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Time to Colonoscopy and Risk of Colorectal Cancer in Patients With Positive Results From Fecal Immunochemical Tests

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e82. Learning Objective–Upon completion of this activity, successful learners will be able to utilize current evidence to manage patients with positive fecal immunochemical test results for the purpose of colorectal cancer prevention.

BACKGROUND & AIMS: **In patients with positive results from a fecal immunochemical test (FIT), failure to receive a timely follow-up colonoscopy may be associated with higher risks of colorectal cancer (CRC) and advanced-stage CRC. We evaluated the prevalence of any CRC and advanced-stage CRC associated with delays in follow-up colonoscopies for patients with positive results from a FIT.**

METHODS: **We collected data from 39,346 patients (age, 50–69 years) who participated in the Taiwanese Nationwide Screening Program from 2004 through 2012 and had completed a colonoscopy more than 1 month after a positive result from a FIT. Risks of any CRC and advanced-stage CRC (stage III-IV) were evaluated using logistic regression models and results expressed as adjusted odds ratios (aORs) and corresponding 95% CIs.**

RESULTS: **In our cohort, 2003 patients received a diagnosis of any CRC and 445 patients were found to have advanced-stage disease. Compared with colonoscopy within 1–3 months (cases per 1000 patients: 50 for any CRC and 11 for advanced-stage disease), risks were significantly higher when colonoscopy was delayed by more than 6 months for any CRC (aOR, 1.31; 95% CI, 1.04–1.64; 68 cases per 1000 patients) and advanced-stage disease (aOR, 2.09; 95% CI, 1.43–3.06; 24 cases per 1000 patients). The risks continuously increased when colonoscopy was delayed by more than 12 months for any CRC (aOR, 2.17; 95% CI, 1.44–3.26; 98 cases per 1000 patients) and advanced-stage disease (aOR, 2.84; 95% CI, 1.43–5.64; 31 cases per 1000 patients). There were no significant differences for colonoscopy follow up at 3–6 months for risk of any CRC (aOR, 0.98; 95% CI, 0.86–1.12; 49 cases per 1000 patients) or advanced-stage disease (aOR, 0.95; 95% CI, 0.72–1.25; 10 cases per 1000 patients).**

CONCLUSIONS: **In an analysis of data from the Taiwanese Nationwide Screening Program, we found that among patients with positive results from a FIT, risks of CRC and advanced-stage disease increase with time. These findings indicate the importance of timely colonoscopy after a positive result from a FIT.**

Keywords: Prevention; Population; Colon Cancer; Endoscopy.

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; Hb, hemoglobin; OR, odds ratio.

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Most current article

See related editorial on page 1245.

Colorectal cancers (CRC) rank second and third as the leading causes of cancer-related death in men and women, respectively, in the world.[1] To reduce the burden of CRC, colonoscopy is considered an effective method, which can reduce the risk of new-onset CRCs by the removal of adenomatous polyps and can improve CRC survival by the detection of presymptomatic malignancies.[2] In addition to primary screening colonoscopy, a two-stage approach using the fecal immunochemical test (FIT) is increasingly popular because of its ability to identify patients with the highest risk of CRC; in this manner, limited colonoscopist resources can be efficiently allocated.[3,4] Nonetheless, this two-stage approach involves a time lag between a patient's positive FIT result and colonoscopic follow-up. In theory, the longer the time lag, the greater the number of advanced lesions because neoplastic progression is continuous over time, and the anticipated benefit of screening may be reduced.[5] However, knowledge remains limited regarding the extent of neoplastic progression within this relatively short period of time and clinicians are short of evidence about the tolerable waiting time between positive FIT results and colonoscopic follow-up.[6]

To control the rapidly increasing burden of CRC in Taiwan, a nationwide screening program using biennial FIT was launched in 2004; this screening program defined time to diagnostic examinations as a quality assurance indicator in follow-up.[7] Using this nationwide cohort, our primary aim was to associate the risks of any CRC and advanced-stage CRC with the time to colonoscopic follow-up, especially for those patients who did not undergo colonoscopy within the recommended time. Our secondary aim was to identify risk factors that were collected at baseline but associated with the subsequent development of CRC.

What You Need to Know

Background

Colorectal cancer (CRC) screening using the fecal immunochemical test (FIT) is increasingly popular. However, in patients who have positive FIT results, our knowledge remains limited about the association between colonoscopy delays and the risk of any CRC and advanced-stage disease.

Findings

In this cohort study of 39,346 patients with positive FIT results, colonoscopy delays of more than 6 months were significantly associated with higher risks of any CRC and advanced-stage disease.

Implications for patient care

After positive FIT results, timely colonoscopy is required to decrease the number of new-onset CRCs and prevent the stage shifting of already-present CRCs.

