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ORIGINAL ARTICLE

Screening for colorectal cancer in Tianhe, Guangzhou: results of combining fecal immunochemical tests and risk factors for selecting patients requiring colonoscopy

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Abstract

Objective: To explore the performance of a protocol combining fecal immunochemical test (FIT) and a high-risk factor questionnaire (HRFQ) for selecting patients requiring colonoscopy as part of a population-based colorectal cancer (CRC) screening program in China.
Methods: From 2015 to 2016, we conducted a CRC screening program for all residents aged 45 years or older in Tianhe District, Guangzhou City, China. Participants underwent an FIT and received an HRFQ as part of primary screening. Those with positive FIT and/or HRFQ results were considered to be at high risk and were recommended to undergo colonoscopy.
Results: A total of 10 074 subjects were recruited and enrolled in the screening program. In the enrolled population, 17.5% had positive FIT results and 19.4% had positive HRFQ results. Of those recommended to undergo diagnostic colonoscopy, 773 did so. The screening method's overall positive predictive value (PPV) was 4.9% for non-adenomatous polyps, 11.4% for low-risk adenomas (LRAs), 15.9% for high-risk adenomas (HRAs) and 1.6% for CRC. The PPVs of positive FIT results for non-adenomatous polyps, LRAs, HRAs and CRC were 5.2%, 15.9%, 22.5% and 2.5%, respectively. The PPVs of positive HRFQ results for non-adenomatous polyps, LRA, HRA and CRC were 4.1%, 10.2%, 14.3% and 1.4%, respectively. The PPVs associated with combined positive FIT and HRFQ results for non-adenomatous polyps, LRAs, HRAs and CRC were 4.5%, 16.4%, 23.7% and 2.8%, respectively.
Conclusion: Our results suggest that this two-step CRC screening strategy, involving a combination of FIT and HRFQ followed by colonoscopy, is useful to identify early-stage CRC. The high detection rates and PPVs for CRC and adenomas encourage this strategy's use in ongoing screening programs.

Key words: colorectal cancer, screening, fecal immunochemical test, high-risk factors, colonoscopy, positive predictive value

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Introduction

According to the global 2012 cancer statistics, colorectal cancer (CRC) continues to be the third most frequently diagnosed cancer in men and the second most frequent in women, with an estimated 1.4 million cases and 693 900 associated deaths worldwide. The highest incidence is in more developed counties and regions, such as Australia/New Zealand, Europe and North America [1]. However, during the past two decades, there has been a remarkable increase in the incidence of CRC and associated deaths in Asian countries [2]. In China, CRC is the fourth most common carcinoma and the fifth most common cause of mortality, with an estimated 331 300 new cases and 159 300 associated deaths annually [3].

It is increasingly acknowledged that most CRCs originate from adenomas, which develop slowly and sometimes undergo malignant transformation through a series of genetic and epigenetic alterations [4]. A period of at least 10 years may be required for the transition from detectable adenoma to cancer. During this period, CRC screening can identify and allow the removal of adenomas that may be cancer precursors. In addition, the time from early to invasive cancer may span several years. This window provides an opportunity for screening to detect early-stage cancer, when treatment is more effective. This is the rationale for a screening program aimed at reducing the incidence of CRC and associated mortality. Several randomized controlled trials conducted in developed countries showed the effective early detection of cancer and increased long-term survival rates following the use of population-based CRC screening [5–7].

In China, CRC screening began in the 1970s. A randomized, controlled, population-based trial in Jiashan revealed that mass screening effectively reduced rectal cancer mortality by 31.7% [8]. Beginning in 2015, CRC screening was established as a major public health project in Guangzhou; we were responsible for the screening program in Tianhe District. According to the recommendation by the China National Committee of Cancer Early Detection and Treatment, we conducted a two-step screening strategy that involved fecal occult blood test (FOBT) combined with a high-risk factor questionnaire (HRFQ) as the primary screening method. The screening program included follow-up colonoscopies aimed at identifying more premalignant lesions and early CRC cases.

Methods

Patient population

From 2015 to 2016, a CRC screening program was conducted for all residents aged 45 years or older in Tianhe District, Guangzhou City, China. The program was directed by the Chronic Disease Center (CDC) and the Sixth Affiliated Hospital of Sun Yat-sen University. Patients with current or prior CRC were not included in the study. Those who had recently undergone a colon examination (colonoscopy or sigmoidoscopy) were provided with the option to reject the screening invitation.

Study participant recruitment

To promote participation in CRC screening, information was provided to citizens through the media, including television, radio and newspaper advertisements, posters in public places, and distributed pamphlets and brochures. Study participants were recruited at the CDC, with the cooperation of community doctors. The CDC staff explained the screening purpose and process to all participants.

