REVIEW

Diagnostic Accuracy Of Fecal Occult Blood Tests For Detecting Proximal Versus Distal Colorectal Neoplasia: A Systematic Review And Meta-Analysis

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Objective: We conducted a systematic review and meta-analysis aimed at evaluating the differences of diagnostic performance of fecal occult blood tests (FOBTs) in detecting advanced colorectal neoplasms located in the proximal versus distal colorectum.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were searched for eligible articles published before August 17, 2018. Two independent reviewers conducted study assessment and data extraction. Diagnosis-related indicators of FOBT for detecting proximal and distal colorectal neoplasms were summarized, and further stratified by the type of FOBT (guaiac-based FOBT (gFOBT) and immunochemical FOBT (iFOBT)). Pooled sensitivities and specificities were calculated using a random effect model. Summary receiver operating characteristic curves were plotted and area under the curves were calculated.

Results: Overall, 31 studies meeting the inclusion criteria were included in this review. For gFOBT, we found no site-specific difference (proximally vs distally located) of pooled sensitivities observed in the colorectal cancer (CRC), advanced adenomas, and advanced neoplasms groups. As for iFOBT, pooled sensitivities for detecting CRC located in the distal colon/rectum were comparable with that in the proximal colon (proximal vs distal, 0.67, 95% CI 0.62–0.72 vs 0.72, 95% CI 0.68–0.75), while higher pooled sensitivities for detecting advanced adenomas and advanced neoplasms located in the distal colon/rectum than for detecting those in the proximal colon were observed for iFOBT with the values of 0.24 (95% CI 0.22–0.25) vs 0.32 (95% CI 0.30–0.34) and 0.25 (95% CI 0.23–0.28) vs 0.38 (95% CI 0.36–0.40), respectively. Summary receiver operating characteristic curve analyses showed similar patterns for both types of FOBT regarding the diagnostic accuracy for detecting colorectal neoplasms according to the anatomical sites of the colorectum.

Conclusion: iFOBT had higher sensitivity for detecting advanced adenomas and advanced neoplasia located in the distal colon/rectum than that for those in the proximal colon.

Keywords: sensitivity, colorectal cancer, screening test

Introduction

With an estimated 1,849,518 new cases and 880,792 deaths occurring in 2018, colorectal cancer (CRC) is the third most commonly diagnosed cancer and fourth most common cause of cancer-related deaths worldwide.[1] Current practices have suggested that screening for CRC is effective in reducing CRC mortality.[2,3] The fecal occult blood test (FOBT) is a non-invasive CRC screening test that has been widely used in many screening programs and is recommended by current guidelines for CRC screening.[4,5] Overall, there are two types of FOBTs which use different mechanisms to identify fecal occult blood. The traditional one is

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the guaiac-based FOBT (gFOBT) for detecting peroxidase activity of heme. Another type of FOBT is immunochemical FOBT (iFOBT, also referred to as FIT) that uses antibodies to specifically detect human hemoglobin in stool, which make fecal immunochemical tests less likely to result in false-positive results due to the ingredients. The iFOBT has been shown to have better analytical and clinical sensitivity and higher detection ability in terms of CRC and its precursors, improved compliance, and cost-effectiveness, compared to gFOBT.[6]

Previous randomized controlled trials have demonstrated that FOBT-based screening could reduce the mortality associated with CRC.[7,8] In a FOBT-based CRC screening, patients with positive FOBT results are scheduled to undergo subsequent colonoscopies for clinical diagnosis. Therefore, the diagnostic performance of FOBT would strongly affect the efficacy of screening. In a meta-analysis including 19 studies the pooled sensitivity of FOBT for CRC was relatively high at 79% (95% CI, 69–86%), with corresponding pooled specificity of 94%.[9] However, some studies have reported that the diagnostic performance of FOBT varied according to the anatomical site of the colorectum.[10,11] Even with screening colonoscopy, which is considered as the gold standard for CRC screening, a much higher protective effect for distal colon/rectum than proximal colon was observed for colonoscopy-based screening.[12] Therefore, the gradient in the efficacy of population-based screening according to the anatomic site of the colorectal lesions may be larger considering the site-specific sensitivities for colorectal neoplasms. Two systematic reviews in this area were published several years ago although the focus on this issue was constricted due to their limited sample size and incomplete study scope of colorectal neoplasia.[10,11] Based on these studies, we conducted an updated systematic review including all relevant studies to further evaluate the diagnostic accuracy of FOBT for CRC and advanced adenomas according to different anatomical sites.

