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Performance of the Fecal Immunochemical Test for Colorectal Cancer Screening Using Different Stool-Collection Devices: Preliminary Results from a Randomized Controlled Trial

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Background/Aims: We are in the process of conducting a randomized trial to determine whether compliance with the fecal immunochemical test (FIT) for colorectal cancer screening differs according to the stool-collection method. This study was an interim analysis of the performance of two stool-collection devices (sampling bottle vs conventional container). **Methods:** In total, 1,701 individuals (age range, 50 to 74 years) were randomized into the sampling bottle group (intervention arm) or the conventional container group (control arm). In both groups, we evaluated the FIT positivity rate, the positive predictive value for advanced neoplasia, and the detection rate for advanced neoplasia. **Results:** The FIT positivity rates were 4.1% for the sampling bottles and 2.0% for the conventional containers; these values were significantly different. The positive predictive values for advanced neoplasia in the sampling bottles and conventional containers were 11.1% (95% confidence interval [CI], −3.4 to 25.6) and 12.0% (95% CI, −0.7 to 24.7), respectively. The detection rates for advanced neoplasia in the sampling bottles and conventional containers were 4.5 per 1,000 persons (95% CI, 2.0 to 11.0) and 2.4 per 1,000 persons (95% CI, 0.0 to 5.0), respectively. **Conclusions:** The impact of these findings on FIT screening performance was unclear in this interim analysis. This impact should therefore be evaluated in the final analysis following the final enrollment period. **(Gut Liver 2016;10:925-931)**

Key Words: Colorectal neoplasms; Early detection of cancer; Screening; Intervention study; Predictive value of tests

INTRODUCTION

Population-based colorectal cancer (CRC) screening using the fecal occult blood test (FOBT) has been shown to be effective for reducing CRC mortality and incidence.[1,2] Although several countries offer the FOBT in primary screening for CRC, participation has not been satisfactory.[3] In Korea, the National Cancer Screening Program (NCSP) provides a fecal immunochemical test (FIT) every year to individuals who are at least 50 years old, but only 25.7% of those eligible participated in 2012.[4] To overcome poor participation, several studies evaluated the effectiveness of various strategies to improve CRC screening compliance, including CRC screening reminders by mail or telephone, provision of information on CRC screening (leaflets), and sending stool-collection devices to people's homes.[5-7]

To investigate strategies to increase CRC screening compliance using the FIT within the NCSP we are in the process of conducting a randomized trial using a 2×2 factorial design with the factors stool-collection device distribution method (mailing vs visiting the clinic) and type of stool-collection device (sampling bottle vs conventional container). Unlike other interventions, the type of stool-collection device can affect FIT results and CRC screening compliance. Sampling bottles (intervention arm) contain a hemoglobin (Hb)-stabilizing buffer to minimize Hb degradation at ambient temperatures.[8,9] However, the conventional containers (control arm) currently being used at the NCSP do not contain an Hb-stabilizing buffer. Therefore, we hypothesized that the sampling bottles would yield better per-

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formance than conventional containers.

In this study, we present the results of an interim analysis of the performance of the stool-collection devices. We compared FIT positivity rates (PRs) and the positive predictive values (PPVs) and detection rates (DRs) for colonic high-risk adenoma, advanced adenoma, CRC, and advanced neoplasia between the sampling bottles and the conventional containers.

MATERIALS AND METHODS

1. Participants

Study participants (age range, 50 to 74 years) were recruited at the National Cancer Center (NCC) and data were collected from February 2013 to January 2014. To recruit study participants, invitation letters were mailed to the target population. Details of the study protocol were published in Shin *et al*.[10] CRC screening recipients (age range, 50 to 74 years) who were registered in the NCSP were included in the study. Participants were excluded if they had been diagnosed with any cancer, undergone colonoscopy or polypectomy, or had a FIT within the previous year. The Institutional Review Board of the NCC approved the study (NCCNCS-12-683).