Methods

Target Population

Details of Taiwan Nationwide CRC Screening Program have been reported previously, including the accuracy of FIT,[8] colonoscopic referral,[9] colonoscopic quality,[10] and effectiveness on reducing CRC mortality.[7] In brief, beginning in 2004, residents aged 50–69 years were invited to receive free-of-charge biennial FIT. The screening test was delivered via either a community-based outreach or a hospital-based inreach approach.[11] The cutoff concentration for a positive test was 20 μg hemoglobin (Hb)/g feces (Eiken Chemical Co, Tokyo, Japan; or Kyowa Medex Co Ltd, Tokyo, Japan).[8] Those who had positive FIT results were notified by mail and/or telephone by the public health centers or hospitals where the screening test was delivered, and colonoscopic follow-up, which was covered by the reimbursement system of Taiwan's Universal Healthcare Insurance, was arranged.[12] Hospitals performing colonoscopy could be categorized into 3 accreditation levels, including the local hospital and clinic, regional hospital, and medical center, based on the size, capability, and quality of performance.[13] Repeat screen attendees were defined as those who had received prior FIT-based screening.

All screening results, including the coverage rate, positivity rate, number of colonoscopies performed, and colonoscopic results, were transmitted via a virtual private network to a central database that generated standardized indicators to monitor the screening quality. Colonoscopic follow-up was recommended within 3 months after a positive FIT result; this recommendation was made according to the consensus process in 2004, considering the efficiency of the referral system and the manpower of colonoscopists available.

We excluded patients who had a negative FIT, those who did not receive diagnostic examination, or those who underwent suboptimal diagnostic examination (eg, sigmoidoscopy and double-contrast barium enema). We also excluded those who underwent colonoscopy within 2 years before FIT or a colonoscopy within 1 month after positive FIT results; these instances more likely were symptom driven.

Outcomes Measurement

Colonoscopic findings reported were attributed to the first colonoscopy that followed the abnormal FIT result. We recorded the diagnostic details of colonoscopies, including the thoroughness of examination; the anatomic site reached by colonoscopy; the number, size, location, and histopathology of colonic neoplasms; and whether or

not the colonic neoplasms were removed. The histopathology was classified according to the criteria of the World Health Organization.[14] An advanced adenoma was defined as an adenoma ≥10 mm in diameter or having a villous component or high-grade dysplasia.

Information about CRC staging was obtained from Taiwan National Cancer Registry, which has a high degree of coverage (99% of the population; each hospital is required to report all cases of CRC) and accuracy (percentage of death-certificate-only cases of <1% for CRC).[15] The CRC staging was defined according to the American Joint Committee on Cancer 7th staging system; advanced-stage CRC was defined as stage III–IV cancer.[16]

Study Design

We stratified patients by their time to colonoscopy into 5 groups: (1) 1–3 months, (2) 3–6 months, (3) 6–9 months, (4) 9–12 months, and (5) >12 months (1 month was equal to 30.5 days). This stratification was based on equal lengths of time and a sufficient number of patients over different time periods to provide adequate statistical power. We selected the baseline comparator of 1–3 months and hypothesized that the risk of CRC may increase with time. We excluded patients who had colonoscopy within 1 month between FIT and colonoscopy because the symptom-driven referrals had inflated their risk of CRC (Supplementary Table 1).

Statistical Analysis

We first compared patients' baseline characteristics among different groups, including the age, sex, first or repeat screen, baseline fecal Hb concentration, patients' geographic regions, and hospital level to perform the colonoscopy; for these comparisons we used analysis of variation, the Kruskal-Wallis test, or the chi-square test, as appropriate. Second, we calculated the risk of colorectal neoplasms for each group, expressed the results as percentages (% or per 1000 patients), and performed the trend test. The per-person analysis was used, and patients were categorized according to the most advanced lesions found. Third, we applied univariable and multivariable logistic regression models to evaluate the relative risk of any CRC or advanced-stage CRC; we expressed the results as crude and adjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). In addition to the main predictor of time to colonoscopy (categorical and continuous), we also sought to identify the baseline character that might be associated with the subsequent risk of CRC. In a subsidiary analysis, we used the Poisson regression analyses to evaluate the CRC risk of patients who did not undergo colonoscopic follow-up; results were expressed as the relative risks.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All P values were two-sided, and P values of $< .05$ were considered statistically significant.

Results

Study Population

Between 2004 and 2012, a total of 2,914,855 subjects participated in the nationwide screening program. Among 175,164 (6.0%) who had positive FIT results, we excluded 65,782 patients who did not receive confirmatory examinations, 11,123 patients who underwent barium enema study or sigmoidoscopy, 3375 patients who received a colonoscopy within 2 years before the FIT, and 55,538 patients who had colonoscopy within 1 month after the FIT. We included 39,346 patients who had positive FIT results and completed colonoscopic follow-up in our study population.

As shown in Figure 1, of the patients who completed a colonoscopy, most completed the procedure within 3 months. Patients were stratified by their time to colonoscopy into the following 5 groups: (1) 1–3 months (n = 30,695), (2) 3–6 months (n = 6555), (3) 6–9 months (n = 1357), (4) 9–12 months (n = 444), and (5) >12 months (n = 295). After colonoscopy, 2003 and 445 patients were diagnosed with any CRC and advanced-stage CRC, respectively.

