Risk Stratification Score Improves Sensitivity for Advanced Colorectal Neoplasia in Colorectal Cancer Screening: The Oshima Study Workgroup

Masau Sekiguchi, MD, PhD[1,2,3], Yasuo Kakugawa, MD[3], Hiroaki Ikematsu, MD, PhD[4], Kinichi Hotta, MD[5], Kenichi Konda, MD, PhD[6], Yusaku Tanaka, MD[7], Hiroyuki Takamaru, MD, PhD[3], Masayoshi Yamada, MD, PhD[3], Taku Sakamoto, MD, PhD[3], Yutaka Saito, MD, PhD[3], Kenichiro Imai, MD[5], Sayo Ito, MD[5], Yoshikatsu Koga, MD, PhD[8], Motoki Iwasaki, MD, PhD[9], Yoshitaka Murakami, PhD[10] and Takahisa Matsuda, MD, PhD[1,2,3]

INTRODUCTION: **Noninvasive colorectal cancer (CRC) screening methods with higher sensitivity for advanced colorectal neoplasia (ACN) than the fecal immunochemical test (FIT) alone are warranted. This study aimed to elucidate the diagnostic performance of a risk stratification score calculated using baseline individual characteristics and its combination with FIT for detecting ACN.**

METHODS: **This cross-sectional analysis of data from a prospective cohort in Izu Oshima, Japan, included asymptomatic individuals age 40–79 years who underwent both 2-day quantitative FIT and screening colonoscopy. The 8-point risk score, calculated based on age, sex, CRC family history, body mass index, and smoking history, was assessed. Colonoscopy results were used as reference.**

RESULTS: **Overall, 1,191 individuals were included, and 112 had ACN. The sensitivity and specificity of the 1-/2-day FIT (cutoff: 50–200 ng Hb/mL) for ACN were 17.9%–33.9% (4.9%–22.0% for right-sided ACN) and 91.8%–97.6%, respectively. The risk score's c-statistic for ACN was 0.66, and combining the score (cutoff: 5 points) with 1-/2-day FIT (cutoff: 50–200 ng Hb/mL) yielded a sensitivity and specificity for ACN of 46.4%–56.3% (43.9%–48.8% for right-sided ACN) and 76.6%–80.8%, respectively. The specificity of the risk score and FIT combination for all adenomatous lesions was 82.4%–86.4%.**

DISCUSSION: **The 8-point risk score remarkably increased the sensitivity for ACN, particularly for right-sided ACN. Although the specificity decreased, it was still maintained at a relatively high level. The risk score and FIT combination has the potential to become a viable noninvasive CRC screening option.**

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INTRODUCTION

The fecal immunochemical test (FIT) is widely used as a primary noninvasive test for colorectal cancer (CRC) screening based on its diagnostic performance and the effect of fecal occult blood test on CRC-related mortality and incidence reduction (1–11). Nevertheless, the diagnostic performance of the FIT is not perfect and interval cancer is a concern, although imperfect performance can be compensated, to some extent, through periodic test repetition (10–12).

The sensitivity of the FIT for advanced colorectal neoplasia (ACN) is reportedly relatively low (10,11). The diagnostic performance of the FIT can be adjusted by changing the cutoff level of the quantitative FIT and/or by using multiple FIT samples per screening; however, the effects of these adjustments are considered to be limited, and further noninvasive screening methods with higher sensitivity are warranted (10,11). Of the existing tools, a risk score calculated based on easily collectable factors regarding individual characteristics with the ability to stratify screened individuals in ACN risk is expected to be useful, particularly when used in combination with the FIT (13–17). Several risk scores are currently available, including the Asia-

[1]Cancer Screening Center, National Cancer Center Hospital, Tokyo, Japan; [2]Division of Screening Technology, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan; [3]Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan; [4]Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan; [5]Division of Endoscopy, Shizuoka Cancer Center, Shizuoka, Japan; [6]Division of Gastroenterology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [7]Division of Gastroenterology, Keiyu Hospital, Yokohama, Japan; [8]Division of Developmental Therapeutics, EPOC, National Cancer Center, Kashiwa, Japan; [9]Epidemiology and Prevention Group, National Cancer Center, Tokyo, Japan; [10]Department of Medical Statistics, Toho University, Tokyo, Japan. **Correspondence:** Masau Sekiguchi, MD, PhD. E-mail: masekigu@ncc.go.jp. Takahisa Matsuda, MD, PhD. E-mail: tamatsud@ncc.go.jp.