We aimed to evaluate the differences of diagnostic performance of FOBT in detecting colorectal neoplasms located in the proximal versus distal colorectum and to provide important references for designing effective FOBT-based CRC screening programs in the future.

Methods

We conducted a systematic review and meta-analyses following the PRISMA statement.[13]

Data Sources And Search Process

To identify potential studies reporting data on the diagnostic performance of FOBT for detecting colorectal neoplasms of the proximal and distal colon/rectum, two independent investigators searched PubMed, Embase, Cochrane Library, and Web of Science to retrieve studies published before August 17, 2018 using the following combined search terms: [colorectal (or) colon (or) rectum] (and) [cancer (or) neoplasm (or) carcinoma (or) adenoma (or) malignancy] (and) [faecal immunochemical test (or) fecal immunochemical testing (or) fecal immunochemical test (or) faecal immunochemical testing (or) faecal occult blood test (or) FOBT] (and) [detection (or) screening (or) detecting (or) diagnosis]. Detailed search terms and retrieval records are provided in Table S1.

Study Selection

An initial search based on the titles and abstracts was conducted to exclude studies that were not relevant to the study topic. In addition, conference abstracts without full texts or studies written in non-English language were also excluded. For potential relevant articles identified in the initial search, a full-text review was performed using the following inclusion criteria: 1) FOBT results should be reported along with colonoscopy results available as the gold standard of reference; 2) site-specific diagnosis information was provided in detail or the diagnosis-related indicators were accessible to be assessed.

Quality Assessment

Potential risks of bias and applicability of the included studies were assessed according to the Quality Assessment of Diagnostic Accuracy Studies (QUADA-2) scoring system,[14] and the detailed protocol was shown in the supplementary material (Protocol 1).

Data Extraction

Assessment of the included studies was performed independently by two reviewers (ML and XL) during the whole process. When disagreement occurred, consensus was reached through discussion between the authors or referral to the third reviewer (HC and MD). The following information was extracted: year of publication, country, study setting (clinical setting: participants recruited in hospitals or clinics in an opportunistic manner; screening setting: participants recruited in communities in an organized manner), population characteristics (sample size, age, and sex, etc.), diagnostic outcomes, attributes of FOBTs (type, brand, and cut-off value), sensitivity, and specificity.

In this review, we only focused on the diagnostic accuracy of FOBT in one single round of testing. For multiple rounds of FOBT tests, only the first-round result was extracted. Sensitivity was defined as the proportion of FOBT-positive patients among those who were diagnosed with the outcome of interest. As the

main indicator of diagnostic performance, sensitivity was extracted directly according to the anatomical site (proximal and distal colon/rectum) if reported or was calculated based on reported information. Specificity referred to the number of participants with negative FOBT results divided by the number of participants without neoplasms. For quantitative FOBT results with more than one cut-off value reported in the study, the cut-off values recommended by the manufacturer were used. Only patients with targeted tumors located in an isolated side were considered. In this review article, the proximal colon was defined as colon involving the area proximal to the splenic flexure while distal colon including distal to the splenic flexure. Advanced adenoma was defined by at least one adenoma with any of the following features: ≥1 cm in size, tubulovillous or villous components, and high-grade dysplasia. Advanced neoplasms included CRC and advanced adenomas.

Data Synthesis And Statistical Analysis

We first summarized the basic characteristics of all the included studies. Diagnosis-related indicators including sensitivity (true positive rate) and specificity (true negative rate), stratified by anatomical location were extracted or calculated and respective 95% CIs were also reported (the Wilson method was used if not reported in the studies). We applied the random effect model to estimate the pooled sensitivity and specificity. Statistical heterogeneity was assessed by I^2 statistics. Forest plots for the pooled sensitivities of FOBT for detecting colorectal neoplasms in the proximal and distal colon/rectum were generated. Summary receiver operating characteristic (SROC) curves were plotted

to assess the accuracy of FOBT for detecting proximal and distal colorectal neoplasms. Z test was applied to examine the statistical difference of the areas under SROC curves according to the anatomical sites.

