Editorial

Recent advances in colorectal cancer screening

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide.[1] In the United States, 135,430 new cases of CRC were diagnosed in 2017, with 50,260 CRC-related deaths.[2] In the Asia-Pacific region, the incidence varies between regions, with an increasing trend among countries that have undergone rapid development and industrialization. In China, for example, age-standardized incidence of CRC increased from 12.8 in 2003 to 16.8 in 2011 per 100,000 individuals.[3] Timely screening for CRC is critical to reducing CRC-related mortality by detecting the tumor at the early, curable stage. In the United States, large-scale screening programs have led to a significant decrease in CRC morality, highlighting the importance of primary prevention, early detection and treatment.[2,4] Formulating an optimal screening strategy relies upon several important factors, such as local healthcare infrastructure and the availability of medical resources, CRC incidence, the quality of each screening method,

and other context-related factors. In this review, we summarize the recent advances in our understanding of CRC pathogenesis and new development in CRC screening.

Colorectal cancer pathogenesis—a heterogeneous disease with different paradigms

CRC, like other types of malignancy, is fundamentally a genetic disease.[5] It is the consequence of the accumulation of deleterious mutations and epigenetic changes, which ultimately lead to uncontrolled proliferation of malignant cells. Over thirty years ago, Vogelstein and colleagues discovered an important pattern of colorectal carcinogenesis called "adenoma-carcinoma" sequence.[6] (Fig. 1) A predominant feature of this pathway is chromosomal instability with a high percentage of aneuploidy. With accumulation of mutations in genes such as *APC*, *KRAS*, and *p53*, normal colonic mucosa gradually transforms to malignant epithelium in the form of adenomas. This is a multi-step cascade including aberrant crypt foci, low grade dysplasia, high grade dysplasia, and eventually, adenocarcinoma. Because this process typically takes 10 years or longer to complete, screening colonoscopy is recommended every 10 years for average-risk individuals. An exception is the adenomatous polyposis syndromes, characterized by significantly increased

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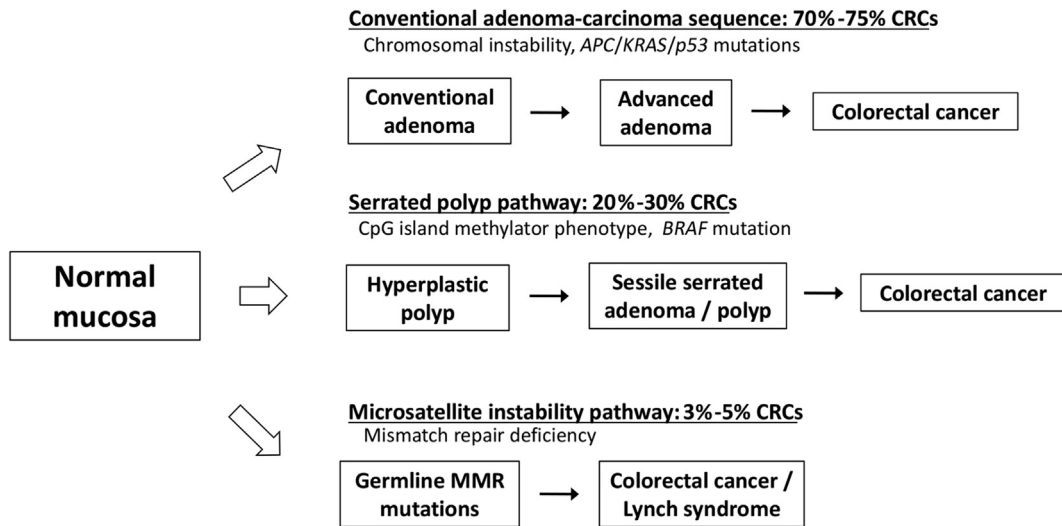Peer review under responsibility of Chinese Medical Association.