2. Study design

This study was an interim evaluation of the performance of stool-collection devices over the course of 1 year, a duration chosen because the FIT is offered annually by the NCSP. Telephone interviews were conducted to screen for participants that met the inclusion criteria and verbal informed consent was obtained from participants before enrolment in the study. Participants were randomly allocated by a computer-generated randomization program to receive either a sampling bottle (intervention arm) or a conventional container (control arm). Participants in the intervention arm were provided with a sampling bottle (Eiken Chemical Co., Ltd., Tokyo, Japan), tissue paper to avoid contact of the stool with toilet water, and instructions for stool collection. The sampling bottle consists of a small tube with a cap. The tube contains 2.0 mL Hb-stabilizing buffer to minimize Hb degradation. Attached to the inside of the cap is a thin, 4.2-cm-long sampling probe used to obtain the stool sample. The sampling bottle collects approximately 10 mg of stool. Participants in the control arm were provided with a conventional container and instructions for stool collection. The conventional container consists of a small plastic container with a 2.0-cm-long sampling probe attached to the inside of the cap and does not contain Hb-stabilizing buffer. All participants were instructed to collect several stool samples from one bowel movement and then to submit the samples for the FIT within 24 hours. At the NCC lab, the collected stool specimens were analyzed in an OC-SENSOR DIANA machine (Eiken Chemical Co., Ltd.), an automated analyzer designed to process the sampling bottles. Therefore, samples collected using conventional containers were transferred into sampling bottles so that they could be tested in the same machine. FIT results were mailed to participants within 3 weeks; those who received positive results were contacted by telephone and recommended for colonoscopy, as per standard medical practice. Research staff obtained informed consent from participants when they submitted their stool specimens at clinics.

3. Outcomes and statistical analysis

The primary outcome was the PR of the FIT based on stool samples collected using the sampling bottle or the conventional container. A positive FIT result was defined as an Hb concentration greater than 100 ng/mL, based on the manufacturer's instructions, and the PR was defined as the percentage of participants with a positive FIT result among all participants. Secondary outcomes were the PPVs and DRs for high-risk adenoma, advanced adenoma, CRC, or advanced neoplasia. The PPV was defined as the percentage of participants with colonic lesions detected during a follow-up colonoscopy among participants with a positive FIT result. The DR was defined as the number of participants with colonic lesions per 1,000 participants. High-risk adenomas were defined based on the United States Multi-Society Task Force CRC guidelines for postpolypectomy surveillance.[11] Briefly, adenomas were classified as high-risk if they had a villous histology, evidence of high-grade dysplasia (HGD) or were at least 10 mm in diameter. The presence of three or more smaller adenomas also fitted the criteria for high-risk. Adenomas were classified as advanced if they had a villous or tubulovillous pattern, evidence of HGD, or were greater than 10 mm in diameter. Advanced neoplasia included advanced adenoma and/or carcinoma. Expert endoscopists measured the size of colonic polyps during colonoscopy. Based on histology, polyps were classified as nonneoplastic polyp, adenoma (tubular, tubulovillous, villous, or serrate) or carcinoma by qualified pathologists.

Differences in primary and secondary outcomes between the two different stool-collection devices were analyzed using the chi-square test or Fisher exact test. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated using multiple logistic regression analyses to compare performance between the stool-collection devices. All statistical analyses were performed using the SAS software version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

In total, 1,701 participants were included in this initial study. A study flow diagram for the enrollment process and outcomes is presented in Fig. 1. Participant characteristics are shown in Table 1. Among the participants, 1,259 and 442 submitted stool samples using the conventional container and the sampling bottle, respectively. There were no differences in general charac-