Baseline Characteristics

As shown in Table 1, we found small differences among the 5 groups in terms of their baseline characteristics; the differences reach statistical significance mainly because of a large sample size. The percentage of patients with repeat screens decreased from the 1–3 months group (15.8%) to the >12 months group (9.8%).

Prevalence of Colorectal Neoplasms

As shown in Table 2, the overall prevalence rates for any adenoma, advanced adenoma, any CRC, and advanced-stage CRC were 47.6%, 13.9%, 5.1%, and 1.1%, respectively. Stratified by the time to colonoscopy, the prevalence rates of nonadvanced adenoma ($P = .12$) and advanced adenoma ($P = .55$) were similar between different groups, but the prevalence rates of early stage CRC ($P < .01$) and advanced-stage CRC ($P < .01$) were significantly different. For the risk of any CRC and advanced-stage disease, there are increasing trends with time (Figure 2; $P < .01$ for the trend test). For any CRC, the risk increased from the baseline group (1528 cases of 30,695 patients = 50 per 1000 patients), 3–6 months (321 cases of 6555 patients = 49 per 1000 patients), 6–9 months (92 cases of 1357 patients = 68 per 1000 patients), and the 9–12 months groups (33 cases of 444 patients = 74 per 1000 patients) to the >12 months group (29 cases of 295 patients = 98 per 1000 patients);

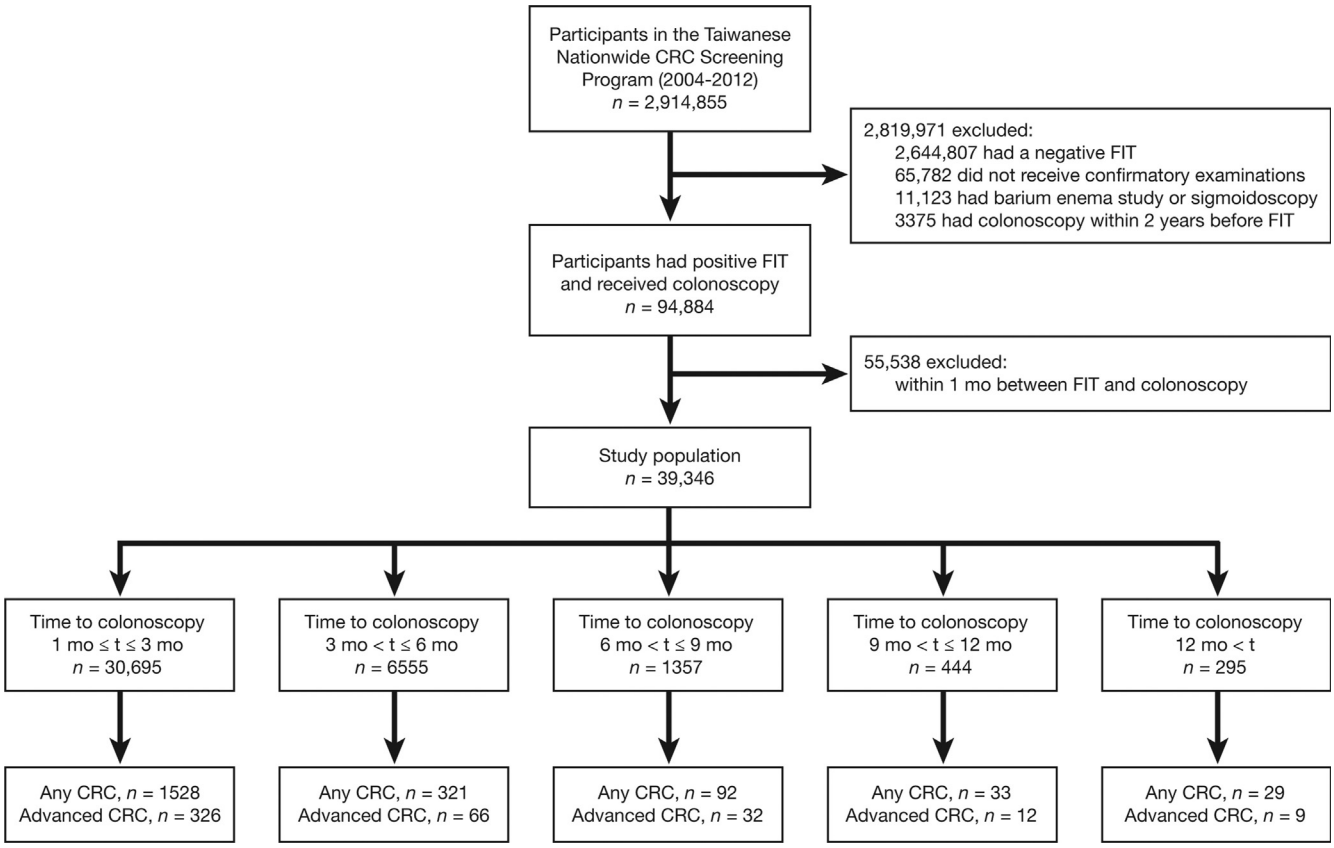

Figure 1. Flow diagram of the study population in the nationwide screening program in Taiwan.

the risk substantially increased when colonoscopy was delayed by more than 6 months. For the advanced-stage CRC, the risk was similar between the baseline group (326 cases of 30,695 patients = 11 per 1000 patients) and 3–6 months group (66 cases of 6555 patients = 10 per 1000 patients), whereas substantial increases were seen from the 6–9 months (32 cases of 1357 patients = 24 per 1000 patients), 9–12 months (12 cases of 444 patients = 27 per 1000 patients), to the >12 months groups (9 cases of 295 patients = 31 per 1000 patients). The consequence of delays for each cancer stage is shown in Supplementary Table 2; similar trends are seen.

