Impact of Fecal Hb Levels on Advanced Neoplasia Detection and the Diagnostic Miss Rate For Colorectal Cancer Screening in High-Risk vs. Average-Risk Subjects: a Multi-Center Study

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OBJECTIVES: The Asia-Pacific Colorectal Screening (APCS) scoring system was developed to identify high-risk subjects for advanced neoplasia. However, the appropriate fecal immunochemical test (FIT) cutoff for high-risk population may be different from that of average-risk population. We aimed to evaluate the FIT performance at different cutoffs in high-risk subjects undergoing colorectal cancer (CRC) screening.

METHODS: We prospectively enrolled asymptomatic subjects aged 50–75 years. Using the APCS score, subjects were stratified into either the average-risk or high-risk groups. All subjects were tested with one-time quantitative FIT and underwent colonoscopy. We compared the FIT performance for advanced neoplasia between two groups using different cutoffs (5 (FIT5), 10 (FIT10), 20 (FIT20), 30 (FIT30), and 40 (FIT40) μg Hb/g feces).

RESULTS: Overall, 1,713 subjects were recruited, and 1,222 (71.3%) and 491 (28.7%) were classified as average-risk and high-risk, respectively. Advanced neoplasia was detected in 90 (7.4%) of the average-risk subjects and 65 (13.2%) of the high-risk subjects. In the high-risk group, by decreasing the cutoff from FIT40 to FIT5, the sensitivity increased by 33.8 percentage points with decreased specificity by 11 percentage points. In the average-risk group, the sensitivity increased by 20 percentage points with decreased specificity by 9.6 percentage points. At the lowest cutoff (FIT5), the number of needed colonoscopies to find one advanced neoplasia was 2.8 and 6.1 for the high-risk and average-risk groups, respectively.

CONCLUSIONS: Using an appropriate FIT cutoff for CRC screening in high-risk subjects could improve CRC screening performance and reduce the unnecessary colonoscopies. To maintain high sensitivity and specificity for advanced neoplasia, the optimal cutoff FIT in the high-risk subjects should be lower than that in the average-risk subjects.

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Subject Category: Colon/Small Bowel

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide. The incidence of CRC is rising on many continents, including Asia. Several guidelines for CRC screening recommend screening to begin at age 50. Fecal occult blood test (FOBT) is widely recommended in an organized screening program, and the results from randomized trials confirmed the reduction in the incidence and mortality of CRC by using guaiac-based FOBT (gFOBT). However, gFOBT has some disadvantages, as it is not specific to hemoglobin and diet restriction is required. In addition, rehydration of stool sample may cause false-positive and -negative results. Previous studies demonstrated that fecal immunochemical test (FIT) for human hemoglobin was superior in sensitivity for advanced neoplasia (34–57%) than gFOBT (14–20%) with comparable specificity (91–95%) to gFOBT(92–97%). A recent recommendations by the US Multi-Society Task Force on CRC screening and the updated Asia-Pacific consensus preferred the use of FIT over gFOBT.

Nevertheless, the population of individuals older than 50 years of age is large and complex with regard to clinical risk factors. In the Asia-Pacific regions, a risk-stratified scoring system (Asia-Pacific Colorectal Screening (APCS) scoring system) based on clinical risk factors for advanced neoplasia in Asian population has been developed and validated.
These calculated items include age (0 ≤ 50, 2 = 50–69, 3 ≥ 70), gender (0 = female, 1 = male), smoking status (0 = never, 1 = current/past), and family history of CRC (0 = absent, 2 = present). The APCS score stratifies subjects into low-risk (score 0–1), moderate-risk (score 2–3), and high-risk (score 4–7) groups (Table 1). The prevalence of advanced neoplasia increased 2.6-fold in the moderate-risk group and 4-fold in high-risk group compared with the low-risk group. Notably, all subjects at age 50 without additional CRC risk factors are classified as moderate-risk by the APCS score; however, they are generally considered average-risk in the standard CRC screening program. Later, the usefulness of the APCS score as a predictor for advanced neoplasia has been studied in different racial population including Chinese, Korean, Vietnamese, Thais and Western population. An evidence based on the use of risk score (APCS score) combining with FIT to prioritize subjects for colonoscopy and to reduce colonoscopy workload is emerging. A previous study from Thailand evaluated the combination of the APCS score and FIT to predict advanced neoplasia and to prioritize colonoscopy. According to APSC score and FIT results, 948 asymptomatic subjects were categorized into four different groups (high-risk with positive FIT, high-risk with negative FIT, average-risk with positive FIT, and average-risk with negative FIT). The prevalence of advanced neoplasia was significantly 6.15-fold higher in the participants with both high-risk and positive FIT compared with the other three groups. Recently, a multi-center prospective study from 12 Asia-Pacific countries including 5,657 asymptomatic subjects who underwent CRC screening showed that by selecting high-risk subjects and low/average-risk subjects with a positive FIT for colonoscopy the colonoscopy workload could be reduced by 50% compared with the strategy of primary colonoscopy in those same subjects.

