Fecal Immunochemical Testing and the Risk of Advanced Colorectal Neoplasia: A Difference-In-Difference Analysis

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ABSTRACT

PURPOSE To evaluate the effectiveness of fecal immunochemical testing (FIT) in colorectal cancer screening.

METHODS We conducted a prospective cohort study among 5,598 participants age 40-74 years between 2012 and 2020 in Tianjin, China. Inverse probability weighting was adopted to adjust for potential imbalanced factors between groups. A Cox proportional hazards model was used to estimate the weighted associations between FIT screening and advanced colorectal neoplasia. A difference-in-difference (DID) model was adopted to compare the incidence rates of advanced colorectal neoplasia between groups.

RESULTS In DID analysis, the rate of incidence was reduced by 0.34 cases per person-years in the screening group as compared with the historical FIT screening group (rate ratio [RR], 0.08 [95% CI, 0.07 to 0.10]) and by 0.06 cases per person-years in the non-FIT screening group as compared with the historical non-FIT screening group (RR, 0.37 [95% CI, 0.29 to 0.48]; $P < .001$ for both comparisons), with a relative reduction of 0.28. Similar benefit effect from FIT screening was observed in sex and age subgroups.

CONCLUSION FIT screening was associated with a reduction in incidence density from advanced colorectal neoplasia.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors, and screening is effective in reducing its incidence and mortality.[1] There are a variety of tests available for CRC screening, including fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy.[2] Fecal immunochemical testing (FIT) is a commonly used screening test worldwide, with advantages such as moderately sensitive, noninvasive, easy to complete, and low cost, and specifically identifies high-risk patients for colonoscopy, rendering it the most popular first-tier test for CRC screening, especially in developing countries and regions where resource and health service settings are constrained.[3]

FIT as the preferred method is recommended in screening programs for CRC by the international expert panels.[2,4] The guideline for CRC screening in China also highly recommends the FIT as an initial test in bowel cancer screening programs for the population age 40 years or older.[5] However, the reduction in the risk of death from CRC was not statistically significant, suggesting that continuing efforts to search for the perfect screening tool were necessarily needed.[6]

Observational studies suggest that FIT could reduce the incidence of CRC.[7] Nevertheless, the effectiveness of FIT screening is still uncertain[8] chiefly because of concern regarding methodologic limitations. The main challenge in quantifying the reduction in incidence from observational screening programs is to provide valid comparison groups because of the nonrandom assignment.[9] As we all know, a simple comparison of people who actually receive FIT screening (attenders) and people who do not (nonattenders) usually differ, substantially in socioeconomic status and the risk of cancer in baseline, which causes self-selection bias in observational studies.[7] In addition, studies often overlook important confounding factors related to chronological trends, such as advancements in CRC awareness and treatment, which can significantly influence the findings.

The difference-in-difference (DID) design is a quasi-experimental research design that compares the outcomes of groups exposed to different policies and environmental factors at different times to offer information about causal relationships, which could be used in scientific research and public health policy analysis when randomized controlled trials are unfeasible or unethical. Therefore, the ingenious

CONTEXT

Key Objective
To assess the efficacy of fecal immunochemical testing (FIT) in colorectal cancer (CRC) screening.

Knowledge Generated
In our study, FIT screening was found to be associated with a significant reduction in the incidence density of advanced colorectal neoplasia. This effect was consistent across subgroups on the basis of sex and age.

Relevance
Our findings provided evidence supporting the effectiveness of FIT screening in reducing the occurrence of advanced colorectal neoplasia. These results have important clinical implications, highlighting FIT as a valuable tool in CRC screening programs for early detection.

design of DID is particularly attractive for evaluation of CRC screening on the basis of FIT.

Leveraging the DID design, we evaluated the effectiveness of FIT in reducing the incidence of advanced colorectal neoplasia with the introduction of FIT to determine what is the contribution of FIT in population-based CRC screening and whether we should continue offering FIT test in population-wide CRC screening. This study may provide a scientific basis for explicating FIT value in the practical CRC screening.

METHODS

Study Setting and Population

The National Health Commission of the People's Republic of China released a document for early diagnosis and treatment of CRC in 2011, outlining an approach to CRC screening. The core detection methodologies incorporated usage of the High-Risk Factor Questionnaire (HRFQ) and FIT. Those individuals who received positive results from either the FIT or risk assessment questionnaire were identified as being at high risk for CRC. These participants were subsequently referred to officially designated hospitals or subjected to colonoscopy examinations for further evaluation. Suspicious lesions were biopsied, and pathological examination was performed to discern patients with precancerous lesions and cancer. The Tianjin CRC screening program was formally initiated in 2012 by the government, implemented as a public health project. It has already provided free CRC screening for more than 4 million residents from 2012 to 2020 and became one of the largest population-based screening programs for CRC in China.