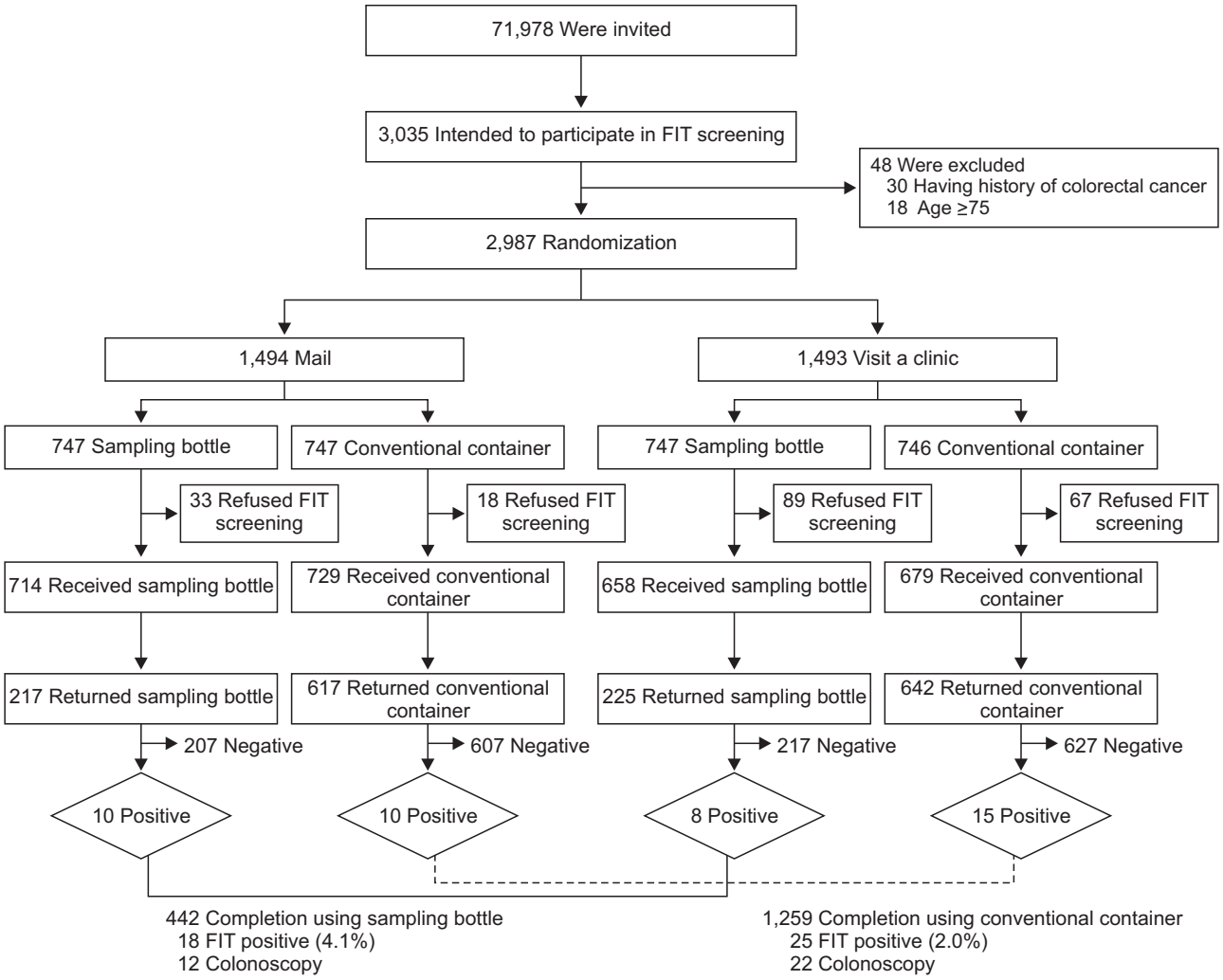

Fig. 1. Flow chart and outcomes of the study.
FIT, fecal immunochemical test.

teristics between the two groups.

Among the 43 participants who had positive FIT results, 34 underwent follow-up colonoscopy. Of the nine FIT-positive participants who did not have a colonoscopy, six were reluctant to have the procedure and three were lost to follow-up. Among those who underwent colonoscopy, 12 (66.7%) were from the sampling bottle group and 22 (88.0%) were from the conventional container group. For both groups, PRs, PPVs and DRs for high-risk adenoma, advanced adenoma, CRC, and advanced neoplasia are shown in Table 2. Among all participants, 43 (2.5%) had a positive FIT result. There were 18 (4.1%) and 25 participants (2.0%) with positive FIT results in the sampling bottle and conventional container groups, respectively. The PR was significantly higher in the sampling bottle group than in the conventional container group (aOR, 1.97; 95% CI, 1.02 to 3.79) after adjusting for sex, age, family history of CRC, medication, and smoking and alcohol consumption history. However, there were no significant differences in the PPVs or DRs for all colonic lesions between the two groups, even high-risk adenomas and advanced neoplasias. In the sampling bottle and conventional container groups, PPVs for high-risk adenoma were 16.7% (95% CI, -0.5 to 33.9) and 12.0% (95% CI, -0.7 to 24.7), respectively. In the sampling bottle and conventional container groups, the PPVs for advanced neoplasia were 11.1% (95% CI, -3.4 to 25.6) and 12.0% (95% CI, -0.7 to 24.7), respectively; the DRs for high-risk adenoma were 6.8 per 1,000 persons (95% CI, -1.0 to 14.0) and 2.4 per 1,000 persons (95% CI, 0.0 to 5.0), respectively, and the DRs for advanced neoplasia were 4.5 per 1,000 persons (95% CI, 2.0 to 11.0) and 2.4 per 1,000 persons (95% CI, 0.0 to 5.0), respectively.