Fig. 1. Main molecular pathways in CRC pathogenesis. CRC: colorectal cancer; MMR: mismatch repair.

number of adenomas in the colon and upper gastrointestinal tract. The most common types of adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) (due to mutations in *APC* gene).[7] FAP is an autosomal dominant condition and accounts for ~1% of all CRC cases. Classical FAP presents with hundreds to thousands of adenomatous polyps throughout the colon and rectum, while attenuated FAP usually presents between 10 and 100 adenomas. CRC screening with colonoscopy should be started at teenage years for FAP patients.[7,8] Prophylactic total colectomy should be considered. Genetic counseling should be provided for at-risk family members.[8]

A different paradigm of colorectal carcinogenesis called "serrated pathway" has been established more recently.[9] The main precursor lesions for the serrated pathway are serrated polyps, particularly sessile serrated adenomas (SSAs, also known as sessile serrated polyps or SSPs). SSA/Ps are predominantly located at the proximal colon and have a flat endoscopic appearance. Histologically, SSA/Ps are characterized by dilatation at the bases of crypts, branched crypts, horizontal extension of crypt bases, or crypts dysmaturation.[10] SSA/Ps frequently harbor *BRAF* mutations and CpG island methylator phenotype, and are responsible for 20%−30% of CRC (Fig. 1).[9,11,12]

Another important cause of CRC is the germline mutations of DNA mismatch repair genes leading to microsatellite instability, a condition called Lynch syndrome (also known as hereditary nonpolyposis CRC, or HNPCC) (Fig. 1).[13] Lynch syndrome is the most common type of hereditary CRC syndromes, representing 2%−4% of all CRC cases. Patients with Lynch Syndrome have up to 80% lifetime risk for CRC and up to 60% risk for endometrial cancer, as well as increased risks for cancers in other organs such as stomach, ovaries, small intestine, hepatobiliary tract, urinary tract, and brain.[14] Individuals diagnosed with Lynch syndrome should have surveillance colonoscopy every 1−2 years, starting at 20−25 years of age or 5 years before the youngest age of diagnosis of CRC in an affected family member, whichever occurs first. Female patients should be advised to consider prophylactic hysterectomy with bilateral salpingo-oophorectomy after their childbearing has been completed. The at-risk family members of Lynch syndrome patients should receive genetic counseling to assess their risk of carrying a deleterious mutation.[15]

In recent years, the availability of multi-gene panel testing has provided a promising tool to more precisely stratify patients for their CRC risks.[16] Identifying individuals carrying germline mutations of cancer susceptibility genes allows clinical providers to provide timely preventive care for these patients and their at-risk family members. In a study of over 10,000 consecutive individuals referred for genetic evaluation using next-generation multi-gene panel testing, 0.9% of patients were found to carry at least one pathogenic mutation or

likely pathogenic variant, and Lynch syndrome/CRC panel (containing *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC* and *MUTYH*) comprised the highest percentage among positive results.[17] In another study of 1058 CRC patients who underwent panel testing including 25 genes, 9.9% carried germline mutations of cancer susceptibility genes, including 3.1% with Lynch syndrome mutations and 7.0% with non-Lynch mutations.[18] In a multi-center study in the U.S., gene panel testing identified germline mutations among 16% of CRC patients who were younger than 50 years.[19] These findings were in line with another recent study showing approximately 1 in 5 individuals with CRC at younger than 50 years of age carried a cancer-associated germline mutation, supporting the notion that all young patients with CRC should be considered for germline testing.[20]

Another progress towards precision medicine is development of individualized CRC risk-scores based on environmental and genetic risk factors. A study by Jeon et al[21] created models to determine the CRC risk based on family history, 19 lifestyle and environmental factors (E-score), and 63 CRC-associated single nucleotide polymorphisms (G-score). The model combining both scores and family history demonstrated greater accuracy in determining an individual's CRC risk compared with using family history alone. These scoring systems represent an important step towards developing individualized CRC prevention strategies that are more accurate than those based on the current screening guidelines.[21]

