Performance of a Colorectal Cancer Screening Protocol in an Economically and Medically Underserved Population

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Abstract

The performance of combining fecal immunochemical tests (FITs) and a high-risk factor questionnaire (HRFQ) in colorectal cancer (CRC) screening in economically and medically underserved populations is uncertain. This study investigated the performance of a CRC screening protocol of combining FITs and an HRFQ as primary screening methods in a rural Chinese population. A CRC mass screening was conducted using FITs and an HRFQ as the first and colonoscopy as the second stage of screening in Jiashan, 2007–2009. The target population was 31,963 residents in three communities. The compliance was 84.7% for HRFQ, 76.4% for FITs, and 78.7% for colonoscopy. The detected rates of cancer, adenoma, nonadenomatous polyps, and advanced neoplasm were 2.7%, 14.8%, 5.9%, and 8.9% by FITs, which were higher than those by HRFQ (0.5%, 9.2%, 4.8%, and 3.8%, respectively). There was no significant difference in detected rate for nonadenomatous polyps between FITs and HRFQ. A total of 41.2% adenomas, 53.2% nonadenomatous polyps, and 29.8% advanced neoplasms were detected by HRFQ but missed by FITs. Positive predictive value of the screening protocol of combining FITs and HRFQ for advanced neoplasm was 5.7%, which was higher than FITs alone. Men had a higher prevalence of advanced neoplasm than women. Results indicate that combining FITs and HRFQ as primary screening methods is an efficient CRC screening strategy in economically and medically underserved populations. *Cancer Prev Res; 4(10); 1572–9.* ©2011 AACR.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer death worldwide. In China, cancer is becoming the first and second leading cause of death in urban and rural areas, respectively. Death due to CRC has continuously increased in the last few decades. CRC mortality has rapidly increased by 36.8% in both urban and rural areas during 1990–2004 (1). Although the etiology of CRC is not completely understood, effective early detection and prevention were successfully achieved and confirmed by 3

large-scale randomized controlled trials of CRC screening, showing a decrease of CRC mortality by 15% to 33% with fecal occult blood tests (FOBT; refs. 2–4). A reduction of CRC mortality in the Unites States was interpreted as due to an increase in colonoscopies for earlier detection (5, 6), and a reduction by 43% in people attending once-only flexible sigmoidoscopy screening in the United Kingdom (7) also reveals a bright future for success in CRC prevention and control. In China, since 1980s, a protocol of CRC screening in Chinese was established and proved by a reduction of CRC mortality with a randomized controlled trial in 2003 (8–11).

From 2007, when a national CRC screening program began, the CRC screening protocol based on the previous protocol was revised by the China National Committee of Cancer Early Detection and Treatment (12), aimed at finding more early CRC cases and premalignant lesions such as adenoma. The first pilot field of this national screening program is in Jiashan County, which is recognized as a high-risk CRC county in China. In Jiashan, the age-standardized CRC incidence was about 13.7 per 100,000 during 1987–1998 (13) and increased to 15.95 per 100,000 during 1998–2007 (data not published), ranked first for women in all sites of cancers. For efficiency, screening must be conducted in a high-risk population. Although the CRC incidence in Jiashan is lower than that in the United States, it is one of the fields with a high

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incidence in China. Thus, a screening was conducted in 3 communities in Jiashan to test the performance of the revised screening protocol of combining FITs and HRFQ as primary screening methods in a medically and economically underserved population.

Methods

Study design and population

All permanent residents in Ganyao, Dayun, and Yaozhuang communities in Jiashan, aged 40 to 74 years, were invited to attend a free CRC screening program, in 2007, 2008, and 2009, respectively. All participants who attended the screening program signed the written consent form. A total of 31,963 (male: 16,169; female: 15,794) participants from 3 communities were enrolled as the target population.