DISCUSSION

The NCSP in Korea has been offering the FIT for primary CRC screening free of charge to individuals who are at least 50 years of age every year since 2004; however, CRC screening

Table 1. Participant Characteristics Based on Stool-Collection Device

Characteristic	Type of stool-collection device		p-value
	Sampling bottle	Conventional container	
Overall	442 (100.0)	1,259 (100.0)	
Sex			0.090
Male	165 (37.3)	528 (41.9)	
Female	277 (62.7)	731 (58.1)	
Age group, yr			0.218
50–64	324 (73.3)	884 (70.2)	
65–74	118 (26.7)	375 (29.8)	
Family history of colorectal cancer			0.620
Absent	399 (90.3)	1,126 (89.4)	
Present	43 (9.7)	133 (10.6)	
Aspirin or NSAID or warfarin			0.368
No	331 (74.9)	942 (74.8)	
Yes	81 (18.3)	262 (20.8)	
No answer	30 (6.8)	55 (4.4)	
Smoking			0.332
Never	275 (62.2)	786 (62.4)	
Ever	125 (28.3)	403 (32.0)	
No answer	42 (9.5)	70 (5.6)	
Drinking			0.617
Never	220 (49.8)	616 (48.9)	
Ever	196 (44.3)	581 (46.2)	
No answer	26 (5.9)	62 (4.9)	

Data are presented as number (%).
NSAID, nonsteroidal anti-inflammatory drug.

compliance is still low compared with screening for stomach, breast, and cervical cancers.[4] System-related barriers decrease participation in CRC screening;[12] therefore, we are in the process of conducting a randomized trial to assess compliance according to stool-collection method. Here, we initially compared the performance of stool-collection devices (sampling bottle vs conventional container) for FIT screening.

The most interesting finding was a higher PR for sampling bottles compared with conventional containers. The PR was twice as high in the sampling bottle group (4.1%) as in the conventional container group (2.0%). According to the 2008 USPSTF, the PR of various commercial FIT brands was 2.0% to 5.9%.[13] Previous studies that used a sampling bottle (OC-Sensor; Eiken Chemical Co., Ltd., Tokyo, Japan) with the same cutoff value (100 ng/mL) as our study reported similar or slightly higher PR values in the Netherlands, 4.8% to 6.0%;[14-18] Italy, 4.2% and 4.5%;[19,20] and Belgium, 4.7%.[21] The lower PR in the conventional container group in our study was consistent with results from a Korean study that reported a PR of 2.5% for NCSP recipients who used a conventional container for the FIT.[22] The lower PR in the conventional container group may have been due to Hb degradation, because the conventional container does not contain Hb-stabilizing buffer.[8] Even in the presence of Hb-stabilizing buffer, fecal Hb degradation can still occur[23] and it has been shown in a clinical laboratory-based study that Hb can on average decrease by 29 ng/mL per day.[24] Thus, stool samples stored in a conventional container without Hb-stabilizing buffer are more likely to result in a negative FIT.

In a buffer-free container, a previous study found that 36.7% of stool specimens that initially had a positive FIT result had a negative result after 24 hours at room temperature. Moreover, six positive stool specimens with Hb concentration of less than 200 ng/mL tested negative within 24 hours.[9] In our study, all participants were instructed to submit their stool specimens to a clinic within 24 hours; however, it is possible that Hb degradation still occurred, resulting in the lower PR value in the conventional container. In addition, the sample probe is longer and thinner in the sampling bottle than in the conventional container and this may have made it easier for participants to sample various parts of stools, as was requested. An image of a stool-collection device is shown in Shin *et al.*[10]