The 16 districts of Tianjin are covered by the CRC screening program, where television, radio, brochures, and social media outlets were used for program advocacy, promoting CRC screening enrollment. According to the eligibility of all the residents who were age 40-74 years, the HRFQ combined with FIT was used for primary screening in the community. The initial screen–positive population was defined as high risk of CRC, and free colonoscopy was recommended for high-risk groups. Participants were excluded if they had a history of CRC, a history of colonic resection, or significant comorbidity not suitable for screening. All participants were fully informed of the risks and benefits of the program, and they provided written informed consent. The study was approved by the ethics committees of Tianjin Health Commission (the ethical approval number is 2023C04).

Screening Procedures

The sequential screening was divided into two stages. In the first stage, FITs and HRFQs were used as the primary screening method.[5] The staff members distributed the FIT test kits to the participants who visited the community health service center and instructed them about the operating procedures. The participants were recommended to complete FIT at home or at the community health service center if possible. Fecal samples were collected by community health workers and tested by experienced technicians in the health centers. The test result of FITs was considered positive when the hemoglobin concentration in at least one sample was ≥100 ng/ml, which corresponds to ≥20 μg Hb/g feces. The HRFQ included basic demographic information, such as age, sex, residence, marital status, and education level, and nine CRC risk factor questions. The administration of the HRFQ was completed by trained general practitioners. A positive result of HRFQ means if (1) individuals had one of the following events: (a) a history of cancer, (b) a history of polyps, or (c) a family history of CRC in a first-degree relative and/or (2) at least two of the following events: (a) chronic diarrhea; (b) chronic constipation; (c) mucoid blood stool; (d) serious unhappy life events, such as the death of a first-degree relative; (e) chronic appendicitis or appendectomy; or (f) chronic cholecystitis or cholecystectom.[10]

Colonoscopy

For the FIT or HRFQ, if either result was positive, the participants were recommended to undergo a colonoscopy and were transferred to designated hospitals, with the capacities

to perform colonoscopies, and CRC multidisciplinary teams in the second stage. All colonoscopies were conducted by experienced gastroenterologists (attending physician or above having extensive experiences of endoscopy). Abnormal findings were recorded during colonoscopy and carefully checked under standard clinical procedures. The biopsies for further pathology diagnosis and clinical information, such as adequacy of bowel preparation, morphological feature, location of distance from the anus and segment, and macroscopic diagnosis size, were collected and documented into the data system. Participants who had inadequate bowel preparation or incomplete colonoscopy were asked to retake the colonoscopy examination for the clinical standard for diagnosis.

Data Management and Quality Control

In this CRC screening program, 42 specifically designated medical institutions have been assigned the responsibility of performing thorough colonoscopies for individuals at high risk. The outcomes of these examinations are then compiled into a dedicated database within a web-based system. The databases encompass the diagnosis and information regarding whether the diagnosis was established before or subsequent to the implementation of the screening program. Both historical and current data have been gathered from this database. Trained staff collected and recorded all research data using standardized forms. For quality control, repeated examination was conducted for 4% of questionnaires and randomly selected stool sample results. All diagnoses during endoscopy were confirmed following up-to-date clinical guidelines. The highly standardized forms were used to collect pathology results by pathologists.

Exposure

The exposure was a change in the screening group (from non-FIT to FIT). All participants filled out the HRFQ. The FIT screening group comprised individuals who had undergone high-risk questionnaires and at least one FIT during the screening program, and the non-FIT group consisted of individuals who received high-risk questionnaire but no FIT throughout the study period.

Outcome

The primary outcome was the incidence rate of advanced colorectal neoplasia, defined as CRC and advanced adenoma.[11] Advanced adenomas are defined as at least one adenoma ≥10 mm, a villous component of at least 25%, or high-grade dysplasia. The final clinical diagnoses were classified according to the most advanced finding reported in colonoscopy. The diagnosis was established according to International Classification of Diseases-10 criteria.

