Original Article

Comparative yield and efficiency of strategies based on risk assessment and fecal immunochemical test in colorectal cancer screening: A cross-sectional population-based analysis

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Abstract

Objective: Integration of risk stratification into fecal immunochemical test (FIT) might aid in the suboptimal detection of advanced neoplasms by FIT in colorectal cancer (CRC) screening. A comparative study was conducted to evaluate the participation and diagnostic yield of the parallel combination of questionnaire-based risk assessment (QRA) and FIT, FIT-only and QRA-only strategies in a CRC screening program in China.

Methods: The study included 29,626 individuals aged 40–74 years and invited to participate in a CRC screening program in China. Participants were first invited to undertake QRA and one-time FIT (OC-sensor). Participants with positive QRA or FIT were deemed to be high-risk individuals who were recommended for subsequent colonoscopy. Participation, detection rate, and resource demand for colonoscopy were calculated and compared.

Results: Of the 29,626 invitees, 20,203 completed the parallel combination, 8,592 completed the QRA-only, and 11 completed the FIT-only strategy. For the parallel combination, FIT-only, and QRA-only strategies, the overall positivity rates were 10.2% (2,928/28,806), 5.4% (1,096/20,214), and 6.8% (1,944/28,795), respectively; the yield of advanced neoplasm per 10,000 invitees were 46.9 [95% confidence interval (95% CI): 39.8–55.4], 36.8 (95% CI: 30.5–44.4), and 12.2 (95% CI: 8.8–16.8), respectively; the positive predictive values for detecting advanced neoplasms among participants who completed colonoscopy were 4.7% (95% CI: 4.0%–5.6%), 9.9% (95% CI: 8.3%–11.9%), and 1.9% (95% CI: 1.3%–2.6%), respectively; the number of colonoscopies required to detect one advanced neoplasm was 11.4 (95% CI: 9.8–13.4), 5.7 (95% CI: 4.8–6.7), and 28.4 (95% CI: 20.7–39.2), respectively.

Conclusions: The parallel combination of QRA and FIT did not show superior efficacy for detecting advanced neoplasm compared with FIT alone in this CRC screening program.

Keywords: Colorectal neoplasm; screening; fecal immunochemical test; risk stratification

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Introduction

Colorectal cancer (CRC) emerged as the third most frequently diagnosed cancer worldwide in 2018 (1). Recently, a rapid increase in the incidence and mortality rates of CRC has been observed in many countries with medium or high human development index, particularly in East Europe, Asia, and South America, possibly due to the wide adoption of westernized lifestyles (2). Given the long sojourn time and relatively high survival rate for patients with localized tumor stage, studies have demonstrated screening as the most effective strategy to reduce the mortality in colorectal cancer patients (3-5). Although the benefits of CRC screening are well acknowledged, designing risk-adapted CRC screening strategies to improve their yield and cost-effectiveness is still a major challenge.

Among the well-established CRC screening modalities, fecal immunochemical test (FIT) is the most widely used tool and has been widely adopted in nationwide CRC screening programs (6,7). A recently published meta-analysis demonstrated that the sensitivities of FIT for CRC and advanced adenoma were 0.91 [95% confidence interval (95% CI): 0.84–0.95] and 0.40 (95% CI: 0.33–0.47), respectively, at a positivity threshold of 10 μg Hb/g (8). Although FIT has strengths such as low cost, ease of use, and high compliance rate, its low sensitivity for detecting advanced adenoma may limit its potential to reduce the incidence of CRC (9). To further improve its diagnostic efficacy, researchers have investigated the potential combination of FIT and other biomarkers, such as fecal DNA and fecal microbial markers (10-12). However, only a few significant biomarkers have been successfully translated into clinical use because of high cost, technical barrier, or deficiency of prospective validation using a large sample size (12).

The potential use of risk stratification models based on established risk factors in CRC screening has been proposed (13,14). In a previous study, the most common risk factors were age, sex, family history in first-degree relatives, body mass index, smoking, and the models generally yielded modest discriminative efficacy with the area under the receiver operating characteristics curves (ROC) ranging from 0.61 to 0.70 (13). To optimize the screening yield, the risk-stratification scoring was recommended for selecting high-risk patients by colonoscopy, and was especially suitable for countries with intermediate disease burden and limited health resources (15,16). Previous retrospective studies have demonstrated that the combined use of FIT and risk-stratification scores could enhance the sensitivity for detecting advanced neoplasm without significantly increasing the workload in colonoscopy (17,18). However, the evidence of such combined strategy in the true screening settings is sparse and needs to be further validated to guide its clinical application.

