JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2020-094
http://journal-arc.jp

Original Research Article

Risk for Colorectal Cancer in Patients with Serially Positive Fecal Immunochemistry Test in an Annual Screening Program

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Abstract

Objectives: There are patients who do not undergo colonoscopy even if the fecal immunochemistry test (FIT) results are positive and even with repeated positive test results the following year. We aimed to investigate colorectal cancer (CRC) risk in examinees with positive FIT results in our annual screening program.

Methods: We analyzed patients who underwent initial colonoscopy from April 2010 to March 2017 because of positive FIT results using an endoscopy database in our hospital. We investigated the difference in the risk of advanced colorectal neoplasia as a surrogate marker of CRC between those who had an initial positive test and those who had repeated positive tests.

Results: A total of 748 patients were included in this analysis. The advanced neoplasia detection rates were 7.6% (50/656) and 18.5% (17/92) for the initial and repeated positive test groups, respectively. Subgroup analysis of those with repeated positive tests revealed that the detection rates in examinees with positive tests 1-2 and >2 years ago were 16.7% (6/36) and 19.6% (11/56), respectively. The odds ratios for advanced neoplasia detection in patients with positive tests 1-2 and >2 years ago compared with those in the initial positive test group were 2.72 (95% confidence interval [CI], 1.04-7.10) and 3.09 (95% CI, 1.47-6.48), respectively.

Conclusions: The risk of CRC appears more than doubled in patients with a repeated positive FIT result. Prompt colonoscopy is recommended for FIT-positive cases.

Keywords

cancer screening, colonic neoplasms, colonoscopy, colorectal neoplasms, occult blood

J Anus Rectum Colon 2021; 5(4): 340-345

Introduction

Population-based colorectal cancer (CRC) screening in Japan has been conducted using the 2-day method via fecal immunochemistry test (FIT)[1,2]. The sensitivity and specificity of the FIT for detecting CRC are reported to be 53%-100% and 87%-95%, respectively[3]; it is considered to be an excellent screening method. However, the positive predictive value of FIT in Japan is reported to be 3.6% (7,830/220,308)[4], with the remaining approximately 96% of FIT-positive individuals not diagnosed with CRC. Because of this low positive predictive rate, some FIT-positive patients do not undergo colonoscopy. It has been reported that only 59.5% of FIT-positive individuals in Japan underwent thorough examination[4]. In addition, because of the recent coronavirus disease 2019 (COVID-19) pandemic, many hospitals refrain from performing colonoscopy unless necessary[5]. As such, FIT-positive patients may not readily be

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Received: November 22, 2020, Accepted: May 11, 2021

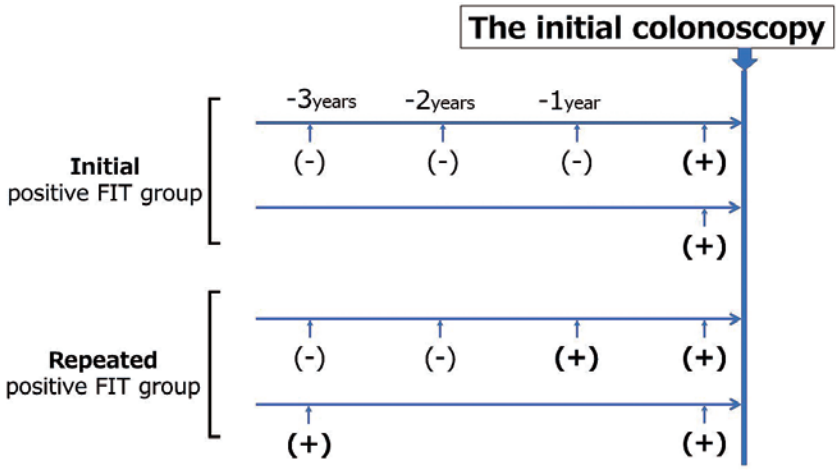

Figure 1. Description of groups.
The initial positive fecal immunochemistry test (FIT) group includes individuals who had previously been tested negative and were positive for the first time or those who were positive in their first test. The repeated positive FIT group includes individuals who had multiple previous positive FIT results prior to colonoscopy.

able to undergo colonoscopy.

