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ORIGINAL ARTICLE

Age-adapted Variation in Screening Interval of Fecal Immunochemical Test May Improve its Participation and Colonoscopy Acceptance

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Goals: We determined appropriate intervals for administering the fecal immunochemical test (FIT) and performance outcomes in an Asian national colorectal cancer (CRC) screening program.

Background: The optimal interval for FIT in CRC screening is unclear, especially in Asian populations.

Study: Between January 2009 and December 2015, 13,480 individuals aged 50 years or older with an initial negative FIT result underwent 2 rounds of FIT screening at intervals of 1 (annual group, 5333), 2 (biennial group, 7363), or 3 years (triennial group, 784). Positive rates of FIT, colonoscopy acceptance, colonoscopy findings, and detection rates for CRC and advanced neoplasia were compared according to FIT intervals.

Results: The overall positivity rate of FIT in the second screening round was significantly higher in men and in older subjects than in the entire sample. Younger subjects were less likely to undergo annual FIT (36.0% vs. 46.4%, $P < 0.001$). The colonoscopy acceptance rate was decreased in the biennial and triennial groups compared with an annual group among younger subjects (odds ratio, 0.56; 95% confidence interval, 0.33-0.95 for the biennial group vs. odds ratio, 0.19; 95% confidence interval, 0.03-1.37 for the triennial group). Detection rates for CRC and advanced neoplasia in the second round were significantly higher and accompanied by increased FIT screening intervals in older, but not younger subjects.

Conclusions: Age-adapted variation in FIT screening intervals, such as annual screening for elderly subjects and biennial screening for younger subject, may improve FIT participation and colonoscopy acceptance.

Key Words: colon cancer, fecal immunochemical test, screening, quality, colonoscopy

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According to the World Health Organization, the incidence of colorectal cancer (CRC) is rapidly increasing in Asian countries, including Korea.[1] The fecal occult blood test has been well-established as a primary screening modality for CRC that decreases mortality.[2–6] The fecal immunochemical test (FIT) is superior to guaiac-based tests for preventing CRC development due to its enhanced detection of advanced neoplasia.[7–9] However, despite the proven benefit of FIT, the optimal interval for screening remains unclear.

Currently, the majority of US organizations recommend annual FIT screening,[10,11] whereas most European countries recommend biennial FIT screening.[12] Recommendations for annual FIT screening may lead to poor year-to-year adherence in clinical practice, with corresponding negative impacts on CRC incidence and mortality. A previous Dutch population–based CRC screening trial[13] failed to show associations between FIT screening interval (1 to 3 y) and detection rates for advanced neoplasia in the second screening round. However, hemoglobin concentration ≥ 50 ng/mL was used as the cutoff for positive FIT results, limiting the application of its findings.

Furthermore, the optimal screening interval for FIT has not been evaluated in an Asian population. The aim of this study was to investigate the appropriate interval for FIT and FIT performance in a national CRC screening program.

METHODS

Population and Study Design

We sought to determine the appropriate interval for FIT and evaluate its performance in the context of a Korean national CRC screening program for asymptomatic people aged 50 years or older who completed 2 consecutive FIT screening rounds (annually, biennially, or triennially) as a part of the National Cancer Screening Program (NCSP)[14] between January 1, 2009 and December 31, 2015.

The NCSP recommends a single annual FIT examination as the initial CRC screening method for people aged 50 years or older,[14] but ultimately, the actual screening interval depends on the participation of the program participants. All participants were notified of their FIT results and those with positive test results in the first round were excluded from the study. Subjects were also excluded if they refused to participate in routine CRC screening or had symptoms or signs indicating the need for colonoscopy. When second round FIT tests revealed positive results, they were invited back for colonoscopy. This study was

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The authors declare that they have nothing to disclose..
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approved by the Institutional Review Board of Kyung Hee University Hospital at Gang Dong (KHNMC IRB 2016-05-014) and the need for informed consent was waived for this retrospective study.

