Digestive and Liver Disease 51 (2019) 589–594

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Association of time to colonoscopy after a positive fecal test result and fecal hemoglobin concentration with risk of advanced colorectal neoplasia

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ARTICLE INFO

Article history:
Received 20 August 2018
Accepted 11 December 2018
Available online 23 December 2018

Keywords:
Advanced colorectal neoplasia
Colorectal cancer
Fecal immunochemical test
Time factors

ABSTRACT

Background: We evaluated the risk of advanced colorectal neoplasia (ACRN) and colorectal cancer (CRC) according to time to colonoscopy after positive fecal immunochemical test (FIT), fecal hemoglobin concentration, and combination of both.
Methods: We analyzed the records of 2362 patients aged ≥50 years who underwent colonoscopy because of a positive FIT result through the National Cancer Screening Program of Korea.
Results: ACRN risk increased with increasing time to colonoscopy after a positive FIT (17.2%, 18.6%, 19.1%, 21.4%, and 27.2% in <30, 30–59, 60–149, 150–179, and ≥180 days; $P = 0.034$), and ACRN and CRC risk increased with increasing fecal hemoglobin concentration (ACRN, 13.2%, 16.9%, 18.5%, 23.2%, and 26.6%; CRC, 1.3%, 1.7%, 4.7%, 5.7%, and 12.8% with 100–200, 200–300, 300–500, 500–1000, and ≥1000 ng Hb/mL; both $P < 0.001$). Even after adjusting for confounders, follow-up after 180 days tended to be associated with a higher ACRN risk (adjusted odds ratio, 1.73; 95% confidence interval [CI], 0.91-3.27), compared with follow-up colonoscopy at <30 days, and fecal hemoglobin 500–1000, and ≥1000 ng Hb/mL were associated with a significantly higher ACRN and CRC risk, compared with 100–200 ng Hb/mL. Moreover, the group with ≥180 days and ≥1000 ng Hb/mL had a much higher CRC risk compared with the group with <180 days and <1000 ng Hb/mL (12.45-fold; 95% CI, 3.73–41.57).
Conclusions: Patients with positive FIT results, especially those with higher fecal hemoglobin levels, should undergo timely follow-up colonoscopy.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer, and its incidence is rapidly increasing in Asian countries, making it the fourth most common cause of cancer-related death in the world [1]. The fecal immunochemical test (FIT) is regarded as the most effective, non-invasive CRC screening strategy currently available [2]. FIT screening can detect a large portion of CRC occurring in asymptomatic average-risk populations and reduce the risk of CRC mortality [2]. Therefore, many countries have adopted the FIT in population-based CRC screening programs [3–5].

As a two-stage screening strategy, the effectiveness of FIT depends on undergoing adequate colon examination for positive results, generally with colonoscopy. However, there are no clear guidelines for the appropriate time interval to colonoscopy after a positive FIT result. Recommendations for how quickly to complete colonoscopy differ and lack supporting data. In practice, there is marked variation in time intervals between a positive FIT result and colonoscopy follow-up [6–8]. Some studies reported that intervals of 6 months or longer are common in actual clinical practice [6,9]. Such delays may result in neoplastic progression and thus may undermine the benefits of CRC screening. However, the relationship between the time interval from the date of a positive FIT result to colonoscopy and colorectal neoplasia (CRN) outcomes is not well-known. Longer time to colonoscopy after a positive FIT result may be associated with higher likelihood of advanced CRN

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https://doi.org/10.1016/j.dld.2018.12.008
1590-8658/

(ACRN), CRC, and advanced-stage disease. A microsimulation modeling study showed that every month added until colonoscopy was associated with a 0.1/1000 person increase in CRC incidence risk (i.e., an increase of 0.3%/month, compared with individuals who underwent colonoscopies within 2 weeks of a positive FIT result) [10]. Given this modeling study's results, patients with a positive FIT result should undergo colonoscopy as soon as possible. However, this requires swift communication of positive results to patients and physicians, sufficient colonoscopy access, and rapid scheduling. It may be difficult to apply this rapid progress to all patients with a positive FIT result in countries with limited resources.