Regression Analyses

The results of univariable and multivariable regression analyses are shown in Table 3. Using the 1–3 months group as the baseline comparator, the ORs of any CRC were 0.99 (95% CI, 0.87–1.11), 1.36 (1.10–1.69), 1.54 (1.07–2.20), and 2.15 (1.46–3.17), respectively, for colonoscopic follow-up at 3–6 months, 6–9 months, 9–12 months, and >12 months. When we used advanced-stage CRC as the outcome variable, the results (95% CI) were 0.95 (0.73–1.24), 2.19 (1.52–3.16), 2.54 (1.42–4.55), and 2.93 (1.50–5.74), respectively. For both any CRC and advanced-stage CRC, the increase was statistically significant when the colonoscopic follow-up was performed after 6 months. Results were remarkably similar when we adjusted for the age, sex, first or repeat screen, baseline fecal Hb concentration, patients' geographic region, and hospital level to receive the colonoscopy.

When we used time to colonoscopy as the continuous variable, there were significantly increasing trends for any CRC (OR, 1.04; 95% CI, 1.02–1.06 per month) and for advanced-stage CRC (OR, 1.07; 95% CI, 1.04–1.11 per month). When we adjusted for the baseline characteristics, the increments were 1% (95% CI, 0%–3%) and 4% (1%–7%) per month, respectively.

Risk Factor Analyses

In addition to the time to colonoscopy, the results for the baseline characteristics are shown in Table 4. Older age, male sex, first screen, higher fecal Hb concentration, and certain geographic regions were associated with higher risks for any CRC. For the advanced-stage disease, similarly, older age, first screen, and higher fecal Hb concentration were associated with higher risks. Medical center and regional hospital were associated with higher risks for the diagnoses of any CRC and advanced-stage disease when compared with local hospital and clinic.

The risk was remarkably higher among patients who had high levels of baseline fecal Hb concentration; for example, in patients with the fecal Hb concentration of 20–49 μg Hb/g feces (n = 13,633), their risks of any CRC and advanced-stage disease were 22 (301 cases of

Table 1. Baseline Characteristics of Participants Stratified by the Time to Colonoscopy After Positive Fecal Immunochemical Test Results in a Nationwide Screening Program

Characteristics	Total (n = 39,346)	1 mo ≤ t ≤3 mo (n = 30,695)	3 mo < t ≤6 mo (n = 6555)	6 mo < t ≤9 mo (n = 1357)	9 mo < t ≤12 mo (n = 444)	12 mo < t (n = 295)	*P* value[a]
Mean age, *y* (SD)	54.0 (5.3)	54.1 (5.3)	53.8 (5.1)	52.9 (4.4)	52.4 (3.7)	53.1 (4.9)	< .01
Male sex, (%)	20,934 (53.2)	16,170 (52.7)	3581 (54.6)	760 (56.0)	270 (60.8)	153 (51.9)	< .01
Repeat screen, n (%)	6014 (15.3)	4853 (15.8)	892 (13.6)	187 (13.8)	53 (11.9)	29 (9.8)	< .01
Baseline fecal hemoglobin concentration, μg Hb/g feces, median (IQR)	73.4 (36.8–199.8)	73.4 (37.0–199.8)	70.2 (35.0–199.8)	82.1 (38.6–200)	92.8 (43.8–200)	80.0 (36.8–200)	< .01
Patients' geographic region, n (%)							< .01
Northern area	15,996 (40.7)	12,925 (42.0)	2377 (36.3)	436 (32.1)	161 (36.2)	97 (32.9)	
Central area	8931 (22.7)	6836 (22.3)	1597 (24.4)	306 (22.5)	110 (24.8)	82 (27.8)	
Southern area	11,926 (30.3)	9168 (29.9)	2022 (30.8)	488 (36.0)	145 (32.7)	103 (34.9)	
Eastern area and offshore islands	2493 (6.3)	1766 (5.8)	559 (8.5)	127 (9.4)	28 (6.3)	13 (4.4)	
Hospital level, n (%)							< .01
Medical centers	14,249 (37.9)	11,368 (38.7)	2206 (35.2)	422 (32.6)	146 (34.5)	107 (38.1)	
Regional hospitals	16,570 (44.0)	12,829 (43.7)	2833 (45.1)	595 (46.0)	202 (47.8)	111 (39.5)	
Local hospitals and clinics	6821 (18.1)	5167 (17.6)	1239 (19.7)	277 (21.4)	75 (17.7)	63 (22.4)	

IQR, interquartile range; SD, standard deviation; t, time.
[a]*P* values were estimated using the analysis of variation test for age, Kruskal-Wallis test for the fecal hemoglobin concentration, and the chi-square test for the categorical data.

