Perspectives

Colorectal Cancer Screening in China: Status, Challenges, and Prospects — China, 2022

Hongda Chen[1]; Bin Lu[1]; Min Dai[1,#]

ABSTRACT

Colorectal cancer (CRC) ranks third among the most commonly diagnosed cancers in China. Despite proof that screening can decrease CRC incidence and mortality, there are still gaps remaining between CRC screening objectives and reality in China. In this review, we provided an overview of the status of CRC screening in China. First, we summarized the current CRC screening programs and strategies in China. Second, we reviewed the authoritative CRC screening and early detection guidelines in China to orient future evidence-based guideline development. Finally, we identified current challenges and further provided some suggestions to improve the implementation of CRC screening programs. To maximize the effectiveness of CRC screening, further research on risk prediction models including polygenic risk scores and prior screening outcomes, novel biomarkers and artificial intelligence, and personalized screening strategies are recommended. Both cohort study and microsimulation techniques are recommended for long-term evaluations of the effectiveness of CRC screening strategies.

INTRODUCTION

According to the recently released data from GLOBOCAN (https://gco.iarc.fr/), an estimated 555,477 newly diagnosed colorectal cancer (CRC) and 286,162 CRC-related deaths occurred in China in 2020 (*1*). With population aging, socioeconomic development, and lifestyle changes, the disease burden of CRC in China has been increasing in the past decades, especially in urban and eastern regions. Numerous practices and studies have demonstrated that the early detection and early treatment of CRC and its precancerous lesions through screening were effective in reducing mortality and incidence for CRC (*2*–*4*). In this article, we first reviewed the current status of CRC screening programs conducted in China; we also summarized the major achievements and challenges regarding the CRC screening practices conducted in China; we further reviewed the current research advances in the aspect of CRC screening and possible further direction. We anticipated that this review could provide evidence to guide future CRC screening programs in China.

CRC SCREENING PROGRAM IN CHINA

Organized cancer screening programs targeting highly prevalent types of cancer (including esophagus, stomach, liver, colorectum, breast, cervix, and nasopharynx) have been conducted in China for over 20 years. To date, there are four organized cancer screening programs in China, which are public health service programs supported by the central government (detailed information is shown in Table 1). Through these programs, over 2,000,000 high-risk individuals have been screened by the end of 2016, and 55,000 were diagnosed with cancer, with an early diagnosis rate of 80% (*5*).

In China, population-based organized CRC screening was first conducted in the 1970s in high-incidence regions of CRC (Jiashan and Haining cities, Zhejiang Province) (*6*). Given the satisfactory screening effectiveness observed in these regions, along with the increasing disease burden of CRC, CRC screening programs have been conducted in many regions. Initiatives included the Cancer Screening Program in Rural Areas [initiated in 2005, covering 234 counties in 31 provincial-level administrative divisions (PLADs) in 2016] and Cancer Screening Program in Urban Areas (initiated in 2012, covered 42 cities in 20 PLADs in 2021) (*7*–*8*). In addition, opportunistic CRC screening during outpatient visits in hospitals and clinics has also been introduced (*9*). In population-based organized screening, the screening costs are typically compensated by the program. However, for the opportunistic CRC screening, the costs are typically paid by the patients or the health

TABLE 1. Description of four major cancer screening programs in China.

Year of initiation	Program	Targeted cancer type	Targeted population	Coverage (year)
2005	Cancer screening program in rural areas	Esophagus, stomach, liver, colorectum, cervix*, nasopharynx, and lung	High-risk population selected by questionnaire-based risk assessment	234 counties in 31 provincial-level administrative divisions (2016)
2007	Cancer screening program in Huaihe River areas	Esophagus, stomach, and liver	High-risk population selected by questionnaire-based risk assessment	32 counties in 4 provinces (2019)
2009	Cervical cancer and breast cancer screening program for women in rural areas	Cervix and breast	Women aged 35 to 64 years	1,448 counties for cervical cancer and 953 counties for breast cancer (2016)
2012	Cancer screening program in urban areas	Esophagus, stomach, liver, colorectum, lung, and breast	High-risk population selected by questionnaire-based risk assessment or prescreening tests among individuals aged 40 to 74 years	42 cities in 20 provincial-level administrative divisions (2021)

* Terminate in 2009.

insurance. Currently, there are no nationwide CRC screening programs that cover all suitable populations in China, but local cancer screening programs supported by the local government have been implemented in many cities.