Meanwhile, FITs allow the quantitation of fecal hemoglobin concentration. Several studies have demonstrated that fecal hemoglobin concentration is related to the severity of CRN [11,12]. Recent studies have also shown that the prevalence of ACRN increases with increasing fecal hemoglobin concentration and suggested that fecal hemoglobin concentration is useful for risk stratification for ACRN [13,14].

Based on these results, we sought to propose that among patients with a positive FIT result, those with higher fecal hemoglobin levels should be given priority to undergo colonoscopy as soon as possible. We hypothesized that longer intervals to undergo colonoscopy after a positive FIT result and higher fecal hemoglobin concentration are associated with increased ACRN and CRC risk, and this combination is associated with much higher ACRN and CRC risk. To confirm this hypothesis, we investigated the ACRN and CRC risk according to time to colonoscopy after a positive FIT, fecal hemoglobin concentration, and combination of both.

2. Patients and methods

2.1. Study population

The National Cancer Screening Program (NCSP) of Korea provides a single annual FIT for adults aged 50 years or older as initial CRC screening and a confirmatory colonoscopy as a secondary test for those with a positive FIT. This study consisted of patients aged ≥50 years who underwent colonoscopy because of a positive FIT result through the NCSP at Kangbuk Samsung hospital in Korea from January 2013 to July 2017.

The exclusion criteria were as follows: a history of CRC or colorectal surgery, a history of inflammatory bowel disease (IBD), and poor bowel preparation. The quality of bowel preparation was assessed using the Boston Bowel Preparation Scale, and poor bowel preparation was defined as a score of 0 or 1 on any colon segment [15].

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for informed consent was waived because only de-identified data were retrospectively assessed.

2.2. Clinical measurements and FIT

Data on medical history and smoking status were collected through a self-administered questionnaire. Family history of CRC was defined as CRC in ≥1 first-degree relatives at any age. The body mass index (BMI) was calculated as weight in kilograms divided by height in square meters.

Participants were instructed to collect a one-time stool sample in a sampling tube (Eiken Chemical Company, Tokyo, Japan) containing 2.0 mL of buffer designed to minimize hemoglobin degradation. The collected fecal material was sent to the laboratory sealed in a plastic bag. Fecal hemoglobin quantitation was performed using OC-SENSOR DIANA (Eiken Chemical Company). FIT results were expressed in nanograms of hemoglobin per milliliter of buffer (ng Hb/mL), and the FIT positivity cutoff value was set at 100 ng Hb/mL (equivalent to 20 mg Hb/g feces) [16].

2.3. Colonoscopy and histologic examination

All colonoscopies were performed by experienced board-certified endoscopists, using the EVIS LUCERA CV-260 colonoscope (Olympus Medical Systems, Tokyo, Japan). Suspicious neoplastic lesions were examined by biopsy or removed by polypectomy or endoscopic mucosal resection. All specimens were histopathologically assessed by experienced gastrointestinal pathologists. Overall CRN was defined as a cancer or any adenoma, and ACRN was defined as a cancer or advanced adenoma. Advanced adenoma was defined as the presence of one of the following features: ≥10 mm diameter, tubulovillous or villous structure, and high-grade dysplasia [17].

2.4. Statistical analysis

Data were stratified into five groups according to time to colonoscopy after a positive FIT (<30, 30–59, 60–149, 150–179, and ≥180 days) and fecal hemoglobin concentration (100–200, 200–300, 300–500, 500–1000, and ≥1000 ng Hb/mL), respectively. Baseline characteristics between groups were compared using chi-square test and one-way analysis of variance for categorical and continuous variables, respectively. Prevalence of CRN between groups was compared using linear-by-linear association tests.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of ACRN and CRC according to time to colonoscopy after a positive FIT and fecal hemoglobin concentration were estimated by multivariate logistic regression analysis, adjusted for potential major confounding factors including age, sex, and family history of CRC, smoking status, BMI, history of hypertension, and history of diabetes. In sensitivity analyses, we repeated the multivariate analyses after excluding those with family history of CRC. All reported P values were two-tailed, and P values < 0.05 were considered statistically significant. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

3.1. Baseline characteristics and prevalence of colorectal neoplasia by time to colonoscopy after a positive FIT and fecal hemoglobin concentration

Between January 2013 and July 2017, a total of 52,376 participants underwent FIT for CRC screening through the NCSP at Kangbuk Samsung hospital and 3229 (6.2%) of them had positive FIT results. Of 3229 participants with positive FIT results, 2362 (73.1%) underwent colonoscopy. Of these participants, 104 were excluded because of a history of CRC or colorectal surgery (n = 28), a history of IBD (n = 25), and poor bowel preparation (n = 51). Ultimately, 2258 patients were analyzed. The mean age of the study population was 64.4 ± 8.4 years, and the proportion of men was 53.2%. Among all patients, the prevalence of overall CRN, ACRN, and CRC was 61.1% (n = 1380), 18.7% (n = 422), and 4.8% (n = 109), respectively.