Recent updates in CRC screening methods

There have been significant advances in our knowledge with respect to the efficacy of different screening methods for CRC over the past decade. In this section, we will focus on the screening strategies for asymptomatic average-risk individuals. In the United States, multiple professional societies recommend screening for CRC in average-risk asymptomatic individuals who are between age 50 and 75 years,[22,23] although the most recent guideline by the American Cancer Society recommends starting CRC screening at age 45 years.[24] The decision to screen for CRC in individuals between age 76 and 85 should be made on an individual basis, taking into account the patient's overall health condition and whether the patient had prior CRC screening. The age to start and stop CRC screening and the choice of method(s) for screening are also affected by the availability of local resources, incidence of CRC, and patient and physician preferences. Commonly-used methods include endoscopic methods (colonoscopy and sigmoidoscopy), radiologic method [computed tomography (CT) colonography], stool based testing [guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT) and FIT-DNA] and blood-based screening tests (Table 1).

Endoscopic methods

Colonoscopy

Colonoscopy is considered the most sensitive method for CRC screening and the reference standard for assessing the performance of other CRC screening tests. It allows direct mucosal inspection of the entire colon. In addition to detecting CRC, it is also able to identify and remove precancerous polyps during a single session. Although no data are yet available from large randomized controlled trials, extensive data from cohort studies and case-control studies demonstrated the efficacy of colonoscopy in reducing CRC incidence and mortality.[25−35] In a population-based case-control study from Germany, history of colonoscopy resulted in 77% reduction in the risk of any CRC, 56% reduction for right-sided CRC and 84% reduction of left-sided CRC.[29] In a large population-based case-control study from Canada, colonoscopy resulted in fewer deaths from left-sided CRC (67% reduction) but not from right-sided CRC.[32] In a large cohort study in the United States with a follow-up period of over 22 years, negative colonoscopy was associated with 56% overall risk reduction in CRC and 27% risk reduction of proximal CRC.[34] The discrepancy between the risk reduction for proximal *vs.* distal CRC is likely related to several factors, including incomplete colonoscopy (which is less likely to investigate the proximal colon), difficult visualization in the proximal colon, poorer bowel prep, and possible differences in biology between proximally and distally located CRCs. Several large randomized trials are still in progress which are expected to generate important information in the coming years with respect to the efficacy of colonoscopy in reducing CRC incidence and mortality.

The quality of colonoscopy has also been a focus of extensive research.[36] A large community-based study showed that colonoscopy withdrawal time of 6 minutes or longer was associated with a higher detection rate of colonic neoplasia.[37] Recently, adenoma detection rate (ADR) has become the most important and widely accepted quality benchmark of colonoscopy. Two large studies demonstrated the inverse association between ADR and incidence of interval CRC (defined as CRC diagnosed between the time of screening colonoscopy and the scheduled time of surveillance colonoscopy).[38,39] In one of the two studies, each 1.0% increase in the ADR was associated with a 3.0% decrease in the risk of cancer.[39] Currently, the professional guidelines in the United States

recommend ADR≥25% overall, or ≥30% for male patients and ≥20% for female patients.[23]

Disadvantages of colonoscopy include the inconvenience of taking a bowel prep prior to the procedure, sedation risks (such as cardiovascular events), and risks of complications associated with the procedure (such as colonic perforation and bleeding). In a meta-analysis, pooled risks of perforation, post-colonoscopy bleeding and death were 0.5 per 1000, 2.6 per 1000 and 2.9 per 100,000, respectively.[40] The complication rates were shown to be lower for screening/surveillance than for diagnostic examinations.[40]

Flexible sigmoidoscopy

Flexible sigmoidoscopy examines the lower half of the colon. Several large randomized trials demonstrated decreased CRC incidence among individuals who underwent sigmoidoscopy screening followed by colonoscopy if precancerous polyps are found, compared with no screening.[41—44] In addition, the majority of these studies showed a mortality benefit. In a large multicenter randomized trial in the U.K. with 17 years of follow-up, there was a 26% reduction of CRC incidence and 30% reduction in CRC-related mortality.[45] Sigmoidoscopy remains a viable option for CRC

screening when the availability of colonoscopy is limited. Current United States Preventive Services Task Force (USPSTF) recommendations endorse screening using flexible sigmoidoscopy every 5 years.[22]

