

Colonoscopy Versus Fecal Immunochemical Test for Reducing Colorectal Cancer Risk: A Population-Based Case–Control Study

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INTRODUCTION: Use of colonoscopy or the fecal immunochemical test (FIT) for colorectal cancer (CRC) prevention is supported by previous studies. However, there is little specific evidence regarding comparative effectiveness of colonoscopy or FIT for reducing CRC risk. In this study, we compared the association of CRC risk with colonoscopy and FIT using a nationwide database.

METHODS: This population-based case–control study used colonoscopy and FIT claims data from the Korean National Health Insurance System from 2002 to 2013. Data were analyzed from 61,221 patients with newly diagnosed CRC (case group) and 306,099 individuals without CRC (control group). Multivariable logistic regression models were used to evaluate the association between CRC and colonoscopy or FIT.

RESULTS: Colonoscopy was associated with a reduced subsequent CRC risk (adjusted odds ratio [OR] 0.29). Stronger associations were found between colonoscopy and distal CRC, compared with proximal CRC (0.24 vs 0.47). In an analysis stratified by sex, the association was weaker in female subjects compared with male subjects (0.33 vs 0.27). Any FIT exposure was associated with CRC risk with an OR of 0.74; this association was stronger for distal cancer. As the frequency of cumulative FIT assessments increased (from 1 to ≥ 5), the OR of FIT exposure for CRC gradually decreased from 0.81 to 0.45.

DISCUSSION: The association of colonoscopy or FIT with reduced CRC risk was stronger for distal CRC than for proximal CRC. FIT showed less CRC risk reduction than colonoscopy. However, as the frequency of cumulative FIT assessments increased, the association with CRC prevention became stronger.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and has become a progressively important public health problem that inevitably leads to an increase in morbidity and medical costs (1). Therefore, many countries have a screening program in place to lower the incidence of CRC. Screening programs vary considerably worldwide; fecal immunochemical tests (FITs), sigmoidoscopy, and colonoscopy are the most widely used screening programs (2). However, it remains unclear that which modality offers the most effective screening of CRC-related morbidity (3). The Korean Ministry of Health and Welfare implemented a national cancer screening program for 5 cancers (stomach, colorectal, liver, breast, and cervical cancer), and national CRC screening is performed for

individuals aged 50 years or older, primarily using FIT (4). In addition, for individuals who want to undergo screening colonoscopy without using the national screening program, opportunistic colonoscopy may be performed after paying a fee. Therefore, the national CRC screening program in Korea co-exists alongside opportunistic colonoscopy screening in people with average risk of CRC (5,6).

There is a risk that the patient will complain of pain during the colonoscopy, and in rare cases, complications such as perforation may develop. However, colonoscopy is more sensitive for the diagnosis of lesions than other methods and has the advantage of treating lesions as soon as they are diagnosed. Colonoscopy is considered the gold standard for detection and prevention of CRC, and population-based

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case-control studies have demonstrated that it greatly reduces the risk of CRC (7–9). A recent systematic review and meta-analysis provided convincing evidence that, based on randomized controlled trials and observational studies, screening colonoscopies reduce mortality from CRC (10). The preventive effect of colonoscopy on CRC is clear, but the participation rate in population-based screening is relatively low because colonoscopy is an invasive procedure that involves substantial cost (2). Therefore, it is often difficult to assess the effect of colonoscopy on CRC in population-based studies involving a large number of subjects.

FIT is a direct measure of human hemoglobin in stool, using antibodies against the globin moiety of hemoglobin (11). FIT directly detects hemoglobin and is not hampered by false positives or false negatives caused by food or medicine (12). However, in some cases, detection by FIT is not possible during early CRC, and colorectal polyps cannot be removed, unlike with colonoscopy. In addition, it has a risk of decreased accuracy at high ambient temperatures (13). Despite these shortcomings, FIT has been recommended for CRC screening in many countries because it is more feasible and less costly than other screening strategies (14–16). FIT-based screening significantly reduces the burden of colorectal disease and CRC mortality (15,17). Nevertheless, FIT has comparatively low sensitivity for CRC detection, and compliance with repeated tests is problematic (18,19).

