection of neoplastic lesions in the colon. It can also be used in patients who have failed colonoscopy, or who do not wish to undergo colonoscopy, and in cases where colonoscopy is contraindicated (112, 113). As with colonoscopy, bowel preparation is performed prior to CCE. Moreover, some colorectal polyps are missed during CCE, with a 31% polyp miss rate, as evidenced by a retrospective multicenter study (114). Unfortunately, it is an expensive test, and no tissue can be taken for examination and endoscopic treatment after lesions are found (115, 116). However, CCE does not require sedation and is well tolerated by most patients (117).

4.7 Blood screening test

Blood-based cancer testing, also known as "liquid biopsy", is an emerging non-invasive CRC screening method that is more convenient than other methods (118) and can detect both left-and right-sided CRC (119). But whether it can be used for first-line screening in individuals with average risk has yet to be approved. Studies have shown that those who refuse a colonoscopy overwhelmingly opt for a blood test. This suggests that this testing method will improve patient engagement and compliance (120, 121).

Some studies have shown that the sensitivity and specificity of serum protein biomarkers for the detection of early colorectal cancer exceed 85% and the positive predictive value exceeds 0.72% (122). Some of the major serum protein markers include DNA methylation markers (e.g., SEPT9, SFRP2, and ALX4), circulating micrornas (e.g., micrNA21), SNPS in microRNA-binding sites (e.g., Rs4596 located in the predicted target regions of Mir-518a-5p and Mir-527), protein markers (such as carcinoembryonic antigen and N-methyltransferase), etc. (123). The Septin 9 DNA plasma assay ((M)SEPT9) is an FDA-approved blood-based screening test for CRC (124). A multi-center study compared the performance of Septin9 DNA methylation based blood test and FIT in CRC screening, and found that the sensitivity of Septin9 and FIT for CRC detection were 73.3% and 68.0%, and the specificity was 81.5% and 97.4%, respectively (125).

4.8 Other screening methods

Both urine-based metabolomic diagnostic tests and fecal-based microbiome tests are emerging fields of CRC screening. The former is characterized by easy collection of specimens, abundant metabolites, and non-invasive detection methods (126). Studies involving 1000 subjects have proposed that a urine-based metabolomic diagnostic test can be used to detect adenomatous polyps with higher sensitivity than a fecal-based test (127). Liquid chromatography (LC) -mass spectrometry (MS) is the most used and informative analytical tool in urine metabolomics. In addition, in addition to LC-MS, other

MS-based techniques, such as direct injection (infusion) mass spectrometry, capillary electrophoresis mass spectrometry and gas chromatography mass spectrometry, have also been used in urine metabolomics (128). The accurate analysis of intestinal microbiota is helpful to assess the risk and prognosis of CRC, and the combination of bacterial markers and conventional tumor markers can improve the diagnostic efficiency of non-invasive diagnosis of CRC (129). However, both tests rely on further colonoscopy, and neither test has yet been approved or formally recommended by the FDA for CRC screening.

5. Quality of colonoscopy

Accurate detection and removal of precancerous lesions relies on high-quality colonoscopy screening, and there are multiple quality indicators to assess the effectiveness of colonoscopy screening. Adenoma detection rate (ADR) is now considered one of the most important quality indicators of colonoscopy. Adenoma detection rate (ADR) is now considered one of the most important evidence-based quality indicators of colonoscopy. ADR is defined as the proportion of endoscopists performing colonoscopy screening who detect at least one histologically confirmed colorectal adenoma or adenocarcinoma (130). For intestinal mucosa, observation is primarily performed when the colonoscope is retracted from the cecum to the rectum, and the ADR can be improved if the duration of detection is 6 minutes or longer (131). Most guidelines recommend a minimum of 20% to 25% ADR at screening colonoscopy. each 1% increase in ADR is associated with a 5% reduction in the risk of interstitial colorectal cancer (132, 133).

Interstitial cancers are colorectal cancers that are not detected at screening but are diagnosed before the next recommended test (134). Interstitial carcinomas originate from sessile serrated polyps, which usually occur in the proximal colon, and the detection of adenomas and sessile serrated polyps by localization can improve the outcome of colonoscopy (135). A recent population-based study found that the proximal serrated polyp detection rate (PSPDR) was negatively associated with intermittent colorectal cancer; therefore, PSPDR can also be used as a quality indicator for colonoscopy, and monitoring PSPDR can optimize colorectal cancer prevention (136).

The polyp detection rate is a simpler indicator to assess the quality of colonoscopy compared to ADR. An observational study found that endoscopists with a lower PDR had a significantly higher incidence of colorectal cancer after performing colonoscopy (137). The clarity of colonoscopy can also affect the detection rate of adenoma. A comparative study observed the differences in PDR and ADR before and after colonoscopy, and found that colonoscopy screening with HD technology significantly improved PDR and ADR (138).