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Pacific Colorectal Screening (APCS) score and 8-point risk score (13–18). The APCS score was developed and validated using data from populations in the Asia-Pacific region (13). The 8-point risk score was recently developed through modification of the APCS score based on data analysis of the Japanese population; the score was expected to have a slightly increased discriminatory ability (15–18). Although these scores have attracted much attention globally, they are not widely used even in the Asia-Pacific region partly because their usefulness has not been fully evaluated (16,17). Noticeably, the diagnostic performance of the FIT and aforementioned risk scores combination has not been sufficiently clarified. There is a need for sensitivity and other important measures of diagnostic performance associated with a risk score, including specificity, to be assessed and compared with those of the currently adopted methods using the FIT with various cutoff levels and different sample numbers per screening.

In this study, we aimed to elucidate the diagnostic performance of a risk stratification score—the 8-point risk score—and its combination with the FIT for ACN and to compare it with that of the 1- and 2-day FIT alone with different cutoff levels, using data on asymptomatic screened individuals who underwent both 2-day quantitative FIT and screening colonoscopy.

METHODS

Study setting and design

This study was approved by the Ethics Committee for Clinical Research of the National Cancer Center Hospital in Tokyo, Japan (No. 2015-175).

This was a cross-sectional analysis of data from a cohort of the Oshima study, a prospective cohort study conducted in Izu Oshima (an island in Japan) that aimed to evaluate the diagnostic ability and effectiveness of CRC screening modalities and biomarkers (19). All residents on the island aged 40–79 years without uncontrollable complications, including unstable angina, acute myocardial infarction, heart failure, chronic respiratory disease, and bleeding tendency, that made the safe performance of colonoscopy difficult were recruited to the Oshima study. After informed consent was obtained, the 2-day FIT and screening colonoscopy were performed for all recruited individuals between November 2015 and June 2017. Participants' baseline characteristics and lifestyle factors were also surveyed using questionnaires to enable calculation of the risk score. The FIT, colonoscopy, and score calculation were conducted without previous knowledge of the results of other tests. Individuals who underwent incomplete colonoscopy (poor bowel preparation and/or not reaching the cecum), did not hand in 2-day FIT samples, had a history of colorectal surgery or colonoscopic treatment, or lacked the information required for score calculation were excluded from this study.

FIT

The FIT was conducted using the 2-day sampling method. Participants were asked to collect 2-day FIT samples and hand them in within 30 days before colonoscopy. The collected samples were preserved in cold conditions and sent to the laboratory of the National Cancer Center East, Kashiwa, Japan, where fecal hemoglobin quantitation was performed using the OC-sensor System (Eiken Chemical, Tokyo, Japan). FIT results, expressed in ng Hb/mL (100 ng Hb/mL is equivalent to 20 μg Hb/g feces), were then obtained.

Colonoscopy procedure

All colonoscopy procedures were conducted to investigate the whole colon and rectum using video colonoscopes with the functions of narrow-band imaging and magnification (CF-HQ290ZI, PCF-Q260AZI; Olympus, Tokyo, Japan). A total of 25 highly experienced endoscopists who were board certified by the Japanese Gastrointestinal Endoscopy Society participated in the study and performed colonoscopy procedures. Polyethylene glycol or magnesium citrate solution was administered in the morning of the day of the procedure for bowel preparation. Colonoscopy was performed after nurses confirmed adequate bowel preparation.

Calculation of the risk score

The 8-point risk score was calculated in this study. The score was calculated based on the following factors: sex (male: 1 point, female: 0), age (40–49 years: 0, 50–59 years: 2, 60–69 years: 3, and