However, the impact of different hemoglobin levels of the FIT on advanced neoplasia, cancer detection, and the diagnostic miss rates between high-risk and average-risk subjects has not been studied. We therefore aimed to evaluate the diagnostic performance of the FIT at different cutoffs in high-risk subjects as defined by the APCS scoring system compared to average-risk subjects. We hypothesized that the optimal cutoff FIT in high-risk subjects should be lower than that in average-risk subjects to maintain the high sensitivity for advanced neoplasia while maintaining the high specificity and minimizing the number of colonoscopies needed.

### METHODS

We conducted a prospective study between December 2014 and December 2016 at six university hospitals across Thailand (Chulalongkorn University Hospital, Siriraj Hospital, Rajavithi Hospital, Chiang Mai University Hospital, Prince of Songkla University Hospital, and Khon Kaen University Hospital). Consecutive subjects who visited in a health promotion program at each hospital were eligible for enrollment. The inclusion criteria were subjects aged 50–75 years. The exclusion criteria were subjects with any of lower gastrointestinal-related symptoms (i.e., bowel habit change, gastrointestinal/rectal bleeding, unexplained anemia, abdominal pain, and weight loss), prior colon examination (colonoscopy/radiologic imaging), and a history of CRC, inflammatory bowel disease, colonic resection, or suspected hereditary CRC (≥1 first-degree relative with CRC before 60 years or ≥2 first-degree relatives with CRC). Subjects with bloating or dyspeptic symptoms that are not suggestive of CRC were recruited. All subjects provided written informed consent. This study was approved by the Institutional Review Board at each hospital (Thai Clinical Trial Registry, TCTR20140228001).

### Risk-stratified scoring system

All subjects were interviewed to assess their clinical risk using the APCS score by trained nurses (Table 1). Originally, the APCS score stratified subjects into three groups: low-risk (score 0–1), moderate-risk (score 2–3), and high-risk (score 4–7; Table 1). Because our study population was aged 50–75, our study only included moderate-risk and high-risk subjects. For instance, women at age 50 (score; 0+2 = 2) and men at age 50 (score; 1+2 = 3) were classified as moderate-risk in the APCS system, and they are considered average-risk in the standard CRC screening program. Women aged 50 or older with a family history of CRC (score; 0+2+2 = 4) and men aged 70 or older who smoke (score; 1+3+1 = 5) were classified as high-risk. We therefore modified the classification into the average-risk (score 2–3) and high-risk groups (score 4–7) accordingly.

### Fecal immunochemical test

A one-time quantitative FIT (OC-SENSOR, Eiken Chemical, Tokyo, Japan) was used. Subjects received an explanation for stool collection. No diet and medication restriction were required. Subjects collected the stool sample within 3 days before the day of the colonoscopy. The date of stool sampling was labeled, and the stool-filled bottle was submitted on the colonoscopy day. The stool-filled bottle was analyzed using an automated analyzer machine (OC-SENSOR DIANA machine) following the manufacturer’s instructions. The samples were stored at 4 °C and then were analyzed within 7 days from the collection date. We assessed the test performance on advanced neoplasia at different cutoffs (5 (FIT5), 10 (FIT10), 20 (FIT20), 30 (FIT30), and 40 (FIT40) μg Hb/g feces).

### Colonoscopy

Colonoscopists were blinded to the APCS score and FIT results. The colonoscopy was performed in all

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**Table 1** APCS Score for prediction of advanced colorectal neoplasia

| Risk factor                          | Criteria                  | Points |
|-------------------------------------|---------------------------|--------|
| Age (years)                         | < 50                      | 0      |
|                                     | 50–69                     | 2      |
|                                     | ≥ 70                      | 3      |
| Sex                                 | Female                    | 0      |
|                                     | Male                      | 1      |
| Family history of CRC in a first-degree relative | Absent                | 0      |
|                                     | Present                   | 2      |
| Smoking                             | Never                     | 0      |
|                                     | Current or past           | 1      |

APCS, Asia-Pacific Colorectal Screening; CRC, colorectal cancer.