CRC SCREENING STRATEGIES IN CHINA

In China, due to the large population and limited healthcare resources, a two-step screening strategy was adopted in most CRC screening programs; i.e., using a non-invasive or minimally invasive approach to select high-risk individuals and those who should undertake colonoscopy (the gold standard for CRC screening) examinations in the following step. Regarding the preselection of the target population, a combination of a questionnaire-based risk assessment tool and fecal occult blood test was typically used. To date, several CRC risk prediction tools have been established, and a detailed description of widely used and recommended CRC risk prediction models in China was listed in Table 2 (*10*–*14*). Earlier risk prediction models usually included risk factors of symptoms and were typically used in an opportunistic screening setting or early diagnosis (*13*). For the risk prediction in asymptomatic population, some models for population-based screening were developed. The Asia-Pacific Colorectal Screening (APCS) score was a commonly used model in Asia-Pacific area which showed medium discriminatory power in identifying high-risk populations with the area under the receiver operating characteristics curve (AUC) of 0.64 (*10*). To further improve the predictive efficiency of APCS, some studies have added scoring items and changed scoring principles. However, the 2 typical developed models only had nearly the same AUC as APCS [0.62 (*12*) and 0.65 (*14*), respectively].

Based on the risk prediction models, researchers also explored novel risk-stratified strategies rather than age-stratified strategies by offering different screening techniques to individuals at different risk strata (*15*). For instance, Asia-Pacific Working Group on Colorectal Cancer has performed a multicenter prospective study to test the use of APCS scoring system combined with fecal immunochemical test (FIT) in CRC screening which showed a reduced colonoscopy workload (*16*). Our team has also conducted a randomized controlled trial (RCT) to comparatively evaluate the effectiveness of colonoscopy, FIT, and a novel risk-adapted screening approach for CRC screening in China (*17*). The baseline results of this trial demonstrated that the proposed risk-adapted screening approach (high-risk populations for colonoscopy and low-risk populations for FIT) had higher participation rates and yielded superior detection rates for advanced colorectal neoplasm than FIT-based screening strategy.

CURRENT CRC SCREENING GUIDELINE AND CONSENSUS IN CHINA

To standardize the screening process and improve the screening yield, a series of guidelines and consensus on CRC screening have been released by authoritative scientific societies (Table 3) (*18*–*24*). The majority of guidelines in China recommended average-risk individuals screening between 50 and 75 years of age using colonoscopy, flexible sigmoidoscopy, or fecal occult blood test (mainly FIT). Colon capsule

TABLE 2. Summary of widely used CRC risk prediction tools in China.

