ABSTRACT

Objectives Quantitative faecal immunochemical tests (FITs) are widely used for colorectal cancer (CRC) screening in the Western countries, whereas qualitative FITs are preferred in China. The present study aimed to compare the screening yield between one-sample quantitative FIT and two-sample qualitative FIT for CRC screening.

Design A cross-sectional study.

Setting A population-based CRC screening programme was conducted in 28 communities in Haining City, Zhejiang Province, China.

Participants Consecutive participants aged 40–74 years were invited to undergo the CRC screening programme. Two-sample qualitative FITs were offered between January 2019 and December 2019, and one-sample quantitative FIT was offered between August 2019 and February 2020.

Primary and secondary outcome measures Primary outcomes were detection rates of advanced neoplasms, including CRCs and advanced adenomas. Secondary outcomes were positivity rates and colonoscopy resource demand for the two FITs. The positivity thresholds were 20 µg and 1–5 µg haemoglobin per gram of faeces for the quantitative and qualitative FITs, respectively.

Results A total of 19 131 and 28 804 invitees were assigned to the two-sample qualitative and one-sample quantitative groups, respectively. Positivity rates were 14.2% for the two-sample qualitative FIT and 5.4% for the one-sample quantitative FIT. Detection rates of advanced colorectal neoplasms at colonoscopy using one-sample quantitative FIT and two-sample qualitative FIT were 17.6% (95% CI: 14.6% to 20.6%) and 10.5% (95% CI: 8.7% to 12.4%), respectively. Both detection rates of cancer and advanced adenoma were higher in the one-sample quantitative FIT group than those in the two-sample qualitative FIT group. Moreover, one-sample quantitative FIT significantly reduced the colonoscopy load for detection of one advanced neoplasm case (5, 95% CI: 5 to 7) than the two-sample qualitative FIT (10, 95% CI: 8 to 11).

Conclusions The one-sample quantitative FIT for CRC screening increases the detection rate of advanced neoplasia and reduces the colonoscopy workload compared with the two-sample qualitative FIT.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death throughout the world. Colorectal cancer screening has been substantially increasing over the past three decades. Evidence from a few randomised controlled trials have evaluated the efficacy of screening for reducing the CRC mortality rate. Faecal occult blood test (FOBT) is a non-invasive stool-based test that is recommended by most CRC screening guidelines. Due to the superior diagnostic accuracy, faecal immunochemical test (FIT) has gradually replaced the traditional guaiac FOBT and has been widely used in current CRC screening programmes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This study provides real-world comparison evidence for the screening yield between one-sample quantitative faecal immunochemical test (FIT) and two-sample qualitative FIT for colorectal cancer (CRC) screening.

This study measured the positivity rates, detection rates of advanced neoplasms and colonoscopy workload for two FIT screening strategies.

This was a cross-sectional design study with inherent limited explanation of cause-and-effect temporality.

The cross-sectional study was conducted in one city, where CRC screening has been implemented for several decades.
In China, a two-stage sequential CRC screening modality combining FIT with questionnaire-based risk assessment was established in 1980s. Its effectiveness in reducing the CRC mortality was ascertained. Afterwards, a revised screening modality was adopted in a national and several regional organised CRC screening programmes. Nevertheless, most FITs used in current screening programmes are qualitative and performed based on two stool samples, which is quite different from the one-sample quantitative FIT in many developed countries. Limited evidence has suggested that a quantitative FIT screening has an advantage in detecting advanced colorectal neoplasms, and some recommendations suggest quantitative FITs over qualitative FITs. However, direct comparisons of quantitative FIT with qualitative FIT in the screening settings are scarce and need to be further validated.

A population-based programme for CRC screening was conducted in rural China, in which one-sample quantitative FIT and two-sample qualitative FIT screening strategies were adopted in different communities. The objective of the study was to evaluate the participation rates, positivity and screening yield of the two types of FITs.

METHODS

Study population and design

The present population-based CRC screening programme was conducted in the Haining City of Zhejiang Province in China. In 2007, the Haining government initiated a municipal CRC screening programme for all residents aged 40–74 years. The first round of screening was conducted between January 2007 and December 2012, and the second round was accomplished between January 2013 and March 2021. A two-stage screening process was provided free of charge to all the invited participants. A combination of a FIT and a risk factor questionnaire was used as the preliminary screening modality in the first stage. The participants either tested positive via FIT or determined to be high-risk using the risk factor questionnaire were recommended to undergo a subsequent colonoscopy. Based on the above screening programme, a cluster sampling comparison study was designed to compare the effectiveness of the quantitative and qualitative FITs in 28 communities in Haining between January 2019 and February 2020. A detailed study protocol for the quantitative FIT screening was previously documented.