For this study, we used an up-to-date data from a population-based CRC screening program conducted in China, in which the strategy of parallel combination of FIT and a questionnaire-based risk assessment (QRA) was adopted to select high-risk participants for further colonoscopy examination. In this study, we aimed to evaluate the participation and screening yield of such a parallel combination in detecting CRC and its precursors and to compare it with the results of simulated FIT-only and QRA-only strategies. We anticipated that the results would provide timely evidence in designing effective CRC screening strategies for future CRC screening programs.

Materials and methods

Study design and study population

In this study, the population-based CRC screening program was conducted in the Haining county of Zhejiang province in China. This population-based organized CRC screening program was a part of the public health service program in which the screening service was provided to eligible inhabitants free of charge. For the present study, a total of 17 villages were selected through cluster random sampling of the whole study population in Haining City. Individuals meeting one of the following criteria were excluded: 1) history of CRC; 2) severe cardiac, pulmonary, brain, or renal dysfunction; 3) psychiatric illnesses; 4) acute phase of enteritis, dysentery, or perianal abscess; 5) diagnosis of lumen stenosis because of peritonitis, enterobrosis, or abdominal adhesion; 6) diagnosis of hepatocirrhosis ascites, mesenteric inflammation, and celianeurysm; or 7) pregnant women. Potential participants were recruited in the selected communities and were checked for eligibility by trained study staff.

For the screening scheme, briefly, a two-step screening process was adopted. Eligible individuals aged 40–74 years were firstly invited to undertake FIT and QRA by trained staff, and participants tested either positive by FIT or evaluated to be high risk by QRA were recommended to

undertake subsequent colonoscopy examination at Haining Hospital of Traditional Chinese Medicine. The study was approved by the Ethics Committee of Haining Hospital of Traditional Chinese Medicine (Approval No. 2019-4). All participants provided written informed consent. From August 2019 to February 2020, 29,626 eligible inhabitants from Haining county were invited to participate in this CRC screening program. There were 820 individuals who declined the invitation, and the remaining 28,806 underwent FIT, QRA, or both. A detailed flow diagram of the study participants is shown in *Figure 1*.

Intervention

FIT procedure

A quantitative FIT (OC-sensor, Eiken Chemical Company, Japan) was used by following the standard operating procedure. Briefly, one fecal sample collection tube containing 2.0 mL of stabilization buffer designed to minimize hemoglobin degradation was distributed to the participants along with an operation brochure. Participants were instructed to collect fecal sample from one bowel movement, and the fecal collection material was sealed in a plastic bag. No medical or dietary restriction was required before conducting the test. The participants were instructed to return the sample collection tube to the community healthcare center in 72 h, where the laboratory tests were performed by the trained staff. For this study, a positivity threshold of 100 ng Hb/mL buffer (equivalent to 20 μg Hb/g feces) was used. The specimens having values ≥20 μg Hb/g feces were classified as positive, and the participants were further recommended to undertake the colonoscopy examination.

QRA procedure

Participants were interviewed using a standardized epidemiological questionnaire by the study staff to collect information including basic demographic factors, lifestyle, risk factor exposure, and disease history. An established CRC risk assessment scoring system recommended by the Chinese consensus of early colorectal cancer screening (2019, Shanghai) was used (19). Briefly, participants meeting one of the following criteria were categorized as potentially high-risk participants for CRC: 1) having a family history of CRC among first-degree relatives; 2) having history of malignancy; 3) having history of polyps; or 4) having ≥2 of the following conditions: chronic constipation, chronic diarrhea, mucous bloody stool, chronic appendicitis or history of appendectomy, history of chronic biliary tract disease, or history of cholecystectomy. Participants assessed to be at high risk for CRC were