Although the effects of colonoscopy or FIT screening have been proven in several studies, only 2 have compared colonoscopy screening with FIT screening in a large number of people (7,20). In addition, these comparative studies were performed only in Western countries. Therefore, we aimed to compare the association of CRC risk with use of colonoscopy or FIT by analysis of data from a nationwide population-based database in Korea.

METHODS

Data source

Data used in our study were acquired from the National Health Information Database (NHID) of the National Health Insurance System (NHIS). The Korean NHIS is the sole source of health insurance in Korea. The NHIS includes nearly all health information (e.g., age, sex, diagnostic code, cancer registry, procedures, prescription drugs, medical care institution data, health screening, and sociodemographic variables) for 97% of the Korean population. Furthermore, the NHIS includes a cancer registration system to facilitate benefit coverage. All patients with cancer are asked to ensure their diagnosis is confirmed by qualified doctors through systematized diagnostic criteria distributed by NHIS. In addition, these procedures are managed and supervised by institutions and NHIS. Therefore, codes registered as cancer in Korea are very reliable. All personal information is deidentified before data processing to comply with the regulations of the Health Insurance Portability and Accountability Act. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (approval no. CR316309). For the analyses, only deidentified and anonymized data were used; therefore, informed consent was not required.

Study population

The data used in our study were from the NHID from 2002 to 2013. The NHID uses an outstanding platform, and details of the

database profile have been reported in previous studies (21,22). By reviewing the codes in the NHID, we identified patients with CRC who had been diagnosed from January 2009 to December 2013; we then identified those who had undergone definitive CRC treatment within 6 months of CRC diagnosis. Patients with a history of CRC during a washout period from 2007 to 2009 were excluded. For the control group, age-, sex-, socioeconomic status-, and smoking history-matched individuals without any cancer were randomly extracted; 5 control participants were matched to each patient with CRC. Randomization for control selection was conducted using a program within SAS software, version 9.4 (SAS Institute, Cary, NC). Finally, 61,221 patients were included in the CRC group, and 306,009 individuals without cancer were included in the control group.

Study variables

Information available from the NHID included data regarding each patient's cancer diagnosis and the date of diagnosis. The definition of CRC included International Classification of Disease-10 codes C18 to C20 (malignant neoplasm of colon, rectosigmoid junction, or rectum) and registration as V code by the NHIS. V code is a particular code system in South Korea; cancer patients are registered for the V code through NHIS. For V codes, 95% of the medical cost is covered by the government for 5 years. Because the government alone performs both registration and monitoring of these codes, the accuracy of CRC diagnosis using both the International Classification of Disease-10 code and V code is very high (23).

Age at baseline was categorized into 3 groups: 49 years or younger, 50–74 years, and 75 years or older. Smoking history was divided into nonsmoker and former smoker. Socioeconomic status was recoded into 5 categories (quintile 1, low 20%; quintile 2, 20%–40%; quintile 3, 40%–60%; quintile 4, 60%–80%; and quintile 5, 80%–100% [high 20%]), according to health insurance premiums. Other clinical information (whether FIT was administered, number of FIT trials, and endoscopic treatment method) was obtained from the claims data in health examination records provided by the NHID. Cancer-associated treatment data, CRC location, and endoscopist specialty were determined from the NHID.

Assessment of FIT and colonoscopy

In South Korea, national CRC screening is indicated for people aged 50 years or older, and FIT is the primary screening method. This method was offered biennially until 2011 and, then, annually beginning in 2012. FIT exposure and frequency were determined using a national CRC screening data set from January 2004 until 12 months before the date of CRC diagnosis. We identified individuals who had at least 1 colonoscopy in the NHIS claims database from January 2002 until 12 months before the date of CRC diagnosis. If an individual was never diagnosed with CRC during the follow-up period, the individual's study end date was the last screening date or the institution visit date. We determined whether patients had undergone diagnostic colonoscopy (E7660), single polypectomy (Q7701), ≥ 2 polypectomies (Q7703), or endoscopic mucosal resection (Q7703) using NHIS codes.