Modified APCS classification: average-risk = score 2–3, high-risk = score 4–7.
the subjects consciously sedated with intravenous midazolam and meperidine/fentanyl. The quality of the bowel preparation was assessed using the Aronchick bowel preparation scales. All identified polyps were removed. The polyp size was measured using 7-mm open jaws of biopsy forceps. Removed polyps were separately labeled and reviewed by local gastrointestinal pathologists at each institution. The cecal intubation rate, withdrawal time, and characteristics of the polyps were recorded. Polyps were classified according to World Health Organization criteria as neoplastic (tubular adenoma, villous adenoma, tubulovillous adenoma, sessile serrated adenoma/polyp (SSA/P), or traditional serrated adenoma) and non-neoplastic. Advanced adenoma was defined as adenoma with high-grade dysplasia, villous adenoma (at least 25%), or adenoma with size ≥10 mm. CRC was defined when malignant cells were observed in intramucosal layer. Advanced neoplasia comprised advanced adenoma and CRC.

Statistical analysis. The colonoscopy results were used as a diagnostic reference standard to determine the FIT performance on advanced neoplasia detection. At the different cutoffs, the positivity, sensitivity, specificity, positive predictive value, and negative predictive value for advanced neoplasia with 95% confidence intervals (CIs) were calculated and compared between the average-risk and high-risk groups. To calculate 95% CIs for a sample proportion, the Wilson score interval method was used. Continuous variables were compared with Student’s t-test, and categorical variables were compared with either the X²-test or Fisher’s exact test. The two-sided statistical tests with a P-value < 0.05 were considered statistically significant. The receiver operating characteristic (ROC) curves and area under the ROC with 95% nonparametric asymptotic CIs were analyzed by using SPSS statistical software (version 23.0; PSS, Chicago, IL, USA). We used the sensitivity of FIT for advanced neoplasia as the primary outcome. We assumed that the sensitivity in the average-risk group was 25% (ref. 24) and that the sensitivity increased 1.5-fold in the high-risk group (37.5%) compared with the average-risk group. For a power of 80% and a two-sided test at alpha = 0.05, 340 high-risk subjects were required. In the Asia-Pacific region, the prevalence of high-risk subjects as defined by the APCS score was ~20%. Therefore, a minimum of 1,700 enrolled subjects were required in this study.

RESULTS

A total of 1,740 subjects were enrolled and 25 subjects were excluded because of missed stool collection (n = 15) and poor bowel preparation (n = 10). Among the remaining 1,715 subjects, the successful cecal intubation rate was 99.9% (1,713/1,715; Figure 1). Thus, 1,713 subjects were included in the analysis. The demographic data of the subjects are shown in Table 2. The mean age was 59.4 ± 7.4 years, and 1,041 subjects (60.8%) were women. One thousand eighty-three (80.7%) had excellent to good bowel preparation and a median withdrawal time of 8 min (interquartile range, 5–12 min). At all FIT cutoffs, there were no significant differences of the median withdrawal time and the proportion of excellent to good bowel preparation between subjects with positive FIT and subjects with negative FIT. Using the APCS score, 1,222 (71.3%) and 491 (28.7%) subjects were classified as average-risk and high-risk, respectively. The prevalence of advanced neoplasia and CRC in the high-risk group was significantly higher than that in the average-risk group ((65 (13.2%) vs. 90

Figure 1  Study enrollment.
The diagnostic accuracy in the high-risk and average-risk groups was analyzed by ROC curves. The area under the ROC curve was 0.74 (95% CI; 0.68–0.81) for the high-risk group and 0.66 (95% CI; 0.60–0.72) for the average-risk group (Figure 3).

**Positivity rate.** In both groups, decreasing the cutoff (from FIT40 to FIT5) increased the positivity rates. The high-risk group had positive rates ranging from 6.3 to 19.1%, and the average-risk group had positive rates ranging from 3.7 to 15.4% (Table 3).