The baseline characteristics and prevalence of CRN by time to colonoscopy after a positive FIT are described in Table 1. The proportion of patients with <30, 30–59, 60–149, 150–179, and ≥180 days was 33.2% (n = 750), 34.1% (n = 769), 26.2% (n = 591), 2.5% (n = 56), and 4.1% (n = 92), respectively. The mean interval from the date of a positive FIT result to colonoscopy was 59 ± 54 days (median, 42 days; maximum, 359 days). Mean age was highest in the ≥180-days group. The proportion of hypertension was highest in the 30–59-days group, and the proportion of diabetes was highest in the 150–179-days group. There was no significant difference in sex, proportion of family history of CRC, smoking status,

Table 1
Baseline characteristics and prevalence of colorectal neoplasia by time to colonoscopy after a positive fecal immunochemical test.

	Total	Time to colonoscopy					*P* value
		<30 days	30–59 days	60–149 days	150–179 days	≥180 days	
Number of subjects	2258	750	769	591	56	92	
Baseline characteristics							
Age	64.4 ± 8.4	63.6 ± 8.3	64.7 ± 8.3	64.9 ± 8.5	63.6 ± 8.5	65.1 ± 8.1	0.027
50–59 years	715 (31.7)	263 (35.1)	233 (30.3)	172 (29.1)	22 (39.3)	25 (27.2)	0.172
60–69 years	853 (37.8)	279 (37.2)	283 (36.8)	236 (39.9)	20 (35.7)	35 (38.0)	
≥70 years	690 (30.6)	208 (27.7)	253 (32.9)	183 (31.0)	14 (25.0)	32 (34.8)	
Male sex	1202 (53.2)	391 (52.1)	416 (54.1)	316 (53.5)	25 (44.6)	54 (58.7)	0.498
Family history of CRC	140 (6.2)	51 (6.8)	45 (5.9)	39 (6.6)	1 (1.8)	4 (4.3)	0.524
Current or ex-smoker[a]	717/1756 (40.8)	223/579 (38.5)	252/579 (43.5)	193/480 (40.2)	18/47 (38.3)	31/71 (43.7)	0.484
BMI (kg/m^2)[b]	24.1 ± 3.1	23.9 ± 3.2	24.2 ± 3.0	24.1 ± 3.1	23.6 ± 3.5	24.4 ± 3.0	0.404
History of hypertension	920 (40.7)	285 (38.0)	321 (47.1)	265 (44.8)	21 (37.5)	28 (30.4)	0.026
History of diabetes	354 (15.7)	88 (11.7)	119 (15.5)	121 (20.5)	12 (21.4)	14 (15.2)	<0.001
Prevalence of CRN							
ACRN	422 (18.7)	129 (17.2)	143 (18.6)	113 (19.1)	12 (21.4)	25 (27.2)	0.034
Cancer	109 (4.8)	34 (4.5)	38 (4.9)	25 (4.2)	5 (8.9)	7 (7.6)	0.294
Intramucosal cancer	20 (0.9)	7 (0.9)	7 (0.9)	4 (0.7)	1 (1.8)	1 (1.1)	0.995
Stage I–II	49 (2.2)	15 (2.0)	16 (2.1)	12 (2.0)	2 (3.6)	4 (1.3)	0.258
Stage III–IV	32 (1.4)	11 (1.5)	10 (1.3)	9 (1.5)	0	2 (2.2)	0.896
Unknown	8 (0.4)	1 (0.1)	5 (0.7)	0	2 (3.6)	0	0.449
Overall CRN	1380 (61.1)	451 (60.1)	470 (61.1)	375 (63.5)	25 (44.6)	59 (64.1)	0.642