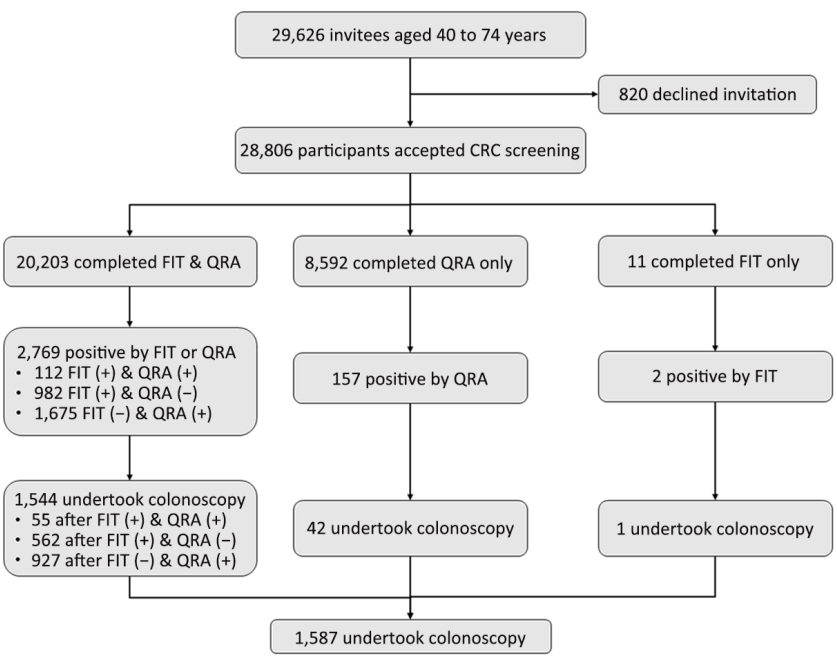

Figure 1 Flow diagram of study participants. CRC, colorectal cancer; FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment.

informed of the results and were further recommended to undertake the colonoscopy examination.

Colonoscopy and pathology

All colonoscopy examinations were conducted by experienced endoscopists. Abnormal findings during colonoscopy were carefully checked under standard clinical procedures and biopsies were collected for further pathology diagnosis. Clinical data such as morphological feature, location (distance from the anus and segment), macroscopic diagnosis, and size were collected from standardized forms. The diagnosis of CRC was made according to the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 edition) (20). Advanced adenomas were defined as at least one adenoma ≥10 mm, at least one adenoma with villous components, or high-grade dysplasia. Advanced neoplasms refer to CRC and advanced adenoma.

Data collection and statistical analysis

Paper-based standardized documentation forms were collected from the trained staff and physicians. Validity of forms was checked by an independent specialist, and any mistakes or inconsistencies were corrected by retrieving the original records. A research database was then constructed in statistical software R for further analysis (21).

Descriptive analysis was performed to summarize the clinical characteristics of the study population. Chi-squared tests were used to analyze the categorical data. Overall and group-specific compliance rates of colonoscopy by age and sex were calculated. To further explore the potential variation of compliance rates among risk, age, and sex groups, multivariate logistic regression models were applied, and odds ratios (OR) along with 95% CIs were calculated and reported. Regarding the evaluation of the diagnostic yield, the yield of advanced neoplasm (CRC and advanced adenoma) or any neoplasm (CRC, advanced adenoma, and non-advanced adenoma) per 10,000 invitees was calculated for three different screening strategies, such as, parallel combination, simulated FIT-only, and simulated QRA-only strategies. The detection rates for positive participants at the one-round screening for three different screening strategies were calculated and compared. In addition, the positive predictive values (PPV) for detecting colorectal neoplasm among participants who completed colonoscopy after undergoing one of the three different screening strategies were calculated and compared. Furthermore, to assess the resource requirement of colonoscopy in the three different screening strategies, we calculated the number of colonoscopies needed to be performed to detect one advanced neoplasm or one any other neoplasm.

Results

Study population characteristics

Of the 28,806 participants, 20,203 completed both FIT and QRA, 8,592 completed QRA-only, and 11 completed FIT-only strategy. Apart from the limited number of participants who underwent FIT only (n=11), the other subgroups had a balanced proportion of both sexes. Approximately 67.5% of the participants were 50–69 years old, 21.4% were 40–49 years old, and only 11.1% were 70–74 years old. Regarding the education background, the majority had completed primary or middle school. Detailed population characteristics in this study are shown in *Supplementary Table S1*.

Characteristics of high-risk population

Figure 1 shows the flow diagram of the study participants. Of the 20,214 participants who completed FIT, 1,096 (5.4%) were tested positive at a cut-off of 20 μg Hb/g feces. Of the 28,795 participants who completed QRA, 1,944 (6.8%) were assessed to be high risk. Notably, of those who completed both FIT and QRA (n=20,203), co-positive results were found in only a small proportion of participants (112/2,769, 4.0%). Among individuals having positive results either by FIT or QRA, the proportions of patients in the age groups of 40–49 years, 50–59 years, 60–69 years, and 70–74 years were 10.9%, 36.0%, 39.9%, and 13.1%, respectively, and the distribution was similar for FIT and QRA (*Figure 2A*). The number of males tested positive was slightly greater than that of females for both FIT and QRA (*Figure 2B*).