Statistical analysis

A descriptive analysis that included all study participants was conducted. The categorical baseline characteristics of the

Table 1. Characteristics of the study population

	Cases (n = 61,221)	Controls (n = 306,099)
Age		
49 yr or younger	6,228 (10.2%)	31,140 (10.2%)
50–64 yr	24,246 (39.6%)	121,230 (39.6%)
65–74 yr	20,334 (33.2%)	101,670 (33.2%)
75 yr or older	10,413 (17.0%)	52,059 (17.0%)
Female sex	23,356 (38.2%)	116,777 (38.2%)
Socioeconomic status ^a		
Quintile 1	9,232 (15.1%)	46,157 (15.1%)
Quintile 2	8,503 (13.9%)	42,515 (13.9%)
Quintile 3	9,858 (16.1%)	49,287 (16.1%)
Quintile 4	13,735 (22.4%)	68,675 (22.4%)
Quintile 5	19,893 (32.5%)	99,465 (32.5%)
Smoking history		
Ever	30,051 (49.1%)	150,255 (49.1%)
Never	29,452 (48.1%)	147,260 (48.1%)
Unknown	1718 (2.8%)	8,584 (2.8%)
Cancer location		
Proximal	12,488 (20.4%)	
Distal	41,313 (67.5%)	
Unknown	7,420 (12.1%)	
Colonoscopies performed	5,686 (9.3%)	77,476 (25.3%)
Type of colonoscopy		
Diagnostic	3,840 (6.3%)	57,245 (18.7%)
One polypectomy	804 (1.3%)	10,217 (3.3%)
≥2 polypectomies or EMR	1,042 (1.7%)	10,014 (3.3%)
Any screening FIT	15,402 (25.2%)	98,941 (32.3%)
Values are expressed as n (%).		
EMR, endoscopic mucosal resection; FIT, fecal immunochemical test.		
^a Socioeconomic status was calculated based on the health insurance premium (from quintile 1 [low] to quintile 5 [high]).		

participants are expressed as numbers (%). Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the incidence of CRC were analyzed using multivariable logistic regression models (adjusted for age and sex) using the undergone any colonoscopy groups (subgroup by age, sex, endoscopist specialty, or colonoscopy type) and the no colonoscopy group as a reference. In addition, the association between FIT frequency and CRC was analyzed with no FIT as a reference. All statistical tests were 2 sided, and the significance level was set at $P < 0.05$. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 summarizes the baseline characteristics of the cancer population (case cohort; n = 61,221) and control cohort (n = 306,099). Because the cohorts were age- and sex-matched, the proportions of age and sex (female subjects: 38.2%) were identical between the 2 groups. CRC was common in the distal

location (67.5%) in the cancer population group. Of the 61,221 patients with cancer, 5,686 (9.3%) underwent colonoscopy. Among the 306,099 controls, 77,476 (25.3%) underwent colonoscopy. In addition, 25.2% of patients with cancer and 32.3% of controls underwent FIT more than 12 months before the diagnosis or reference date.

Table 2 summarizes the associations between a history of any colonoscopy and CRC risk by age at diagnosis, sex, endoscopist specialty, colonoscopy type, and location. Compared with no colonoscopy, the OR of any colonoscopy for all CRC was 0.29 (95% confidence interval [CI]: 0.28–0.30). This association with CRC prevention was stronger for distal CRC (OR: 0.24, 95% CI: 0.23–0.24) than for proximal CRC (OR: 0.47, 95% CI: 0.44–0.49). In a stratified analysis by age at diagnosis, the association was weaker in participants aged 75 years or older (OR: 0.43, 95% CI: 0.40–0.46) and in female subjects (OR: 0.33, 95% CI: 0.31–0.34). The OR of colonoscopy performed by a gastroenterologist (OR: 0.26, 95% CI: 0.24–0.28) was lower than that of colonoscopy performed by another provider (surgeon [OR: 0.40, 95% CI: 0.38–0.42]). The OR of previous diagnostic colonoscopy (OR: 0.27, 95% CI: 0.26–0.28) was lower than that of previous therapeutic colonoscopy (1 polypectomy [OR: 0.31, 95% CI: 0.29–0.34] and ≥ 2 polypectomies or EMR [OR: 0.41, 95% CI: 0.38–0.44]). These results suggest that cancer prevention by colonoscopy may be affected by the expertise of the physician or the examinee’s risk of CRC (adenoma or otherwise).