Reference	Year	Outcome	Scoring items / scoring principles	Discriminatory power
Yeoh et al. (2011) (*10*)	2004	ACN	Age, years (<50: 0; 50–69: 2; ≥70: 3) Gender (male: 1; female: 0) Family history of CRC in a first-degree relative (no: 0; yes: 1) History of smoking (never-smoker: 0; current or past smoker: 1)	0.66 (0.62–0.70) in derivation set; 0.64 (0.60–0.68) in validation set
Cai et al. (2012) (*11*)	2006–2008	ACN	Age, years (40–49: 0; 50–59: 1; 60–69: 2; >69: 3) Sex (male: 2; female: 0) Smoking (0–20 pack-years: 0; >20 pack-years: 2) DM (no: 0; yes: 1) Green vegetables (occasional: 1; regular: 0) Pickled food (occasional: 0; regular: 2) Fried food (occasional: 0; regular: 1) White meat (occasional: 2; regular: 0)	Sensitivity: 82.8% in derivation set; 80.3% in validation set; Specificity: 50.8% in derivation set; 51.2% in validation set; AUC: 0.74 (0.70–0.78) in derivation set; 0.74 (0.70–0.78) in validation set
Wong et al. (2014) (*12*)	2008–2012	CN	Age, years (50–55: 0; 56–70: 1) Sex (male: 2; female: 0) Family history of CRC in a first-degree relative (no: 0; yes: 1) History of smoking (no-smoker: 0; current or past smoker: 1) BMI (<25 kg/m^2: 0; ≥25 kg/m^2: 1) DM (no: 0; yes: 1)	0.62 (0.61–0.63) in derivation set; 0.62 (0.61–0.63) in validation set
Ye et al. (2017) (*13*)	2007–2014	CRC	Age is defined as ≥ 40 years and ≤ 74 years and have one or more of the following items: 1) history of intestinal polyps; 2) history of cancer; 3) family history of CRC in first-degree relatives; 4) 2 or more of the following items: (a) chronic diarrhea; (b) chronic constipation; (c) stressful life events that caused psychiatric trauma in the last two decades (e.g., divorce, death of relatives); (d) mucous and bloody stool; (e) history of appendicitis or appendectomy; (f) history of chronic cholecystitis or cholecystectomy	Sensitivity: 24.51% (19.61%–30.16%) Specificity: 89.78% (89.59%–89.97%)
Sung et al. (2018) (*14*)	2008–2012	ACN	Age, years (50–54: 0; 55–64: 1; 65–70: 2) Sex (male: 2; female: 0) Family history of CRC in a first-degree relative (no: 0; yes: 1) History of smoking (never-smoker: 0; current or past smoker: 1) BMI (<23 kg/m^2: 0; ≥23 kg/m^2: 1)	0.65 (0.61–0.69) in validation set

Abbreviations: ACN=advanced colorectal neoplasm; AUC=area under the curve; BMI=body mass index; CN=colorectal neoplasia; CRC=colorectal cancer; DM=diabetes mellitus; iFOBT=immunochemical fecal occult blood test.

endoscopy, Computed Tomography Colonography (CTC), and multi-target DNA, et al. were also recommended in some guidelines or consensus. For the next steps, it was essential to promote the application of the guidelines to clinicians who were involved in CRC screening and to update the recommendation regularly based on the accumulating newly high-rank evidence of CRC screening (*25*).

CHALLENGES OF CRC SCREENING IN CHINA

Although CRC screening programs have reached certain social benefits, to further optimize the screening effectiveness and reduce the disease burden in the future, there are still many challenges that need to be addressed. We summarized some major challenges of CRC screening in China from the perspectives of screening the target population, clinicians, and service providers.

Screening the Target Population

The current guidelines typically recommended having CRC screening in the average-risk population above a certain age (mostly 50 years old). However, such a whole population strategy may not be suitable for China given the large population and restrained healthcare resources. Therefore, the establishment of precise risk-prediction models and precise identification of high-risk populations who may benefit most from screening is a major task for researchers. Previous studies have proposed a series of risk prediction models based on the sociodemographic and lifestyle factors, but only yielded modest predictive efficacy (*26*). Recent studies have revealed that genetic

TABLE 3. Summary of current China colorectal cancer screening guidelines.

Guideline	Year	Starting age, years	Stopping age, years	Sex and race	Endorsed screening tests	Preferred screening test
NCC (*20*)	2020	50 (low and medium risk) 40 (high risk)	75	No tailoring	FIT, mtFIT-DNA, colonoscopy, CTC, FS	Colonoscopy
CSO (*24*)	2020	40	74	No tailoring	FIT, mtDNA, colonoscopy	Colonoscopy
NCRCDD (*21*)	2019	50	75	No tailoring	FIT, gFOBT, mtFIT-DNA, colonoscopy, CTC, FS, CCE, mSEPT9 test, M2-PK test	FIT, mtFIT-DNA, colonoscopy
Colon Cancer Society of CACA (*18*)	2018	40	74	No tailoring	FOBT, mtDNA, colonoscopy, CTC, FS, questionnaire assessment, M2-PK test, mSEPT9 test	FIT, mtDNA, colonoscopy, questionnaire assessment
Multi-Collaborative Group of CMA (*19*)	2014	50	74	No tailoring	FIT, colonoscopy, questionnaire assessment, DRE, chromoendoscopy, electronic chromoendoscopy	None
CSDE, Oncology Endoscopy Society of CACA (*22*)	2014	50	75	No tailoring	FIT, gFOBT, mtDNA, colonoscopy, FS, CCE, mSEPT9 test, VC	Three-tier: gFOBT, FIT, colonoscopy
CSGE (*23*)	2011	50	74	No tailoring	FOBT, questionnaire assessment, colonoscopy, FS	Two-tier: questionnaire assessment + FIT, colonoscopy