In Japan, there are patients who ignore a positive FIT result and even undergo a second FIT the following year without colonoscopy. CRC risk would be high with serially positive results, but exactly how high is unclear. The present study aimed to determine the risk of CRC in subjects who have never had a colonoscopy and who repeatedly tested positive for FIT.

Methods

Study design

This study was a single-center, retrospective, observational study. The study design was approved by the institutional review board of Kyoto Second Red Cross Hospital (Sp2019-19) and conducted in compliance with the tenets set by the Declaration of Helsinki. All patients who underwent initial colonoscopy at our hospital between April 2010 and March 2017 because of a positive FIT result were potentially included. The potentially included subjects of this study were stated on the website of our hospital and asked to contact the hospital if they did not want their information to be used. Patients younger than 40 years and those who had their FIT for reasons other than our opportunistic screening program were excluded from the analysis. The primary outcome was the incidence of advanced neoplasia as a surrogate marker for CRC. Advanced neoplasia was defined as follows: tubular adenoma ≥ 10 mm, adenoma with a villous histology, high-grade adenoma, intramucosal cancer, or invasive cancer. We investigated the difference in the risk of advanced neoplasia between those who had an initial positive FIT (initial positive FIT group) and previous positive FIT, no colonoscopy, and then a second positive FIT (repeated positive FIT group; Figure 1). In the initial positive FIT group, all patients underwent colonoscopy within 1 year of testing positive for FIT. Even in the repeated positive FIT group, the interval between the last positive FIT and colonoscopy was less than 1 year. The repeated positive FIT group had at least two repeated positive FITs, but more than that were also included.

Data extraction

Solemio ENDO (Olympus Co., Tokyo, Japan) was used as the endoscopic database. Data collected for this study included the indication for colonoscopy and a screen for previous colonoscopy. Our database contains colonoscopies performed at our hospital in the past 20 years. Colonoscopy history was confirmed from the interview and endoscopy database. We selected patients who underwent initial colonoscopy because of positive FIT results. Meanwhile, FIT data were stored in a separate local database of the screening program in our hospital. Both FIT and colonoscopy data were linked by hospital identification number in our hospital. No sample size calculation was used as all colonoscopies performed during the study period in our hospital were potentially included.

FIT and the colonoscopy method

The FIT kit used in our annual opportunistic screening program was the FOBIT Wako (FUJIFILM Wako Pure Chemical Industries), with a 2-day FIT method. The cutoff value was set at 30 ng/mL (7.5 μg hemoglobin/g feces)[6]. For cases of positive FIT results in at least one of the two

samples, a recommendation for colonoscopy was written on the result explanation form and sent by mail. In addition, we mailed a confirmation letter a month later inquiring if the patient had undergone colonoscopy.

Informed consent was obtained from all patients before colonoscopy was performed. In preparation for colonoscopy, magnesium citrate (Magcorol® P 50 g, Horii Pharmaceutical Ind., Ltd., Osaka, Japan) and/or sodium picosulfate hydrate (Laxoberon® Solution 0.75% 10 mL, Teijin Pharma, Ltd., Tokyo, Japan) was orally administered the night before. We also instructed the patient to take 2 L of polyethylene glycol (Muben® liquid state, Nihon Pharmaceutical Co., Ltd., Tokyo, Japan) on the morning of the colonoscopy. If preparation was deemed inadequate, an enema was administered using 500 mL of saline solution just before colonoscopy. Colonoscopy was performed by doctors certified by the Japan Gastroenterological Endoscopy Society or an equivalent.

Statistical analysis

Patient background characteristics were compared between the two groups using the chi-square test or t-test. The detection rates of advanced neoplasia in the initial and repeated positive FIT groups were likewise compared using the chi-square test. In addition, multiple logistic regression analysis was performed to calculate odds ratios adjusted for age, sex, and family history of CRC. The IBM SPSS statistical analysis software (version 22; SPSS Inc., Chicago, IL, USA) was used for all statistical procedures.

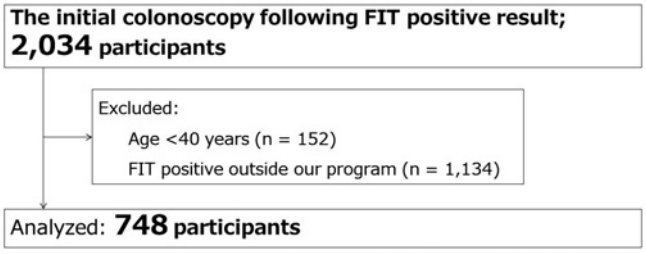

Figure 2. Study flow.
The figure depicts the inclusion and exclusion criteria for the study. All patients who had undergone colonoscopy following a positive fecal immunochemistry test (FIT) result were initially included in the study. Patients were excluded if they were under 40 years or if they had their FIT performed outside of our hospital program.