Values are presented as mean ± standard deviation or number (%).
CRC, colorectal cancer; BMI, body mass index; CRN, colorectal neoplasia; ACRN, advanced colorectal neoplasia.
Chi-square test and one-way analysis of variance were used to compare baseline characteristics, and linear-by-linear association tests were used to compare prevalence of CRN.
[a] Missing values for 502 individuals.
[b] Missing values for 653 individuals.

and BMI between the groups. The prevalence of ACRN increased linearly with increasing time to colonoscopy (17.2%, 18.6%, 19.1%, 21.4%, and 27.2% in <30, 30–59, 60–149, 150–179, and ≥180 days; $P = 0.034$). The prevalence of CRC tended to be higher in the 150–179 and ≥180 days groups (8.9% and 7.6%, respectively) compared with the <30, 30–59, and 60–149 day groups (4.5%, 4.9% and 4.2%, respectively), but it did not reach statistical significance ($P = 0.294$).

The baseline characteristics and prevalence of CRN by fecal hemoglobin concentration are described in Table 2. The proportion of patients with 100–200, 200–300, 300–500, 500–1000, and ≥1000 ng Hb/mL was 33.3% (n = 752), 18.6% (n = 420), 15.1% (n = 340), 11.6% (n = 263), and 21.2% (n = 478), respectively. Mean age was highest in the 500–1000 ng Hb/mL group. The baseline characteristics including sex, family history of CRC, smoking status, BMI, hypertension, and diabetes were not different between the groups. The prevalence of ACRN and CRC increased linearly with increasing fecal hemoglobin concentration (ACRN, 13.2%, 16.9%, 18.5%, 23.2%, and 26.6%; CRC, 1.3%, 1.7%, 4.7%, 5.7%, and 12.8% in 100–200, 200–300, 300–500, 500–1000, and ≥1000 ng Hb/mL; both $P < 0.001$). The time to colonoscopy after a positive FIT and fecal hemoglobin concentration did not show a significant relationship with the prevalence of overall CRN.

3.2. Risk of colorectal neoplasia according to combination of time to colonoscopy after a positive FIT and fecal hemoglobin concentration

With the combination of time to colonoscopy (<180 and ≥180 days) and fecal hemoglobin concentration (<1000 and ≥1000 ng Hb/mL), patients were classified into four groups; 1711 (75.8%) were categorized into G1 (<80 days and <1000 ng Hb/mL), 69 (3.1%) were categorized into G2 (≥180 days and <1000 ng Hb/mL), 455 (20.2%) were categorized into G3 (<180 days and ≥1000 ng Hb/mL), and 23 (1.0%) were categorized G4 (≥180 days and ≥1000 ng Hb/mL) (Table 3). The prevalence of ACRN in the four groups (G1–G4) was 16.2%, 26.1%, 26.4%, and 30.4%, respectively, and the prevalence of CRC was 2.6%, 4.3%, 12.5%, 17.4%, respectively. G2 and G3 had a significantly higher detection rate of ACRN than G1, and G3 and G4 had a significantly higher detection rate of CRC than G1 (Fig. 1).

3.3. Multivariate analysis for risk of colorectal neoplasia according to time to colonoscopy and fecal hemoglobin concentration

Multivariate analyses were performed to identify whether time to colonoscopy after a positive FIT and fecal hemoglobin concentration is independently associated with ACRN and CRC risk (Table 4). Even after adjusting for potential confounding factors, compared to patients with <30 days, those with ≥180 days tended to have a higher ACRN risk (adjusted OR, 1.73; 95% CI, 0.91–3.27), and compared to patients with <100–200 ng Hb/mL, those with 500–1000, and ≥1000 ng Hb/mL had a significantly higher ACRN risk. In addition, compared to patients with <100–200 ng Hb/mL, those with 300–500, 500–1000, and ≥1000 ng Hb/mL had a significantly higher CRC risk.