Individuals who were unable to complete the informed consent form on their own and those who did not undergo a subsequent colonoscopy were excluded if the following criteria were satisfied: (i) presence of severe cardiac, pulmonary, brain or renal dysfunction; (ii) psychiatric illness diagnosis; (iii) patient was in acute phase of enteritis, dysentery or perianal abscess; (iv) diagnosis of lumen stenosis due to peritonitis, perforation or abdominal adhesion; (v) diagnosis of cirrhosis ascites, mesenteric inflammation and abdominal aortic aneurysm; and (vi) pregnancy.

Interventions

One-sample quantitative FIT

A quantitative FIT was conducted using the OC-Sensor FIT manufactured by Eiken Chemical (Tokyo, Japan). One flat faecal sample collection tube containing 2.0 mL of stabilisation buffer designed to minimise haemoglobin (Hb) degradation, along with instructions that were stored in a plastic Ziploc bag, were distributed to the participants. The participants collected a faecal sample from one bowel movement according to the instructions. The participants were requested to return the sample collection tube to the community healthcare centre within 72 hours at 10:00 or 16:00 on a daily basis. The sample was stored at ambient temperature (20°C–25°C), and the laboratory tests were performed daily by a trained staff using the OC-Sensor IO analyser. For the present study, a positivity threshold of 100 ng Hb/mL buffer (equivalent to 20 µg Hb/g faeces) was used. The specimens with values of ≥20 µg Hb/g faeces were classified as positive and the participants were further recommended to undergo a colonoscopy examination.

Two-sample qualitative FIT

Qualitative FIT kits (Abon Biopharm, Hangzhou, China) were used for two tests at an interval of 1 week. The sampling device was filled with 0.5 mL of preservative buffer and sealed with a lid. According to the instructions, the spiral tip of the sampling probe was inserted into three different sites of the stool sample to collect 10–50 mg of faeces and placed into the preservative buffer. The sample was then stored at ambient temperature (20°C–25°C). The laboratory tests were performed daily by a trained staff. The FIT results were reported via visual interpretation as positive or negative using the colloidal gold strip method at a threshold specified by the manufacturer (100 ng Hb/mL, equivalent to 1–5 µg Hb/g faeces). Either of the two FITs presenting positive was classified as a positive result, and the participants were further recommended to undergo a colonoscopy examination.

Colonoscopy and pathology

After the completion of the risk-questionnaire test and FIT, colonoscopy was offered to all positive individuals by the endoscopists from the Haining Hospital of Traditional Chinese Medicine. All colonoscopy examinations were conducted by experienced endoscopists. Abnormal findings during colonoscopy were carefully checked using standard clinical procedures and biopsies were collected for a further pathology diagnosis. Clinical information, such as morphological feature, location (distance from the anus to the segment), macroscopic diagnosis and size, was collected from the standardised case report forms. An adenoma with a size of ≥10 mm and with tubulovillous or villous histology or with high-grade dysplasia in the absence of invasive CRC was referred to as an advanced adenoma. An advanced neoplasm referred to CRC and advanced adenoma.
Outcomes and statistical analysis
A descriptive statistical evaluation of the results was performed. Means and SD were used to compute continuous variables, which were compared using t-tests. The characteristics of the study population were also summarised. Categorical data were expressed as percentages and compared using χ² tests. Overall and group-specific colonoscopy compliance rates were calculated by age and gender. The detection rates of advanced neoplasm (advanced adenoma and cancer) for positive subjects were calculated and compared using the two FITs. In addition, positive predictive values (PPVs) for detecting colorectal neoplasms among the subjects who completed a colonoscopy evaluation after undergoing two FITs were calculated and compared. Furthermore, to assess the colonoscopy resource requirement, the numbers of colonoscopies needed to be performed to detect one case of advanced neoplasm were calculated. Moreover, comparisons of the first and second qualitative FIT (defined as FIT-1 and FIT-2, respectively), a single positive test result and both positive test results for qualitative FITs and different thresholds for the quantitative FIT (online supplemental tables A1–A3) were performed. All statistical analyses were conducted using the SAS (V.9.4). P values ≤0.05 were considered statistically significant.

Patient and public involvement
The patients and the public were not involved in the design, conduct or reporting in the present study.