Follow-Up

The follow-up was defined as the date from the primary FIT screening or the questionnaire date in the screening group to the date of CRC diagnosis, lost to follow-up, or the set end of follow-up (December 31, 2020). All participants were followed up by trained study recruiters to promote follow-up.

Statistical Analysis

The baseline characteristics of the study population were described as mean with standard deviation (SD) or median with IQR for continuous variables and the number (No.) and proportion (%) for categorical variables. We used standardized differences between the FIT screening and non-FIT screening groups. Standardized differences were calculated as the difference in means or proportions divided by the pooled SD, where values ≥0.1 denote meaningful difference.[12] The distribution of categorical variables between groups was also evaluated by using the χ^2 test. The inverse probability weighting (IPW) method used inverse probability of the FIT screening group weights to reduce imbalance in potential confounding factors.[13] A multivariable logistic regression analysis was performed in the population, with having an FIT as the dependent variable and the aforementioned baseline characteristics (including demographic variables, a family history of CRC, previously detected colonic polyp, and gastrointestinal clinical symptoms) as independent variables. The probability of having FIT could be predicted. Furthermore, the weights for individuals were calculated as the inverse of the probability of receiving the FIT for the participants in the screening group who actually had accepted FIT and the inverse of the probability of not receiving the FIT in the nonscreening group. After weighting, we assessed the balance of baseline characteristics between the FIT screening and non-FIT screening groups by calculating the standardized difference. A standardized difference after inverse probability of treatment weighting (IPTW) <0.1 is acceptable.

To estimate the association of FIT screening with advanced colorectal neoplasia, we used a Cox proportional hazards model and estimated the weighted association between FIT screening and the outcome by applying the individual weights in models. Significance tests and CIs for estimates were generated using robust standard errors (SEs) to account for the clustering of observations within individuals by community, and hazard ratios (HRs) and 95% CIs are reported.

DID estimates were calculated to estimate the effect of the FIT intervention. The DID design, a quasi-experimental design, has already been used in public health policies. Our (DID) design estimated the outcomes before and after the introduction of FIT and then compared this difference with the difference in the non-FIT screening group. To do this, we constructed two groups pre-post differences, referred to as DID. DID is determined by the difference in incidence density in the FIT screening group before and during the intervention minus the difference in incidence density in the comparison group before and during the intervention. First, we compared the non-FIT screening current group with

their historical counterparts, which aimed to determine the temporal change in incidence that was not attributable to the introduction of the FIT screening program but that was likely to reflect advanced treatment and/or earlier clinical diagnosis. Then, we also compared the FIT screening current group with their historical counterparts to determine the change in incidence after implementation of the screening program. In this second comparison, the difference in the rate of incidence between the two groups can be attributed both to the screening program and to temporal incidence trends in that were irrelevant to the screening program. Stratified analyses according to sex and age were also performed. We estimated rates of incidence from advanced colorectal neoplasia in the four study groups according to sex (female, male) and age at diagnosis (40-49 years, 50-59 years, 60-69 years, 70 years and older). All statistical analyses were two-sided using the statistical software R version 4.0.2 (RStudio Inc, Boston, MA), and *P* value of <.05 was considered to indicate statistical significance.

RESULTS

DID Design

Overall, 4,033,926 eligible participants were recruited, and of those at high risk for CRC (n = 282,944), 94,789 participants accepted colonoscopy. In total, 5,598 participants were included in this study. For the study group, people were invited to the program, and they accepted diagnosis of CRC from the beginning to 2020. For the control group, participants were those who did not attend the FIT program in two periods: before and after the longitudinal follow-up, but accepted colonoscopy. For the historical control group, participants were those who did not attend the FIT program before the introduction of the FIT program. A flow diagram showing the recruitment of the study population is depicted in Figure 1.

Baseline Characteristics of Participants

Between January 1, 2012, and December 31, 2020, a total of 94,789 participants accepted colonoscopy, and after excluding 68,917 participants who accepted FIT in the first screening and 19,308 participants who did not meet the DID analysis criteria after further evaluation, 5,598 participants were included for the final analysis. Among them, 4,400 individuals were in the FIT screening group and 1,198 individuals in the nonscreening group, with a total follow-up period of 19,195 person-years, and the median follow-up time was 3.0 years (maximum, 8.7 years; Fig 1).

Baseline characteristics of participants in the FIT screening group and nonscreening group are shown in Table 1. The mean age was 65.8 years (SD, 8.14) across the entire population. Compared with those in the nonscreening group, participants in the FIT screening group were more likely to be male and older ($P < .05$ and standardized difference more than 0.1 for each). After IPW, the standardized differences were <0.1 for all confounder factors, suggesting that the FIT screening and nonscreening groups were well balanced.