FOBT

All participants provided written informed consent to undergo FOBT. After providing instructions on stool sampling, each participant was asked to collect samples from six areas of a stool specimen, place the samples in a small container filled with buffer fluid (provided by the CDC) and immediately send the samples to a community hospital laboratory. Laboratory assistants tested each stool sample for occult blood using a qualitative fecal immunochemical test (FIT) kit (Wanhua-Puman Biol. Tech Ltd Company, China), with a detection threshold of 100 ng/mL. If the first FIT result was negative, participants underwent a second FIT screening. There were no dietary restrictions during the test.

HRFQ

Information regarding risk factors was collected using a questionnaire. A positive HRFQ indicated that the participant had one of the following: a family history of CRC in a first-degree relative, a history of polyps, chronic constipation, chronic diarrhea, a history of appendicitis or appendectomy, chronic cholecystitis or cholecystectomy, a history of cancer or a history of psychiatric trauma within the past 20 years. HRFQs were completed by well-trained physicians who met the participant at a convenient time that did not interfere with the participant's work. The questionnaires were checked for completeness and entered into a database by CDC staff.

Colonoscopy

Following a positive FIT or HRFQ result, participants were offered a free colonoscopy. Colonoscopy examinations were performed by expert gastroenterologists at the endoscopy center of the Sixth Affiliated Hospital of Sun Yat-sen University or at other hospitals in Guangzhou. The day before the colonoscopy, participants were provided with instructions for bowel preparation over the phone, which involved a low-fiber diet and the consumption of hypertonic polyethylene glycol solution (2 L). If a colonoscopy failed due to incomplete bowel preparation or other reasons, a second diagnostic colonoscopy would be performed.

The number, size, location and morphology of any detected polyps were recorded. If the polyp diameter was <2 cm, the polyp was removed endoscopically and sent for histopathologic examination after the patient provided written consent. Surgery was recommended for patients with lesions suspected to be cancerous or that were too large or too complicated for endoscopic removal. The major complications were also documented.

Histological classification

Low-risk adenomas (LRAs) were defined as adenomas showing the following features: one or two lesions, size <10 mm, tubular histology and low-grade dysplasia. High-risk adenomas (HRAs) were defined as either adenomatous polyps measuring ≥ 10 mm in size, more than two adenomas, any adenoma with tubulovillous or villous histology or high-grade dysplasia; carcinoma *in situ* was also classified as HRA. The non-adenomatous polyps included serrated polyps, juvenile polyps, inflammatory polyps and hyperplastic polyps.

Statistical analysis

SPSS 16.0 (IBM, Armonk, NY, USA) and Excel (Microsoft, Redmond, WA, USA) were employed for data analyses. Differences in rates and proportions were calculated using Chi-square tests. Percentages and corresponding 95%

confidence intervals (CIs) were used to assess differences. Statistical significance was defined as $p < 0.05$.

Results

A total of 10 074 subjects were recruited and enrolled in the screening program, including 4080 men and 5994 women. The mean age of the participants was 67.4 years. Each participant completed both an HRFQ and at least one FIT. Table 1 shows the characteristics of the recruited population.

Primary screening results

Overall, 27.4% of the participants had positive results in the first stage of screening; 17.5% had positive FIT and 19.4% had positive HRFQ results. When stratified by sex, the overall positive rate was higher among men (29.9%) than among women (25.8%). The rates of positive HRFQ results were similar between men and women; however, the FIT-positive rates were higher among men than among women. When stratified by age, the overall positive rates (FIT and HRFQ) were higher for individuals ≥60 years old than for those <60 years old (Table 2).

There were 2763 participants with positive FIT and/or HRFQ results who were referred for colonoscopy. The average age was 64.4 ± 9.4 and 1219 were males. Among them, 617 (76.3%) with positive FIT, 706 (70.6%) with positive HRFQ and 667 (69.9%) with both positive FIT and HRFQ results refused to undergo colonoscopy examinations. Therefore, 773 participants underwent diagnostic colonoscopy, including 192 FIT-positive individuals, 294 HRFQ-positive individuals and 287 who were both FIT- and HRFQ-positive.

Colonoscopy findings

Of the 773 patients undergoing colonoscopy, the colonoscopy procedures were completed to the cecum in 753 patients (cecal intubation rate, 97.4%). Colonoscopy was not completed due to incomplete bowel preparation, neoplastic stenosis, discomfort or technical issues. No serious colonoscopy complications occurred, except for a minor perforation that occurred during endoscopic polyp removal in one participant; surgery was not required in this patient and there was no serious outcome.

During colonoscopy screening, neoplasms were found in 259 (33.5%) individuals and included adenomas, non-adenomatous polyps and CRC. When stratified by sex, the detection rates for LRAs and HRAs were 14.3% and 20.2%, respectively, among men; the detection rates were lower for women (LRAs, 8.9%; HRAs, 12.2%). There were no differences in the detection rates of non-adenomatous polyps and CRC between men and women. When stratified by age, the detection rates for non-adenomatous polyps, LRAs and HRAs were higher for individuals ≥60 years old than for those <60 years old. However, we did not observe a higher CRC detection rate for individuals ≥60 years old than for younger individuals (Table 3).