A 2-stage screening design was used. Fecal immunochemical tests (FITs) and investigation of a high-risk factor questionnaire (HRFQ) were used as primary screening methods in the first stage. FITs (test kits were purchased from W.H.P.M., Inc.) was repeated twice at an interval of 1 week. HRFQ positive means (i) individuals having one of the following events: (a) a history of cancer, (b) a history of polyps, and/or (c) a family history of CRC in first-degree relatives; and/or (ii) at least 2 of the following events: (a) chronic coprostasis, (b) chronic diarrhea, (c) phlegmatically blood feces, (d) serious unhappy life events such as death among first-degree relatives, (e) chronic appendicitis or appendectomy, and/or (f) chronic cholecystitis or cholecystectomy (12, 14). If either the FIT or HRFQ was positive, a colonoscopy was recommended in the second stage. Polyethylene glycol electrolyte powder was used as a preparation drug for the colonoscopy. If a colonoscopy examination failed because of inadequate bowel preparation, or the cecum could not be reached for some reason, a subsequent colonoscopy was carried out within 1 month. All of these examinations were administered free to participants. The investigation of high-risk factors of CRC was completed by well-trained physicians who went to the community at a convenient time for participants in order not to affect their work. Fecal samples were collected by community health workers and tested in a local hospital by contracted experienced technicians.

All participants in the study population were followed using administrative databases for at least 2 years, and all cancer cases (including death and newly diagnosed) were enrolled into the Jiashan Cancer Registration System. A flowchart of CRC screening is presented in Figure 1.

Histopathologic examination

If colonoscopy showed a positive result, a biopsy and histopathologic diagnosis were done after the patient signed the consent form and paid for a biopsy and histopathologic examination. All cancer cases were confirmed by the Jiashan Cancer Registration System with histopathologic diagnosis. On the basis of the International Classification, CRC was defined as the invasion of malignant cells beyond the muscular mucosa. Patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia. Histologic classification of total polyps included adenoma and nonadenomatous polyps (tubular, tubulovillous, or villous). Pathologic slides of positive lesions were reexamined and diagnosed by consensus of at least 2 independent pathologists.

Data source

Demographic information including age, gender, and community obtained from the local demographic administrative department was transferred into an electronic file. The primary screening results of FITs and HRFQ were merged into the file. Colonoscopy and histopathologic results were recorded and entered into the same file. To ensure data quality, data were checked twice after the final file was created.

Statistical analysis

SPSS 16.0 software was used for data analysis. Differences in proportions between primary screening methods and colonoscopy findings were calculated using a χ^2 test. If more than 20% of the events have expected frequencies below 5, Fisher's exact test was used in 4-fold tables and a rank test was used in multicontingency tables. Advanced adenoma was defined as adenoma of 10 mm or more or with a history showing either a 20% or more villous component or high-grade dysplasia. CRC and advanced adenoma were defined as advanced neoplasm and CRC, adenoma, and polyps were defined as total neoplasm in the analyses. FITs+ means 1 or 2 positive FITs results regardless of HRFQ results. HRFQ+ means a positive HRFQ result regardless of FITs results. Either FITs+ or HRFQ+ was regarded as positive in the first screening stage.

Results

Compliance rate

The mean age of the target population ($N = 31,963$; $n = 13,426$ from Ganyao, $n = 7,990$ from Dayun, and $n = 10,547$ from Yaozhuang) was 53.9 years with a SD of 9.5. There was no difference in age and gender of the target population among the 3 communities. A total of 27,076 participants completed a HRFQ and 24,409 completed at least one FIT. Frequencies by age and gender among all participants are shown in Table 1. A total of 4,075 participants whose results were positive in the first stage were eligible for a colonoscopy. Among them, 3,205 participants with positive results in the first-stage screening completed a colonoscopy. The overall compliance rate was 84.7 (77.7%, 89.5%, and 90.1% in Ganyao, Dayun, and Yaozhuang, respectively) in the first stage and 78.7% (76.2%, 76.1%, and 82.7% in the 3 communities, respectively) in the second stage.