In the multivariate analysis, compared with G1, G3 and G4 had a significantly higher ACRN risk (adjusted OR, 2.23; 95% CI, 1.64–3.02 and 3.13; 1.12–8.74, respectively). Compared with G1, G3 and G4 also had a significantly higher risk of CRC (adjusted OR, 7.31; 95% CI, 4.44–12.03 and 12.45; 3.73–41.57, respectively). Additionally, even in sensitivity analyses where we excluded those with family history of CRC, compared with G1, G3 and G4 had a higher ACRN risk (adjusted OR, 2.31; 95% CI, 1.68–3.17 and 3.17; 1.13–8.93, respectively) and CRC risk (adjusted OR, 7.10; 95% CI, 4.26–11.85 and 12.16; 3.63–40.72, respectively).

4. Discussion

In this study, we found that longer time to colonoscopy after a positive FIT and higher fecal hemoglobin concentration were associated with increased ACRN and CRC risk. ACRN risk increased with increasing time to colonoscopy after a positive FIT, and ACRN and

Table 2
Baseline characteristics and prevalence of colorectal neoplasia by fecal hemoglobin concentration.

	Total	Fecal hemoglobin concentration (ng Hb/mL)					*P* value
		100–200	200–300	300–500	500–1000	≥1000	
Number of subjects	2258	752	420	340	263	478	
Baseline characteristics							
Age	64.4 ± 8.4	64.4 ± 8.2	64.6 ± 8.4	64.8 ± 8.2	65.3 ± 8.9	63.2 ± 8.2	0.005
50–59 years	715 (31.7)	240 (31.7)	128 (30.5)	104 (30.6)	74 (28.1)	169 (35.4)	0.070
60–69 years	853 (37.8)	285 (37.6)	161 (38.3)	120 (35.3)	95 (36.1)	192 (40.2)	
≥70 years	690 (30.6)	232 (30.6)	131 (31.2)	116 (34.1)	94 (35.7)	117 (24.5)	
Male sex	1202 (53.2)	395 (52.2)	215 (51.2)	189 (55.6)	139 (52.9)	264 (55.2)	0.630
Family history of CRC	140 (6.2)	48 (6.3)	21 (5.0)	21 (6.2)	20 (7.6)	30 (6.3)	0.743
Current or ex-smoker[a]	717/1756 (40.8)	243/595 (40.8)	140/335 (41.8)	113/267 (42.3)	89/208 (42.8)	132/351 (37.6)	0.697
BMI (kg/m^2)[b]	24.1 ± 3.1	24.1 ± 3.2	24.2 ± 3.3	23.9 ± 2.7	24.0 ± 3.1	24.2 ± 3.1	0.739
History of hypertension	920 (40.7)	323 (42.7)	165 (39.3)	138 (40.6)	112 (42.6)	182 (38.1)	0.507
History of diabetes	354 (15.7)	108 (14.3)	64 (15.2)	56 (16.5)	51 (19.4)	75 (15.7)	0.392
Prevalence of CRN							
ACRN	422 (18.7)	100 (13.2)	71 (16.9)	63 (18.5)	61 (23.2)	127 (26.6)	<0.001
Cancer	109 (4.8)	10 (1.3)	7 (1.7)	16 (4.7)	15 (5.7)	61 (12.8)	<0.001
Intramucosal cancer	20 (0.9)	2 (0.3)	1 (0.2)	5 (1.5)	5 (1.9)	7 (1.5)	0.003
Stage I–II	49 (2.2)	4 (0.5)	4 (1.0)	7 (2.1)	4 (1.5)	30 (6.3)	<0.001
Stage III–IV	32 (1.4)	3 (0.4)	1 (0.2)	2 (0.6)	5 (1.9)	21 (4.4)	<0.001
Unknown	8 (0.4)	1 (0.1)	1 (0.2)	2 (0.6)	1 (0.4)	3 (0.6)	0.135
Overall CRN	1380 (61.1)	471 (62.2)	246 (58.6)	215 (63.2)	157 (59.7)	291 (60.9)	0.737

Values are presented as mean ± standard deviation or number (%).
CRC, colorectal cancer; BMI, body mass index; CRN, colorectal neoplasia; ACRN, advanced colorectal neoplasia.
Chi-square test and one-way analysis of variance were used to compare baseline characteristics, and linear-by-linear association tests were used to compare prevalence of CRN.
[a] Missing values for 502 individuals.
[b] Missing values for 653 individuals.

Table 3
Prevalence of colorectal neoplasia according to combination of time to colonoscopy and fecal hemoglobin concentration.