**Sensitivity and specificity for advanced neoplasia.** The performance of the FIT for advanced neoplasia at the different cutoffs between the two groups is summarized in Table 3. At every cutoff, the high-risk group yielded comparable specificity for advanced neoplasia as that in the average-risk group (85.9% vs. 86% for FIT5, 89.7% vs. 91.2% for FIT10, 93.7% vs. 95.2% for FIT20, 94.8% vs. 96.2% for FIT30, and 95.5% vs. 97.2% for FIT40, P > 0.05 for all comparisons, respectively). Meanwhile, two different FIT cutoffs in the high-risk group yielded significantly higher sensitivities than those in the average-risk group (FIT5 (52.3% vs. 34.4%, P = 0.03) and FIT20 (32.3% vs. 17.8%; P = 0.04), respectively). For the remaining cutoffs, the sensitivities tended to be higher in the high-risk group, but the differences were not statistically significant (Figure 2). The diagnostic accuracy in the high-risk and average-risk groups was analyzed by ROC curves. The area under the ROC curve was 0.74 (95% CI; 0.68–0.81) for the high-risk group and 0.66 (95% CI; 0.60–0.72) for the average-risk group (Figure 3).

### Table 2 Demographics of study population

|                  | Number of subjects (N=1,713; %) |
|------------------|----------------------------------|
| **Age (mean ± s.d., years)** |                                  |
| 50–59            | 952 (55.6%)                      |
| 60–69            | 589 (34.4%)                      |
| 70–75            | 172 (10.0%)                      |
| **Sex**          |                                  |
| Male             | 672 (39.2%)                      |
| Female           | 1,041 (60.8%)                    |
| **BMI (mean ± s.d., kg/m²)** |                                |
| 23.8±3.8         |                                  |
| **Smoking**      |                                  |
| Smoking          | 188 (11.0%)                      |
| **First-degree family history of colorectal cancer** | |
| Daily aspirin and/or NSAID user | 159 (9.3%)                 |
| **Risk stratification (APCS score)** |                             |
| Average-risk     | 1,222 (71.3%)                    |
| High-risk        | 491 (28.7%)                      |
| **Prevalence of colorectal neoplasia** |                        |
| Adenoma          | 602 (35.1%)                      |
| Advanced neoplasia | 155 (9.0%)                |
| Colorectal cancer | 15 (0.9%)                   |

APCS, Asia-Pacific Colorectal Screen; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.

(7.4%), P < 0.01) and (10 (2%) vs. 5 (0.4%); P < 0.01), respectively.

**Discussion**

This multi-center study shows the impact of different FIT cutoffs on advanced neoplasia detection between the high-risk and average-risk groups. In contrast to the average-risk group, the high-risk subjects showed increased sensitivity (true-positive rates) when decreasing the FIT cutoff while minimally increasing the false-positive rates. Our study demonstrated that from FIT40 to FIT5, the sensitivity for advanced neoplasia in the high-risk group increased by 33.8 percentage points with decreased specificity by 11 percentage points. In the average-risk group, the sensitivity for advanced neoplasia increased by only 20 percentage points with decreased specificity by 9.6 percentage points. In addition, the NNC for one advanced neoplasia detection was 2.8 in the high-risk group compared to 3.5 to 6.1 in the average-risk group.

**Serrated polyp detection.** Among 1,713 subjects, a total of 12 SSA/Ps were found. There were four large SSA/Ps (≥10 mm) and four SSA/Ps located at the proximal colon (>5 mm). Using the lowest cutoff (FIT5), three SSA/Ps (3/12) were detected; one large SSA/P (1/4) and two proximal SSA/Ps (≥5 mm; 2/4). A total of 23 large hyperplastic polyps (≥10 mm) were found. Three (3/23) were detected by FIT5. No traditional serrated adenoma was found. In the high-risk group, a total of two SSA/Ps and five large hyperplastic polyps were found. All had negative FIT at all cutoffs. In the average-risk group, a total of 10 SSA/Ps and 18 large hyperplastic polyps were found. Three SSA/Ps were detected by FIT5 and FIT10. One SSA/P was detected by FIT20. Three large hyperplastic polyps were detected by FIT5; two were detected by FIT10 and one by FIT20.