Positive rate and detected rate

The overall positive rate (Table 2) in the first screening stage was 15.1% (4,075 of 27,076), 7.2% for FITs and 9.8% for HRFQ. In the second stage, the positive
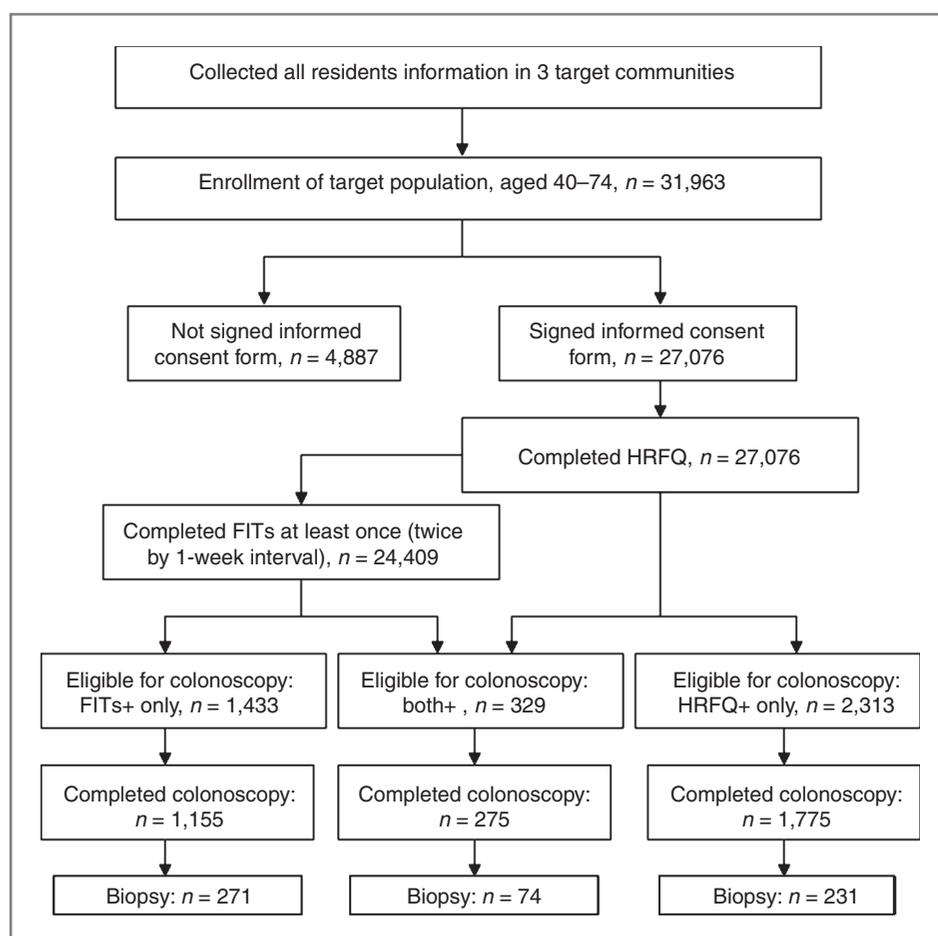
Figure 1. Flowchart of study participants in a colorectal neoplasm screening in a rural population in Jiashan County, China, 2007–2009.

rate of total colorectal neoplasm including CRC, adenoma, and nonadenomatous polyps was 19.3% (618 of 3,205) in the total study population. When stratified by gender, overall positive rate was higher among women (16.2%) than among men (13.9%) in the first phase and higher among men (23.7%) than among women (12.6%) in the second stage. Positive rates of FITs were similar between men and women, but the positive rate of HRFQ

Table 1. Participants who finished first-phase screening by age group and gender in 3 communities in Jiashan County in China, 2007–2009

Community	Gender	Age group, n (%)	
		40–54 y	55–74 y
Ganyao	Man	2,816 (54.7)	2,333 (45.3)
	Woman	2,952 (55.9)	2,328 (44.1)
	Subtotal	5,767 (55.3)	4,662 (44.7)
Dayun	Man	2,136 (59.4)	1,461 (40.6)
	Woman	2,046 (57.6)	1,506 (42.4)
	Subtotal	4,182 (58.5)	2,967 (41.5)
Yaozhuang	Man	2,540 (53.7)	2,193 (46.3)
	Woman	2,531 (53.1)	2,234 (46.9)
	Subtotal	5,071 (53.4)	4,427 (46.6)
Total		15,021 (55.5)	12,055 (44.5)