	ACRN		Cancer		Overall CRN	
	Prevalence	*P* value	Prevalence	*P* value	Prevalence	*P* value
Time to colonoscopy						
<180 days (n = 2166)	397 (18.3)	0.033	102 (4.7)	0.204	1321 (61.0)	0.545
≥180 days (n = 92)	23 (27.2)		7 (7.6)		59 (64.1)	
Fecal hemoglobin concentration						
<1000 ng Hb/mL (n = 1780)	295 (16.6)	<0.001	48 (2.7)	<0.001	1089 (61.2)	0.905
≥1000 ng Hb/mL (n = 478)	127 (26.6)		61 (12.8)		291 (60.9)	
Time to colonoscopy and FIT results						
G1: <180 days and <1000 ng Hb/mL (n = 1711)	277 (16.2)	<0.001	45 (2.6)	<0.001	1043 (61.0)	0.773
G2: ≥180 days and <1000 ng Hb/mL (n = 69)	18 (26.1)		3 (4.3)		46 (66.7)	
G3: <180 days and ≥1000 ng Hb/mL (n = 455)	120 (26.4)		57 (12.5)		278 (61.1)	
G4: ≥180 days and ≥1000 ng Hb/mL (n = 23)	7 (30.4)		4 (17.4)		13 (56.5)	

ACRN, advanced colorectal neoplasia; CRN, colorectal neoplasia; FIT, fecal immunochemical test.

CRC risk increased with increasing fecal hemoglobin concentration. Moreover, these associations remained significant even after adjusting for potential confounding factors.

The median time intervals between a positive FIT result and colonoscopy follow-up vary widely, range from 103 to 202 days, in practice [6–8,18–20]. However, most of studies investigating the intervals were conducted in Western countries [6–8,18–20]. In the present study, the mean and median waiting times from positive FIT result to colonoscopy were 59 days and 42 days, respectively and the intervals were relatively shorter compared to previous Western studies. This may be because the colonoscopy access in Korea is more easier and sufficient than that in Western countries. In Korea, the medical cost for colonoscopy is low and the number of colonoscopists is relatively sufficient compared to other countries. Therefore, rapid colonoscopy scheduling may be possible compared with other Western countries. Nevertheless, only one-third of patients with a positive FIT result underwent a follow-up colonoscopy within 30 days and some patients underwent a follow-up colonoscopy after 6 months.

Recommendations for time intervals between a positive FIT result and colonoscopy follow-up vary. In 2006, a Canadian consensus group recommended follow-up colonoscopy within 2 months of a positive FIT result [21]. In 2012, European guidelines recommended that follow-up colonoscopy after a positive FIT result should be scheduled within 31 days of referral [22]. In the same year, Spanish guideline recommended that waiting time from positive FIT to colonoscopy should be within 6 weeks [23]. However, all of these recommendations lack supporting data. Given the lack of supporting evidence for recommendations and the difficulties of rapidly schedule, US guideline provide no recommendation on the time interval between a positive FIT result and follow-up colonoscopy [24].

There are few data on the consequences of different times to colonoscopy after a positive result from a FIT. To date, only a few studies have investigated this topic. An analysis of 100 patients referred for colonoscopy after a positive FIT result found no association between duration of lag and CRC stage or mortality [25]. A study including 231 patients reported that each additional 30-