Stool-based tests

gFOBT and FIT

Multiple randomized clinical trials have demonstrated that screening with gFOBT reduces CRC-related mortality.[46] Several large randomized controlled trials evaluating the effectiveness of annual or biennial screening using Hemooccult II showed reduction in CRC-related mortality.[47—49] One trial in the United States demonstrated a 32% reduction in mortality over 30 years of follow up.[50] High-sensitivity gFOBT has a sensitivity of 62%—79% and a specificity of 87%—96% for detecting CRC.[46] gFOBT can be falsely positive due to the presence of blood from red meat or certain food (such as turnips or raw horseradish). In contrast, FIT uses antibody technology to detect intact human hemoglobin in stool; therefore, it does not require dietary restrictions. Several studies have shown superior sensitivity and specificity of FIT for CRC screening in comparison with gFOBT.[51—53] In a

Table 1
Options of CRC screening for average-risk individuals.[a]

Screening method	Frequency	Efficacy	Main issues for informed decisions
Endoscopic methods			
Colonoscopy	Every 10 years	Reduction in mortality in a prospective cohort study	Most sensitive. May require sedation. Can detect precancerous lesions. Requires full bowel preparation.
Sigmoidoscopy	Every 5 years	Reduction in mortality in RCTs	Only part of colon examined. Can detect precancerous lesions. Require limited bowel preparation.
Stool-based tests			
gFOBT	Every year[b]	Reduction in mortality in RCTs	Performed at home but should be repeated annually. Limited ability in detecting precancerous lesions. Needs follow-up colonoscopy if result is positive.
FIT	Every year[c]	Higher sensitivity and specificity in detecting CRC than gFOBT, but RCTs lacking	Performed at home but should be repeated annually. Limited ability in detecting precancerous lesions. Needs follow-up colonoscopy if result is positive.
FIT-DNA	Every 1—3 years?	More sensitive but less specific than FIT only. Effect on mortality unknown.	Performed at home. More expensive than gFOBT and FIT. Limited ability in detecting precancerous lesions. Needs follow-up colonoscopy if result is positive.
Radiologic method			
CT colonography	Every 5 years	Effect on mortality unknown	Needs bowel preparation. Lower risk than colonoscopy but less sensitive. Needs follow-up colonoscopy if polyp(s) detected.
Biomarker			
Septin9 DNA	Unknown	Effect on mortality unknown	First FDA approved serum test for CRC screening. Less sensitive and less specific than colonoscopy. May be more convenient than other screening tests.

CRC: colorectal cancer; RCT: randomized controlled trial; gFOBT: guaiac-based fecal occult blood test; FIT: fecal immunochemical test; CT: computed tomography.

[a] Most recommendations in this table are based on the current U.S. Preventive Service Task Force guidelines and U.S. Multi-Society Task Force recommendations.[23,46] Guidelines may vary in different counties.

[b,c] The consensus from the International Agency for Research on Cancer (IARC) Handbook Working Group recommends screening every 2 years with gFOBT without rehydration and every 1—2 years with higher sensitivity guaiac tests (with rehydration). IARC also recommends screening with FIT every 2 years.[55]

meta-analysis by Lee et al[52] which included the results of 19 studies evaluating FIT as a screening tool for CRC among average-risk individuals, the pooled sensitivity of FIT for CRC was 79% [95% confidence interval (*CI*), 69%–86%], and a specificity of 94% (95% *CI*, 92%–95%). The main advantage of stool-based tests is the convenience to perform the tests. These tests are noninvasive, without the need for bowel preparation and can be done at home. If the result is positive, a colonoscopy should follow. A recent study showed that colonoscopy performed more than 10 months after a positive FIT was associated with a higher risk of CRC and advanced-stage disease.[54] Currently, USPSTF and U.S. Multi-Society Task Force recommend annual FIT as a CRC screening test, while recent review by the International Agency for Research on Cancer (IARC) supports screening with FIT every 2 years which has been shown to reduce CRC mortality.[22,23,55]