Abbreviations: CACA=China Anti-Cancer Association; CCE=colon capsule endoscopy; CMA=Chinese Medical Association; CSDE=Chinese Society of Digestive Endoscopology; CSGE=Chinese Society of Gastroenterology; CSO=Chinese Society of Oncology; CTC=computed tomography colonography; DRE=digital rectal examination; FIT=fecal immunochemical test; FS=flexible sigmoidoscopy; gFOBT=guaiac-based fecal occult blood test; mtDNA=multi-target DNA; NCC=National Cancer Center of China; NCRCDD=National Clinical Research Center for Digestive Diseases; VC=visual colonoscopy.

variants, stool- or blood-based biomarkers may help to identify individuals with an elevated risk of CRC (*15*,*27*).

Another important issue is the low participation rate of colonoscopy screening in China. In a multicenter CRC screening program covering 12 PLADs conducted from 2012–2015 (*7*), the overall uptake rate of screening colonoscopy among high-risk populations was only 14.0%. In the most recent CRC screening trial conducted in 6 centers (*17*), the participation rate of screening colonoscopy was 42.5%, which was higher than other studies but was much lower than FIT-based screening in the same studies (94.0%). All the evidences suggested that although colonoscopy was regarded as the gold standard of CRC screening, it was not feasible to be used as the first-line screening modality in a population-based CRC screening program. Implementation of health promotion campaigns to improve the population awareness of screening and using effective non- or minimally invasive approaches to firstly select high-risk populations suitable for subsequent colonoscopy screening may help to improve the overall screening uptake rate.

Clinician

Clinicians played an essential role in CRC screening. First, clinicians could evaluate the patient's risk during their hospital visit. For patients with an elevated risk of CRC, professional advice on choosing appropriate screening techniques could be provided. Though such personal consultation typically occurred in an opportunistic screening setting, the uptake rate of screening may be strongly improved. Second, the clinicians could target patients who might benefit from chemoprevention and other targeted prevention strategies such as lifestyle modification to reduce the future risk of CRC. Third, the effectiveness of screening strongly depend on the quality of examination and diagnosis made by the clinicians. As shown in previous studies, strong heterogeneity of diagnostic performance among endoscopists who performed screening colonoscopy existed in multi-center screening programs (*28*).

To optimize the screening effectiveness, the following aspects need to be addressed in the future: 1) clinicians should be familiar with the well-established risk assessment tool and cancer screening techniques; 2) clinicians should provide tailored CRC screening advice based on the risk assessment results and patients' preference; 3) only experienced clinicians should be involved in the screening, who should also routinely attend training to master the most recent advances regarding diagnosis and treatment; and 4) the quality of screening endoscopy and pathology should be routinely reviewed by an independent scientific panel.

Service Provider

The major challenge from the service provider's perspective is the healthcare legislation on improving the access to CRC screening. The only access to free CRC screening is through organized CRC screening programs initiated by the central and local government, which are limited by their budget. It is therefore urgent to formulate new policies on tackling the scheme of screening payments for eligible individuals to improve the overall attendance rate of CRC screening. In addition, it is also necessary to implement health promotion campaigns to enhance the population's awareness of cancer prevention.

Cost-effectiveness analysis about CRC screening is essential for policymakers and there have been a series of relevant studies being published in China. Wang et al. (*29*) reported a systematic review which included 12 studies of the economic evaluation evidence of CRC screening in mainland China, and this study concluded that CRC screening was generally cost-effective in Chinese population, but the optimal technology and strategy was not conclusive. To maximize the screening yield of CRC screening under limited health expenditure, high-quality health economic evaluations addressing the optimal screening strategy for different populations in China are still needed.