FITs

We used quantitative FIT (OC-Sensor DIANA; Eiken Chemical Co. Ltd, Tokyo, Japan) with 1-day sampling. Hemoglobin concentration ≥ 100 ng/mL was used as the cutoff value for a positive result.[14–17] All participants were instructed to sample their stool while preventing contact with water or urine, but there were no restrictions related to diet or use of medication.

Definition of Variables

The screening interval was defined as the time between 2 FIT screenings. We defined screening-detected cancers as CRCs diagnosed within each interval of positive FIT results

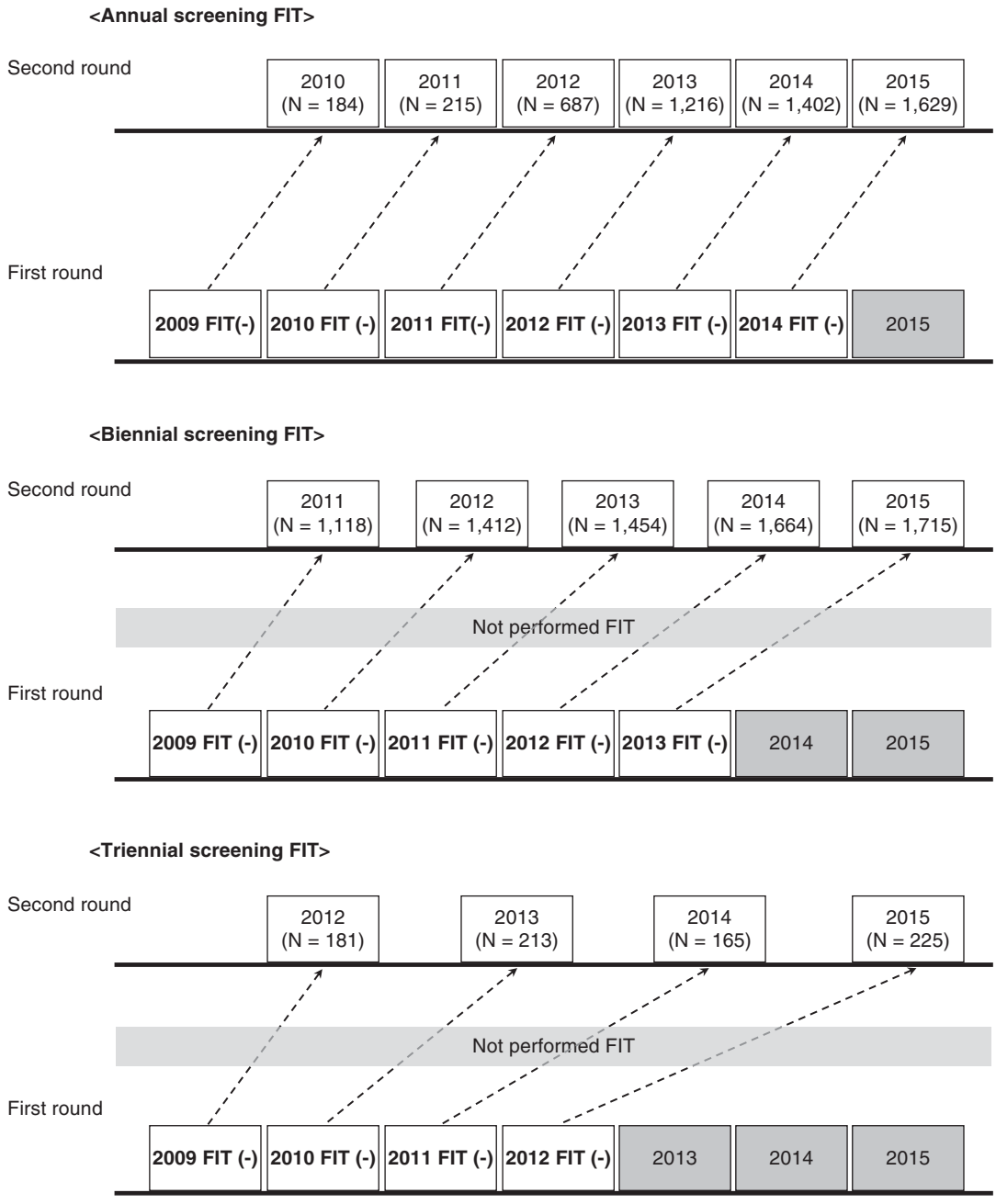

FIGURE 1. Overview of study design. The study included subjects with negative index FIT screening results from 2009 to 2015. Annual FIT screening, 1-year interval between index and subsequent round; biennial FIT screening, 2-year interval between index and subsequent round after negative index FIT; triennial FIT screening, 3-year interval between index and subsequent round. FIT indicates fecal immunochemical test.

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TABLE 1. Characteristics of Screening Participants, 2009-2015

	2009			2010			2011		
Variables	**Total**	**FIT (+)**	**OR (95% CI)**	**Total**	**FIT (+)**	**OR (95% CI)**	**Total**	**FIT (+)**	**OR (95% CI)**
Gender [n (%)]									
Male	1278	28 (2.2)	Ref	1547	25 (1.6)	Ref	1562	28 (1.8)	Ref
Female	2574	22 (0.9)	0.39 (0.22-0.68)	2919	15 (0.5)	0.31 (0.17-0.60)	3153	27 (0.9)	0.47 (0.28-0.81)
Age group [n (%)] (y)									
50-65	2925	33 (1.1)	Ref	3383	22 (0.7)	Ref	3307	34 (1.0)	Ref
65-75	782	15 (1.9)	1.71 (0.93-3.17)	919	15 (1.6)	2.54 (1.31-4.91)	1155	12 (1.0)	1.01 (0.52-1.96)
75 +	145	2 (1.4)	1.23 (0.29-5.16)	164	3 (1.8)	2.85 (0.84-9.61)	253	9 (3.6)	3.55 (1.68-7.49)

CI indicates confidence interval; FIT, fecal immunochemical test; OR, odds ratio; Ref, reference.