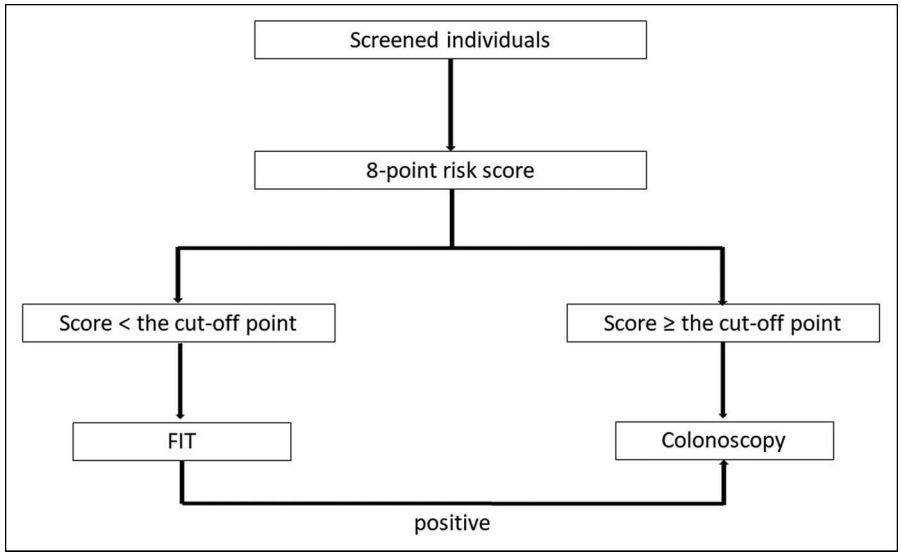

Figure 1. Screening method with combined use of the 8-point risk score and the FIT. FIT, fecal immunochemical test.

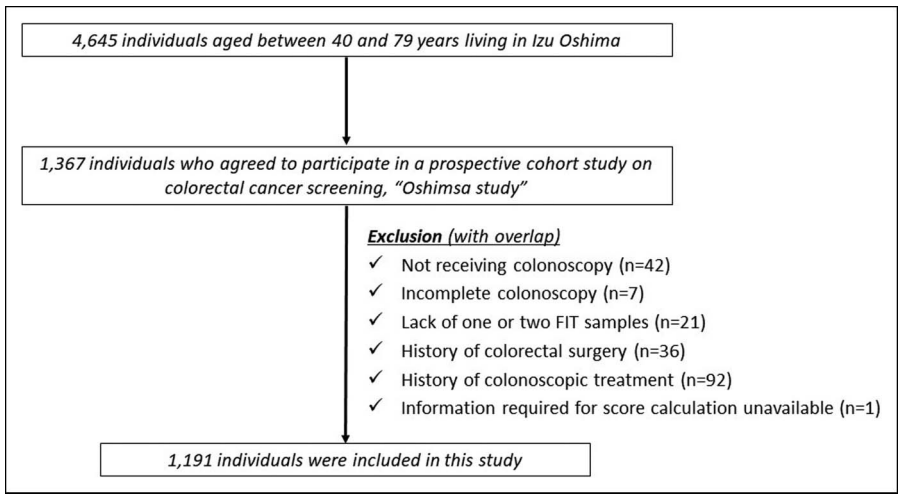

Figure 2. Flow chart showing the inclusion of study participants. FIT, fecal immunochemical test.

≥70 years: 3.5), CRC family history (presence of ≥2 first-degree relatives with CRC: 2, others: 0), body mass index (kg/m^2) (≤22.5: 0, >22.5: 0.5), and smoking history (≤18.5 pack-years: 0, >18.5: 1) (15,18). This score categorizes screened participants into 3 subgroups, i.e., the low-risk (<3 points), moderate-risk (≥3 to <5 points), and high-risk (≥5 points) groups.

Assessment of the diagnostic performance of FIT and risk score

The diagnostic performance of the FIT and 8-point risk score was evaluated using the colonoscopy results as a reference. The sensitivity, specificity, positive predictive value, and negative predictive value for ACN and the sensitivities for CRC, advanced adenoma, and right- and left-sided ACN were assessed. The specificity for all adenomatous lesions, including nonadvanced adenomas, was examined because ACN-negative cases included nonadvanced adenoma cases that might benefit from colonoscopy and polypectomy in CRC prevention (20,21). ACN comprised CRC (with invasion beyond the muscularis mucosa) and advanced adenoma (an adenoma with a diameter ≥10 mm, high-grade dysplasia, or prominent villous component), and its final diagnosis was confirmed pathologically (22,23). Right- and left-sided ACNs were defined as those located in the proximal colon (the cecum and ascending and transverse colon) and distal colon (the descending and sigmoid colon and rectum), respectively.

The diagnostic accuracy of 4 noninvasive screening methods using the FIT and the 8-point risk score was evaluated. First, the 1-day FIT alone (results of the FIT on the first day) with the different cutoff levels of 50–200 ng Hb/mL. Second, the 2-day FIT alone with the different cutoff levels of 50–200 ng Hb/mL. Third, the 8-point risk score alone. Fourth, combination of the 8-point risk score and FIT. This combination is a method in which the FIT is offered to individuals with risk scores lower than the cutoff point, and colonoscopy is offered to those with higher risk scores and those with positive FIT after lower risk scores (Figure 1) (14).