In the subgroup analysis of the clinical risk factors for SSA/Ps among 188 smokers, the prevalence of SSA/P was 0.5% and the prevalence of SSA/P in non-smokers was not much higher (0.7%, P = 1.00). Likewise, the prevalence of large hyperplastic polyp was low and comparable (0.5% vs. 1.4%; P = 0.12, respectively). Among 92 obese subjects (BMI ≥ 30 kg/m²), there was no significant difference on the prevalences of SSA/P and large hyperplastic polyp between obese subjects and non-obese subjects (0% vs. 0.7%; P = 1.00 for SSA/Ps and 1.2% vs. 3.3%; P = 0.12 for large hyperplastic polyp), respectively.
Table 3: Diagnostic performance of the different FIT cutoffs for advanced neoplasia in the average-risk group (n=1,222) and high-risk group (n=491)

| Diagnostic test | Risk stratification | FIT (μg Hb/g feces) | 5 | 10 | 20 | 30 | 40 |
|-----------------|---------------------|---------------------|---|----|----|----|----|
| Positivity rate (%; 95% CI) | Average-risk | 15.4% (13.5–17.5%) | 10.2% (8.6–12.0%) | 5.7% (4.6–7.2%) | 4.7% (3.6–6.0%) | 3.7% (2.8–4.9%) |
| | High-risk | 19.1% (15.9–22.9%) | 14.1% (11.3–17.4%) | 9.8% (7.5–12.7%) | 7.3% (5.3–10.0%) | 6.3% (4.5–8.8%) |
| Accuracy (%; 95% CI) | Average-risk | 86.1% (84.0–88.1%) | 91.2% (89.4–92.8%) | 95.2% (93.8–96.4%) | 96.2% (94.9–97.2%) | 97.2% (96.0–98.1%) |
| | High-risk | 85.9% (82.3–89.1%) | 89.7% (86.4–92.4%) | 93.7% (90.9–95.8%) | 94.8% (92.3–96.7%) | 95.5% (93.1–97.3%) |
| Sensitivity (%; 95% CI) | Average-risk | 52.3% (39.5–64.9%) | 38.5% (26.7–51.4%) | 32.3% (21.2–45.1%) | 21.5% (12.3–33.5%) | 16.5% (9.9–30.0%) |
| | High-risk | 44.6% (31.7–58.2%) | 30.2% (16.6–47.9%) | 28.0% (14.6–44.5%) | 22.6% (10.5–40.1%) | 18.8% (9.5–32.0%) |
| Specificity (%; 95% CI) | Average-risk | 86.1% (84.0–88.1%) | 91.2% (89.4–92.8%) | 95.2% (93.8–96.4%) | 96.2% (94.9–97.2%) | 97.2% (96.0–98.1%) |
| | High-risk | 85.9% (82.3–89.1%) | 89.7% (86.4–92.4%) | 93.7% (90.9–95.8%) | 94.8% (92.3–96.7%) | 95.5% (93.1–97.3%) |
| PPV (%; 95% CI) | Average-risk | 16.5% (12.5–21.4%) | 19.4% (14.0–26.2%) | 22.9% (15.0–33.2%) | 24.6% (15.6–36.4%) | 28.9% (18.1–42.7%) |
| | High-risk | 17.1% (13.2–21.2%) | 20.3% (15.2–27.6%) | 24.0% (16.4–32.2%) | 26.8% (18.1–37.0%) | 31.5% (20.5–45.7%) |
| NPV (%; 95% CI) | Average-risk | 94.3% (93.4–95.1%) | 94.0% (93.2–94.7%) | 93.6% (93.0–94.1%) | 93.5% (92.9–94.0%) | 93.5% (92.9–94.0%) |
| | High-risk | 92.2% (90.1–93.9%) | 90.5% (88.7–92.1%) | 90.1% (88.4–91.5%) | 88.8% (87.4–90.0%) | 88.5% (87.2–89.6%) |
| Cancer miss rate (%; 95% CI) | Average-risk | 0% (0.0–43.5%) | 0% (0.0–43.5%) | 20% (3.6–62.5%) | 20% (3.6–62.5%) | 40% (11.8–76.9%) |
| | High-risk | 20% (5.7–51.0%) | 20% (5.7–51.0%) | 20% (5.7–51.0%) | 20% (5.7–51.0%) | 30% (10.8–60.3%) |
| Number needed to screen | Average-risk | 39.4 | 39.4 | 39.4 | 39.4 | 39.4 |
| | High-risk | 14.4 | 14.4 | 14.4 | 14.4 | 14.4 |
| Number needed to colonoscope | Average-risk | 6.1 | 6.1 | 6.1 | 6.1 | 6.1 |
| | High-risk | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 |

95% CI, 95% confidence interval; FIT, fecal immunochemical test; Number needed to screen, number needed to colonoscope to find one case of advanced neoplasia; PPV, positive predictive value; NPV, negative predictive value.