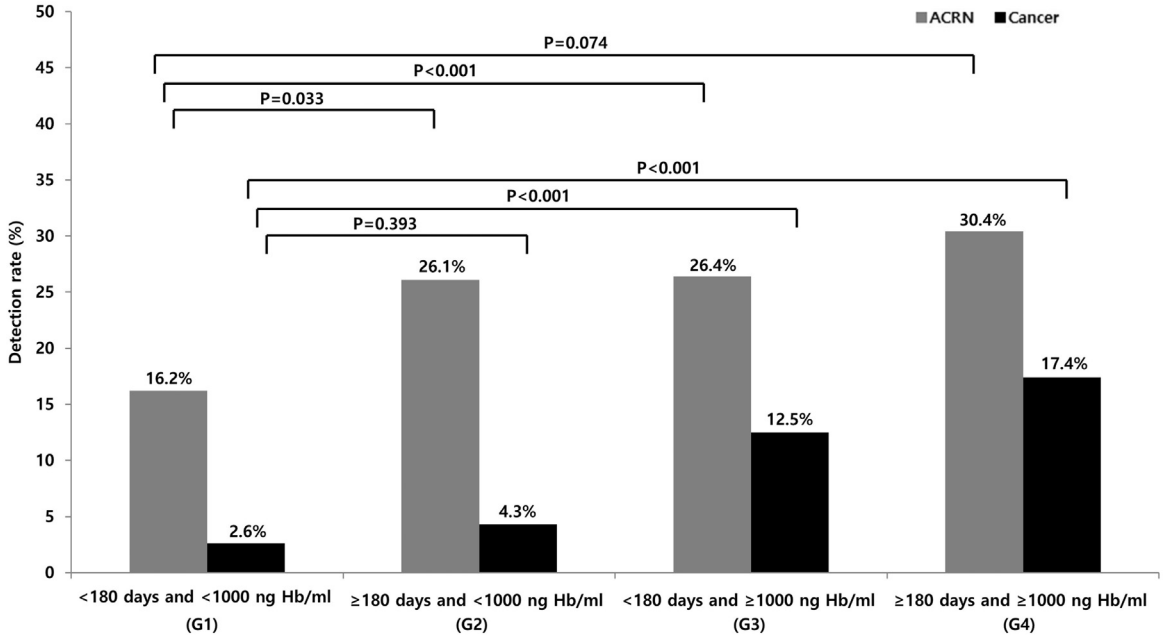

Fig. 1. Detection rate of advanced colorectal neoplasia (ACRN) and cancer classified by combining time to colonoscopy and fecal hemoglobin concentration.

Table 4
Multivariate analysis for risk of colorectal neoplasia according to time to colonoscopy and fecal hemoglobin concentration.

	ACRN		Cancer	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Time to colonoscopy				
<30 days	1 (Reference)		1 (Reference)	
30–59 days	1.01 (0.73–1.39)	0.958	0.91 (0.52–1.58)	0.727
60–149 days	1.05 (0.75–1.48)	0.775	0.63 (0.33–1.21)	0.168
150–179 days	1.18 (0.50–2.81)	0.710	2.10 (0.69–6.39)	0.193
≥180 days	1.73 (0.91–3.27)	0.093	1.93 (0.75–4.93)	0.172
Fecal hemoglobin concentration				
100–200 ng Hb/mL	1 (Reference)		1 (Reference)	
200–300 ng Hb/mL	1.38 (0.93–2.06)	0.114	1.20 (0.34–4.30)	0.778
300–500 ng Hb/mL	1.48 (0.97–2.26)	0.070	4.69 (1.74–12.69)	0.002
500–1000 ng Hb/mL	1.58 (1.01–2.48)	0.044	4.23 (1.48–12.10)	0.007
≥1000 ng Hb/mL	2.80 (1.96–4.01)	<0.001	16.19 (6.81–38.53)	<0.001
Time to colonoscopy and FIT results				
G1: <180 days and <1000 ng Hb/mL	1 (Reference)		1 (Reference)	
G2: ≥180 days and <1000 ng Hb/mL	1.67 (0.78–3.54)	0.185	1.92 (0.44–8.46)	0.388
G3: <180 days and ≥1000 ng Hb/mL	2.23 (1.64–3.02)	<0.001	7.31 (4.44–12.03)	<0.001
G4: ≥180 days and ≥1000 ng Hb/mL	3.13 (1.12–8.74)	0.030	12.45 (3.73–41.57)	<0.001

Values were adjusted for age, sex, and family history of colorectal cancer, smoking status, BMI, history of hypertension, and history of diabetes.
ACRN, advanced colorectal neoplasia; OR, odds ratio; CI, confidence interval; FIT, fecal immunochemical test.

day wait for colonoscopy after a positive FIT result was associated with an increased risk of overall CRN (OR, 1.10; $P = 0.01$), but did not achieve statistical significance for ACRN (OR, 1.07; $P = 0.14$) [7]. However, both studies were underpowered to detect effects on CRN outcomes because the sample size was too small. Recently, a modeling study estimated that, compared with colonoscopy within 2 weeks of a positive FIT result, delays of up to 12 months can reduce the total years of life gained from screening up to nearly 10% [10]. The modeling study reported a steady increase in risk between the duration of the delay and screening benefits lost [10]. Another recent large-scale study found that among patients with a positive FIT result, compared with follow-up colonoscopy at 8–30 days, follow-up after 10 months was associated with a higher risk of CRC and more advanced-stage CRC [26].