Table 3 tabulates that participants with exposure to FIT had a lower OR (0.74 [95% CI: 0.73–0.76]) for CRC than those without FIT. In a stratified analysis, the association between FIT and CRC risk reduction was weaker in participants aged 75 years older than in younger individuals (49 years or younger [OR: 0.62, 95% CI: 0.41–0.92], 50–74 years [OR: 0.70, 95% CI: 0.69–0.72], and 75 years or older [OR: 0.94, 95% CI: 0.90–0.99]). As the frequency of cumulative FIT assessments increased from 1 to ≥ 5 during the previous 10 years, the OR of FIT exposure for CRC decreased from 0.81 (95% CI: 0.80–0.83) to 0.45 (95% CI: 0.39–0.51). This suggests the efficacy of continuous and repeated, rather than 1-time, FITs and emphasizes the need for continuous and systematic population-level cancer screening. Moreover, the association was stronger for distal cancer (OR: 0.41, 95% CI: 0.35–0.48) than for proximal cancer (OR: 0.58, 95% CI: 0.46–0.74).

DISCUSSION

To our knowledge, this is the first study to evaluate the risk of CRC in an Asian population by comparing colonoscopy with FIT, using population-based claims data. The first strength of our study is that it included a large number of participants, by using data from the NHID. Thus far, only 2 large-scale studies have been published regarding simultaneous comparisons of the preventive effects of colonoscopy and FIT on CRC (7,20); none have been conducted in Asia. In this study, colonoscopy and cumulative FIT assessments were associated with 71% and 55% reduced risk of CRC, respectively. In addition, as the frequency of cumulative FIT assessments increased, its association with CRC prevention became stronger. In particular, our results demonstrated that the risk of CRC was effectively reduced because FIT tests were repeated over 10 years at the population level.

Table 2. Association between previous colonoscopy and risk of CRC in various subgroups

Group	All CRC OR (95% CI)	Proximal CRC OR (95% CI)	Distal CRC OR (95% CI)	Unknown site of cancer OR (95% CI)
Total	0.29 (0.28–0.30)	0.47 (0.44–0.49)	0.24 (0.23–0.24)	0.33 (0.30–0.36)
Age				
49 yr or younger	0.35 (0.32–0.39)	0.56 (0.46–0.68)	0.29 (0.25–0.33)	0.44 (0.33–0.61)
50–74 yr	0.27 (0.26–0.28)	0.42 (0.40–0.45)	0.22 (0.21–0.23)	0.31 (0.28–0.34)
75 yr or older	0.43 (0.40–0.46)	0.66 (0.58–0.74)	0.35 (0.31–0.38)	0.41 (0.32–0.51)
Sex				
Female subjects	0.33 (0.31–0.34)	0.49 (0.46–0.54)	0.26 (0.24–0.28)	0.35 (0.30–0.41)
Male subjects	0.27 (0.26–0.28)	0.45 (0.42–0.48)	0.23 (0.22–0.24)	0.32 (0.28–0.35)
Endoscopist specialty				
GI	0.26 (0.24–0.28)	0.39 (0.34–0.44)	0.22 (0.20–0.24)	0.25 (0.20–0.32)
Non-GI IM	0.27 (0.26–0.28)	0.43 (0.41–0.47)	0.21 (0.20–0.22)	0.31 (0.28–0.35)
Surgery	0.40 (0.38–0.42)	0.62 (0.56–0.69)	0.33 (0.31–0.35)	0.45 (0.38–0.54)
Others	0.28 (0.25–0.32)	0.45 (0.35–0.57)	0.23 (0.19–0.28)	0.31 (0.20–0.48)
Colonoscopy type				
Diagnostic colonoscopy	0.27 (0.26–0.28)	0.42 (0.39–0.44)	0.22 (0.21–0.23)	0.31 (0.28–0.35)
One polypectomy	0.31 (0.29–0.34)	0.52 (0.46–0.59)	0.25 (0.23–0.28)	0.33 (0.26–0.42)
≥2 polypectomies or EMR	0.41 (0.38–0.44)	0.73 (0.65–0.81)	0.32 (0.29–0.35)	0.43 (0.35–0.53)

CRC, colorectal cancer; EMR, endoscopic mucosal resection; GI, gastrointestinal; IM, internal medicine; OR, odds ratio.