Average-risk defined by Asia-Pacific Colorectal Screening score 2–3 and high-risk defined by Asia-Pacific Colorectal Screening score 4–7. *P < 0.05.
high-risk group when screened using FIT; this was 2.7-fold lower when compared with primary colonoscopy strategy without using the risk score and FIT (NNC, 7.6). However, the NNC for one advanced neoplasia detection was 6.1 in the average-risk group as screened by FIT, which was 2.2-fold lower than that of individuals screened using the primary colonoscopy strategy (NNC, 13.6). This finding indicates that the use of FIT in both high-risk subjects and average-risk subjects and recruiting those with positive FIT for colonoscopy can significantly reduce colonoscopy workload.

Because having first-degree relatives with CRC is associated with two- to threefold increased risk of CRC, these individuals are considered high-risk subjects by default; thus, primary screening colonoscopy is recommended by most professional societies. However, a recent randomized trial comparing an annual FIT at 10 μg Hb/g feces with primary colonoscopy in familial CRC members demonstrated that three rounds of FIT detected all the CRCs and 61% of advanced adenomas, which was equivalent to a one-time colonoscopy. The authors reported that more than 70% of colonoscopies in the colonoscopy group had either normal or insignificant findings. In other words, using FIT as a primary screener in familial CRC members could reduce the colonoscopy workload by 86%. In addition, the NNC for one advanced neoplasia detection was four times lower (four in the FIT group vs. 18 in the colonoscopy group).

Previous studies have recommended that the FIT cutoff should be individualized based on risk factors to enhance effective FIT-based CRC screening. A population-based study from Spain illustrated the impact of different age- and gender-specific cutoffs. Among 663 subjects with a positive FIT at thresholds of 20 and 40 μg Hb/g feces who underwent colonoscopy, decreasing the cutoffs (FIT40 to FIT20) in men or individuals ≥60 years of age increased the CRC detection rate. In addition to age and gender, adding other important CRC risk factors in the APCS scoring system, including familial history of CRC and smoking status, our study demonstrated that lower FIT cutoffs in high-risk subjects could increase the detection rate for CRC from 70 to 80% and for advanced neoplasia from 18 to 52%.

Although there have been earlier studies on different FIT cutoffs in high-risk subjects, these population-based studies only performed colonoscopies in subjects with a positive FIT result; subjects with a negative FIT were not offered a colonoscopy. By this inherent limitation, the sensitivity for advanced neoplasia detection and the CRC miss rate could not be analyzed. In our study, all subjects underwent colonoscopy regardless of the FIT results, which allowed us to calculate the sensitivity for advanced neoplasia detection and the CRC miss rate at all cutoffs. On the basis of the results...
of our study, the lowest cutoff at 5 μg Hb/g feces for screening high-risk subjects provided the highest sensitivity at 52.3% (95% CI, 39.5–64.9%) but still maintained high specificity 85.9% (95% CI, 82.3–89.1%). Because the CRC miss rate is an important concern, our study results should be interpreted with caution because of the small number of detected CRC cases in both groups. Of note, using the lowest FIT5 in the high-risk group still elicited a significant CRC miss rate (n = 2/10)—the two missed cancers were polyps with carcinoma in situ. In the average-risk group, all the CRCs were detected when FIT5 was used. By contrast, at a FIT cutoff of 20 μg Hb/g feces (which is the commonly used cutoff), we missed one cancer (TNM stage IIA).

Although colonoscopy is still the gold-standard diagnostic tool for advanced neoplasia detection and can provide a method of treatment via endoscopic resection, colonoscopies incur high costs and increased workload in the health-care system. In this study, the NNC for one advanced neoplasia detection under the primary colonoscopy strategy in the high-risk group was 7.6. For the FIT-based screening, the NNCs for one advanced neoplasia detection in the high-risk group at each cutoff were 2.8 at FIT5, 2.8 at FIT10, 2.3 at FIT20, 2.6 at FIT30, and 2.6 at FIT40. When using the primary colonoscopy strategy as the reference, the calculated reduction in the NNC for one advanced neoplasia detection was 63% for FIT5, 63% for FIT10, 70% for FIT20, 66% for FIT30, and 66% for FIT40.