Statistical analysis

Diagnostic performance measures of the screening tests are expressed with 95% confidence intervals (CIs). The discriminatory abilities of the 8-point risk score for ACN and right- and left-sided ACN were examined using receiver operating characteristic curves and c-statistics. To assess the diagnostic performance of

Table 1. Characteristics of study participants

Characteristics	Study participants (n = 1,191)
Age, yr	63 (53–70)
Age groups, yr	
40–49	210 (17.6%)
50–59	256 (21.5%)
60–69	415 (34.8%)
≥70	310 (26.0%)
Sex	
Male	518 (43.5%)
Female	673 (56.5%)
BMI, kg/m^2	22.8 (20.8–25.0)
Smoking	
Nonsmoker	570 (47.9%)
Current/past smoker	621 (52.1%)
Alcohol	
Nondrinker	435 (36.5%)
Current/past drinker	756 (63.5%)
Family history of CRC	
Absent	1,058 (88.8%)
One first-degree relative with CRC (+)	128 (10.7%)
2 or more first-degree relative with CRC (+)	5 (0.4%)
No. of individuals with neoplastic lesions	
With ACN	112 (9.4%)
With CRC	10 (0.8%)
With advanced adenoma	102 (8.6%)
With right-sided ACN	53 (4.5%)
With left-sided ACN	70 (5.9%)
With adenomatous lesions	612 (51.4%)

Data are presented as median (interquartile range) or n (%).
ACN, advanced colorectal neoplasia; BMI, body mass index; CRC, colorectal cancer.

the 8-point risk score, the cutoff score was set at 5 points, which is the cutoff score for the high-risk group among the 3 subgroups stratified by the score, as proposed in previous studies (15,18). The number of colonoscopies needed to detect one ACN lesion for a given screening method was calculated as the number of colonoscopies in which ACN was detected divided by the total number of colonoscopies performed for individuals with a positive noninvasive screening test.

All data analyses were performed using SPSS software, version 26.0 (IBM, Armonk, NY), and EZR, version 1.4.1 (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (24).

RESULTS

Characteristics of the study participants

A flow chart of participant inclusion is shown in Figure 2. In total, 1,191 individuals (518 [43.5%] men) with a median age of 63.0 years (interquartile range: 53.0–70.0) were included. The characteristics of the participants are summarized in Table 1. Of the 1,191 participants, 112 (9.4%) had ACN and 612 (51.4%) had at least one adenomatous polyp.

Diagnostic accuracy of the FIT

The diagnostic accuracy of the FIT and number of colonoscopies needed to detect one ACN lesion are summarized in Table 2. The sensitivity and specificity for ACN of the 1-day FIT with cutoff levels of 50–200 ng Hb/mL were 17.9%–24.1% and 95.0%–97.6%, respectively. The corresponding values for the 2-day FIT (cutoff levels: 50–200 ng Hb/mL) were 22.3%–33.9% and 91.8%–96.5%, respectively. The sensitivities of the 1- and 2-day FIT (cutoff levels: 50–200 ng Hb/mL) for right-sided ACN were 4.9%–12.2% and 7.3%–22.0%, respectively.

Discriminatory ability of the 8-point risk score for ACN

The findings on the discriminatory ability of the 8-point risk score for ACN and right- and left-sided ACN are shown in Table 3. The receiver operating characteristic curve of the risk score for ACN is described in Figure 3, with the c-statistics of 0.66 (95% CI: 0.61–0.72). The c-statistics of the score for right-sided ACN and left-sided ACN were 0.71 (95% CI: 0.65–0.78) and 0.63 (95% CI: 0.56–0.69), respectively.

Diagnostic performance of the risk score and its combination with the FIT

Table 4 summarizes the diagnostic performance of the 8-point risk score and its combination with the FIT. When the score (cutoff: 5 points) was used alone, the sensitivity and specificity for ACN were 35.7% and 82.8%, respectively, and the sensitivities for CRC, advanced adenoma, right-sided ACN, and left-sided ACN were 40.0%, 35.3%, 39.0%, and 31.0%, respectively.