Table 2. Participants and results by gender, age, screening test, and stage in CRC screening in a rural population in Jiashan, China, 2007–2009

Gender/age	Screening test	Participant, n	Result	n (%)	Eligible, n	Participant, n (%)	CRC	Adenomas (n[a])	Nonadenomatous (n[b])	Advanced[c]
Male	FITs	11,962	FITs+	841 (7.0)	841	663 (78.8)	23	139 (54)	45 (11)	77
	HRFQ	13,478	HRFQ+	1,184 (8.8)	1,184	892 (75.3)	7	108 (41)	63 (25)	48
	HRFQ with FITs	11,962	FITs+/HRFQ−	687 (5.7)	687	537 (78.2)	16	113 (47)	32 (6)	63
			FITs−/HRFQ+	922 (7.7)	922	721 (78.2)	0	81 (33)	49 (19)	33
			FITs+/HRFQ+	154 (1.3)	154	126 (81.8)	7	26 (7)	13 (5)	14
	HRFQ without FITs	1,516	HRFQ+	108 (7.1)	108	45 (41.7)	0	1 (1)	1 (1)	1
	Subtotal	13,478	Any +	1,871 (13.8)	1,871	1,429 (76.4)	23	221 (88)	95 (31)	111
Female	FITs	12,447	FITs+	921 (7.4)	921	767 (83.3)	16	72 (34)	40 (7)	56
	HRFQ	13,598	HRFQ+	1,458 (10.7)	1,458	1,158 (79.4)	4	81 (26)	36 (17)	30
	HRFQ with FITs	12,447	FITs+/HRFQ−	746 (6.0)	746	618 (82.8)	12	57 (28)	34 (7)	40
			FITs−/HRFQ+	1,196 (9.6)	1,196	959 (80.2)	0	63 (19)	28 (17)	19
			FITs+/HRFQ+	175 (1.4)	175	149 (85.2)	4	15 (6)	6 (0)	10
	HRFQ without FITs	1,151	HRFQ+	87 (7.6)	87	50 (57.5)	0	3 (1)	2 (0)	1
	Subtotal	13,598	Any +	2,204 (16.2)	2,204	1,776 (80.6)	16	138 (54)	70 (24)	70
Age <55 y	FITs	13,397	FITs+	810 (6.0)	810	692 (85.4)	5	74 (36)	38 (8)	41
	HRFQ	15,021	HRFQ+	1,213 (8.1)	1,213	967 (79.7)	0	72 (17)	39 (20)	17
	HRFQ with FITs	13,397	FITs+/HRFQ−	683 (5.1)	683	582 (85.2)	5	62 (33)	30 (5)	38
			FITs−/HRFQ+	979 (7.3)	979	799 (81.6)	0	58 (13)	29 (17)	13
			FITs+/HRFQ+	127 (0.9)	127	110 (6.6)	0	12 (3)	8 (3)	3
	HRFQ without FITs	1,624	HRFQ+	107 (6.5)	107	58 (54.2)	0	2 (1)	2 (0)	1
	Subtotal	15,021	Any +	1,896 (12.6)	1,896	1,549 (81.7)	5	134 (50)	69 (25)	55
Age ≥55 y	FITs	11,012	FITs+	951 (8.6)	921	737 (77.5)	34	137 (52)	47 (10)	86
	HRFQ	12,055	HRFQ+	1,429 (11.9)	1,458	1,083 (75.8)	11	117 (50)	60 (22)	61
	HRFQ with FITs	11,012	FITs+/HRFQ−	750 (6.8)	750	573 (76.4)	23	108 (52)	36 (8)	65
			FITs−/HRFQ+	1,139 (10.3)	1,139	881 (77.3)	0	86 (39)	48 (19)	39
			FITs+/HRFQ+	202 (1.8)	202	165 (81.7)	11	29 (10)	11 (2)	21
	HRFQ without FITs	1,043	HRFQ+	88 (8.4)	88	37 (42.0)	0	2 (1)	1 (1)	1
	Subtotal	12,055	Any +	2,179 (18.1)	2,179	1,656 (76.0)	34	225 (92)	96 (30)	126