There are certain limitations in this study. First, we enrolled all the subjects from the health promotion program at each hospital. Therefore, we cannot avoid self-referral bias. However, the characteristics of our study population were comparable to those previously reported in other population-based studies. The percentage of the high-risk subjects (28%) in our study was also comparable to that in another large multi-center APCS study. Second, this study was based on only one round of FIT screening as a result and did not completely comply with the recommended clinical practice guideline that advises the use of repeated FITs screening to enhance advanced neoplasia detection. There has been an increase in lines of evidence to support the use of one-sample FIT screening. A meta-analysis evaluating the performance of different number of FIT samples on CRC screening showed similar pooled sensitivities for CRC detection (one-sample FIT, two-sample FIT, and three-sample FIT had sensitivities at 79%, 77%, and 80%, respectively). In addition, a cost-effective study comparing between the performance of one-sample and two-sample FIT for CRC by Goede et al. showed that using one-sample FIT in the short interval (1 year) approach was equal to or more cost-effective when compared with the two-sample FIT approach. Recently, the US Multi-Society Task Force on Colorectal Cancer suggests one-sample annual FIT approach for FIT screening. Third, the results of these cutoff values were based on the CRC prevalence in Thailand. Although our prevalence was in line with previously reports from other Asia-Pacific countries, these may not be applicable to other countries with a different CRC prevalence. Fourth, although we had only a handful number of SSA/Ps, our simple analysis on the association between SSA/Ps and FIT results was still keeping with those from the larger study by Chiu HM et al. They demonstrated that the performance of FIT on SSA/P was lower than that of FIT on advanced adenoma. At FIT10, the sensitivity for large SSA/P was 18.4%, whereas the sensitivity for advanced adenoma was 32.4%. Therefore, FIT-based colonoscopy appears to be a suboptimal screening tool for SSA/P detection; perhaps, low risk of blood shredding in SSA/P is the main factor. Imperiale et al. showed the performance of multitarget DNA stool testing compared with FIT on 9,989 participants undergoing screening colonoscopy. They reported that the multitarget DNA test yielded higher sensitivity for SSA/P (42.4%) compared with that for FIT (5.1%) (P < 0.001). The specificity for SSA/P of the multitarget DNA and FIT was 86.6% and 94.9%, respectively. Thus, more studies on other stool tests such as DNA tests may be helpful to predict SSA/P before colonoscopy.

In conclusion, this study indicates that lowering FIT cutoff in high-risk subjects could improve the sensitivity while...
maintaining the same level of specificity for advanced neoplasia similar to the average-risk group. However, in the country with limited resource like Thailand the cost-effectiveness analysis is needed as the number of colonoscopy workload could be higher.

**CONFLICT OF INTEREST**

Guarantor of the article: Rungsun Rerknimitr, MD, who is the corresponding author, accepts the full responsibility for this study.

**Specific author contributions:** Rungsun Rerknimitr: study conception and design, selecting the articles, critical revision of the manuscript. Satimai Aniwat: writing the proposal, submitting the proposal to the Institutional Review Board, analyzing the data, selecting the articles, drafting the manuscript, and submitting the manuscript to CTG. Thaweewis Singsopas: performing colonoscopy and collecting data. Supot Pongprasobchai: performing colonoscopy and collecting data. Ong-Ard Prasontarangkul: performing colonoscopy. Pises Ponponsa: performing colonoscopy and collecting data. Pisaln Wisedopas: histological assessment. Pinit Mairiang: performing colonoscopy. Apichat Sangchan: performing colonoscopy and collecting data. Jaksin Sottisuporn: performing colonoscopy and collecting data. Naruemon Wisedopas: histological assessment. Prin Kullavanijaya: facilitating the study. All authors have approved the final draft of the submitted manuscript.

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**Study Highlights**

**WHAT IS CURRENT KNOWLEDGE**

- The fecal immunochemical test (FIT) is widely recommended as an organized screening program.
- Combining the risk stratification with the FIT is useful for prioritizing colonoscopies and decreasing the colonoscopy workload.

**WHAT IS NEW HERE**

- The optimal cutoff FIT in high-risk subjects should be lower than that in average-risk subjects to provide high sensitivity in detecting advanced neoplasia while maintaining a low colorectal cancer (CRC) miss rate.
- Selecting an appropriate FIT cutoff for CRC screening in high-risk subjects could improve advanced neoplasia detection and may reduce the number of unnecessary colonoscopies.

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