The combination of the risk score with the FIT yielded higher sensitivities for the lesions than the risk score alone. The sensitivities of the combination for ACN and CRC were 46.4%–50.0% and 70.0%–80.0%, respectively, with 1-day FIT (cutoff: 50–200 ng Hb/mL) and 49.1%–56.3% and 100%, respectively, with 2-day

Table 2. Diagnostic performance of the 1-day and 2-day FIT with different cutoff levels

	1-day FIT				2-day FIT			
FIT cutoff value (ng Hb/mL)	50	100	150	200	50	100	150	200
Sensitivity for ACN, %	24.1 (16.5–33.1)	22.3 (15.0–31.2)	18.8 (12.0–27.2)	17.9 (11.3–26.2)	33.9 (25.3–43.5)	30.4 (22.0–39.8)	24.1 (16.5–33.1)	22.3 (15.0–31.2)
For CRC, %	80.0 (44.4–97.5)	80.0 (44.4–97.5)	70.0 (34.8–93.9)	60.0 (26.2–87.8)	100.0 (74.1–100.0)	100.0 (74.1–100.0)	100.0 (74.1–100.0)	90.0 (55.5–99.7)
For advanced adenoma, %[a]	18.6 (11.6–27.6)	16.7 (10.0–25.3)	13.7 (7.7–22.0)	13.7 (7.7–22.0)	27.5 (19.1–37.2)	23.5 (15.7–33.0)	16.7 (10.0–25.3)	15.7 (9.2–24.2)
For right-sided ACN, %[b]	12.2 (4.1–26.2)	7.3 (1.5–19.9)	7.3 (1.5–19.9)	4.9 (0.6–16.5)	22.0 (10.6–37.2)	14.6 (5.6–29.2)	12.2 (4.1–26.2)	7.3 (1.5–19.9)
For left-sided ACN, %[c]	29.3 (18.1–42.7)	29.3 (18.1–42.7)	24.1 (13.9–37.2)	24.1 (13.9–37.2)	41.4 (28.6–55.1)	39.7 (27.0–53.4)	31.0 (19.5–44.5)	31.0 (19.5–44.5)
Specificity for ACN, %	95.0 (93.5–96.2)	96.5 (95.2–97.5)	97.2 (96.1–98.1)	97.6 (96.5–98.4)	91.8 (89.9–93.3)	94.3 (92.7–95.6)	95.6 (94.2–96.8)	96.5 (95.2–97.5)
PPV for ACN, %	33.3 (23.2–44.7)	39.7 (27.6–52.8)	41.2 (27.6–55.8)	43.5 (28.9–58.9)	29.9 (22.1–38.7)	35.4 (25.9–45.8)	36.5 (25.6–48.5)	39.7 (27.6–52.8)
NPV for ACN, %	92.3 (90.6–93.8)	92.3 (90.6–93.8)	92.0 (90.3–93.5)	92.0 (90.2–93.5)	93.0 (91.3–94.5)	92.9 (91.2–94.3)	92.4 (90.7–93.9)	92.3 (90.6–93.8)
No. of colonoscopies needed to detect one ACN lesion	3.0	2.5	2.4	2.3	3.3	2.8	2.7	2.5

Data on sensitivity, specificity, PPV, and NPV are presented with their 95% confidence intervals.
ACN, advanced colorectal neoplasia; FIT, fecal immunochemical test; NPV, negative predictive value; PPV, positive predictive value.
[a]Cases with advanced adenoma (not having CRC) were assessed.
[b]Cases with right-sided ACN (not having left-sided ACN) were assessed.
[c]Cases with left-sided ACN (not having right-sided ACN) were assessed.

Table 3. Prevalence of advanced colorectal neoplasia according to the 8-point risk score and the score's discriminatory ability

8-Point risk score	ACN	Right-sided ACN	Left-sided ACN
≥0, <1	4.1% (4/98)	0.0% (0/98)	4.1% (4/98)
≥1, <2	3.0% (2/66)	1.5% (1/66)	1.5% (1/66)
≥2, <3	3.9% (6/155)	1.3% (2/155)	3.2% (5/155)
≥3, <4	7.4% (27/367)	2.7% (10/367)	4.9% (18/367)
≥4, <5	11.8% (33/279)	6.8% (19/279)	6.8% (19/279)
≥5, <6	17.9% (34/190)	8.4% (16/190)	10.5% (20/190)
≥6	16.7% (6/36)	13.9% (5/36)	8.3% (3/36)
Low (≥0, <3)	3.8% (12/319)	0.9% (3/319)	3.1% (10/319)
Intermediate (≥3, <5)	9.3% (60/646)	4.5% (29/646)	5.7% (37/646)
High (≥5)	17.7% (40/226)	9.3% (21/226)	10.2% (23/226)
C-statistics	0.66 (0.61–0.72)	0.71 (0.65–0.78)	0.63 (0.56–0.69)

Data on c-statistics are presented with 95% confidence intervals. The other data are presented as proportion with actual number of cases per total number.
ACN, advanced colorectal neoplasia.