Compared with cumulative FIT assessments, colonoscopy was more strongly associated with a reduced risk of CRC. Notably, our results differ from those of previous studies regarding risk reduction of CRC after colonoscopy or FIT (7,20). In a previous well-designed randomized controlled trial (7), the diagnostic yield for CRC screening was not significantly different, when using colonoscopy or FIT. Another study showed that the CRC detection rates were similar for colonoscopy and FIT in an as-screened analysis (20); in that study, cumulative FIT assessments detected significantly more CRC than colonoscopy. Our data differ from those of other studies for several reasons. First, the previous studies were prospective studies, whereas this study was a nationwide population-based case-control analysis using claims data. These fundamental differences in study design may have affected the relevance of multiple variables, leading to different study results. As demonstrated in this study, research using claims data is advantageous in that it is easy to derive research results for a large number of individuals at the national level, with relatively little effort and time. In particular, another advantage of this study type is that it provides real-world evidence involving a greater number of people, compared with randomized controlled trials. Therefore, this is an attractive method because it offsets the large investment of capital and human resources involved in prospective randomized controlled trials. Second, in the previous studies, the rate of participation was significantly higher in the FIT group than that in the colonoscopy group (7,20). The participation rate of CRC screening may differ depending on the socioeconomic situation, medical system, and culture (24,25). Therefore, it is difficult to interpret heterogeneous results that depend on the participation rate in each study. Notably, low participation may affect the diagnostic yield in the previous

studies. Finally, compared with previous studies, our study contained much larger groups of patients and controls (30,007 and 57,404 vs 367,320) (7,20). Differences in the numbers of participants may also have influenced the conclusions of studies regarding CRC, which has a low incidence. Therefore, this study may be more reliable because the 95% CI ranges were small, compared with those of other studies.

This study demonstrated that preceding colonoscopy was associated with a 71% lower risk for CRC. Our findings are consistent with those of previous studies, which showed reduction of CRC risk after colonoscopy (8,10,26–30). Furthermore, our study supports the hypothesis that colonoscopy considerably reduces CRC risk in the real-world setting. A recent meta-analysis indicated that the effects of colonoscopy on CRC tended to improve over time (from 2005 to 2013) (10); our study also showed superior risk reduction, compared with studies published before 2010 (27,28). This is because factors such as the development of colonoscopy technology, establishment of training, and increased consistency of quality management have led to improved colonoscopies. Colonoscopy can prevent CRC but is uncomfortable and requires additional equipment. Furthermore, it is associated with adverse events and higher costs. As such, not all screening methods for CRC can be replaced by colonoscopy. Current ongoing large-scale prospective clinical trials will clearly aid in determining the effectiveness of population-based colonoscopy vs FIT screening (31,32). Furthermore, a population-based cohort study with a long-term follow-up is needed to determine when to start and stop screening, to maximize the likelihood of CRC prevention.

In this study, the risk reduction of CRC after colonoscopy in the distal colon was substantially greater than the risk reduction

Table 3. Association between previous screening FIT and risk of CRC in various subgroups