Association Between FIT and Colorectal Neoplasia

Cox proportional hazard models were used to evaluate potential risk factors. The adjusted HRs for the association between the FIT screening and advanced colorectal neoplasia from unweighted and weighted Cox regression models after IPW are shown in Table 2. The FIT screening group had

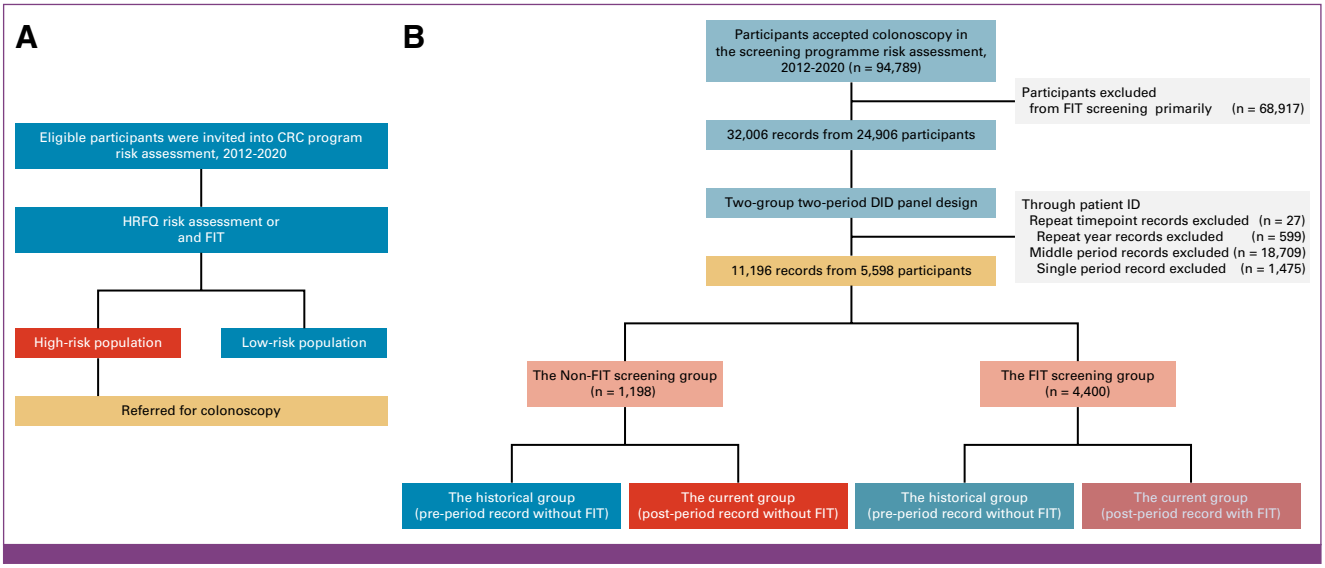

FIG 1. Overall study design and flow diagram for the study populations in CRC DID analysis. (A) CRC screening strategies and (B) the study population inclusion in the DID analysis. CRC, colorectal cancer; DID, difference-in-difference; FIT, fecal immunochemical testing; HRFQ, High-Risk Factor Questionnaire; ID, identification.

TABLE 1. Baseline Characteristics of the CRC Screening Study Population

Characteristic	Non-FIT Screening (n = 1,198)	FIT Screening (n = 4,400)	Before IPW		After IPW	
			P^a	SMD	P^b	SMD[c]
Age, years						
Mean (SD)	64.31 (8.8)	66.25 (7.88)	<.001	0.232	.433	0.027
40-49, No. (%)	83 (6.9)	185 (4.2)				
50-59, No. (%)	273 (22.8)	716 (16.3)				
60-69, No. (%)	467 (39.0)	1,710 (38.9)				
>70, No. (%)	375 (31.3)	1,789 (40.8)				
Sex, No. (%)						
Male	571 (47.7)	2,112 (48.0)	.861	0.007	.441	0.027
Female	627 (52.3)	2,288 (52.0)				
Education, No. (%)						
Below high school	168 (14.1)	1,074 (24.4)	<.001	0.317	.930	0.013
High school	784 (65.4)	2,785 (63.3)				
Postsecondary	246 (20.5)	541 (12.3)				
Work, No. (%)						
Administrators/technicians	444 (37.1)	1,549 (35.2)	.084	0.084	.956	0.019
Service industry	88 (7.3)	272 (6.2)				
Production/transport devices staff	459 (38.3)	1,855 (42.2)				
Unemployment/unknown	207 (17.3)	724 (16.4)				
Previously detected colonic polyp, No. (%)						
No	974 (81.3)	3,981 (90.5)	<.001	0.266	.691	0.012
Yes	224 (18.7)	419 (9.5)				
Family history of CRC, No. (%)						
No	1,094 (91.3)	4,127 (93.8)	.003	0.094	.991	<0.001
Yes	104 (8.7)	273 (6.2)				