FIT (cutoff: 50–200 ng Hb/mL). The sensitivities of the combination for right-sided ACN and left-sided ACN were 43.9%–46.3% and 44.8%–48.3%, respectively, with 1-day FIT (cutoff: 50–200 ng Hb/mL) and 43.9%–48.8% and 50.0%–58.6%, respectively, with 2-day FIT (cutoff: 50–200 ng Hb/mL). The specificity of the combination for ACN varied between 79.1% (FIT cutoff: 50 ng Hb/mL) and 80.8% (FIT cutoff: 200 ng Hb/mL) with 1-day FIT and between 76.6% (FIT cutoff: 50 ng Hb/mL) and 80.0% (FIT cutoff: 200 ng Hb/mL) with 2-day FIT. The prevalence of nonadvanced adenomas among false-positive cases for ACN using the risk score and its combination with the FIT was approximately 60%. The specificity of the risk score and FIT combination for all adenomatous lesions, including nonadvanced adenomas, was 82.4%–86.4%.

DISCUSSION

This study elucidated the diagnostic performance of the 8-point risk score and its combination with the FIT in CRC screening. Our study clearly shows that the screening sensitivity of the FIT alone for ACN is low even if the cutoff levels and number of samples are changed and that the use of the risk score can enhance the screening sensitivity.

All examined screening approaches using the risk score had higher sensitivities for ACN than that observed with the FIT alone. However, using the risk score alone (without FIT) was problematic because it presented low sensitivity for CRC (40.0%). Thus, combining the risk score with the FIT is strongly considered a more favorable option. Some previous studies have demonstrated the improved detectability of ACN with the additional use of a risk score to the FIT (14,25–27). Our study confirmed the improved sensitivity with the use of a risk score; notably, our study newly clarified that the improvement of the screening sensitivity with the use of the risk score is more remarkable for right-sided ACN. The observed sensitivities for right-sided ACN of the FIT alone (1-/2-day FIT with cutoff levels of 50–200 ng Hb/mL) and the combined use of the risk score (cutoff: 5 points) with the FIT (1-/2-day FIT with a cutoff level of 50–200 ng Hb/mL) were 4.9%–22.0% and 43.9%–48.8%, respectively. It is postulated that the low screening sensitivity of the FIT for right-sided ACN can be compensated by using the risk score. Several strengths further distinguish our studies from other previous studies.

An important strength of this study is that in addition to sensitivity, other measures of diagnostic accuracy, including specificity, were elucidated. Specificity is an important measure for screening tests; however, it is often difficult to evaluate because of lack of data on screened individuals with negative primary screening test results. However, colonoscopy was performed for all participants, regardless of the FIT and risk score results. Therefore, the specificity of the tests could be assessed using colonoscopy results as a reference. Moreover, because each examination (the FIT, risk score calculation, and colonoscopy) was

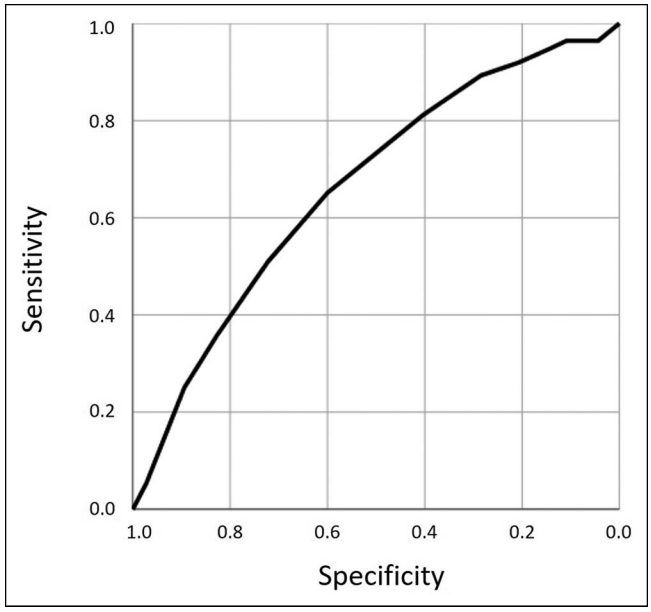

Figure 3. The receiver operating characteristic curve of the 8-point risk score for advanced colorectal neoplasia.