13,633 patients) and 2 (33 cases of 13,633 patients) cases per 1000 patients, respectively, whereas in patients with the fecal Hb concentration of ≥100 μg Hb/g feces (n = 16,140), the risks were 88 (1415 cases of 16,140 patients) and 23 (373 cases of 16,140 patients) cases per 1000 patients, respectively. Using patients with the fecal Hb concentration of 20–49 μg Hb/g feces as the baseline comparator, the adjusted ORs (95% CI) for any CRC and advanced-stage disease were 4.28 (3.87–4.72) and 6.73 (5.28–8.57), respectively, for patients with the fecal Hb concentration of ≥100 μg Hb/g feces. When we used fecal Hb concentration as the continuous variable, significantly increasing risks were noted for any CRC and advanced-stage disease, with the respective increment of 9.9% (95% CI, 9.4%–10.5%) and 12.7% (11.5%–13.9%) per 10 μg Hb/g feces.

Risk of Patients Who Did Not Undergo Colonoscopy After Positive Fecal Immunochemical Test Results

After exclusion of 5999 patients who received colonoscopy within 2 years before FIT, there were 59,783 patients who did not undergo colonoscopy after positive FIT results (Supplementary Table 3). During the mean follow-up time of 4.16 years, there were 2485 CRCs (42 cases per 1000 patients) and 1124 advanced-stage diseases (19 cases per 1000 patients) obtained from the cancer registry. Compared with colonoscopy referrals, the relative risks of the nonreferrals were 0.82 (95% CI, 0.77–0.86) and 1.66 (95% CI, 1.49–1.85), respectively, for any CRC and advanced-stage disease (Supplementary Figure 1); results were similar when we adjusted for the baseline characteristics (Supplementary Table 4).

Discussion

In the present study, we found that, in patients who had a positive FIT result but failed to receive timely colonoscopic follow-up, the risks of any CRC or advanced-stage CRC increased with time. Compared with those who underwent colonoscopy within 1–3 months, patients who underwent colonoscopic follow-up after 6 months had a significantly increased risk of any CRC and advanced-stage disease. Higher fecal Hb concentrations at baseline were substantially associated with the subsequent risk of CRC. Collectively, our findings indicate the tolerable waiting time of colonoscopy following positive FIT results and provide an approach that may help set priorities for these colonoscopy candidates.

In a FIT-based screening program, the main target is the colorectal neoplasm that can shed a sufficient amount of blood above the predefined level. Using the cutoff concentration in our study, about 80%–90% of CRCs and 50% of advanced adenomas could be detected.[3,4] The high sensitivity of FIT and the population characteristics (eg, the high percentage of first screen

Table 2. Risks of Colorectal Neoplasms Stratified by the Time to Colonoscopy After Positive FIT Results in a Nationwide Screening Program

		Any adenoma		Advanced adenoma		Any CRC		Advanced-stage CRC	
Time to colonoscopy	Positive FIT, n	n	%	n	%	n	per 1000	n	per 1000
1 mo ≤ t ≤3 mo	30,695	14,536	47.4	4287	14.0	1528	50	326	11
3 mo < t ≤6 mo	6555	3145	48.0	882	13.5	321	49	66	10
6 mo < t ≤9 mo	1357	676	49.8	202	14.9	92	68	32	24
9 mo < t ≤12 mo	444	227	51.1	69	15.5	33	74	12	27
12 mo < t	295	138	46.8	44	14.9	29	98	9	31
Overall	39,346	18,722	47.6	5484	13.9	2003	51	445	11

CRC, colorectal cancer; FIT, fecal immunochemical test; t, time.

attendees) may explain why colorectal neoplasms were so prevalent in our FIT-positive population. In addition to patients' higher risk at baseline, another factor that accounts for our observations is the magnitude of transition rates. In a computer-simulation study, researchers found that, compared with patients who received colonoscopies within 2 weeks of positive FIT results, patients who received colonoscopies 12 months later had increased risks of any CRC and CRC-related death by about 4% and 16%, respectively.[17]

In an organized screening program, the diagnoses of CRC could be increased by multiple and not necessarily clinical factors, including the presence of clinical symptoms, higher disease awareness, better health behaviors, prompting and reminding activities of healthcare workers, and the expertise of endoscopists.[18] Nonetheless, when we attempted to reduce these confounders, our findings of increased risks of 1% and 4% for each additional month of delay for any CRC and advanced CRC, respectively, were similar to the results from a population-based study from Kaiser Permanente (Northern California Division of Research), which demonstrated the increments of 3% and 5%, respectively.[6]