Subgroup analyses were also performed to estimate the effect of study setting (clinical setting vs screening setting) and type of iFOBT (qualitative vs quantitative) on the diagnostic performance of FOBT. Potential publication bias was evaluated for studies using gFOBT and iFOBT separately by Deeks' funnel plot.

All the analyses were conducted using Meta-Disc software 1.4 and Stata 12.0. Statistical tests presented were two-sided, and P-value <0.05 was considered statistically significant.

Results

Literature Search Result

As shown in Figure 1, 9066 studies were identified from the initial literature search. After removal of 3694 duplicates, a first round of title and abstract review was conducted, and 4888 articles unrelated to the review topic, 421 non-English language articles and 11 articles having no full-text were excluded. For the 52 remaining articles, a full-text review was conducted and 21 of them were excluded due to the following reasons: 1) site-specific diagnostic indicators could not be calculated (n=16); 2) colonoscopy conducted for participants with positive FOBT results only (n=4); and 3) repeated information contained in the previous articles by the same study group (n=1). Finally, 31 eligible studies were included in this review.
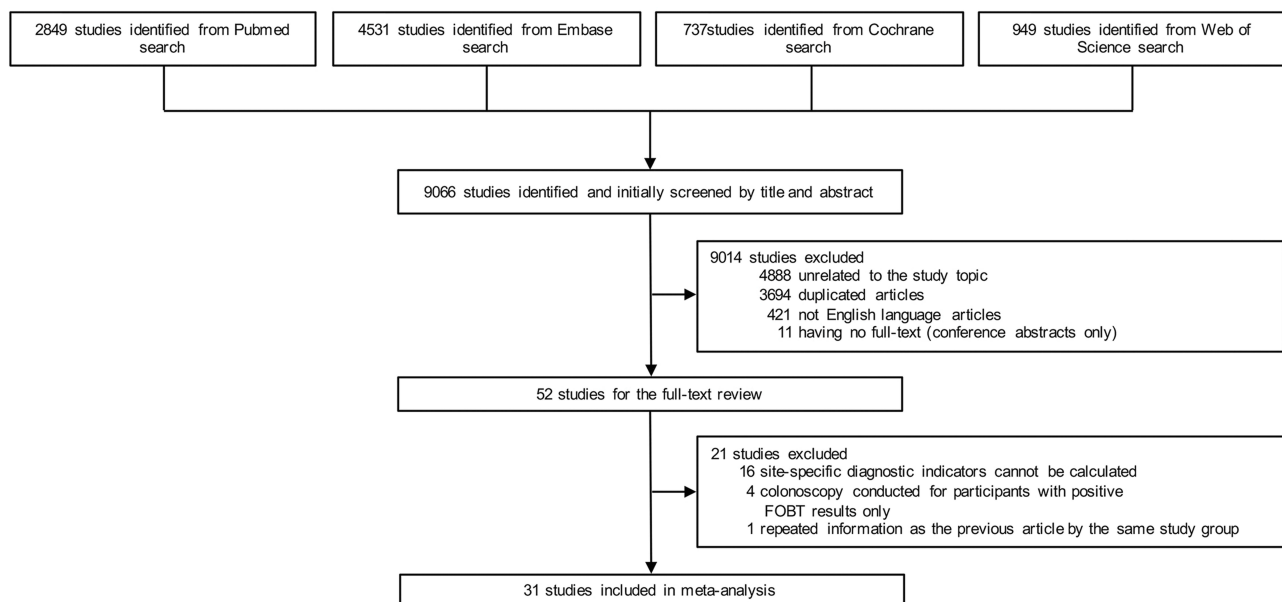
Figure 1 Flow chart of search strategy and selection of reports (search until August 20, 2018).