FIT-DNA

Multitarget stool DNA combined with FIT as a screening test for CRC (Cologuard) has been approved by the U.S. Food and Drug Administration (FDA).[56] This test combines FIT with testing for DNA markers that are shed into the stool. A positive result should be followed by colonoscopy. One-time FIT-DNA testing has been shown to have a higher sensitivity for detecting CRC than FIT (92.3% *vs.* 73.8%) with lower specificity (86.6% *vs.* 94.9%).[56] A major disadvantage of FIT-DNA test is its lower specificity than FIT, which is associated with higher likelihood of false positive results requiring follow-up colonoscopy. In addition, data on the mortality benefit of FIT-DNA as a CRC screening test are still lacking. In the United States, although the Center for Medicaid & Medicare Services approved the test for reimbursement and recommends FIT-DNA at 3-year intervals, the optimal frequency of using FIT-DNA for CRC screening is still to be determined. In addition, the cost of FIT-DNA is substantially higher than FIT, which may be a barrier against its use as a screening tool.

Radiographic test—CT colonography

CT colonography is a radiologic method of CRC screening.[57,58] If polyps are detected, follow-up colonoscopy should be performed. In comparison with barium enema, CT colonography is more sensitive and better tolerated.[59,60] CT colonography has a sensitivity of 82%–92% for adenomas ≥1 cm in size.[23] The per-person sensitivity of CT colonography to detect adenomas ≥1 cm in size ranges from 67% to 94% and specificity ranges from 86% to 98%.[46] In a European study, CT colonography reaches sensitivities comparable with colonoscopy for polyps >5 mm.[61] CT colonography also has an advantage of lower risk of perforation compared with colonoscopy. However, the sensitivity of small polyps by CT colonography is inferior to colonoscopy, and the detection rate of flat polyps (such as proximally located serrated polyps) is unsatisfactory.[62] There are several other issues related to CT colonography, including radiation exposure, frequent detection of incidental extracolonic findings that need additional follow-up,[46] and requirement of bowel preparations (in most centers in the United States). However, no published randomized trials have assessed the effect of CT colonography on CRC incidence or mortality.[55] Despite its disadvantages, CT colonography may have its niche as a CRC screening tool, particularly for those who are at an increased risk of colonoscopy-associated complications, or those who are reluctant to consider colonoscopy. Currently, the U.S. Multi-Society Task Force recommends a 5-year screening interval using CT colonography, and that individuals with colonic polyps ≥6 mm on CT colonography should undergo colonoscopy.[23] However, the IARC Handbook Working Group considered the evidence supporting CT colonography as a screening tool still very limited.[55]

Blood-based screening tests (liquid biopsy)

In the recent years, a new concept in diagnosing cancer, called "liquid biopsy", has drawn increasing attention.[63] Liquid biopsy refers to the analysis of circulating tumor cells (CTCs), cell-free tumor DNA (ctDNA) and/or protein markers which are detectable in the blood.[64] Potential applications of liquid biopsy are broad, including early detection of cancer, monitoring minimal residual disease and response to treatment, and providing guidance for treatment.[64,65] In addition, liquid biopsy as a blood test offers significant convenience compared with other tests (such as stool-based methods or colonoscopy), which may increase the compliance of screening.

The first FDA approved serum test for CRC screening is the methylated Septin9 DNA assay. In a study using colonoscopy as the reference standard, the Septin9 assay had a sensitivity of 48.2% and a specificity of 91.5%.[66] The sensitivity for CRC stage I-IV was 35.0%, 63.0%, 46.0% and 77.4%, respectively, but the sensitivity for advanced adenomas was only 11.2%.[66] As a serum assay, Septin9 test has an advantage of being convenient for patients, which may improve their willingness to undergo CRC screening. A major disadvantage of Septin9 test is the low sensitivity for detecting CRC and poor performance in detecting advanced adenomas.[67] In a recent meta-analysis of 14 studies, the pooled sensitivity of Septin9 in diagnosing CRC was only 67%, with a specificity of 89% in discriminating CRC patients from cancer-free individuals.[68] In addition, data evaluating the efficacy of Septin9 as a screening test on CRC incidence and mortality are lacking.