RESEARCH ADVANCES AND PROSPECT

Despite the idea of risk-adapted CRC screening having been introduced nearly 30 years (*30*), no national screening program adopted it so far with the need for reliable risk prediction models. A cost-effectiveness analysis has shown that a discriminatory performance of at least 0.65 is required for risk-adapted screening to be more cost-effective than uniform screening (*31*). To promote the discriminatory power of the model, a combination of traditional risk factors with novel indicators might be a promising direction in the future. The polygenic test can be used to estimate personal polygenic risk score (PRS) based on the absence or presence of specific risk alleles. Jeon et al. (*32*) found that the model combined lifestyle, environmental, and PRS yielded better discrimination than model only included environmental-score with the AUC of 0.63 and 0.59, respectively. Except for the estimation of background risk, an alternative type of potential indicator was the outcomes of prior screening. Several studies have shown that fecal hemoglobin concentrations in previous screening rounds were highly predictive for future detection of advanced neoplasia (*33*–*34*) and risk prediction models combining this factor were being developed (*35*).

Apart from the risk assessment model, novel screening techniques like biomarkers and artificial intelligence (AI) could also optimize CRC risk-adapted screening. Food and Drug Administration (FDA) in the US has approved several novel screening techniques, for example, multi-target stool DNA test known as Cologuard (*36*), gut microbiota known as Lifekit (*37*), and methylated SEPT9 test known as the Epi proColon (*38*). These new screening techniques available in the US offered new options for developing screening guidelines with a diagnostic efficacy similar to or superior to FIT (*39*).

Coloclear, a multi-target stool DNA test method approved by the National Medical Products Administration for registration of innovative Class III medical devices in 2020, is known as the first certification of the CRC screening method in China. The registration of Coloclear indicated the development and implementation potential of biomarkers in CRC screening in China. Most AI tools in CRC screening aim at increasing detection of small abnormalities to increase screening sensitivity and referred to as computer-aided detection (CADe). In China, Wang et al. (*40*–*41*) did both nonblinded and blinded RCT to assess the effectiveness of a CADe system that avoided potential operational bias and found a significant increase in the number of diminutive adenomas detected.

Traditional cohort studies and RCTs need long duration and high cost in verifying the long-term cost-effectiveness of a new screening strategy, in addition, screening strategies with a broad variation of test characteristics are too many to evaluate. To avoid these drawbacks, several countries adopt the way of model simulation to evaluate the effect of screening strategies. The microsimulation model, which simulates individual disease histories using stochastic parameters describing transitions between specified health states, could flexibly and quickly conduct estimation. In the US, the results from microsimulation model studies have assisted policymakers in decision-making relative to screening guideline (*3*). Hence, the long-term reality study and microsimulation study will both provide solid evidence for decision-making in CRC screening. To date, the application of microsimulation model in CRC screening in China is sparse.

CONCLUSION

Pilot population-based CRC screening programs have been implemented in most PLADs of China and have served as a good policy informing platform for future CRC screening practices. Authoritative scientific societies have formed a series of CRC screening and early detection guidelines or expert consensus to ensure overall quality and effectiveness. To orient future screening practices and effectively reduce the disease burden, future research addressing the aspects of population risk prediction and stratification, novel effective screening and early detection biomarkers, development of personalized screening strategy, long-term evaluation of the effectiveness of different screening strategies using cohort and microsimulation techniques should be highly recommended.

Conflicts of Interest: No conflicts of interest.

Funding: Supported by the National Natural Science Foundation of China (82173606), the Natural Science Foundation of Beijing Municipality (7202169) and the Beijing Nova Program of Science and Technology (Z191100001119065).

doi: 10.46234/ccdcw2022.077

[#] Corresponding author: Min Dai, daimin2002@hotmail.com.

[1] Medical Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

Submitted: January 16, 2022; Accepted: March 10, 2022

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