Positive predictive values for the primary screening methods

In this study, the overall positive predictive values (PPVs) were 4.9% for non-adenomatous polyps, 11.4% for LRAs, 15.9% for HRAs and 1.6% for CRCs. The FIT PPVs for non-adenomatous polyps, LRAs, HRAs and CRCs were5.2%, 15.9%, 22.5% and 2.5%, respectively. The HRFQ PPVs for non-adenomatous polyps, LRAs, HRAs and CRCs were 4.1%, 10.2%, 14.3% and 1.4%, respectively. For individuals with both positive FIT and HRFQ results, the PPVs for non-adenomatous polyps, LRAs, HRAs and CRCs were 4.5%, 16.4%, 23.7% and 2.8%, respectively. The FIT PPVs for LRAs and HRAs were higher than those for HRFQ (Table 4). However, using HRFQ, we found that 30.6% of non-adenomatous polyps (11/36), 13.6% of LRAs (12/88) and 12.2% (15/123) of HRAs were missed by the FIT method.

Except for non-adenomatous polyps, the PPVs for each method, individually or combined, were higher for men than for women. PPVs were also higher for all lesion types in participants ≥60 years than in those <60 years.

Table 1. Characteristics of recruited participants

Characteristics	No. (%)
Sex	
Male	4080 (40.5%)
Female	5994 (59.5%)
Age, years	
Male	
Range	45–82
Mean±SD	67.6±11.2
Female	
Range	45–78
Mean±SD	67.2±10.8
Positive items	
Fecal immunochemical test	1763 (17.5%)
Family history of colorectal cancer	440 (4.4%)
Chronic constipation	1035 (10.3%)
Chronic diarrhea	472 (4.7%)
History of appendicitis or appendectomy	712 (7.1%)
History of cancer	256 (2.5%)
History of psychiatric trauma	1213 (12.0%)

Discussion

Our results suggest that a CRC screening program, involving FIT and HRFQ combined with follow-up colonoscopy, allows early detection of CRC. The high detection rates and PPVs for CRCs and adenomas encourage the use of this strategy in ongoing screening programs.

The FOBT, recommended in both the European Union and the USA [8,9], is the most widely used CRC screening test. The test is inexpensive, non-invasive and easy to use at home. Currently, two major approaches are available: the guaiac-based FOBT (gFOBT) and FIT. Compared to the gFBOT, FIT has a higher sensitivity and better specificity for both CRC and advanced adenoma detection [10,11]. However, FIT misses disease associated with non-bleeding or intermittent bleeding lesions. Thus, the HRFQ may be a complement to that test. Our results showed that the PPV of combined positive FIT and HRFQ results was higher for HRAs than that of a positive FIT alone; the difference did not reach statistical significance. This may due to the small number of individuals participating in the colonoscopy screening. A limitation of our study is the low response rate for patients undergoing follow-up colonoscopies. Participation rates in primary colonoscopy screenings are generally suboptimal [12]. Because <70% of the eligible patients participated in the colonoscopy screening, our results may have been biased.

The HRFQ investigation aims to identify participants with an increased risk of CRC owing to a family history or a predisposing condition. In our screening program, the FIT PPVs for LRAs and HRAs were higher than the HRFQ PPVs for the same lesions. However, using the HRFQ, we found that 30.6% of non-adenomatous polyps, 13.6% of LRAs and 12.2% of HRA were missed by

Table 2. Sex- and age-specific rates of positive fecal immunochemical tests (FITs) and high-risk factor questionnaires (HRFQs)

Screening test	Male (n=4080)	Female (n=5994)	P-value	<60 years (n=3716)	≥60 years (n=6358)	P-value
FIT, n (%)	765 (18.8)	998 (16.6)	0.006	592 (15.9)	1171 (18.4)	0.002
HRFQ, n (%)	811 (19.9)	1143 (19.1)	0.314	676 (17.2)	1278 (20.7)	0.019
FIT/HRFQ, n (%)	1219 (29.9)	1544 (25.8)	<0.001	924 (24.9)	1839 (28.9)	<0.001

Table 3. Sex- and age-specific colonoscopy results

Screening test	Male (n=356)	Female (n=417)	P-value	<60 years (n=269)	≥60 years (n=504)	P-value
Non-adenomatous polyp, n (%)	19 (5.3)	17 (4.1)	0.41	6 (2.2)	30 (6.0)	0.019
Low-risk adenoma, n (%)	51 (14.3)	37 (8.9)	0.017	19 (7.1)	69 (13.7)	0.006
High-risk adenoma, n (%)	72 (20.2)	51 (12.2)	0.002	24 (8.9)	99 (19.6)	<0.001
Colorectal cancer, n (%)	7 (2.0)	5 (1.2)	0.39	3 (1.1)	9 (1.8)	0.47