Results

During the study period, 2,034 subjects underwent an initial colonoscopy because of FIT-positive results. We analyzed a total of 748 cases, excluding subjects younger than 40 years and those who were identified as positive for FIT in programs other than ours (Figure 2). The breakdown of patients was 656 (87.7%) for the initial positive FIT group and 92 (12.3%) for the repeated positive FIT group. There were no significant differences in mean age or family history of CRC between groups, but the repeated positive FIT group had significantly more men (Table 1). The primary outcome of advanced neoplasia detection rate was 7.6% (50/656) in the initial positive FIT group and 18.5% (17/92) in the repeated positive FIT group, and this difference was significant (p = 0.003). The incidence rates of invasive cancer were 1.8% (12/656) in the initial positive FIT group and 8.7% (8/92) in the repeated positive FIT group. In the repeated positive FIT group, the advanced neoplasia detection rates were 16.7% (6/36) for those who had been noted as FIT-positive 1-2 years ago and 19.6% (11/56) for those who had been noted positive >2 years ago. In multivariate analysis, the odds ratios for advanced neoplasia detection compared with those the initial positive FIT group were 2.72 (95% confidence interval [CI], 1.04-7.10) and 3.09 (95% CI, 1.47-6.48) for those who had been noted positive for FIT 1-2 and >2 years ago, respectively (Figure 3).

Discussion

The present study showed that the risk of advanced neoplasia was 2-3 times higher in subjects who did not undergo colonoscopy despite a positive FIT result and who were again found FIT-positive the following year or later. There is evidence that screening by fecal occult blood test reduces CRC mortality[7-12]. Therefore, it is problematic that FIT positivity is ignored. In the present study, 92 (12.3%) patients who underwent initial colonoscopy because of a recent positive FIT result had ignored previous positive FIT results at least once in the past. Although this study confirmed that the risk of CRC increases with repeated positive

Table 1. Patient Characteristics.

	Initial positive FIT group (n = 656)	Repeated positive FIT group (n = 92)	p value
Sex			0.01
Male, n (%)	333 (51)	60 (65)	
Female, n (%)	323 (49)	32 (35)	
Mean age (years)	57.7	57.6	0.87
Family history of CRC, n (%)	58 (9)	10 (11)	0.53

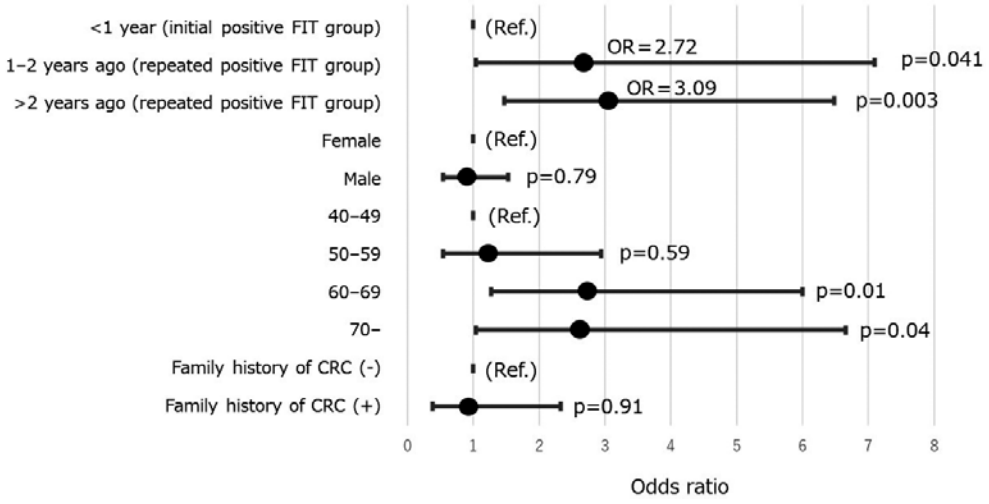

Figure 3. Results of the multivariate analysis.
The odds ratios for advanced neoplasia detection in the repeated positive FIT group compared with those in the initial positive FIT group were significantly higher.