RESULTS
Study population characteristics
A total of 47,935 residents aged 40–74 years agreed to participate in the CRC screening programme between January 2019 and February 2020. Of these, 19,131 were included in the qualitative FIT screening group and 28,804 in the quantitative FIT screening group. Demographic characteristics for all participants were similar with respect to sex, history of previously detected colonic polyps and history of CRC in first-degree relatives (all p values>0.05), except for age (p<0.001; table 1).

Positivity rates for two FITs and colonoscopy compliance rates
A total of 20,212 (70.2%) returned the quantitative FIT versus 14,437 (75.5%) returned at least one qualitative FIT (p<0.001). Fewer participants tested positive at the threshold of 100 ng Hb/mL with a quantitative FIT: 1097 (5.4%) versus 2048 (14.2%) patients with a positive result with one of two-sample qualitative FITs. However, for individuals who tested positive, similar adherence for the colonoscopy examination was found in the quantitative FIT group (619, 56.4%) compared with the qualitative FIT group (1091, 53.3%, p=0.09; figure 1).

Detection rates for advanced neoplasms using two screening strategies
For participants who actually underwent the screening, the detection rate for advanced neoplasms during colonoscopy for the quantitative FIT (17.6%, 95% CI: 14.6% to 20.6%) was significantly higher than that for the qualitative FIT (10.5%, 95% CI: 8.7% to 12.4%). The quantitative FIT identified more patients with CRC (2.4%, 95% CI: 1.2% to 3.6%) and advanced adenoma (15.2%, 95% CI: 12.4% to 18.0%) than the qualitative FIT (0.9%, 95% CI: 0.4% to 1.5% and 10.5%, 95% CI: 7.9% to 11.4%, respectively; table 2).

Resource load for colonoscopy to detect one advanced neoplasm
Compared with the qualitative FIT strategy, the quantitative FIT strategy significantly reduced the colonoscopy load to detect one case of CRC (42, 95% CI: 28 to 91 vs 111, 95% CI: 67 to 250, p=0.013), advanced adenoma (6, 95% CI: 5 to 8 vs 10, 95% CI: 9 to 13, p<0.013) and advanced neoplasm (5, 95% CI: 5 to 7 vs 10, 95% CI: 8 to 11, p<0.01). Detailed results are shown in table 2.

Table 1 Study characteristics of all invitees

| Qualitative FIT group (n=19131) | Quantitative FIT group (n=28804) | P value |
|----------------------------------|----------------------------------|---------|
| Age, mean (SD)                   | 57.1 (9.1)                       | 57.5 (8.8) | <0.001  |
| Age group, n (%)                 |                                 | <0.001  |
| 40–49                            | 4601 (24.1)                      | 6162 (21.4) |         |
| 50–59                            | 6753 (35.3)                      | 10 749 (37.3) |       |
| 60–74                            | 7777 (40.7)                      | 11 893 (41.3) |       |
| Gender, n (%)                    |                                 | 0.882    |
| Male                             | 9588 (50.1)                      | 14 416 (50.0) |       |
| Female                           | 9543 (49.9)                      | 14 388 (50.0) |       |
| Previously detected colonic poly*p, n (%) |                             | 0.283    |
| No                               | 18 257 (95.6)                    | 27 472 (95.4) |       |
| Yes                              | 835 (4.4)                        | 1319 (4.6)   |         |
| History of CRC in first-class relative*, n (%) |           | 0.461    |
| No                               | 18 878 (98.9)                    | 28 447 (98.8) |       |
| Yes                              | 214 (1.1)                        | 344 (1.2)    |         |

*pPercentage was calculated after excluding participants with missing information.
CRC, colorectal cancer; FIT, faecal immunochemical test.
Subgroup analysis
Similar results for detection rate and PPV of advanced neoplasms were demonstrated in the subgroup analyses by gender and age. Quantitative FIT was superior to qualitative FIT in detecting more advanced neoplasms in males (p<0.001) and the elder age group (p=0.025 for 50–59 year group and p<0.001 for 60–74 year group), whereas no significant differences were found in women (p=0.317) and the younger age group (p=0.825). Detailed results are shown in Table 3.

DISCUSSION
Although the quantitative FIT is common for CRC screening in developed countries, the qualitative FIT has been predominantly adopted in China. This population-based study preliminarily compared the effectiveness between one-sample quantitative FIT and two-sample qualitative FIT in a CRC screening setting. The positivity rate for the quantitative FIT was lower than that for the qualitative FIT, whereas the detection rate and PPV for advanced neoplasms were higher in the quantitative FIT group. Generally, the quantitative FIT used in CRC screening had higher detection rates of advanced neoplasms and a lower colonoscopy workload.