Table 4. Positive predictive values for the different screening tests used in colorectal cancer screening

Screening test	No.	Positive predictive value, n (%)			
		Non-adenomatous polyps	Low-risk adenomas	High-risk adenomas	Colorectal cancer
FIT only	479	25 (5.2)	76 (15.9)	108 (22.5)	12 (2.5)
HRFQ only	581	24 (4.1)	59 (10.2)	83 (14.3)	8 (1.4)
FIT and HRFQ	287	13 (4.5)	47 (16.4)	68 (23.7)	8 (2.8)
FIT or HRFQ	773	36 (4.9)	88 (11.4)	123 (15.9)	12 (1.6)

FIT, fecal immunochemical test; HRFQ, high-risk factor questionnaire.

the FIT method. Thus, HRFQ is a supplemental method for CRC screening.

Colonoscopy allows direct observation of the total colonic and rectal mucosa. Moreover, tissue biopsy and polyp removal from the colorectum can be completed during the same procedure. These features may enable colonoscopy to be a reliable tool for the early detection of CRC and also allow prevention of the progression of other lesions to CRC. Many Western countries include colonoscopy in their CRC screening programs [13,14]. Although the program was widely advertised before the start of screening, our reported colonoscopy compliance rate was unsatisfactory. Colonoscopy is invasive, is associated with potential complications and procedural discomfort, and requires prior bowel preparation. A small proportion of population was aware that colonoscopy is a useful method for detecting CRC. Together, these factors may have contributed to the low percentage of our study population choosing to undergo colonoscopies. Therefore, much more needs to be done to improve colonoscopy participation rates in the target population.

To achieve successful colonoscopy screening outcomes, the quality of the colonoscopy procedure is a key factor. Several studies have shown that the most important cause of interval CRC is related to colonoscopy quality. Approximately half of interval CRCs seem to result from lesions that were missed during colonoscopy [15]. Some studies have indicated that variations among endoscopists and endoscopy centers lead to changes in the quality of colonoscopy procedures. Corley *et al.* reported that the adenoma detection rate (ADR) ranges from 7.4% to 52.5%, based on a review of over 300 000 colonoscopies performed by 136 different gastroenterologists [16]. In our screening program, the ADR was 32.6% in men and 20.4% in women, corresponding to the target ADR recommended by the 2014 American Society for Gastrointestinal Endoscopy for populations undergoing screening colonoscopies. Moreover, the cecal intubation rate, a measure of the endoscopists' ability to reach the cecum, was 97.4% in our screening program; no serious complications were observed. These two parameters indicate that high-quality colonoscopies were being performed.

In our study, male sex and older age contributed to the high rate of positive colonoscopy screenings. These observations correspond to the fact that colorectal neoplasms occur more often in men and in older individuals. However, some authors have reported that younger age is also associated with higher rates of positive CRC screenings [17,18].

In this study, the overall PPVs were 1.6% for CRCs, 15.9% for HRAs and 33.5% for total colorectal neoplasms. These results mean that patients with positive results on primary screening would have a 1.6% possibility of having CRC, 15.9% possibility of having an HRA and a 33.5% possibility of any type of colorectal neoplasm. The PPV results in our study were consistent with those from the Tianjin CRC screening program [19], but were relatively high compared to the results from rural Zhejiang [20]. Lifestyle and dietary habit changes between urban and rural areas in China may contribute to the high PPVs that have been observed. Additionally, physician experience, bowel preparation quality, sedation and instrument quality may also contribute to the different detection rates. However, 66.5% (false-positive rate) of participants without colorectal neoplasms underwent colonoscopies. If this false-positive rate can be reduced, the screening efficiency would be greatly improved. A new, more efficient method is still needed for CRC screening.

Patients prefer non-invasive options such as FOBT instead of colonoscopy for CRC screening. Nevertheless, the sensitivity of FIT for detecting colorectal neoplasms is unsatisfactory, leading to the active exploration of other non-invasive screening modalities. Fecal DNA testing is based on the identification of specific genetic alterations in the adenoma cancer sequence. A study by Imperiale *et al.* reported that the sDNA panel

demonstrated a 92.3% sensitivity for detecting cancer in comparison to a 73.8% sensitivity for FIT. Similarly, the sDNA panel had a 42.4% sensitivity for detecting HRAs, compared with 23.8% for FIT [21]. Other non-invasive screening tests, such as microRNA, plasma-based DNA and stool protein tests, are being investigated for their potential use [22]. The unremitting exploration of non-invasive tests will probably greatly improve the efficiency of CRC screening.

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