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical testing; IPW, inverse probability weighted; SD, standard deviation; SMD, standardized mean difference.
[a]*P* values before IPW.
[b]*P* values after IPW.
[c]Standardized differences after inverse probability weighting, lower than 0.1 were balanced.

significantly lower advanced colorectal neoplasia risk (22.0% lower) than the nonscreening group (HR, 0.78 [95% CI, 0.62 to 0.98]). Compared with the male participants, significant advanced colorectal neoplasia incidence reductions were observed in female participants (HR, 0.58 [95% CI, 0.47 to 0.72]). The risk of advanced colorectal neoplasia in participants increases with age (HR, 1.05 [95% CI, 1.03 to 1.07]). Although an increased risk among participants with a family history of CRC or a history of polyps was still observed, it was not statistically significant.

Effectiveness of FIT

In the FIT screening group, the incidence density was 0.031 per person-years, compared with 0.366 per person-years among their historical counterparts, for a difference of 0.34 cases per person-years (rate ratio [RR], 0.08 [95% CI, 0.07 to 0.10]). In the nonscreening group, the incidence density was 0.036 per person-years, compared with 0.095 per person-years among their historical counterparts, for a difference of 0.06 cases per person-years (RR, 0.37 [95% CI, 0.29 to 0.48]), with a relative reduction of 0.28 (Table 3; Fig 2).

In stratified analyses according to sex and age, among male participants, there was a significant relative reduction of 0.34 after the introduction of the FIT screening program. Among female participants, the corresponding reduction was 0.23 (Table 3; Fig 3). Among participants between age 40 and 49 years, the significant relative reduction was 0.25 after the introduction of the FIT screening program. Among participants between age 50 and 59 years, the relative reduction was 0.12. Among participants between age 60 and 69 years, the relative reduction was 0.26. Among participants age 70 years and older in the screening group, the relative reduction was 0.32 (Table 3; Fig 4).

DISCUSSION

Previous studies have found that CRC screening is effective in reducing disease burden but did not distinguish whether the

TABLE 2. Multivariable Analysis of Factors Associated With Advanced Colorectal Neoplasia Incidence Rate

	Model 1[a]		Model 2[b]	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*
Group				
Non-FIT screening	1.00 (reference)		1.00 (reference)	
FIT screening	**0.79 (0.64 to 0.98)**	**.028**	**0.78 (0.62 to 0.98)**	**.030**
Age, years	**1.05 (1.04 to 1.06)**	**<.001**	**1.05 (1.03 to 1.07)**	**<.001**
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	**0.66 (0.56 to 0.78)**	**<.001**	**0.58 (0.47 to 0.72)**	**<.001**
Education				
Below high school	1.00 (reference)		1.00 (reference)	
High school	1.21 (0.98 to 1.48)	.070	1.16 (0.86 to 1.56)	.345
Postsecondary	1.05 (0.78 to 1.42)	.727	1.05 (0.71 to 1.56)	.734
Work				
Administrators/technicians	1.00 (reference)		1.00 (reference)	
Service industry	1.01 (0.73 to 1.40)	.940	1.29 (0.87 to 1.91)	.331
Production/transport devices staff	1.06 (0.88 to 1.28)	.532	1.15 (0.90 to 1.47)	.180
Unemployment/unknown	1.09 (0.85 to 1.41)	.481	1.22 (0.90 to 1.66)	.209
Previously detected colonic polyp				
No	1.00 (reference)		1.00 (reference)	
Yes	1.13 (0.89 to 1.44)	.310	0.85 (0.65 to 1.12)	.234
Family history of CRC				
No	1.00 (reference)		1.00 (reference)	
Yes	1.34 (0.99 to 1.81)	.060	0.78 (0.54 to 1.13)	.196