The PPVs and DRs for advanced neoplasia were slightly high-

Table 2. Performance of Sampling Bottles and Conventional Containers

	Sampling bottle (n=442)	Conventional container (n=1,259)	Sampling bottle vs conventional container
			aOR (95% CI)
FIT positive, n (%)	18 (4.1)	25 (2.0)	1.97 (1.02–3.79)
Colonoscopy after positive FIT	12 (66.7)	22 (88.0)	-
Positive predictive value, % (95% CI)			
Nonadvanced adenomas	16.7 (-0.5 to 33.9)	28.0 (10.4 to 45.6)	0.58 (0.08 to 4.07)
High-risk adenoma by USMSTF guidelines*	16.7 (-0.5 to 33.9)	12.0 (-0.7 to 24.7)	1.33 (0.07 to 26.61)
Advanced adenomas†	5.6 (-5.0 to 16.2)	4.0 (-3.7 to 11.7)	-
CRC	5.6 (-5.0 to 16.2)	8.0 (-2.6 to 18.6)	-
Advanced neoplasia‡	11.1 (-3.4 to 25.6)	12.0 (-0.7 to 24.7)	3.46 (0.13 to 87.78)
Detection rate per 1,000 (95% CI)			
Nonadvanced adenomas	6.8 (-1.0 to 14.0)	5.6 (1.0 to 10.0)	1.32 (0.34 to 5.19)
High-risk adenoma by USMSTF guidelines*	6.8 (-1.0 to 14.0)	2.4 (0.0 to 5.0)	3.57 (0.70 to 18.22)
Advanced adenomas†	2.3 (-2.0 to 7.0)	0.8 (-1.0 to 2.0)	3.82 (0.23 to 64.56)
CRC	2.3 (-2.0 to 7.0)	1.6 (-1.0 to 4.0)	1.46 (0.13 to 16.27)
Advanced neoplasia‡	4.5 (2.0 to 11.0)	2.4 (0.0 to 5.0)	2.16 (0.36 to 13.10)

The models were adjusted for sex, age, family history of colorectal cancer, medications, smoking, and alcohol consumption.
aOR, adjusted odds ratio; CI, confidence interval; FIT, fecal immunochemical test; USMSTF, United States Multi-Society Task Force; CRC, colorectal cancer.
*High-risk included advanced adenoma, adenoma with villous histology, high-grade dysplasia (HGD), ≥3 adenomas, or size ≥10 mm; †Advanced adenoma: size ≥10 mm, villous histology, or high-grade dysplasia (HGD); ‡Advanced neoplasia included advanced adenoma and CRC.

er in the sampling bottle group than in the conventional container group; however, these differences were not statistically significant. Also, the values for both study groups were lower than those of previous studies using a sampling bottle (OC-sensor; Eiken Chemical Co., Ltd.) with a cutoff Hb concentration of 100 ng/mL.[16-18,20,25-27] The low values may be due to the large percentage of participants aged 50 to 64 years, whereas other studies included older subjects.[15,16] Advanced neoplasias were found more frequently with increasing age.[28] In addition, while the diagnostic yield was higher in males than in females,[15,28] our study included a high proportion of females.

Our study has several limitations. First, the sample size was small; thus, comparison of the performance between stool-collection devices was limited. The higher PR in the sampling bottle group may result in an increase of the false positive rate, which caused subjects to undergo unnecessary colonoscopies, thus generating unnecessary costs. However, as we are still recruiting study participants, we will evaluate this performance again at the end of the study. Second, the conventional container group had a greater number of participants than that of the sampling bottle group. The data used in the present study were part of a 2×2 factorial intervention trial: (1) sampling bottle received by mail; (2) conventional container received by mail; (3) sampling bottle received at the clinic; and (4) conventional container received at the clinic. To date, the rate of compliance of those who received a sampling bottle at the clinic or via mail was lower than that in those who received the conventional container. We assume that the participants were accustomed to the use of the conventional container, because the NCSP has been offering it since 2004. Third, follow-up colonoscopy compliance after a positive FIT was lower in the sampling bottle group (66.7%) than in the conventional container group (88.0%) and previous studies,[21,27] even though participants were encouraged (via telephone) to have a colonoscopy. Nevertheless, DRs were slightly higher in the sampling bottle group, albeit not significantly so, which suggests that a similar follow up colonoscopy compliance rate in the two groups would have facilitated comparison of the performance.

Despite these limitations, our study had several strengths. First, we used a randomized design, which minimizes bias so that the groups can be reliably compared. Second, to our knowledge, this was the first study to evaluate the performance of different stool-collection devices for CRC screening within a population-based screening program and thus we can apply the study results to the target population in the NCSP system. Additionally, our study used a cutoff Hb concentration of 100 ng/mL, which is consistent with the cutoff level of the majority of healthcare facilities that use the OC-SENSOR analyzer. Therefore, the results of this study may be applicable to the target population for CRC screening using current technological methods.

In conclusion, the PR was significantly higher in the sampling bottle group. However, the PPV and DR ware not different between the sampling bottle and conventional container groups.

These findings may have resulted in large numbers of false positives, leading to the need for more colonoscopies and increasing costs. Therefore, the impact of our findings on the performance of FIT screening was not clear in this interim analysis; it should be further evaluated in the final analysis after the end of the final enrollment to contribute to the development of evidence-based strategies for CRC screening.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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