First stage (FITs and HRFQ) | Second stage (colonoscopy) — Result

(Continued on the following page)

Table 2. Participants and results by gender, age, screening test, and stage in CRC screening in a rural population in Jiashan, China, 2007–2009 (Cont'd)

| | | | First stage (FITs and HRFQ) | | | | Second stage (colonoscopy) | | | |
| | | | | | | | | Result | | |
Gender/age	Screening test	Result	Participant, n	n (%)	Eligible, n	Participant, n (%)	CRC	Adenomas (n[a])	Nonadenomatous (n[b])	Advanced[c]
All	FITs	FITs+	24,409	1,762 (7.2)	1,762	1,430 (81.2)	39	211 (88)	85 (18)	127
	HRFQ	HRFQ+	27,076	2,642 (9.8)	2,642	2,050 (77.6)	11	189 (67)	99 (42)	78
	HRFQ with FITs		24,409							
		FITs+/HRFQ−		1,433 (5.9)	1,433	1,155 (80.6)	28	170 (75)	66 (13)	103
		FITs−/HRFQ+		2,118 (8.7)	2,118	1,680 (79.3)	0	144 (52)	77 (36)	52
		FITs+/HRFQ+		329 (1.4)	329	275 (83.6)	11	41 (13)	19 (5)	24
	HRFQ without FITs	HRFQ+	2,667	195 (7.3)	195	95 (48.7)	0	4 (2)	3 (1)	2
	Subtotal	Any +	27,076	4,075 (15.1)	4,075	3,205 (78.7)	39	359 (142)	165 (55)	181

NOTE: Compliance by gender and age in total 3 communities is as follows: (i) all men: eligible for screening = 16,169; compliance at first stage = 84.1% (13,598 of 16,169), compliance at second stage = 76.4% (1,429 of 1,871); (ii) all women: eligible for screening = 15,794; compliance at first stage = 86.1% (13,598 of 15,794), compliance at second stage = 80.1% (1,776 of 2,204); (iii) total study population: eligible for screening = 31,963; compliance at first stage = 84.7% (27,076 of 31,963), compliance at second stage = 78.7% (3,205 of 4,075).

[a]Number in parenthesis is the number of participants who had advanced adenoma.

[b]Number in parenthesis is the number of participants who were diagnosed with nonadenomatous polyps by colonoscopy without histopathologic results.

[c]Advanced neoplasm includes CRC and advanced adenomas.

was higher among women than among men. When stratified by age, overall positive rate was higher among people 55 years or older than those younger than 55 years.

The detected rates (Table 2) of cancer, adenoma, non-adenomatous polyps, and advanced neoplasm were 2.7% (95% CI: 1.9–3.6), 14.8% (95% CI: 12.9–16.6), 7.2% (95% CI: 5.9–8.5), and 8.9% (95% CI: 7.4–10.4) by FITs, which were higher than those by HRFQ [0.5% (95% CI: 0.2–0.9), 9.2% (95% CI: 8.0–10.5), 6.9% (95% CI: 5.8–8.0), 3.8% (95% CI: 3.0–4.6), respectively]. There was no significant difference in detected rate for nonadenomatous polyps between FITs and HRFQ.

Using HRFQ, we found that 41.2% (148 of 359) adenomas (FITs+ only: 47.4% and both FITs+ and HRFQ+: 11.4%), 53.2% (117 of 220) nonadenomatous polyps (FITs+ only: 35.9% and both: 10.9%), and 29.8% (54 of 181) advanced neoplasm (FITs+ only: 56.9% and both: 13.3%) were missed by FIT methods.

Positive predictive value

In this rural population, the positive predictive value (PPV; Table 3) of this study protocol for CRC was 1.2%, PPV for adenoma was 11.2%, PPV for nonadenomatous polyps was 6.9%, PPV for advanced neoplasm was 5.7%, and PPV for total colorectal neoplasm was 19.3%. PPV for adenoma was the highest among all kinds of colorectal neoplasm.