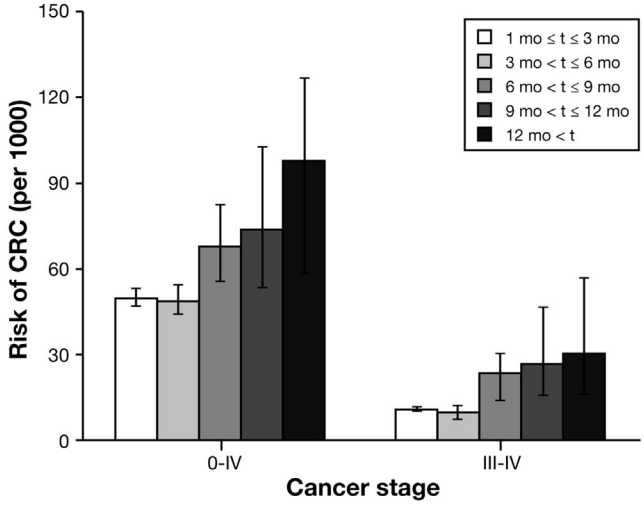

Figure 2. The risks of any CRC and advanced-stage CRC stratified by the time to colonoscopy; error bars indicate the 95% confidence intervals. *P* values for the trend test are < .01 for both the any CRC and advanced-stage disease.

Also in the Kaiser Permanente study (number of FIT-positive patients: 70,124), researchers found that colonoscopy >10 months after positive FIT results was associated with a statistically significant increase in any CRC (adjusted OR, 1.47) and advanced-stage CRC (adjusted OR, 1.95) compared with the baseline of 8–30 days.[6] In our study with a comparable sample size (number of FIT-positive patients: 39,346), we identified the similarly increased risks for any CRC (adjusted OR, 2.17) and advanced-stage CRC (adjusted OR, 2.84) after 12 months compared with the baseline of 1–3 months. However, not only the sample size, the length of tolerable time before a statistically significant difference is observed also depends on the transition rates. In both studies, the magnitude of risk was higher for the advanced-stage CRC than any CRC, which may be explained by the more rapid transition from early stage to advanced-stage CRC compared with that from adenoma to CRC. Our findings indicate that after positive FIT results, early colonoscopic follow-up is required to decrease the risk of new-onset CRCs and stage shifting of already-present CRCs.

Knowing that lack of colonoscopic follow-up can be considered the most extreme form of delay, we made a comparison between those who did and did not receive colonoscopic follow-up. Consistently, we found that the risk in the nonreferrals increased over time and the risk of advanced-stage CRC soon outnumbered that of the referrals (Supplementary Figure 1). Regarding the risk of any CRC, the protective effect from the colonoscopy (detection and removal of polyps), however, required longer follow-up time to become observable because the incidence rate in the referrals had been rapidly inflated by the colonoscopic screening.

European and Canadian Guidelines recommend that colonoscopy should take place within 1 and 2 months, respectively, after positive results of fecal occult blood tests.[19,20] However, when a FIT-based screening program is administered on a regional or national scale, a large number of FIT-positive results are generated simultaneously, so patients may be queued in the process of

Table 3. Risks of Any CRC or Advanced-Stage CRC According to the Time to Colonoscopy Using the Logistic Regression Models

	Any CRC				Advanced-stage CRC			
Time to colonoscopy	OR	95% CI	aOR[a]	95% CI	OR	95% CI	aOR[a]	95% CI
1 mo ≤ t ≤3 mo	1	—	1	—	1	—	1	—
3 mo < t ≤6 mo	0.99	0.87–1.11	0.98	0.86–1.12	0.95	0.73–1.24	0.95	0.72–1.25
6 mo < t ≤9 mo	1.36[b]	1.10–1.69	1.31[b]	1.04–1.64	2.19[b]	1.52–3.16	2.09[b]	1.43–3.06
9 mo < t ≤12 mo	1.54[b]	1.07–2.20	1.32	0.91–1.92	2.54[b]	1.42–4.55	1.97[b]	1.06–3.65
12 mo < t	2.15[b]	1.46–3.17	2.17[b]	1.44–3.26	2.93[b]	1.50–5.74	2.84[b]	1.43–5.64
Continuous time, per mo	1.04[b]	1.02–1.06	1.01[b]	1.00–1.03	1.07[b]	1.04–1.11	1.04[b]	1.01–1.07

aOR, adjusted odds ratio; CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; t, time.
[a]Adjusted for age, sex, first or repeat screen, baseline fecal hemoglobin concentration, patients' geographic region, and hospital level to receive the colonoscopy.
[b]*P* value < .05.

colonoscopic confirmation because of the limited number of colonoscopists available. In our study, we found that the significant progression might occur 6 months after positive FIT results, which indicated that short delays are much less likely to be associated with significant transitions of disease. Also, we provided a novel approach for priority setting by demonstrating a significant association between the quantitative value of FIT and the subsequent risk of any CRC and advanced-stage disease. This finding was consistent with our previous work showing that fecal Hb concentrations of 50–99 μg Hb/g feces and ≥100 μg Hb/g feces were associated with the 2.21- and 2.53-fold increases in the risk of CRC-related death, respectively, if patients did not comply with orders for colonoscopic follow-up.[9]