that were registered in the Korea Central Cancer Registry.[18] Positive rates of FIT were calculated as the proportions of subjects with a positive test result on second round examination. Colonoscopy acceptance was defined as colonoscopy following a positive FIT result. The younger population was defined as patients aged 50 to 64.9 years, and the older population was defined as patients aged 65 years or older according to the World Health Organization guidelines. Advanced neoplasia was defined as the presence of lesions >10 mm with a villous component, high-grade dysplasia, or carcinoma.

Statistical Analysis

The primary outcomes of this study were advanced neoplasia detection rate and cancer detection rate per FIT interval. Secondary outcomes were participation rates, positive rates of FIT, and colonoscopy acceptance rates for 1-, 2-, and 3-year interval groups.

Continuous variables were compared using 2-tailed Student *t* tests, and categorical variables were compared using 2-tailed χ^2 tests or the Fisher exact tests. FIT positivity at each year, cancer detection rate, and advanced neoplasia detection rate were evaluated by logistic regression. We computed odds ratios and 95% confidence intervals using logistic regression. All *P*-values were 2 tailed, and $P < 0.05$ were considered statistically significant. Data analyses were conducted using SPSS software, version 21.0 (SPSS, Chicago, IL).

RESULTS

We identified 25,682 individuals invited to participate in the NCSP FIT screening program at our center during the study period. Of these individuals, 5333 in the annual group, 7363 in the biennial group, and 784 in the triennial group were selected. The outcomes of annual FITs were compared with those for biennial and triennial FITs. The study design is detailed in Figure 1. During 2009 to 2015, the positive rate of FIT each year was higher in men and in older subjects (Table 1).