Another example of recent advances in liquid biopsy research is the development of a blood test (CancerSEEK) which was able to detect eight common cancer types based on the levels of circulating proteins and mutations in ctDNA.[69]

Among 1005 patients with nonmetastatic (stage I to III) cancers of ovary, liver, stomach, pancreas, esophagus, colorectum, lung or breast, the median sensitivity of CancerSEEK was 73% for stage II cancers, 78% for stage III cancers and 43% for stage I cancers. It had a high specificity of >99% with a positive score found in only 7 of the 812 healthy individuals. The cost of this test was estimated to be <\$500. Although this study has shown great promise of using liquid biopsy as a screening tool in the future, the clinical utility of blood-based screening tests will depend on the results of prospective studies in large populations to determine their performance (such as sensitivity and specificity). In addition, management of false positive results may be challenging.

Colorectal cancer screening: organized versus opportunistic approach

At the population level, CRC screening can be performed through an organized or opportunistic approach. In opportunistic screening, patients are offered CRC screening when they visit a physician's office for a checkup or for unrelated medical issues. Those who visit doctors regularly are more likely to have the opportunity to undergo CRC screening than those who do not.[70] In contrast, organized CRC screening involves a systematic process aimed to screen all eligible members within a target population, with appropriate follow-up of those with positive screening results.[71] The IARC defines the following elements as essential for an organized screening program[72]: an explicit policy with specified age categories, screening method and screening interval; a defined target population; a management team responsible for implementation; a healthcare team for decisions, care and follow-up of patients with positive screening tests; a quality assurance structure for every step in the process; a process for monitoring, evaluating and identifying cancer occurrence in the population.

Compared with opportunistic screening, organized screening has several advantages, including a well-defined target population (e.g. average-risk individuals between 50 and 75 years of age), the ability to monitor the quality of screening process, and the infrastructure to arrange appropriate follow-up of abnormal results.

There are substantial variations with respect to implementation of organized or opportunistic CRC screening programs in different countries or regions around the world. Currently, the approach to CRC screening in the United States is largely opportunistic but organized screening programs also exist. An example of successful organized screening programs comes from Kaiser Permanente Northern California (KPNC), a healthcare delivery system covering over 4 million members in Northern California. At KPNC, organized screening outreach was established since 2007, targeting screening eligible individuals 51–75 years old. This organized screening program significantly increased the rate of CRC screening, from 38.9% in 2000 to 82.7% in 2015, accompanied by a 25.5% reduction in annual CRC incidence and a 52.4% reduction in cancer mortality.[73] In Europe, 24 out of 28 European Union countries either had established or planned to establish an organized or opportunistic CRC screening program as of 2015.[71] In the Asia-Pacific region, several countries have developed population-based CRC screening programs, including China, Japan, Korea and Singapore. The proportion of the populations covered by these screening programs may vary significantly, secondary to available resources and infrastructure.[71]

Conclusion

The last decade has witnessed significant advances in our knowledge of CRC. Meanwhile, accumulating clinical evidence on CRC screening methods has led to important modifications of our screening strategies. Besides the technical parameters of each screening method described above, the optimal strategy of CRC screening also depends on multiple other factors including the availability of medical resources, readiness of the local infrastructure for organized screening and follow-up, cost-effectiveness of screening, socio-economic factors, and cultural influences. The increasing availability of genetic testing may help us more accurately predict a given individual's future risk of developing CRC, with a personalized plan in terms of when (at what age) and how (which method to use) to perform CRC screening, and at what interval. A combination of evidence-based strategies and precision medicine will further enhance our ability to reduce the incidence and mortality related to CRC.

Conflicts of interest

The author declares no conflicts of interest.

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Edited by Pei-Fang Wei