Strengths of our study include its nationwide scale and long follow-up time that provided sufficient statistical power to overcome the difficulties of insufficiently powered studies in which most FIT-positive patients received colonoscopic follow-up within the recommended time but only a small subset could be used for hypothesis testing. However, our study also has limitations. First, although we have quantified the course of CRC development and progression, some potentially important confounding factors have not adjusted; for example, smokers, which can promote progression, may be less likely to come timely for colonoscopy. Second, contaminations from symptomatic patients cannot be completely ruled out. The differences observed between groups comprising 3–6 months compared with 1–3

Table 4. Association Between Baseline Characteristics and the Risks of Any CRC and Advanced CRC in the Multiple Logistic Regression Analyses

	Any CRC		Advanced-stage CRC	
Factors	aOR[a]	95% CI	aOR[a]	95% CI
Age, *y*	1.01[b]	1.00–1.02	1.02[b]	1.00–1.03
Male vs female	1.19[b]	1.11–1.29	0.93	0.80–1.08
FIT+ during first screen vs repeat screen	1.72[b]	1.52–1.94	2.07[b]	1.57–2.73
Baseline fecal hemoglobin concentration (μg Hb/g feces)				
20–49	1	—	1	—
50–99	1.50[b]	1.32–1.70	1.62[b]	1.18–2.23
≥100	4.28[b]	3.87–4.72	6.73[b]	5.28–8.57
Patients' geographic region				
Northern area	1	—	1	—
Central area	0.83[b]	0.75–0.92	0.95	0.78–1.15
Southern area	1.11[b]	1.02–1.20	1.09	0.91–1.29
Eastern area and offshore island	0.78[b]	0.65–0.93	0.85	0.59–1.22
Hospital level				
Medical center	1	—	1	—
Regional hospital	0.96	0.88–1.04	0.91	0.78–1.07
Local hospital and clinic	0.71[b]	0.63–0.79	0.76[b]	0.60–0.95

aOR, adjusted odds ratio; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test.
[a]Adjusted for time to colonoscopy, age, gender, first or repeat screen, baseline fecal hemoglobin concentration, patients' geographic region, and hospital level to receive the colonoscopy.
[b]*P* value < .05.

months did not rise to the level of statistical significance, which may be caused by contamination of risk from the baseline group; nonetheless, there was evidence of trend when the colonoscopy delay was prolonged. The higher hospital level associated with the higher CRC risk may suggest that those who underwent the screening service in the hospital-based program may carry a higher possibility of clinical symptoms.[11] Third, although we have identified the tolerable waiting time when the statistically significant increases of risk occurred, these were surrogates for the CRC-specific mortality. Theoretically, the high risk of CRC may be associated with higher mortality rates in patients whose time to colonoscopy is prolonged; however, our follow-up time remained insufficient to assess this endpoint. Fourth, during our study period, priority setting based on the quantitative fecal Hb concentration has not yet been applied; whether this approach can generate greater health benefits as a result of screening deserves further trials. Finally, the recommended time to colonoscopy applied in our study was population specific, so the extent to which the results can be generalized to other populations requires further observations.

In conclusion, in patients who have positive FIT results but do not undergo timely colonoscopy, our findings define risk over time and suggest the risk becomes more significant with prolonged delay. Results of this nationwide study have important implications regarding how to maximize the benefit generated from a FIT-based screening program to reduce the enormous burden of CRC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2018.10.041.

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Conflicts of interest
The authors disclose no conflicts.

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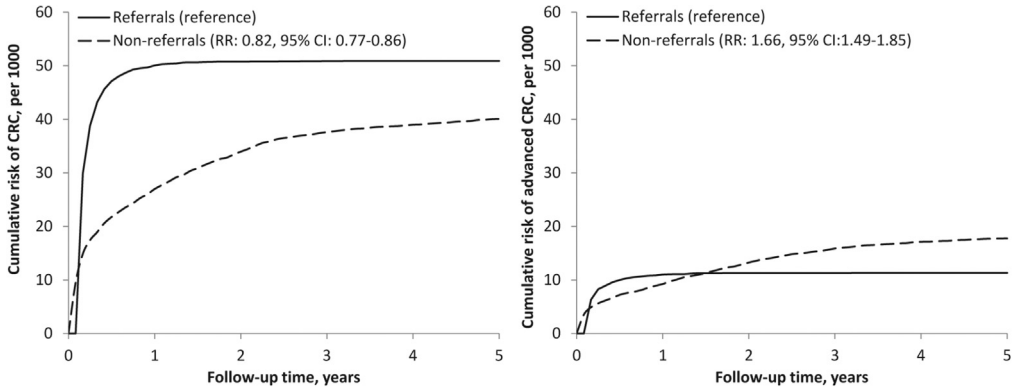

Supplementary Figure 1. Cumulative risks of CRC and advanced-stage CRC according to the colonoscopy referrals and nonreferrals after positive fecal immunochemical test results. Both the incidence rates of any CRC and advanced-stage disease in the nonreferrals increased over time. The risk of advanced-stage CRC soon outnumbered that of the colonoscopy referrals mainly because of the progression of pre-existing CRCs (*right side*). However, the protective effect of colonoscopy on the risk of any CRC (the effect from detection and removal of polyps on the new-onset CRCs) required a longer follow-up period to become observable because the incidence rate in the referrals had been rapidly inflated by the active colonoscopic screening within the initial 2 years (*left side*).