We further categorized the quantitative FIT values (*Figure 2C*). Overall, 87.6% of the participants had FIT values <10 μg Hb/g feces. In the positive cases, the proportions of participants with FIT values in the range of 20.0–29.9, 30.0–39.9, and ≥40.0 μg Hb/g feces were 1.6%, 0.7%, and 3.1%, respectively. According to the criteria of QRA, 67.8% (1,319/1,944) had history of polyp, 17.7% had history of CRC among first-degree relatives, 13.0% had history of malignancies, and 10.8% had ≥2 conditions related to elevated risk of CRC. Detailed information is

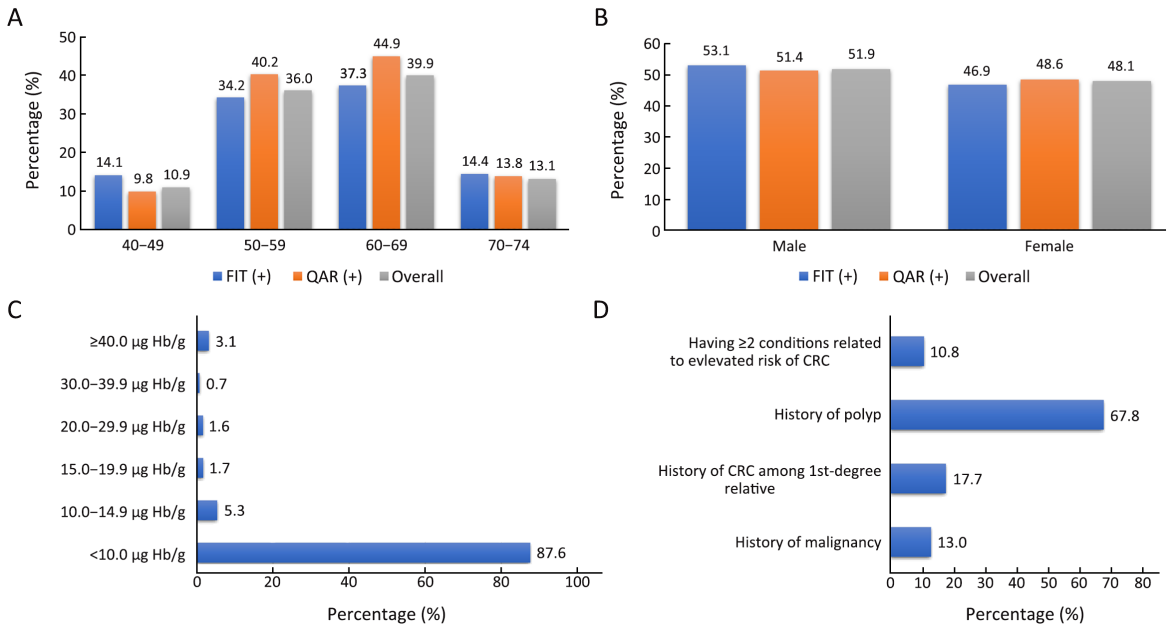

Figure 2 Characteristics of participants conducting FIT or QRA. (A) Age distribution for subjects with positive FIT results or assessed to be high risk; (B) Sex distribution for subjects with positive FIT results or assessed to be high risk; (C) Distribution of quantitative FIT values for subjects who completed FIT; (D) Condition of criteria for subjects who assessed to be high risk of CRC. FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; CRC, colorectal cancer.

shown in *Figure 2C,D*.

Compliance of colonoscopy

Participants having positive FIT or QRA were recommended for subsequent diagnostic colonoscopy. Of the 2,928 positive participants, 1,587 (54.2%) finished colonoscopy as per the study protocol at the designated hospital, and 866 individuals with abnormal colonoscopy findings received biopsy check for further pathological diagnosis. We further explored the variations in the compliance rate of colonoscopy between subgroups. By applying multivariate logistic regression, the results showed that, compared with participants having positive-QRA and negative-FIT results, participants having positive-FIT and negative-QRA results were more willing to accept colonoscopy, with OR of 1.25 (95% CI: 1.07–1.47; P=0.006). In addition, the compliance rates increased with age, and no significant difference was found between males and females. Detailed results are shown in *Figure 1*, *Supplementary Table S2*.