FIT, it does not mean that colonoscopy is not necessary if the patient does not have repeated positive FIT. If there is no previous colonoscopy and the FIT result is positive, colonoscopy should be immediately performed.

Recently, many hospitals have refrained from providing colonoscopy services because of the COVID-19 pandemic. In a report from Italy, it has been noted that 46.7% of gastroenterology divisions have entirely postponed CRC screening[5]. As such, many patients at the time of writing may have not been able to undergo a colonoscopy even if they are noted to be FIT-positive and were desirous of one. Longer time between FIT positivity and follow-up colonoscopy has been reported to increase the risk of CRC[13]. Corley et al. reported that follow-up colonoscopy more than 10 months after FIT positivity was associated with a higher risk of CRC, with the odds ratio for CRC in patients who had undergone colonoscopy at more than 12 months after a positive FIT result being 2.25[14]. A report from Taiwan indicated an increased risk for CRC at more than 6 months after a positive FIT result was noted, with the odds ratio for CRC more than 12 months after a positive FIT result being 2.15[15]. A study from Italy similarly reported an increased risk for CRC at more than 9 months after a positive FIT result, with the odds ratio for CRC at more than 270 days after a positive FIT result being 1.75[16]. The results of these reports are consistent with those of the present study. Although a temporary postponement of screening operations due to the COVID-19 pandemic is unavoidable, from the perspective of CRC screening, a prompt resumption of screening operations is desirable[17].

Recent analyses suggest that interrupted CRC screening is feared to have a significant impact on CRC morbidity and mortality in the long term[18]. Therefore, performing catch-up screening as much as possible is important. Especially, when a patient has not had a colonoscopy although they were noted to be FIT-positive, prompt colonoscopy is desirable. However, if the resources for colonoscopy are extremely limited, the results of our study suggest that providing top priority to patients with repeated positive FIT results is acceptable. However, colonoscopy should eventually be recommended for subjects with an initial positive FIT result even if the second FIT result is negative.

The cutoff value used in our program (7.5 μg hemoglobin/g feces) was lower than the general cutoff value (e.g., 20 μg hemoglobin/g feces). If the patient has not had a colonoscopy in the past, the detection rate of lesions increases as the fecal hemoglobin concentration increases[6]. In a program with a general cutoff value, the detection rate of lesions may further increase if there are consecutive positive results. Whether the present results can be applied to many programs requires further study in the future.

The present study has several limitations. First, this study was a single-center, retrospective study and; thus, was subject to the regular limits of its design. We included only those whose most recent FIT was performed at our institution and excluded those whose positive FIT result was noted at other institutions; however, whether the patients had previously been noted to be FIT-positive at other institutions is unclear. Furthermore, the known risk factors for CRC, such as frequent smoking history and increased body mass index[19-22], were not considered because we did not have these data in our database. Second, all subjects in the present study had a positive FIT result within at least a year. Thus, even if a previous positive FIT result was ignored; those who had a recent subsequent negative FIT result were not included in the study. Third, we used advanced neopla-

sia as a primary outcome in this study. The purpose of FIT is to detect CRC, not to detect advanced neoplasia. Although advanced neoplasia is an excellent surrogate that has been frequently used in previous studies[23], it is a limitation in interpreting the data because not all advanced neoplasia is cancerous. Despite these limitations, the present study has shown some evidence of CRC risk in individuals who repeatedly test positive for FIT. Prompt colonoscopy is recommended for FIT-positive patients who did not have experience of colonoscopy.

Acknowledgements

The authors would like to thank the staff of the screening and endoscopy centers at Kyoto Second Red Cross Hospital for their health screening services. We would also like to thank Editage (www.editage.jp) for English language editing.

Conflicts of Interest

There are no conflicts of interest.

Source of Funding

This study was self-funded.

Author Contributions

TK: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. KA, NI, NS, YO, KS, and MK: acquisition of data. KT: acquisition of data and technical support. KN, KU, and KY: study supervision. All authors approved the final version of this manuscript.

Approval by Institutional Review Board (IRB)

Sp2019-19 (the institutional review board of Kyoto Second Red Cross Hospital)

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