In the present study, ACRN risk increased with increasing time to colonoscopy, and patients with follow-up colonoscopy ≥180 days tended to have a significantly higher ACRN risk, compared with those with follow-up colonoscopy <30 days. Patients with time interval to colonoscopy follow-up of 150–179 and ≥180 days also tended to have a higher risk of CRC compared with those with <30 days, but the difference did not achieve statistical significance. The nonsignificant increase for CRC is likely due to the small number of CRC patients. Delays in colonoscopy after a positive FIT result may result in neoplastic progression and this may be lead to higher ACRN or CRC risk. Considering these points, patients with a positive FIT result may have to undergo colonoscopy as soon as possible. However, this increases patient and physician burdens and requires sufficient colonoscopy access and rapid scheduling. Therefore, it may be difficult to get a colonoscopy quickly for all patients with a positive FIT result, especially in countries with limited medical resources. As the medical resources such as colonoscopy access and physicians can be vary from country to country, it may be better to recommend the intervals between a positive FIT result and colonoscopy follow-up for each country rather than recommending the same interval uniformly to all countries.

In CRC screening programs, FIT is used as a binary result ("negative" or "positive") to identify individuals with levels above a predetermined cut-off concentration chosen to suit the requirements of colonoscopy. However, FIT allows quantitation of fecal hemoglobin, and recent some studies have reported a linear increase in ACRN and CRC risk with higher level of fecal hemoglobin [11–13]. Similarly, our study also demonstrated that ACRN and CRC risk increased with increasing fecal hemoglobin concentration. Based on these results, we would like to suggest that among patients with positive FIT result, those with higher fecal hemoglobin concentration should be given priority to undergo colonoscopy as soon as possible if the number of institutions offering colonoscopy is limited. Indeed, we found that the combination of longer time to colonoscopy and higher fecal hemoglobin levels is associated with a much higher ACRN and CRC risk. In particular, the risk of CRC was 12.5-fold higher in G4 than in G1, which supports our suggestion.

To the best of our knowledge, this is the first study to evaluate CRN risk according to combination of longer time to colonoscopy after a positive FIT and higher fecal hemoglobin concentration and to show that this combination is associated with a much higher ACRN and CRC risk. Nevertheless, the current study has several limitations. First, this was a retrospective study with a corresponding potential bias in design. Second, this study was hospital based rather than population based, and thus, there was likely some degree of selection bias. Third, because most patients with positive FIT result underwent colonoscopy within 150 days and only a few patients (6.6%, n = 148/2258) underwent colonoscopy after 150 days, there was a limit to evaluate the effects of long delayed colonoscopy. Fourth, the number of CRC patients was too small to assess the relationship between time to colonoscopy after a positive FIT result and CRC outcomes. Further large-scale studies are needed to clarify their association. Finally, the sample sizes based on the combination of time to colonoscopy (<180 and ≥180 days) and fecal hemoglobin concentration (<1000 and ≥1000 ng Hb/mL) was uneven. However, the prevalence of ACRN was similar between groups with <30, 30–59, 60–149, and 150–179 days and the prevalence of CRC was also similar between groups with <30, 30–59, and 60–149 days. In other words, the prevalence of ACRN increased steeply in group with ≥180 days and the prevalence of CRC increased steeply in group with ≥150 days. Additionally, regarding fecal hemoglobin concentration, the prevalence of CRC increased steeply in group with ≥1000 ng Hb/mL. Therefore, although the sample size were uneven, we classified patients into groups with <180 and ≥180 days and groups with <1000 and ≥1000 ng Hb/mL, considering the clinical aspects.

In conclusion, longer time to colonoscopy after a positive FIT and higher fecal hemoglobin concentration were associated with increased ACRN or CRC risk. In particular, patients who underwent follow-up colonoscopy after 180 days despite fecal hemoglobin ≥1000 ng Hb/mL were much more at risk for CRC. Our results indicate the importance of timely follow-up colonoscopy in patients with a positive FIT result, especially those with higher fecal hemoglobin levels.

Conflicts of interest

None declared.

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