NOTE. Bold values indicate statistical significance.
Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical testing; HR, hazard ratio.
[a]HRs were adjusted for age, sex, education, work, a history of cancer, a history of polyps, a family history of CRC, chronic diarrhea, chronic constipation, mucoid blood stool, chronic appendicitis or appendectomy, chronic cholecystitis, or cholecystectomy.
[b]Except for the factors included in model 1, adjusted HRs are from weighted Cox regression models after inverse probability weighting.

benefit comes from initial FIT or colonoscopy screening. The highlight of our research is differentiating the net benefits of FIT. Therefore, when we took into account the effect of colonoscopy screening and time trends in the incidence change of advanced colorectal neoplasia caused by other factors, to determine the net benefits of FIT, we designed a counterfactual model. In our study, with long follow-up, the incidence density from advanced colorectal neoplasia was reduced after the introduction of a FIT screening program in Tianjin, China. Indeed, the critical result was that FIT screening was associated with an absolute reduction of 0.28 in the incidence density from advanced colorectal neoplasia. This population-based, prospective study evaluated incidence reduction associated with FIT screening, which corroborated the few previous observational studies on the effectiveness of FIT screening in reducing CRC incidence. Two Italian studies demonstrated significant reductions of about 20%.[14,15] Recently, another large cohort study from Italy found attendance to FIT screening with a self-selection adjusted decrease of 33% in men and 21% in women in CRC incidence.[16] Similar to what was discovered by Levin et al, the decrease was estimated to be 25%.[17] In a Taiwanese FIT screening program, a 34% reduction in the incidence of advanced-stage CRC was observed on long-term results.[18]

In our study, we focused on advanced colorectal neoplasia as we believe that this should be the critical lesion and an attractive target for screening. Early detection of advanced neoplasia promotes preventive screening by polypectomy, interrupting the progression to carcinoma. As advocated in an expert consensus statement, this aim of preventing high-risk lesions endows a higher level preventive meaning and brings greater benefit in the CRC screening population compared with case finding.[19] Whether it could be an important surrogate end point, more information about its natural develop history needs to be known. The reduction of advanced colorectal neoplasia incidence density shown in this study is acceptable. Generally, in the beginning, there was an increase in the incidence of CRC since there is an active search going on among long time screening. However, the number of CRC found during a primary period is only a portion of those detected because of symptoms. The crucial point is that advanced adenoma is the most important precursor of CRC, and such precancerous lesions

TABLE 3. Comparison of Rates of Cases of Advanced Colorectal Neoplasia According to the FIT Screening Group

	Non-FIT Screening Groups		FIT Screening Groups		Difference		
Group and Incidence Data	Historical Group	Current Group	Historical Group	Current Group	Non-FIT Screening Groups[a]	FIT Screening Groups[b]	Between-Group Difference[c]
Total population							
No. of cases/No. of person year	114/1,198	119/3,339	512/1,399	445/14,456			
Incidence density	0.095	0.036	0.366	0.031	0.06	0.34	0.28
RR for case (95% CI)					0.37 (0.29 to 0.48)	0.08 (0.07 to 0.10)	0.29
Sex group							
Male							
No. of cases/No. of person-year	78/572	79/1,615	304/657	266/7,095			
Incidence density	0.136	0.049	0.463	0.037	0.09	0.43	0.34
RR for case (95% CI)					0.36 (0.26 to 0.49)	0.08 (0.07 to 0.10)	0.28
Female							
No. of cases/No. of person-year	36/626	40/1,724	208/742	179/7,361			
Incidence density	0.058	0.023	0.280	0.024	0.03	0.26	0.23
RR for case (95% CI)					0.40 (0.26 to 0.63)	0.09 (0.07 to 0.11)	0.31
Age group, years							
40-49							
No. of cases/No. of person-year	6/94	5/248	15/49	11/584			
Incidence density	0.064	0.020	0.360	0.019	0.04	0.29	0.25
RR for case (95% CI)					0.32 (0.10 to 1.03)	0.06 (0.03 to 0.13)	0.26
50-59							
No. of cases/No. of person-year	12/267	11/847	41/251	38/2,355			
Incidence density	0.045	0.013	0.163	0.016	0.03	0.15	0.12
RR for case (95% CI)					0.29 (0.13 to 0.65)	0.10 (0.06 to 0.15)	0.19
60-69							
No. of cases/No. of person-year	55/471	57/1,326	199/515	164/5,546			
No. of cases/person-year	0.117	0.043	0.386	0.030	0.07	0.36	0.26
RR for case (95% CI)					0.37 (0.25 to 0.53)	0.08 (0.06 to 0.09)	0.29
>70							
No. of cases/No. of person year	41/304	46/915	257/583	232/5,970			
Incidence density	0.135	0.050	0.441	0.039	0.08	0.40	0.32
RR for case (95% CI)					0.37 (0.24 to 0.57)	0.09 (0.07 to 0.11)	0.28

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical testing; RR, rate ratio.