A complete and accurate colonoscopy must test all the colon including the cecum. The rate of cecum intubation is one of the indicators to assess the quality of colonoscopy, and the high rate of intubation affects the outcome of CRC screening (139). A low cecum intubation rate is associated with a high incidence of proximal cancer after colonoscopy (140, 141). Effective endoscopists should achieve a cecum insertion rate of at least 90% (142, 143). Therefore, endoscopists should be aware of cecum markers such as ileocecal flap and appendiceal opening during colonoscopy.

Other quality measures, such as adequate bowel preparation and bowel scoring system records, are also described. Adequate bowel preparation was defined as bowel preparation sufficient to identify polyps larger than 5 mm. Good bowel preparation is an important part of high-quality colonoscopy. Unsatisfactory bowel cleaning will not only prolong the examination time, reduce the rate of cecal intubation, and increase the related costs, but also increase the

risk of missing polyps or adenomas (144). A prospective study found that inadequate Boston Bowel Preparation Scale (BBPS) scores were associated with a higher incidence of polyps during subsequent colonoscopy within a short period of time, as well as an increased risk of missed polyps diagnosis (145).

The effectiveness of endoscopic resection of adenomas is an emerging area for assessing the quality of colorectal cancer screening. Incomplete excision of polyps can lead to the development of interstitial carcinoma, and this may diminish the effectiveness of screening (146). A meta-analysis found that for polyps of 1-20 mm there would be incomplete resection, with a greater risk of incomplete resection for polyps of 10 mm or larger (147). Of course the discomfort and the occurrence of complications associated with the patient after colonoscopy are also important in assessing the quality of colonoscopy screening.

6. Artificial intelligence

Artificial intelligence is a hot topic at present, and its application in the field of medicine has been widely concerned, especially in the field of computer-aided diagnosis of colonoscopy (148). The integration of artificial intelligence with endoscopy to improve polyp and adenoma detection rates is being explored (149-151). A prospective randomized controlled trial that included 659 patients and compared adenoma detection rates in the automated quality control system (AQCS) and control groups found that AQCS significantly improved polyp and adenoma detection rates and improved endoscopist outcomes (152). A study using convolutional neural networks (CNN; a deep learning model for image analysis) to test the ability of computer-aided image analysis noted that CNN detected polyps with an accuracy of 96.4% (153). Artificial intelligence can increase the detection rate of colorectal tumors by improving lesion recognition, and reduce the pathological cost by improving optical diagnosis (154), so as to improve the screening effect of colonoscopy. Artificial intelligence assists endoscopists to improve ADR and reduce interstage colorectal cancer, but its application in practice needs to be validated by more prospective studies (155).

7. Interventions to improve screening compliance

Screening can reduce CRC morbidity and mortality. However, the effectiveness of screening depends not only on accurate detection, but also on patient compliance, quality of screening and analysis of results. Although various screening modalities for colorectal cancer are available, they are not fully utilized by all (156, 157). There are various reasons for the low screening rate, such as low awareness of the importance and benefits of screening, cost issues, lack of health awareness, inadequate promotion in hospitals and medical screening centers, and fear or resistance to the test itself (5, 158). There are several ways to improve CRC screening adherence, such as enhancing patient education and disease surveillance awareness by distributing brochures or videos (159).

The testing of screening items, interpretation of results, and follow-up of positive results should be done by a medical professional (160, 161). One study suggests that 10% of positive patients after colorectal cancer screening do not comply with screening recommendations for follow-up. Providing individualized counseling for this group of patients may improve compliance rates (162). Patient decision aids coupled with patient coaching may also improve CRC screening completion rates (163). Some studies have found that telephone or text message reminders and mailing of free FIT kits can improve CRC screening rates (164, 165). In a randomized controlled trial conducted in the Netherlands, van et al. compared the difference in adherence to colorectal cancer screening between two different invitations: sending an advance notification letter significantly increased

adherence relative to the usual standard invitation (166).

Removing structural barriers, such as simplifying access to stool test cards and extending or increasing the length of non-standard clinic visits, is effective in increasing CRC screening rates (167, 168). Also physician-patient communication increases screening rates, as a randomized controlled trial showed that patients who received physician counseling participated in CRC screening at a significantly higher rate than those who only received information leaflets on CRC screening (169). It is crucial that health systems need to develop policies that encourage colorectal cancer screening.

8. Conclusion

CRC remains a major burden of health problems worldwide, and there are currently multiple modalities available for CRC screening, and several screening strategies have been shown to reduce CRC mortality. However, the use of screening methods is low, which is mainly related to low patient engagement and compliance and socioeconomic level. Primary care doctors should know the characteristics of all kinds of screening methods, such as the advantages and limitations of each screening options, but also to learn how to the risk stratification of patients, give patients reasonable screening recommendations, in short in all kinds of ways to improve patients compliance, and increase the rate of screening, and ultimately to reduce colorectal cancer incidence and mortality, the purpose of improving people's health.

Declarations

1) Consent to publication

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4) Authors' contributions

FYD, ZQY, and XPT contributed to this review with the design. FYD, ZQY and JL reviewed the references. FYD and ZQY wrote the manuscript. FYD, ZQY and MHA designed and produced the tables and figures. All authors read and approved the manuscript for publication.

5) Competing interests

The authors declare that they have no competing interests.

6) Authors' biography

None.

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