The overall PPV of FITs+ only for CRC was 2.7% and of HRFQ+ only was 0.5%. Overall PPV of FITs+ only was 14.8% for adenoma, 7.2% for nonadenomatous polyps, 8.9% for advanced neoplasm, and 24.7% for total colorectal neoplasm, and of HRFQ+ only was 9.2% for adenoma, 6.9% for nonadenomatous polyps, 3.8% for advanced neoplasm, and 16.6% for total colorectal neoplasm. PPVs of FITs+ only for CRC, adenoma, advanced neoplasm, and total colorectal neoplasm were higher than those of the HRFQ+ only ($P < 0.05$).

When stratified by gender and age, PPVs of both FITs and HRFQ were higher among men than among women except for CRC and nonadenomatous polyps that did not reach statistical significance and were higher among those 55 years or older than those younger than 55 years.

Gender and age distributions of advanced neoplasm

Men overall have a significantly higher prevalence rate of advanced neoplasm than women (6.9 per 1,000 men and 4.4 per 1,000 women) and a higher prevalence of CRC (1.6 per 1,000 men and 0.9 per 1,000 women) than women. The age distribution of advanced neoplasm was parabolic with a peak in the 55 to 59 age group. There were 2 CRC cases who were younger than 50 years, including one CRC case who was younger than 44 years, accounting for 5.1% (2 of 39) in the total 3 communities, and 21 cases with advanced neoplasms who were younger than 50 years accounting for 11.6% (21 of 181).

Discussion

More and more countries are encouraging a nationwide CRC screening program. Several easy and efficient screening strategies for colorectal neoplasm are now available (15). Screening strategies can be chosen on the basis of individual risk, personal preference, and access (16). Our screening program used both FITs and HRFQ as primary mass screening methods and colonoscopy as a secondary screening method based on a screening protocol recommended and put forward in 2006 by the China National Committee of Cancer Early Detection and Treatment. We repeatedly tested this screening protocol in 3 community populations from 2007 to 2009 to determine its effectiveness in the population.

The effectiveness of a screening program depends on compliance (17–19). In this study, the compliance rate in each community is satisfactory in both screening stages,

Table 3. PPV (%) of different screening tests in CRC screening in total study population ($N = 27,076$) in Jiashan, China, 2007–2009

Positive result	N	CRC		Adenoma		Nonadenomatous polyps[a]		Advanced neoplasm[b]		Total CR neoplasm[c]	
		n	PPV (95% CI)	n	PPV (95% CI)	n	PPV (95% CI)	n	PPV (95% CI)	n	PPV (95% CI)
FITs+ only	1,430	39	2.7 (1.9–3.6)	211	14.8 (12.9–16.6)	103	7.2 (5.9–8.5)	127	8.9 (7.4–10.4)	353	24.7 (22.5–26.9)
HRFQ+ only	2,050	11	0.5 (0.2–0.9)	189	9.2 (8.0–10. 5)	141	6.9 (5.8–8.0)	78	3.8 (3.0–4.6)	341	16.6 (15.0–18.3)
FITs+/HRFQ–	1,250	28	2.2 (1.4–3.0)	174	13.9 (12–15.8)	83	6.6 (5.3–8.0)	105	8.4 (6.9–9.9)	285	22.8 (20.5–25.1)
FITs–/HRFQ+[d]	1,680	0	–	144	8.6 (7.2–9.9)	113	6.7 (5.5–7.9)	52	3.1 (2.3–3.9)	257	15.3 (13.6–17.0)
FITs+/HRFQ+	275	11	4.0 (1.7–6.3)	41	14.9 (10.7–19.1)	24	8.7 (5.4–12.1)	24	8.7 (5.4–12.1)	76	27.6 (22.4–32.9)
Total	3,205	39	1.2 (0.8–1.6)	359	11.2 (10.1–12.3)	220	6.9 (6.0–7.7)	181	5.7 (4.9–6.5)	618	19.3 (17.9–20.7)

[a]The number of participants who were diagnosed with nonadenomatous polyps by colonoscopy.
[b]Included CRC and advanced adenomas.
[c]Total colorectal neoplasm including CRC, adenomas, and nonadenomatous polyps.
[d]FITs–/HRFQ+ including HRFQ+ without FITs result group.

which ensures that our results can be generalized to the rural population in China. The high compliance is due to strong support from the local government and the screening interviewers going to the community at a convenient time for residents.