Group	All CRC OR (95% CI)	Proximal CRC OR (95% CI)	Distal CRC OR (95% CI)	Unknown site of cancer OR (95% CI)
Total	0.74 (0.73–0.76)	0.80 (0.77–0.83)	0.72 (0.70–0.73)	0.80 (0.75–0.85)
Age				
49 yr or younger	0.62 (0.41–0.92)	0.46 (0.16–1.28)	0.67 (0.42–1.07)	0.57 (0.17–1.90)
50–74 yr	0.70 (0.69–0.72)	0.73 (0.69–0.76)	0.68 (0.67–0.70)	0.76 (0.71–0.81)
75 yr or older	0.94 (0.90–0.99)	1.08 (0.99–1.12)	0.88 (0.83–0.93)	1.00 (0.87–1.15)
Sex				
Female subjects	0.76 (0.74–0.79)	0.78 (0.74–0.83)	0.74 (0.71–0.77)	0.83 (0.75–0.92)
Male subjects	0.73 (0.71–0.75)	0.81 (0.77–0.86)	0.70 (0.68–0.72)	0.78 (0.72–0.85)
Frequency of FIT				
FIT × 1	0.81 (0.80–0.83)	0.86 (0.83–0.91)	0.79 (0.77–0.81)	0.86 (0.80–0.92)
FIT × 2	0.71 (0.68–0.73)	0.75 (0.70–0.79)	0.68 (0.66–0.71)	0.77 (0.70–0.85)
FIT × 3	0.60 (0.57–0.63)	0.68 (0.63–0.75)	0.56 (0.53–0.60)	0.67 (0.58–0.78)
FIT v 4	0.50 (0.46–0.53)	0.63 (0.55–0.73)	0.44 (0.40–0.49)	0.59 (0.45–0.77)
FIT × ≥5	0.45 (0.39–0.51)	0.58 (0.46–0.74)	0.41 (0.35–0.48)	0.34 (0.20–0.58)

CRC, colorectal cancer; FIT, fecal immunochemical test; OR, odds ratio.

after colonoscopy in the proximal colon. These findings are consistent with the results of previous studies, which showed a higher percentage of missed adenomas in the proximal colon. These results are related to the flat and serrated morphology of adenomas in the proximal colon, which are often hidden behind haustral folds and exhibit different molecular biological properties (33–35). Because colonoscopy screening for proximal CRC prevention has been ineffective in a few studies (36,37), it is important to clarify the benefits and limitations of colonoscopy screening regarding proximal CRC.

There was a difference in the risk of CRC according to colonoscopy by sex. Overall, female subjects tended to have higher OR values than male subjects. This is a clinically relevant finding, and the underlying reasons are as follows: First, colonoscopy in female subjects is generally more difficult than in male subjects for various reasons, including a longer colon and previous gynecological surgery (38,39). Such technical difficulty can adversely affect the adenoma detection rate, which can reduce the CRC-prevention effect of colonoscopy. Second, adenomas were more likely to present as nonpolypoid lesions in female subjects compared with male subjects (40). Because nonpolypoid polyps are easy to miss during colonoscopy, the effect of colonoscopy may be reduced in female subjects. Third, the rate of new or missed CRC after negative colonoscopy is reportedly higher in female subjects than that in male subjects, especially in the proximal colon (41,42). In addition, proximal serrated polyp is a main cause of interval CRC and tends to be more prevalent in female subjects (43,44). In this study, the OR of proximal CRC after colonoscopy in female subjects was 0.49.

The low risk reduction effect of colonoscopy on proximal CRC can be attributed to the tumor, aforementioned patient factors and operator-dependent factors (45). This is supported by our finding that a stronger association of colonoscopy with CRC risk reduction was observed for procedures performed by gastroenterologists rather than surgeons. In addition, adjusted ORs for

proximal CRC showed a greater difference depending on the operator. Considering that postcolonoscopy CRC occurs more commonly in the proximal colon, this finding supports the need for endoscopy quality control through appropriate training and active feedback for endoscopists (46).

Another significant finding we noted was that the association between FIT and CRC risk was weaker in older participants. In particular, the prevention effect of CRC risk by FIT was small among participants aged 75 years or older. First, older age itself is an important risk factor for CRC. It is possible that patients with undiagnosed CRC were included in the group of participants aged 75 years or older, and these patients did not receive a coded diagnosis during the study period. Therefore, the preventive effects of colonoscopy and FIT for CRC may seem to be inferior for these participants, compared with other age groups. Second, previous studies documented an elevated incidence of proximal CRC in elderly patients, which is less likely to be detected by stool tests or colonoscopy (47,48). Therefore, the efficacy of FIT may be reduced in elderly individuals because the sensitivity for detecting CRC is lower at the proximal colon than that at the distal colon in the general population (49). Third, age may have affected FIT accuracy. Although the findings were not statistically significant, a recent meta-analysis demonstrated a trend toward reduced sensitivity with age (sensitivity of CRC detection was 85% for individuals aged 50–59 years and 73% for individuals aged 60–69 years) (50). Another study showed that older age was associated with a higher incidence of interval CRC after a negative FIT result (51).