Table 4. Diagnostic performance of the 8-point risk score and its combination with the FIT

The cutoff point of the risk score	5 points								
The sample number of FIT	None	1-day FIT				2-day FIT			
FIT cut-off value (ng Hb/mL)	—	50	100	150	200	50	100	150	200
Sensitivity for ACN, %	35.7 (26.9–45.3)	50.0 (40.4–59.6)	49.1 (39.5–58.7)	46.4 (37.0–56.1)	46.4 (37.0–56.1)	56.3 (46.6–65.6)	54.5 (44.8–63.9)	50.0 (40.4–59.6)	49.1 (39.5–58.7)
For CRC, %	40.0 (12.2–73.8)	80.0 (44.4–97.5)	80.0 (44.4–97.5)	70.0 (34.8–93.9)	70.0 (34.8–93.9)	100.0 (74.1–100.0)	100.0 (74.1–100.0)	100.0 (74.1–100.0)	100.0 (74.1–100.0)
For advanced adenoma, %[a]	35.3 (26.1–45.4)	47.1 (37.1–57.2)	46.1 (36.2–56.2)	44.1 (34.3–54.3)	44.1 (34.3–54.3)	52.0 (41.8–62.0)	50.0 (39.9–60.1)	45.1 (35.2–55.3)	44.1 (34.3–54.3)
For right-sided ACN,** %[b]	39.0 (24.2–55.5)	46.3 (30.7–62.6)	43.9 (28.5–60.3)	43.9 (28.5–60.3)	43.9 (28.5–60.3)	48.8 (32.9–64.9)	46.3 (30.7–62.6)	46.3 (30.7–62.6)	43.9 (28.5–60.3)
For left-sided ACN, %[c]	31.0 (19.5–44.5)	48.3 (35.0–61.8)	48.3 (35.0–61.8)	44.8 (31.7–58.5)	44.8 (31.7–58.5)	58.6 (44.9–71.4)	56.9 (43.2–69.8)	50.0 (36.6–63.4)	50.0 (31.7–58.5)
Specificity for ACN, %	82.8 (80.4–85.0)	79.1 (76.6–81.5)	80.0 (77.5–82.3)	80.5 (78.0–82.9)	80.8 (78.3–83.1)	76.6 (74.0–79.1)	78.2 (75.6–80.7)	79.2 (76.7–81.6)	80.0 (77.5–82.3)
PPV for ACN, %	17.7 (13.0–23.3)	19.9 (15.4–25.1)	20.3 (15.7–25.6)	19.8 (15.2–25.2)	20.1 (15.4–25.5)	20.0 (15.7–24.8)	20.6 (16.1–25.7)	20.0 (15.5–25.2)	20.3 (15.7–25.6)
NPV for ACN, %	92.5 (90.7–94.1)	93.8 (92.1–95.3)	93.8 (92.0–95.3)	93.5 (91.8–95.0)	93.6 (91.8–95.1)	94.4 (92.7–95.8)	94.3 (92.6–95.7)	93.9 (92.1–95.3)	93.8 (92.0–95.2)
No. of colonoscopies needed to detect one ACN lesion	5.7	5.0	4.9	5.0	5.0	5.9	4.9	5.0	4.9
Prevalence of nonadvanced adenomas among false-positive cases for ACN, %	63.4 (56.1–70.4)	60.9 (54.2–67.3)	61.1 (54.3–67.7)	61.9 (55.0–68.5)	61.8 (54.8–68.5)	59.5 (53.2–65.6)	59.6 (53.0–65.9)	61.2 (54.4–67.6)	61.1 (54.3–67.7)
Specificity for all adenomatous lesions (including nonadvanced adenomas), %	88.3 (85.3–90.8)	84.8 (81.6–87.6)	85.5 (82.4–88.3)	86.2 (83.1–88.9)	86.4 (83.3–89.0)	82.4 (79.0–85.4)	83.6 (80.3–86.5)	85.0 (81.8–87.8)	85.5 (82.4–88.3)

Data on sensitivity, specificity, PPV, and NPV are presented with their 95% confidence intervals.
ACN, advanced colorectal neoplasia; FIT, fecal immunochemical test; NPV, negative predictive value; PPV, positive predictive value.
[a]Cases with advanced adenoma
(not having CRC) were assessed.
[b]Cases with right-sided ACN
(not having left-sided ACN) were assessed.
[c]Cases with left-sided ACN
(not having right-sided ACN) were assessed.