Screening yield of different screening strategies

Table 1 and *Figure 3* present results of the screening yield of three screening strategies. The combined strategy included participants who completed either FIT, QRA, or both. The number of eligible participants included in the combined, FIT-only, and QRA-only strategies was 28,806, 20,214, and 28,795, respectively, yielding the participation rate of 97.2% (95% CI: 97.0%–97.4%), 68.2% (95% CI: 67.7%–68.8%), and 97.2% (95% CI: 97.0%–97.4%), respectively. The positivity rate of the combined strategy was significantly higher than that of the FIT-only and QRA-only strategies (10.2%, 5.4%, and 6.8%, respectively). With respect to the screening yield, the yield of advanced neoplasm per 10,000 invitees for the combined, FIT-only, and QRA-only strategies were 46.9 (95% CI: 39.8–55.4), 36.8 (95% CI: 30.5–44.4), and 12.2 (95% CI: 8.8–16.8), respectively; and the yield of any neoplasm per 10,000 invitees for the combined, FIT-only, and QRA-only strategies were 101.6 (95% CI: 90.8–113.7), 61.4 (95% CI: 53.2–71.0), and 43.9 (95% CI: 37.0–52.1), respectively.

For participants who actually underwent different screening strategies, PPV of advanced neoplasm at colonoscopy for the FIT-only strategy (9.9%, 95% CI: 8.3%–11.9%) was significantly higher than that for both combined (4.7%, 95% CI: 4.0%–5.6%) and the QRA-only strategy (1.9%, 95% CI: 1.3%–2.6%) (*Table 1*). However, compared with the FIT-only strategy, the combined

Table 1 Detection rates and positive predictive values of colorectal neoplasms in different screening scenarios

Outcomes	Combined strategy		FIT-only strategy		QRA-only strategy	
	$N_{positive}$/N	Rate [% (95% CI)]	$N_{positive}$/N	Rate [% (95% CI)]	$N_{positive}$/N	Rate [% (95% CI)]
Detection rate at colonoscopy						
Advanced neoplasm	139/1,587	8.8 (7.5–10.3)	109/618	17.6 (14.8–20.8)*	36/1,024	3.5 (2.6–4.8)*
CRC	15/1,587	0.9 (0.6–1.6)	15/618	2.4 (1.5–4.0)*	0/1,024	0 (0–0.4)*
Advanced adenoma	124/1,587	7.8 (6.6–9.2)	94/618	15.2 (12.6–18.3)*	36/1,024	3.5 (2.6–4.8)*
Non-advanced lesions	727/1,587	45.8 (43.4–48.3)	243/618	39.3 (35.5–43.2)*	509/1,024	49.7 (46.7–52.8)
Non-advanced adenoma	162/1,587	10.2 (8.8–11.8)	73/618	11.8 (9.5–14.6)	94/1,024	9.2 (7.6–11.1)
Other benign lesion†	565/1,587	35.6 (33.3–38.0)	170/618	27.5 (24.1–31.2)*	415/1,024	40.5 (37.6–43.6)*
No findings	721/1,587	45.4 (43.0–47.9)	266/618	43.0 (39.2–47.0)	479/1,024	46.8 (43.7–49.8)
PPV						
Advanced neoplasm	139/2,928	4.7 (4.0–5.6)	109/1,096	9.9 (8.3–11.9)*	36/1,944	1.9 (1.3–2.6)
Any neoplasm	866/2,928	29.6 (28.0–31.3)	352/1,096	32.1 (29.4–34.9)	509/1,944	26.2 (24.3–28.2)*

CRC, colorectal cancer; PPV, positive predictive value; FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; 95% CI, 95% confidence interval; †, Other benign lesions included hyperplastic polyps, inflammatory polyp and chronic inflammation; *, Significant differences of detection rate or positive predictive values were observed when compared to the combined strategy.