Because CRC is a strictly surveillance disease in the Cancer Registration System in China, all newly diagnosed and dead cancer cases will be entered into the Cancer Registration System, that is to say that CRC data are complete in this study. The data of all sites of cancer incidence and mortality in Jiashan County have been cited by International Agency for Cancer Research for at least 10 years (20). Therefore, the results in this study are valid and reliable.

Overall PPV is 1.2% for CRC and 19.3% for total colorectal neoplasm, which means that one whose result is positive in the first-stage screening would have a 1.2% possibility of CRC and 19.3% of any colorectal neoplasm. However, there are 80.7% (false-positive rate) of participants without colorectal neoplasm undergoing a colonoscopy. If this false-positive rate can be reduced, screening efficiency would be greatly improved. A new more efficient method is still needed for CRC screening.

Gender is a factor affecting PPV for colorectal neoplasm. Men have higher PPVs than women. PPV is higher among an old age group than among a young age group, which is in accordance with the fact that colorectal neoplasm incidence is higher among men and old age groups. In the future, men should be encouraged to get CRC screening.

Although a colonoscopy allows a complete examination of the large bowel, it has the risk of perforation (21), let alone its acceptability, availability, and expensiveness (16, 22). Therefore, colonoscopy is not routinely used as a first choice for screening but mostly as a follow-up examination after other less invasive tests or used for surveillance after the detection of positive lesions (23), especially in a medically and economically underserved rural population. Therefore, a simple and economical method for CRC screening should be explored.

Investigation of high-risk factors by HRFQ has been used in the diagnosis of CRC in clinical processes (24, 25), but it is rarely used in CRC mass screening. From previous studies, HRFQ could be one of the primary screening methods for colorectal neoplasm in the population (8); however, fewer data were reported. In our study, PPVs of HRFQ for CRC, adenoma, advanced neoplasm, and total colorectal neoplasm are significantly lower than those of the FITs in this study population, but using HRFQ, we found that 41.2% of adenomas, 53.2% of nonadenomatous polyps, and 29.8% of advanced neoplasms were missed by the FITs method. There was no significant difference in the detected rate for nonadenomatous polyps between FITs and HRFQ. Although CRC detection rate is not improved by HRFQ,

it can be used as a complementary primary screening method for colorectal adenoma and nonadenomatous polyps to make up for a deficiency of FITs.

Up till now, FIT is still one of the most efficient screening methods to capture CRC cases without obvious risk and complications. But it misses adenoma and nonadenomatous polyps without bleeding, which may be caught by HRFQ. From our result, the PPV of the screening protocol of combining FITs and HRFQ for advanced neoplasm is 5.7% in this study population, which was higher than that of FITs (2.2%) or guaiac FOBT (1.2%) alone reported in the previous studies of meta-analysis results (26), which implies that combination of FITs and HRFQ is more effective than FITs alone. Although HRFQ has a limitation of a relatively high false-positive rate that increases the number of colonoscopies, it is cheap, accessible, of no obvious risk, and has a considerable capacity for finding colorectal adenoma and nonadenomatous polyps, especially advanced adenoma, which is very important to a medically and economically underserved rural population. HRFQ found about 30% of advanced adenomas in this study, which is of vital importance to prevent and control CRC for its apt malignancy transforming.

HRFQ and FITs have shown their considerable capacity in colorectal neoplasm screening, especially for economically and medically underserved populations. Combination of HRFQ and FITs improved the detection capacity of colorectal neoplasm compared with FITs alone.

Disclosure of Potential Conflicts of Interest

Authors have no conflicts of interest with any individuals or organizations.

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