[a]For the non-FIT screening groups, the value means the difference between the rate of case in the historical group and that in the current group. This difference represents changes in incidence over time as a result of increased CRC awareness, improved therapy, and the management of treatment.

[b]For the FIT screening groups, the value shown is the difference between the rate of case in the historical group and that in the current group. This difference represents changes in incidence both over time and after introduction of the CRC screening program.

[c]For the comparison of the non-FIT screening groups with the FIT screening groups, the value shown is the difference between the two rate-of-case differences. This value represents the effect of introducing the FIT screening.

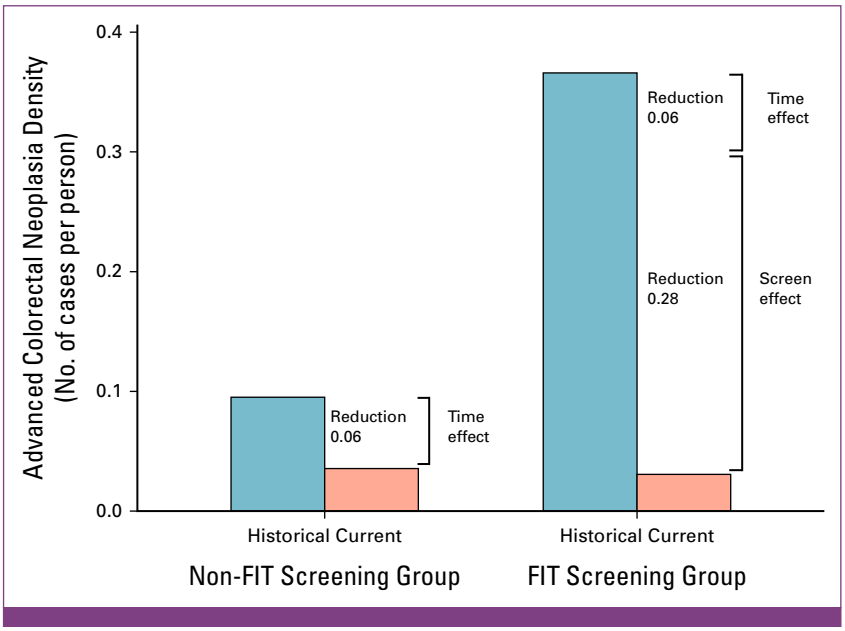

FIG 2. Difference in incidence density of advanced colorectal neoplasia between non-FIT screening and FIT screening groups. Blue bar represents the historical group. Red bar represents the current group. FIT, fecal immunochemical testing.

are ablated, leading to a decrease in the incidence of advanced colorectal neoplasia.[20]

In subgroup analyses by sex and age group, similar beneficial effects of FIT screening were observed. Notably, our study found that people age 40-49 years in the screening group were also effective. Worldwide, most national and international screening guidelines recommend that screening program should initiate at age 50 years.[21] However, in recent years, the incidence of early-onset CRC is increasing steadily.[22] Recently,

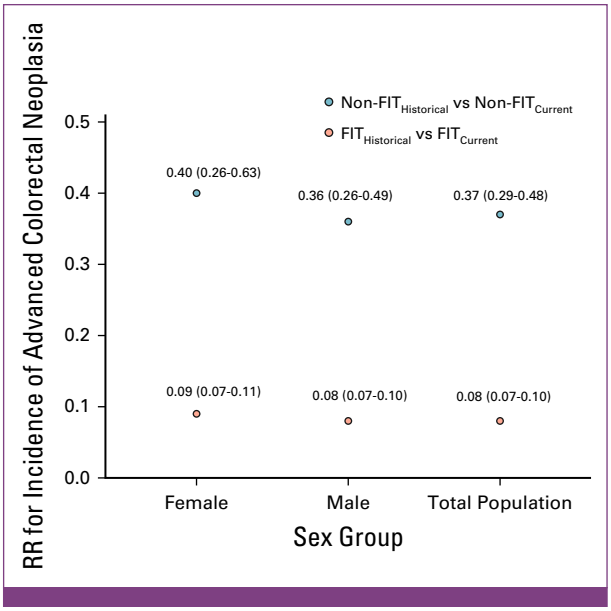

FIG 3. Comparison of RR for incidence of advanced colorectal neoplasia between the FIT screening group and historical group by sex group. Blue dot represents RR for case between the current and historical groups in the non-FIT screening group. Red dot represents RR for case between the current and historical groups in the FIT screening group. FIT, fecal immunochemical testing; RR, rate ratio.