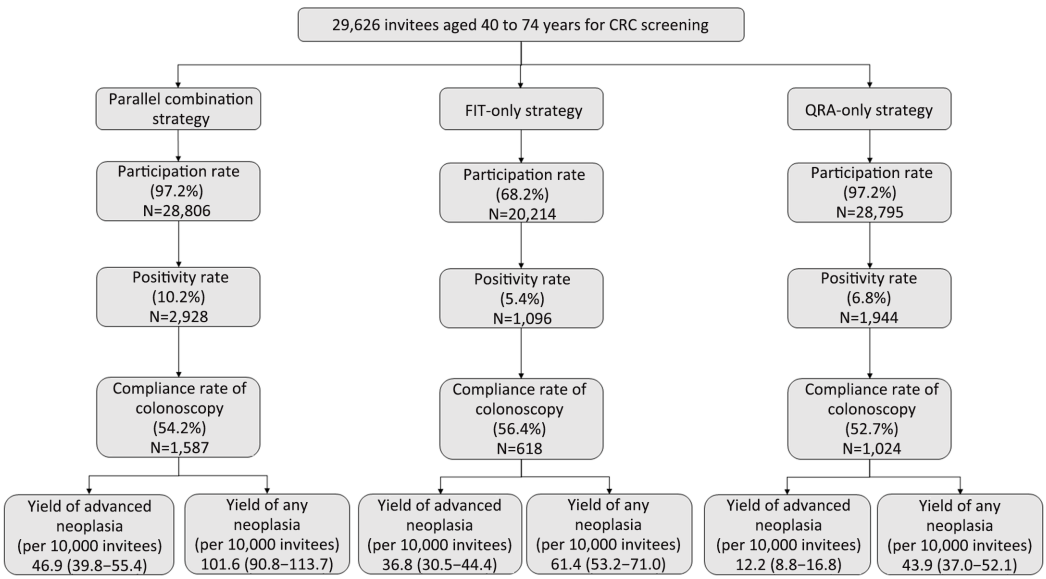

Figure 3 Screening yield of different screening strategies. CRC, colorectal cancer; QRA, questionnaire-based risk assessment.

strategy identified more patients with non-advanced lesions. This observation was further strengthened in the subgroup of participants finishing both FIT and QRA, as shown in *Supplementary Table S3*. Approximately 40% of the abnormal findings identified by QRA were benign lesions such as inflammatory polyps and chronic inflammation. Taking the compliance rate into consideration, the detection rates for advanced neoplasm and any neoplasm in the FIT-only strategy were significantly higher than that of the combined strategy and the QRA-only strategy. For instance, PPV for detecting advanced neoplasm for the FIT-only, combination, and QRA-only strategies was 9.9% (95% CI, 8.3%–11.9%), 4.7% (95% CI, 4.0%–5.6%), and 1.9% (95% CI, 1.3%–2.3%), respectively.

Resource load of colonoscopy to detect one colorectal lesion

Compared with the FIT-only strategy, the combined

strategy additionally detected 30 advanced adenomas, 89 non-advanced adenomas, and 395 other benign lesions, at a cost of 969 additional colonoscopies. Regarding the number of colonoscopies needed to detect one advanced neoplasm, the FIT-only strategy was the most cost-efficient compared with other two strategies with 5.7 (95% CI, 4.8–6.7), 11.4 (95% CI, 9.8–13.4), and 28.4 (95% CI, 20.7–39.2) colonoscopies required for the FIT-only, combined, and QRA-only strategies, respectively. Detailed results are shown in *Table 2*.

Discussion

In this population-based CRC screening program in China, we comparatively evaluated the participation and screening yield of the parallel combination of FIT and QRA, simulated FIT-only, and simulated QRA-only strategies. The FIT-only strategy had considerably lower participation rate than the other two strategies. However, in terms of screening yield, the FIT-only strategy had superior detection rate and PPV for detecting advanced neoplasms than the other two strategies. The FIT-only strategy was more cost-efficient than the combination strategy in terms of significantly lower resource demand for colonoscopy. Our study therefore provided important empirical evidence regarding the feasibility and efficacy of the parallel combination of FIT and QRA in a real-world CRC screening setting.

Accurate risk stratification is essential for CRC screening in the era of precise medicine. Taking feasibility and practicality into consideration, most risk prediction models were constructed based on easy-to-collect risk factors associated with CRC; however, such models had the modest diagnostic performance in detecting CRC and advanced adenoma (13). Peng *et al.* conducted a head-to-head comparison of 17 risk prediction models for advanced neoplasms in two German cohorts and found that the areas under ROC curves ranged from 0.57 to 0.65 (22). Similarly, in our study, the detection rate of advanced neoplasm was suboptimal for the QRA, and most patients having abnormal findings were actually diagnosed with non-advanced adenoma or other benign lesions in subsequent colonoscopy examination. One potential explanation is that nearly 70% of the high-risk population had a history of polyps. Removal of such lesions yielded a reduced risk of CRC and advanced adenomas as demonstrated by previous studies, and the 5-year recurrence rate of advanced adenoma after polypectomy was relatively low (4). In addition, having symptoms of digestive tract disorders such as chronic diarrhea and constipation may not reflect the presence of advanced neoplasm in the single round of screening, which should, however, be monitored in the long term.