The positivity rate of FITs reflects the Hb concentrations in faeces, which affects the detection of colorectal lesions by colonoscopy. In the present study, the positivity rate of quantitative FIT (OC-Sensor) was 5.4% at the threshold of 20 µg Hb/g faeces, which was similar to data in previous studies. Potential underlying reasons could be the differences in the sample collection process and storage of various FIT products. After converting the cut-off value units, the threshold for the qualitative FIT was 1–5 µg Hb/g faeces, which was much lower than 20 µg Hb/g faeces for the quantitative FIT. If the cut-off values were reduced to 10 µg Hb/g faeces and 5 µg Hb/g faeces, the positivity values for the quantitative FIT in the present study were.

Results for the comparisons between FIT-1 and FIT-2 of the two-sample qualitative FITs, single positive test and both positive tests for qualitative FITs and different thresholds for the quantitative FITs are provided in the online supplemental table A1–A3.

Table 2  Comparison of screening yield characteristics between qualitative and quantitative FITs

| Indicator                      | Qualitative FIT strategy (N=19 131) | Quantitative FIT strategy (N=28 804) | P value |
|-------------------------------|-------------------------------------|--------------------------------------|--------|
| Detection rate at colonoscopy, % (95% CI) |                                       |                                       |        |
| Colorectal cancer             | 0.9 (0.4 to 1.5)                    | 2.4 (1.2 to 3.6)                     | 0.013  |
| Advanced adenoma              | 9.6 (7.9 to 11.4)                   | 15.2 (12.4 to 18.0)                  | <0.001 |
| Advanced neoplasm             | 10.5 (8.7 to 12.4)                  | 17.6 (14.6 to 20.6)                  | <0.001 |
| Positive predictive value, % (95% CI) |                                       |                                       |        |
| Colorectal cancer             | 0.5 (0.2 to 0.8)                    | 1.4 (0.7 to 2.1)                     | 0.008  |
| Advanced adenoma              | 5.1 (4.2 to 6.1)                    | 8.6 (6.9 to 10.2)                    | <0.001 |
| Advanced neoplasm             | 5.6 (4.6 to 6.6)                    | 9.9 (8.2 to 11.7)                    | <0.001 |
| Colonoscopies needed to detect one lesion, number (95% CI) |                                       |                                       |        |
| Colorectal cancer             | 111 (67 to 250)                     | 42 (28 to 91)                        | 0.013  |
| Advanced adenoma              | 10 (9 to 13)                        | 6 (5 to 8)                           | <0.001 |
| Advanced neoplasm             | 10 (8 to 11)                        | 5 (5 to 7)                           | <0.001 |

FIT, faecal immunochemical test.
12.4% and 38.6%, respectively. Li et al. have compared the performance of 15 qualitative FITs and 2 quantitative FITs, and found that there were great variations among various FIT products, including the volume and composition of the preservative buffer, sampling probe and mass of faeces dissolved in the preservative buffer. Huang et al. have reported that the performance of qualitative FIT could be improved after the optimisation of faecal sampling device. Lu et al. have used data from a CRC screening trial in China and demonstrated differences in the diagnostic performance for qualitative and quantitative FITs using the same threshold, although this heterogeneity was eliminated from the threshold adjustment. Therefore, when comparing the effectiveness of various FIT products, the Hb concentration in faeces should be used instead of the buffer concentration.

Although a large number of studies have evaluated the performance of one-sample quantitative FIT screening, few studies have made comparisons of qualitative and quantitative FITs in a real-world screening setting. Although a lower positivity rate was found for the quantitative FIT in the present study, the detection rate and positive prediction value for advanced neoplasms were significantly higher than those for the qualitative FIT. One prior study has reported similar results using data from a Korean national CRC screening programme. The positivity rates were 8.1% for the qualitative FIT and 2.5% for the quantitative FIT, and the detection rates of suspicious cancer were 5.2% for the qualitative FIT and 14.4% for the quantitative FIT. In addition, another study compared the quantitative and qualitative FITs when screening 6494 patients in Jiashan County, which is adjacent to the current study site. They have demonstrated significantly higher PPVs of large adenomas and CRC for the quantitative FIT than the qualitative FIT. In addition, when comparing individual effects of two-sample qualitative FITs, the detection rates of advanced neoplasms differed (online supplemental table A1), which suggested the instability of qualitative FIT screening. However, although the quantitative FIT reduced the colonoscopy workload, the screening yield of CRC and advanced adenoma cases was 3.78‰ in the quantitative FIT group, which is lower than 6.01‰ in the qualitative FIT group. This issue should be addressed in the future. A higher threshold inevitably implies higher specificity and PPV, but also lower sensitivity with risk of false negative results. The higher positivity rate of the qualitative FIT may also imply diagnostic delays due to unavailability of endoscopic resources to perform colonoscopies in every positive case. The pros and cons of a higher threshold in FITs should be balanced in a large-scale screening setting.