FIT Performance

The participation rate was dramatically decreased in the triennial group compared with the annual and biennial groups (20.8% annual vs. 28.7% biennial and 3.1% triennial). The median screening intervals for FIT were 12.3 [interquartile range (IQR) 4.1] months in the annual group, 24.4 (IQR, 4.4) months in the biennial group and 36.2 (IQR, 5.2) months in the triennial group. The younger (age, 50 to 65 y) subjects underwent annual FIT less frequently compared with the elderly subjects ($P < 0.001$) (Table 2). Approximately 4% of all subjects reported a family history of CRC (Table 2).

FIT positivity was not significantly different among the 3 groups ($P = 0.974$). The quantitative value (median, IQR) of FIT was significantly higher in the annual group compared with the biennial group (217.0, 600.0 vs. 250.0, 482.0, $P < 0.001$); however, it was similar in the annual and triennial groups ($P = 0.724$). The median time from positive FIT to colonoscopy was within 1 month for all groups (Table 2). Among patients with positive FIT results, the colonoscopy acceptance rate was significantly higher in the annual than the biennial or triennial groups (82.0% annual vs. 67.9% biennial and 66.7% triennial). Colonoscopic findings for the annual screening group were not significantly different from those of the biennial or triennial groups. The detection rates for advanced neoplasia were 15.9% for annual versus 20.0% for biennial and 0% for triennial (Table 2).

FIT Performance According to Screening Interval and Age Group

FIT positivity, colonoscopy acceptance, and detection rate of advanced neoplasia or CRC were compared for the biennial and triennial groups against the annual group according to age (Table 3). Compared with the annual group, FIT positivity was decreased in the biennial and triennial groups, regardless of age group. The colonoscopy acceptance rate was decreased in the biennial or triennial group compared with the annual group in younger subjects, but was increased in older subjects. The detection rate for advanced neoplasia was increased with age and screening interval.

DISCUSSION

FIT screening is usually recommended annually or biennially to reduce mortality and morbidity from CRC. As FIT has a higher detection rate and sensitivity for CRC than guaiac-based screening, the optimal FIT screening interval may vary from the interval for guaiac-based screening, based on the current guidelines.[12,19,20] Recently, van Roon et al[13] showed that the total number of advanced neoplasias found on repeat FIT screening is not influenced by interval length within a range of 1 to 3 years. However, this Dutch study was limited by the use of ≥50 ng/mL hemoglobin concentration as a cutoff value for positive FIT instead of the standard 100 ng/mL.[14–17] Therefore, little is known about the optimal screening intervals and performance of FIT in population-

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TABLE 1. *(continued)*

2012			2013			2014			2015		
Total	**FIT (+)**	**OR (95% CI)**	**Total**	**FIT (+)**	**OR (95% CI)**	**Total**	**FIT (+)**	**OR (95% CI)**	**Total**	**FIT (+)**	**OR (95% CI)**
Gender [n (%)]											
2293	22 (1.0)	Ref	2344	41 (1.7)	Ref	2604	37 (1.4)	Ref	2607	39 (1.5)	Ref
3653	29 (0.8)	0.83 (0.47-1.44)	3885	42 (1.1)	0.61 (0.40-0.95)	4220	39 (0.9)	0.65 (0.41-1.02)	3992	46 (1.2)	0.77 (0.50-1.18)
Age group [n (%)] (y)											
4056	32 (0.8)	Ref	4048	43 (1.1)	Ref	4426	36 (0.8)	Ref	4041	40 (1.0)	Ref
1533	16 (1.0)	1.33 (0.73-2.42)	1751	34 (1.9)	1.84 (1.17-2.90)	1920	24 (1.2)	1.54 (0.92-2.60)	2030	33 (1.6)	1.65 (1.04-2.63)
357	3 (0.8)	1.07 (0.33-3.50)	430	6 (1.4)	1.32 (0.56-3.12)	478	16 (3.3)	4.22 (2.33-7.67)	528	12 (2.3)	2.33 (1.21-4.46)

based screening programs using standard cutoff levels, especially in an Asian population. This is the first study exploring appropriate FIT intervals and FIT performance in a national CRC screening program using a standard cutoff level.