Some previous studies have tried to construct multivariate risk prediction models by including FIT and CRC-related risk factors, the results of which showed that adding risk-based stratification increased the accuracy for detecting advanced neoplasms in FIT-based screening (17,23,24). However, such combined risk prediction models lacked prospective validation in a true screening setting. Another simple approach was combining risk assessment and FIT in parallel, as demonstrated in the present study. The significant findings of our study are in line with a recently published study by Roos *et al.* who evaluated an online family history questionnaire in addition to the FIT in 6,000 Dutch screening-naïve individuals and demonstrated that the addition of the questionnaire assessment to one round of FIT screening did not increase the detection rate of advanced neoplasm compared with the FIT-only approach (25). However, unlike the study by Roos *et al.*, who evaluated the risk assessment in individuals qualifying for suspected Lynch syndrome or familial CRC syndrome, the QRA used in the present study covered more high-risk populations without the restriction of family history. Therefore, our study provided an essential evidence of the real-world application of parallel combination from a different aspect. Our analysis also

Table 2 Number of colonoscopies needed to be performed to detect one colorectal lesion for different screening scenarios

Screening scenarios	Number of colonoscopies needed to be performed to detect [n (95% CI)]	
	One advanced neoplasm	One any neoplasm
Combined strategy	11.4 (9.8–13.4)	1.8 (1.8–1.9)
FIT-only strategy*	5.7 (4.8–6.7)	1.8 (1.6–1.9)
QAR-only strategy	28.4 (20.7–39.2)	7.9 (6.7–9.3)

FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; 95% CI, 95% confidence interval; *, Quantitative FIT (OC-sensor, Eiken, Japan) was used in the present study, and the positivity threshold used was 20 μg Hb/g feces.

showed that the co-positivity rate between QRA and FIT was low in our study population. Further studies comparing the positivity rates between other established risk prediction models and FIT are necessary in the future.

Recently, researchers also proposed risk-adapted screening, that is, to provide appropriate CRC screening technique based on the risk stratification, to optimize the efficiency of CRC screening in terms of performance and cost. For instance, high-risk patients were recommended to undertake colonoscopy, and intermediate- or low-risk patients were recommended to undertake FIT screening (17,26,27). Chiu *et al.* evaluated the risk-adapted approach combining the Asia-Pacific Colorectal Screening (APCS) score and FIT in 5,657 participants from 12 Asia-Pacific regions, and the results showed that the APCS score-based algorithm was effective in triaging participants for FIT or colonoscopy and could substantially reduce colonoscopy workload (17). Recently, our research team also conducted a large-scale randomized controlled trial to comparatively evaluate the effectiveness of colonoscopy, FIT, and a novel risk-adapted screening approach in CRC screening (26). The interim baseline results demonstrated that the risk-adapted screening approach had a high participation rate, and its diagnostic yield was superior to that of FIT at a similarly low load of colonoscopy (28). Therefore, exploration of personalized screening strategies based on effective risk stratification deserves further attention in the future.

Our study also provided up-to-date data regarding the feasibility and effectiveness of FIT-based screening in China, which could be referenced for other countries with a similar CRC burden. This study used the quantitative FIT (OC-sensor), which has been widely used in previous studies. The positivity rate in our study population was 5.4% at the positivity threshold of 20 μg Hb/g feces, and the positivity rate could be further increased to 7.1% or 12.4% if the positivity threshold was lowered to 15 μg Hb/g feces or 10 μg Hb/g feces, respectively. For other screening programs, the optimal positivity threshold should be determined based on the targeted positivity rate and resource load of colonoscopy (29-31). Variation regarding the detection rate for colorectal neoplasm needs to be explored further. The PPV for detecting advanced neoplasm in our study was lower than that described in previous studies conducted in western countries, possibly due to the relatively low prevalence of colorectal neoplasm in China (29,31).

Specific strengths and limitations should be taken into consideration when interpreting the results. As major strengths, the study was prospectively conducted in a true clinical screening setting to comparatively evaluate three different strategies in CRC screening. In addition, rigorous standards were adopted to ensure the quality of research data. There are also several limitations. First, our study only included results of single round of screening. However, considering the unfavorable results of the combined strategy, we did not anticipate that the conclusion would change if repeated screening was performed. Second, the compliance rate of colonoscopy for positive participants (either FIT or QRA) was suboptimal, which may affect the overall detection rates. For instance, the compliance rate of colonoscopy for participants with positive QRA but negative FIT was slightly lower than that for participants with positive FIT but negative QRA, such differences may underestimate the overall screening efficacy of QRA-based strategy. Although we observed that the compliance rates were similar among the three strategies in a simulated approach, the true participation rates and screening yield of the proposed strategies should be prospectively evaluated in further studies from a true screening setting. Third, the FIT-only and QRA-only strategies were simulated among participants undertaking FIT or QRA, meaning that the FIT-only approach may also have participants having available QRA, and *vice versa*. However, we postulated such simulation might have little bias when estimating the participation rate of FIT, given that most participants having strong willingness to accept QRA in this population-based screening program. Fourth, the positivity rate of FIT depends on characteristics of the study population. Therefore, the positivity rate of FIT among participants in other populations with different characteristics needed to be further evaluated.