conducted in a manner that was blinded to the results of the other examinations, the diagnostic test performance was evaluated without any bias related to the other test results. Our study demonstrated that the use of the risk score resulted in a lower specificity for ACN than that with the use of the FIT alone. In addition to the higher sensitivity, the lower specificity with the use of the risk score should be considered. However, even with the use of the risk score, the relatively high specificity for ACN (approximately 80%) was maintained, and the number of colonoscopies needed to detect one ACN lesion was not very high. Furthermore, the specificity for all adenomatous lesions, including nonadvanced adenomas, was higher. Even among false-positive cases for ACN using the score, nonadvanced adenomas were detected in more than half of the cases for which colonoscopy performance can be justified because of the effect of lowering CRC incidence and mortality through polypectomy (20,21). Given this, the combined use of the risk score and FIT is believed to have the potential to become a viable noninvasive screening option with higher ACN sensitivity than the FIT alone if the colonoscopy capacity allows.

Another strength of this study is that detailed findings on the diagnostic accuracy of the FIT with different cutoff levels and numbers of samples per screening were elucidated. This was possible because all study participants received the 2-day quantitative FIT. The limited effect of different cutoff levels and sample numbers on the diagnostic performance of the FIT was clearly confirmed herein. Even the 2-day FIT with a low cutoff level showed a low sensitivity for ACN, particularly right-sided ACN. This finding emphasizes the importance of wider screening options with a higher sensitivity that can be provided along with the use of the risk score.

Regarding a risk stratification score, the 8-point risk score was examined in this study (15,18). Our study's significance is that the moderate discriminatory ability of this risk score for ACN was proven in a population independent from that used for its development. A recent study analyzing several risk scores using the German population data also demonstrated similar results regarding the discriminatory ability of this risk score (17). Considering that the discriminatory ability of the 8-point risk score has been proven in several different populations, the use of the score and FIT has the potential to improve CRC screening not only in Japan but also in other regions through the provision of wider screening options.

This study has several limitations. First, although the results of the colonoscopy, the most reliable modality for detecting colorectal lesions, were used as a reference for the analyses, it is possible that some colorectal neoplastic lesions may have been overlooked. However, there is little possibility that ACNs were overlooked in this study because all colonoscopy procedures were performed by highly experienced endoscopists from advanced Japanese institutions. Given the high adenoma detection rate (51.4%), the colonoscopy quality in this study is believed to be high. Second, our study used data collected from the population of 1 Japanese island, which may limit its generalizability. Although further studies involving other types of populations are warranted, it is believed that our findings have sufficient potential to be applicable to various populations, considering that the moderate discriminatory ability of the risk score has been reported in different populations (15,17). Third, only the 8-point risk score was examined as a risk stratification score in this study because we judged that this score was most suitable for the study participants. It is warranted to assess other existing scores' diagnostic performance using various types of populations in the future. Considering that any existing scores' diagnostic ability is reportedly not perfect at present, the improvement of a risk score by finding and incorporating a novel scoring item is another issue to be challenged (16,17). If a higher specificity for ACN of the combined use of an improved risk score with the FIT is achieved, this combination may become the standard screening method.

In conclusion, the use of the 8-point risk score remarkably increased the screening sensitivity for ACN and particularly for right-sided ACN, compared with the FIT alone, despite decreasing the specificity. However, the specificity was also maintained at a relatively high level, particularly when considering all adenomatous lesions. The risk score and FIT combination has the potential to become a viable noninvasive screening option with a higher sensitivity for ACN than the FIT alone, allowing for the selection of a more suitable screening method based on the colonoscopy resource capacity.

CONFLICTS OF INTEREST

Guarantor of the article: Masau Sekiguchi, MD, PhD.

Specific author contributions: M.S. and T.M.: designed the study, and collected and analyzed the data. M.S.: drafted the article. All authors contributed to the interpretation of the data. Y.K., H.I., K.H., K.K., Y.T., H.T., M.Y., T.S., Y.S., K.I., S.I., Y.K., M.I., Y.M., and T.M.: contributed to the critical revision of the article for important intellectual content. All authors approved the final version of the article.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Screening sensitivity of the fecal immunochemical test (FIT) for advanced colorectal neoplasia (ACN) is relatively low.
- ✓ Further noninvasive screening methods with higher sensitivity are warranted.

WHAT IS NEW HERE

- ✓ Risk stratification score, 8-point risk score, remarkably increases sensitivity for ACN, particularly right-sided ACN, compared with FIT alone.
- ✓ Although risk score lowers the specificity, it remains at a reasonably high level.

TRANSLATIONAL IMPACT

- ✓ Combining risk score and FIT may become a noninvasive screening option with a higher sensitivity for ACN than FIT alone.

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