As expected, the positivity rate of FIT in our study was higher in males and elderly subjects, consistent with the findings of a previous study.[21] Participation is a key indicator determining the potential effectiveness of population-based screening programs for CRC. A major advantage of FIT over guaiac-based tests is its higher participation rate.[22] The annual participation rate of FIT in this study (20.8%) was lower than those reported for Western countries (37.9% to 55.8%),[23,24] but higher than that reported in a Japanese study (17.0%).[25] In our study, annual participation in FIT (20.8%) was lower than biennial participation (28.7%), but higher than triennial participation (3.1%). Our findings may justify annual or biennial rather than triennial screening intervals for all age groups. However, optimal screening intervals may be tailored to local participation rates.

The colonoscopy acceptance rate for participants with positive FIT test is also an important component of FIT-based screening. Our colonoscopy acceptance rate was higher than those seen in US studies,[26–28] but significantly lower in biennial and triennial than in annual screening groups (67.9% biennial, 66.7% triennial, 75.6% annual). This result might be explained by the inclusion of annual FIT-group subjects who were more health-conscious than those in the biennial and triennial groups. Therefore, optimal FIT screening intervals should be tailored to colonoscopy acceptance rate as well as FIT participation rate.

Our results indicate that the total number of advanced neoplasias found with repeat FIT screening was not influenced by interval length within a range of 1 to 3 years, consistent with the findings of the aforementioned Dutch study.[13] However, when we focused on elderly subjects aged 65 or older, the detection rate for advanced neoplasia and CRC was significantly higher for biennial than annual screening. In younger subjects, however, the detection rate for advanced neoplasia was not higher in subjects undergoing biennial compared with annual screening. Furthermore, the FIT screening interval was significantly longer and the colonoscopy acceptance rate was significantly lower in the younger group compared with the older group. Our findings suggest that a greater emphasis should be placed on improving FIT participation and colonoscopy acceptance in younger patients. On the basis of our observations, age-adapted variation in FIT screening intervals may be beneficial, specifically annual screening for those aged 65 or older and biennial screening for younger

TABLE 2. Comparative Analysis of Fecal Immunochemical Test Performance in 3 Screening Intervals

Variables	Annual Group	Biennial Group	*P*	Annual Group	Triennial Group	*P*
Participation [n (%)]	5333 (20.8)	7363 (28.7)		5333 (20.8)	784 (3.1)	
Time from index FIT [median (IQR)] (mo)	24.4 (4.4)	12.3 (4.1)	< 0.001	24.4 (4.4)	36.2 (5.2)	< 0.001
Age at index FIT [median (IQR)] (y)			< 0.001			< 0.001
50-65	3206 (60.1)	5122 (69.6)		3206 (60.1)	567 (72.3)	
65-75	1733 (32.5)	1912 (26.0)		1733 (32.5)	186 (23.7)	
75 +	394 (7.4)	329 (4.5)		394 (7.4)	31 (4.0)	
Family history of CRC [n (%)]			< 0.001			< 0.001
Yes	191 (3.6)	306 (4.2)		191 (3.6)	32 (4.1)	
No	4732 (88.7)	7023 (95.4)		4732 (88.7)	751 (95.8)	
Unknown	410 (7.7)	34 (0.4)		410 (7.7)	1 (0.1)	
FIT positivity [n (%)]	59 (1.1)	81 (1.1)	0.974	59 (1.1)	6 (0.8)	0.385
Quantitative value of FIT [median (IQR)]	217 (600)	250 (482)	< 0.001	217 (600)	200 (104)	0.724
Colonoscopy acceptance [n (%)]	44 (0.8)	55 (0.7)	0.297	44 (0.8)	4 (0.5)	< 0.001
Colonoscopic findings			0.679			0.221
Normal	11 (25.0)	13 (23.6)		11 (25.0)	2 (50.0)	
Benign/nonadvanced adenoma	26 (59.1)	31 (56.4)		26 (59.1)	2 (50.0)	
Advanced neoplasia	7 (15.9)	11 (20.0)		7 (15.9)	0 (0.0)	
Time to colonoscopy [median (IQR)] (d)	27.0 (28.0)	26.5 (39.0)	0.935	27.0 (28.0)	24.0 (134.0)	0.932

CRC indicates colorectal cancer; FIT, fecal immunochemical test; IQR, interquartile range.