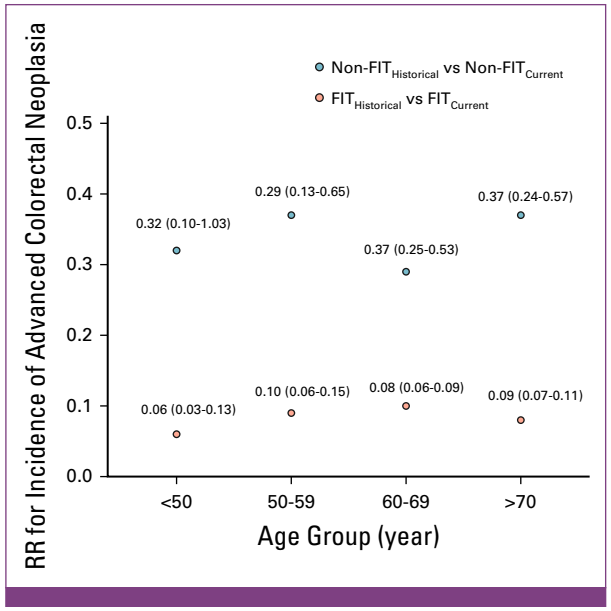

FIG 4. Comparison of RR for incidence of advanced colorectal neoplasia between the FIT screening group and historical group by age group. Blue dot represents RR for case between the current and historical groups in the non-FIT screening group. Red dot represents RR for case between the current and historical groups in the FIT screening group. FIT, fecal immunochemical testing; RR, rate ratio.

CRC screening guidelines from the American Cancer Society[23] recommended initiation of screening at age 45 years for individuals at average risk. The United States Preventive Services Task Force and American College of Gastroenterology also lowered the age at which to initiate screening to 45 years, although it was based on very limited quality evidence.[2,4] There is still a lack of direct and causal evidence. Our results supported that lowering the starting age for CRC screening to younger than 50 years is also applicable to a two-tier screening setting on the basis of FIT and colonoscopy as a sequential screening tool. Moreover, considering that young-onset CRC is growing in the Asia-Pacific region, using FIT-based screening starting at a younger age may be worthwhile.

The study design has several strengths, including a diverse, stable community-based population and data for more than 8 years covering the periods before and after implementation of organized screening. The cohort size allowed evaluation of screening effect by age and sex, especially in early-onset CRC. In the assessment of screening program effectiveness, cohort and case-control studies may be affected by the often-intractable challenges of self-selection bias. Regarding attributable to FIT screening effect that would influence the incidence rate of advanced colorectal neoplasia, in our study, we calculated DID to estimate the screening effect. Most importantly, the apparent benefit conveyed by the ingenious study design may be available to apply to other evaluation of cancer screening. DID is a novel methodological approach in assessment of cancer screening effectiveness.[24] More studies had shown that the credibility of the method to support valid estimates of screening effectiveness mainly applied in mammography screening.[25-28] Our study also has limitations. First, the limited follow-up time may be too short to show the full potential of the screening program. Second, despite adjusting for important confounding variables, there may still be a lack of measurement of potentially significant covariates at the individual level, such as smoking, drinking, or physical activity. Third, this study involved a single geographic area but reduces confounding by sociodemographic factors. Future studies would be carried out on the basis of a longer follow-up period by controlling for more covariates objectively measured and adjusted and of a larger, multicenter design to verify our findings.

We conclude that our results support the evidence that FIT screening reduces the rate of incidence density from advanced colorectal neoplasia. In summary, the magnitude of this benefit seems clear in high-risk individuals by the screening program we evaluated. In the future, more larger and multisite districts studies of FIT implementation strategies are required to test its effectiveness and comparisons with other CRC screening strategies to help further optimize CRC screening.

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DATA SHARING STATEMENT

The data sets generated and/or analyzed during this study are not publicly available because of privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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