Conclusions

The parallel combination of QRA and FIT showed improved screening yield for advanced neoplasm than FIT-only and QRA-only strategies. However, the parallel combination was not efficient than the FIT-only strategy in terms of resource demand for colonoscopy. Novel risk-adapted screening approaches that are both effective and cost-effective need to be developed in the future.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Study population characteristics

Characteristics	n (%)			
	Invitees accepted screening (N=28,806)	Participants conducted FIT & QRA (N=20,203)	Participants conducted QRA only (N=8,592)	Participants conducted FIT only (N=11)
Age (year)				
40–49	6,162 (21.4)	3,386 (16.8)	2,775 (32.3)	1 (9.1)
50–59	10,749 (37.3)	7,662 (37.9)	3,082 (35.9)	5 (45.5)
60–69	8,707 (30.2)	6,826 (33.8)	1,877 (21.8)	4 (36.4)
70–74	3,188 (11.1)	2,329 (11.5)	858 (10.0)	1 (9.1)
Sex				
Male	14,417 (50.0)	9,694 (48.0)	4,715 (54.9)	8 (72.7)
Female	14,389 (50.0)	10,509 (52.0)	3,877 (45.1)	3 (27.3)
Education background*				
Uneducated	2,500 (13.5)	2,267 (14.3)	233 (8.9)	1 (9.1)
Primary or middle school	14,703 (79.6)	12,581 (79.3)	2,121 (81.4)	8 (72.7)
High school or above	1,272 (6.9)	1,020 (6.4)	252 (9.7)	2 (18.2)

FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; *, the percent was calculated after excluding participants with missing information.

Table S2 Comparison of compliance rates of colonoscopy for different scenarios of FIT and QRA (N=2,928)

Groups	n	Completed colonoscopy (n)	Compliance rate (%)	OR (95% CI)	P*
Risk assessment					
QAR (+) and FIT (–)	1,832	969	52.9	Ref	
QAR (–) and FIT (+)	984	563	57.2	1.25 (1.07–1.47)	0.006
Both QAR (+) & FIT (+)	112	55	49.1	0.87 (0.59–1.27)	0.467
Age (year)					
40–49	320	127	39.7	Ref	
50–59	1,055	572	54.2	1.86 (1.44–2.41)	<0.001
60–69	1,169	685	58.6	2.23 (1.73–2.88)	<0.001
70–74	384	203	52.9	1.75 (1.30–2.37)	<0.001
Sex					
Male	1,520	826	54.3	Ref	
Female	1,408	761	54.0	1.01 (0.88–1.17)	0.849

FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; OR, odds ratio; 95% CI, 95% confidence interval; *, logistic regression models were applied to calculate OR, 95% CI and P.

Table S3 Detection of colorectal neoplasms for subgroup of individuals who finished both FIT and QRA

Groups	No. of participants having positive results	No. of colonoscopies	Detection rate at colonoscopy examination [n (%)]			
			CRC	Advanced adenoma	Non-advanced adenoma	Other benign lesions
FIT (+) & QRA (+)*						
All	112	55	0 (0)	6 (10.91)	5 (9.09)	20 (36.36)
Male	62	31	0 (0)	5 (16.13)	3 (9.68)	9 (29.03)
Female	50	24	0 (0)	1 (4.17)	2 (8.33)	11 (45.83)
FIT (+) & QRA (−)*						
All	982	562	15 (2.67)	87 (15.48)	68 (12.10)	150 (26.69)
Male	519	300	7 (2.33)	67 (22.33)	38 (12.67)	68 (22.67)
Female	463	262	8 (3.05)	20 (7.63)	30 (11.45)	82 (31.30)
FIT (−) & QRA (+)*						
All	1,675	927	0 (0)	29 (3.13)	87 (9.39)	378 (40.78)
Male	839	471	0 (0)	18 (3.82)	49 (10.40)	178 (37.79)
Female	836	456	0 (0)	11 (2.41)	38 (8.33)	200 (43.86)

FIT, fecal immunochemical test; QRA, questionnaire-based risk assessment; CRC, colorectal cancer; *, Quantitative FIT (OC-sensor, Eiken, Japan) was used in the present study, and the positivity threshold used was 100 ng Hb/mL. High-risk or low-risk individuals were assessed by QRA.