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TABLE 3. Odds Ratios (95% Confidence Interval) of Fecal Immunochemical Test Performance According to Age Groups and Screening Intervals

		Age at Index FIT			
Performance Characteristics	**FIT Interval**	**Age 50-65 y**	**Age 65-75 y**	**Age 75 + y**	**Overall**
FIT positivity					
	Annual	Ref	Ref	Ref	Ref
	Biennial	0.69 (0.44-1.09)	1.66 (0.90-3.05)	2.09 (0.81-5.38)	0.99 (0.71-1.39)
	Triennial	0.47 (0.14-1.53)	1.17 (0.27-5.11)	1.84 (0.22-15.48)	0.69 (0.30-1.60)
Colonoscopy acceptance					
	Annual	Ref	Ref	Ref	Ref
	Biennial	0.56 (0.33-0.95)	2.10 (1.00-4.42)	1.51 (0.40-5.65)	0.91 (0.61-1.35)
	Triennial	0.19 (0.03-1.37)	1.87 (0.41-8.61)	3.25 (0.35-30.00)	0.62 (0.22-1.72)
Detection of advanced neoplasia					
	Annual	Ref	Ref	Ref	Ref
	Biennial	0.73 (0.25-2.17)	1.91 (1.85-1.97)	1.20 (0.08-19.23)	1.14 (0.44-2.94)
	Triennial	NA	NA	NA	NA
Detection of colorectal cancer					
	Annual	Ref	Ref	Ref	Ref
	Biennial	3.13 (0.36-26.82)	1.91 (1.85-1.97)	1.84 (1.72-1.96)	2.54 (0.53-12.22)
	Triennial	NA	NA	NA	NA

FIT indicates fecal immunochemical test; NA, not applicable; Ref, reference.

subjects. As longer screening intervals lead to higher adherence to rescreening,[2,33] age-adapted variation in FIT screening intervals may improve participation and the cost-effectiveness of FIT. This hypothesis warrants further investigation.

This study has 3 advantages. First, it was based on a population-level, national CRC screening program and included a population that included only asymptomatic participants. The clinical implications of our study may be greatest for countries with FIT-based CRC screening programs. Second, we presented performance data for FIT from 2009 to 2015. The use of a segmentation method with long-term data could minimize potential confounding variables associated with investigating only a single point in time and could increase consistency and reliability in clinical contexts by using data from multiple timepoints. Third, our data were high in quality despite the study's retrospective design, as questionnaires included items about family history of CRC, prior CRC screening, and prior diagnoses of colorectal neoplasm. The limitations of our study may also merit discussion. First, it was a retrospective, nonrandomized study. However, a randomized, controlled study would not reflect the general characteristics of a population-based screening program, and such studies would require large numbers of subjects. Second, this study was conducted in a single referral center participating in the NCSP, therefore potentially vulnerable to bias. Third, the repeat FIT intervals are not assigned but rather self-selected by patients who may have different risk factors for CRC such as a family history. However, patients with risk factors for CRC are likely to be included to biennial or triennial group than annual group in real population-based CRC screening program. Therefore, self-selection rather than assignment is close to real clinical practice. Finally, sample size of our study was small, especially in the triennial group, which may have been underpowered to detect the difference between the age groups. Therefore, prospective, large-scale, nationwide studies are warranted to assess FIT screening intervals after negative FIT results.

In conclusion, age-adapted variation in FIT screening intervals, such as annual screening for elderly subjects and biennial screening for younger subject, may improve FIT participation and colonoscopy acceptance. Prospective, large-scale, nationwide studies are warranted for age-adapted variation in FIT screening intervals for the population-based CRC screening.

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