Regardless of the cancer site, cumulative FIT assessments significantly reduce the risk of CRC; therefore, as the cumulative number of FIT assessments increases, the cumulative detection rate of CRC also increases. Recent studies also showed similar results (15,52). Zorzi et al. (15) demonstrated that repeated FIT significantly reduced the burden of CRC and advanced adenoma;

after 5 rounds of FIT, the cumulative detection rate was comparable with that of colonoscopy. Another study also showed that the cumulative number of FIT assessments was associated with a higher detection rate of advanced neoplasia (1.6% for 1 test and 3.5% for 4 tests) (52). According to a systematic meta-analysis study, the relative risk of developing interval CRC per FIT screening round decreased significantly as the number of FIT rounds increased (53). Our results clearly indicate that the effectiveness of FIT depends on adherence to the test. Therefore, a national screening strategy is needed to increase the effectiveness of screening; this strategy should emphasize rigorous implementation of FIT at the current 1-year or 2-year intervals.

The NHID, which contains a large amount of data, allowed us to conduct research and estimate the national volume of colonoscopy and FIT. Therefore, the results are generalizable because of the population-based design of our study. However, our study had the following limitations: First, the NHID does not include specific colonoscopy details, such as colonoscopy quality indicators (e.g., withdrawal time, cecal intubation, adenoma detection rate, and adverse events). Thus, there was a lack of standardization regarding colonoscopy. Second, claims data from the NHID do not contain the comprehensive clinical findings for each patient. Because the variables used in our study were limited, we could not consider other potential confounding factors (e.g., family history or obesity) associated with risk of CRC. Third, we did not analyze the data in detail according to the cancer location. Finally, in South Korea, even for younger people (younger than 50 years) who do not have suspicious findings or a family history of disease, colonoscopy is frequently performed for screening purposes. The main reason for this is that the cost of colonoscopy is relatively low (about 60\$) in Korea and hospital access is high. The situation regarding CRC screening in South Korea is different from that in other countries, which limits the applicability of the results of this study to other countries.

In conclusion, we observed a significant reduction in the risk of CRC that was associated with colonoscopy or cumulative FIT assessments. Colonoscopy was the most effective for preventing CRC, especially for distal CRC. FIT showed less CRC risk reduction than colonoscopy. However, multiple rounds of cumulative FIT assessments reduced the risk of CRC to a level similar to that of colonoscopy by nonexperts. These results highlight the importance of active and continuous participation and colonoscopy quality control in CRC screening at the population level.

CONFLICTS OF INTEREST

Guarantor of the article: Hyun-Soo Kim, MD, PhD.

Specific author contributions: S.Y.K. wrote the manuscript. H-S.K. contributed to the study concept and design. H.J.P. and H.M.K. collected the data and acquired material support for the study. Y.T.K., J.K.L., and D.R.K. conducted statistical analysis for our study.

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Potential competing interests: None reported.

Study Highlights

WHAT IS KNOWN

- ✓ Colonoscopy and fecal immunochemical test (FIT) are important methods for prevention of colorectal cancer (CRC).
- ✓ There is little specific evidence regarding the comparative effectiveness of colonoscopy or FIT for reducing CRC risk.

WHAT IS NEW HERE

- ✓ In South Korea, colonoscopy and cumulative FITs reduced the risk of CRC by 71% and 55%, respectively.
- ✓ The risk of CRC decreased with increasing number of FITs.

TRANSLATIONAL IMPACT

- ✓ This study indicated that colonoscopy and FIT screening lower the risk of CRC and are, therefore, effective screening tools for use in South Korea.
- ✓ Our findings supported the importance of systematic quality management of colonoscopy along with continued participation in fecal occult blood tests for the CRC prevention at the population level.

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