Colonoscopy workload is an important element when implementing a population CRC screening programme. Generally, a decrease in the threshold of FIT might result in a detection rate increase at the cost of more colonoscopy examinations. In the present study, the number of colonoscopies needed to detect a case of advanced neoplasm was 10 (95% CI: 8 to 11) for the quantitative FIT strategy, which was consistent with the result from a multicentre randomised controlled trial conducted in China. Owing to a lower positivity rate and higher detection rate of advanced neoplasms, the quantitative FIT reduced the colonoscopy load by half. In addition, quantitative FIT offers an advantage of flexible threshold adjustment, which is an improvement in the detection of advanced neoplasms along with higher thresholds.

### Table 3 Detection rate and positive predictive value of advanced neoplasms by gender and age group

| Indicator | Qualitative FIT (N=19131) | Quantitative FIT (N=28804) | P value |
|-----------|---------------------------|---------------------------|---------|
| Positive predictive value, % (95% CI) | | | |
| Gender | | | |
| Male | 6.6 (5.1 to 8.1) | 13.6 (10.8 to 16.3) | <0.001 |
| Female | 4.4 (3.1 to 5.8) | 5.8 (3.8 to 7.9) | 0.237 |
| Age group | | | |
| 40–49 | 1.8 (0.4 to 3.2) | 2.6 (0.1 to 5.1) | 0.806 |
| 50–59 | 5.4 (3.8 to 7.0) | 8.5 (5.7 to 11.4) | 0.045 |
| 60–74 | 7.1 (5.5 to 8.7) | 12.9 (10.1 to 15.6) | <0.001 |
| Detection rate at colonoscopy, % (95% CI) | | | |
| Gender | | | |
| Male | 12.4 (9.7 to 15.0) | 23.8 (19.2 to 23.4) | <0.001 |
| Female | 8.3 (5.9 to 10.8) | 10.5 (6.9 to 14.0) | 0.317 |
| Age group | | | |
| 40–49 | 4.0 (0.9 to 7.0) | 5.6 (0.3 to 11.0) | 0.825 |
| 50–59 | 9.4 (6.6 to 12.2) | 15.4 (10.5 to 20.3) | 0.025 |
| 60–74 | 13.4 (10.5 to 16.3) | 21.5 (17.1 to 25.8) | 0.002 |

FIT, faecal immunochemical test.
of the quantitative FIT (online supplemental table A3). This is useful when balancing the screening performance and colonoscopy workload in various screening settings. Some studies have also suggested that there are differences in FIT performance due to gender and age and have determined the optimal age-specific and sex-specific FIT thresholds.\textsuperscript{23} \textsuperscript{24} \textsuperscript{29}

Some limitations need to be noted when interpreting the present study results. A higher proportion of older participants was enrolled in the quantitative FIT group than in the qualitative FIT group, which might affect the positivity rate of FIT, colonoscopy compliance and lesion detection rates. The colonoscopy compliance rate in the present study was higher than that in large-scale population-based CRC screening programmes,\textsuperscript{31} \textsuperscript{12} \textsuperscript{21} \textsuperscript{30} but lower than that in randomised trials,\textsuperscript{4} \textsuperscript{31} which affected the colorectal lesion detection rate. Although two-sample tests were requested for each participant in the qualitative FIT group, fewer than 60% participants returned two samples, which might lead to misclassification of the positivity rate and subsequent screening yield. Third, the natural gap in the positivity rate of the two FITs affects the detection rate of colorectal neoplasms during colonoscopy. In addition, no significant differences between the two FITs in women and the younger age group were found in the present study, which could be attributed to insufficient statistical efficiency due to small sample size and relatively low CRC incidence background. Lastly, population-based CRC screening programmes have been implemented for more than 30 years in Haining, and the overall awareness of and willingness to undergo CRC screening were quite different from other places, which restricts the extrapolation of the current study results.

In conclusion, the present study implied that the one-sample quantitative FIT was superior to the two-sample qualitative FIT for CRC screening in improving the detection of advanced neoplasia and reducing the colonoscopy workload. However, more studies should pay attention to long-term effectiveness and economic issues of quantitative FIT for CRC screening in China.

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