Supplementary Table 1. Risks of Colorectal Neoplasms Stratified by the Time to Colonoscopy After Positive FIT Results Within The Recommended Time to Colonoscopy

		Any adenoma		Advanced adenoma		Any CRC		Advanced-stage CRC	
Time to colonoscopy	Positive FIT, n	n	%	n	%	n	per 1000	n	per 1000
1 d $<$ t $\leq$7 d	5133	2293	44.7	657	12.8	358	70	114	22
7 d $<$ t $\leq$1 mo	50,405	23,320	46.3	6713	13.3	2923	58	702	14
1 mo $<$ t $\leq$2 mo	23,459	11,040	47.1	3237	13.8	1205	51	253	11
2 mo $<$ t $\leq$3 mo	7236	3496	48.3	1050	14.5	323	45	73	10

CRC, colorectal cancer; FIT, fecal immunochemical test; t, time.

Supplementary Table 2. Consequence of Delays in Colonoscopy for each CRC Stage

	Total (n = 39,346)	1 mo < t ≤3 mo (n = 30,695)	3 mo < t ≤6 mo (n = 6555)	6 mo < t ≤9 mo (n = 1357)	9 mo < t ≤12 mo (n = 444)	12 mo < t (n = 295)
CRC stage (%)						
0	414 (1.1)	321 (1.0)	70 (1.1)	14 (1.0)	6 (1.4)	3 (1.0)
I	572 (1.5)	442 (1.4)	95 (1.4)	20 (1.5)	6 (1.4)	9 (3.1)
II	251 (0.6)	194 (0.6)	37 (0.6)	10 (0.7)	5 (1.1)	5 (1.7)
III	363 (0.9)	275 (0.9)	47 (0.7)	24 (1.8)	9 (2.0)	8 (2.7)
IV	82 (0.2)	51 (0.2)	19 (0.3)	8 (0.6)	3 (0.7)	1 (0.3)
Unknown	321 (0.8)	245 (0.8)	53 (0.8)	16 (1.2)	4 (0.9)	3 (1.0)
Overall	2003 (5.1)	1528 (5.0)	321 (4.9)	92 (6.8)	33 (7.4)	29 (9.8)

CRC, colorectal cancer; t, time.

Supplementary Table 3. Baseline Characteristics of Participants Stratified by Colonoscopy Referrals and Nonreferrals After Positive Fecal Immunochemical Test Results

Characteristics	Referrals (n = 39,346)	Nonreferrals (n = 59,783)[a]	*P* value[b]
Mean age, *y* (SD)	54.0 (5.3)	52.2 (3.8)	< .01
Male sex, n (%)	20,934 (53.2)	33,154 (55.5)	< .01
Repeat screen, n (%)	6014 (15.3)	5792 (9.7)	< .01
Baseline fecal hemoglobin concentration, μg Hb/g feces, median (IQR)	73.4 (36.8–199.8)	78.0 (37.6–200)	< .01
Patients' geographic region, n (%)			< .01
Northern area	15,996 (40.7)	23,631 (39.5)	
Central area	8931 (22.7)	16,040 (26.8)	
Southern area	11,926 (30.3)	16,622 (27.8)	
Eastern area and offshore islands	2493 (6.3)	3490 (5.9)	

IQR, interquartile range; SD, standard deviation.
[a]After excluding 5999 patients who received colonoscopy within 2 years before fecal immunochemical test.
[b]*P* values were estimated using the Student *t* test for age, Mann-Whitney test for the fecal hemoglobin concentration, and the chi-square test for the categorical data.

Supplementary Table 4. Risks of CRC and Advanced-Stage CRC According to the Colonoscopy Referrals and Nonreferrals After Positive FIT Results Using the Poisson Regression Model

Factors	Any CRC		Advanced-stage CRC	
	aRR[a]	95% CI	aRR[a]	95% CI
Nonreferrals vs referrals	0.89[b]	0.83–0.96	1.75[b]	1.55–1.99
Age, *y*	1.01[b]	1.01–1.02	1.01[b]	1.00–1.02
Male vs female	1.12[b]	1.05–1.20	0.92	0.82–1.02
FIT+ during first screen vs repeat screen	1.59[b]	1.35–1.85	2.38[b]	1.61–3.57
Baseline fecal hemoglobin concentration (μg Hb/g feces)				
20–49	1	—	1	—
50–99	1.50[b]	1.32–1.70	1.77[b]	1.38–2.26
≥100	4.56[b]	4.14–5.01	7.08[b]	5.85–8.58
Patients' geographic region				
Northern area	1	—	1	—
Central area	0.74[b]	0.68–0.81	0.86[b]	0.74–0.99
Southern area	1.01	0.93–1.08	1.07	0.94–1.21
Eastern area and offshore island	0.67[b]	0.57–0.79	0.71[b]	0.54–0.93

aRR, adjusted relative risk; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test.
[a]Adjusted for colonoscopy referral, age, sex, first or repeat screen, baseline fecal hemoglobin concentration, and patients' geographic region.
[b]*P* value $< .05$.