Study Characteristics

Table 1 shows the main characteristics of the studies included in this review.[15–45] Overall, most studies were carried out in Western countries (16 of 31), while only some of them were conducted in East Asia (12 of 31). With regards to the study setting, most of the included studies (20 of 31) were conducted in a screening setting. The sample sizes varied greatly across the studies, ranging from 112 to 21,805. The mean ages of the population in these studies ranged from 48 to 69 years. Regarding the types of FOBT, 2 studies used gFOBT, 21 studies used iFOBT, and 8 studies had results available for both types of FOBT. The brands of the FOBT also varied greatly, with a total number of 24. Among these 31 studies, 24 (77.4%) studies had already excluded patients with incomplete bowel examination by colonoscopy,[17,18,20–29,31–33,35,36,39,41–44] while 7 (22.6%) studies did not report such exclusion.[19,20,30,34,37,38,40]

Diagnostic Accuracy Of gFOBT

The summaries of the diagnostic performance of FOBT for detecting colorectal neoplasms according to the anatomical locations of all the included studies were shown in detail in Tables S2–S4. Forest plots showing the pooled sensitivities of FOBTs for detecting proximal and distal colorectal neoplasms are shown in Figures 2 and 3. For studies using gFOBT, the pooled sensitivity for detecting CRC located in the proximal colon was comparable with the pooled sensitivity of that located in the distal colon/rectum, with values of 0.60 (95% CI 0.45–0.74) and 0.70 (95% CI 0.57–0.80), respectively. The diagnostic accuracy of gFOBT for detecting advanced adenomas was typically low, and there was no difference between detection of advanced adenomas located at the proximal colon (0.10, 95% CI 0.07–0.14) and that at the distal colon/rectum (0.11, 95% CI 0.07–0.15) and for detection of proximally and distally located advanced neoplasms (0.18, 95% CI 0.14–0.22 vs 0.2, 95% CI 0.17–0.24). The corresponding pooled specificities of gFOBT for CRC, advanced adenomas, and advanced neoplasms according to the anatomic site were equal, with the values of 0.88 (95% CI 0.87–0.89), 0.91 (95% CI 0.90–0.92), and 0.95 (95% CI 0.95–0.96), respectively.

Diagnostic Accuracy Of iFOBT

For studies using iFOBT, the sensitivities for detecting colorectal neoplasms were higher than that with traditional gFOBT. For detecting CRC, comparable sensitivities of iFOBT for detecting CRC located in the proximal colon and distal colon/rectum were observed (0.67, 95% CI 0.62–

0.72 and 0.72, 95% CI 0.68–0.75, respectively). However, higher sensitivities were observed for detecting advanced adenomas or advanced neoplasms located in the distal colon/rectum than that for the ones located in the proximal colon, with the values of 0.24 (95% CI 0.22–0.25) and 0.32 (95% CI 0.30–0.34) for proximally and distally located advanced adenomas, respectively, and with values of 0.25 (95% CI 0.23–0.28) for proximally located advanced neoplasms vs 0.38 (95% CI 0.36–0.40) for distally located advanced neoplasms. The corresponding pooled specificities of iFOBT for CRC, advanced adenomas, and advanced neoplasms were equal in terms of anatomic site, with the values of 0.95 (95% CI 0.94–0.95), 0.93 (95% CI 0.93–0.93), and 0.94 (95% CI 0.94–0.94), respectively.

Summary Operating Characteristics Analyses

We further constructed SROC curves to compare the overall diagnostic performance of gFOBT and iFOBT for detecting colorectal neoplasms located in the proximal or distal colorectum (Figure 4). For gFOBT, the areas under the SROC curve for CRC, advanced adenomas, and advanced neoplasms located in the distal colon/rectum were not significantly higher than that for those in the proximal colon/rectum (CRC, proximal vs distal, 0.853 vs 0.896; advanced adenomas, proximal vs distal, 0.588 vs 0.531; advanced neoplasms, proximal vs distal, 0.683 vs 0.728). For iFOBT, the results confirmed a significantly better diagnosis performance for advanced neoplasms (proximal vs distal, 0.760 vs 0.822; *P*=0.02) located in the distal colon/rectum than for that in the proximal colon, while similar results were not observed for CRC and advanced adenomas (CRC, proximal vs distal, 0.929 vs 0.942; advanced adenomas, proximal vs distal, 0.671 vs 0.733).

Subgroup Analyses

To evaluate the potential effect of two factors including the type of iFOBT (qualitative or quantitative) and the study setting (clinical setting or screening setting), we further conducted subgroup analyses stratified by these factors and the results are shown in Figures S1A–S3B. Regarding the types of iFOBT, both qualitative and quantitative iFOBTs had higher sensitivities for detecting colorectal neoplasms located in the distal colon/rectum than for those located in the proximal colon/rectum. Regarding the study setting, higher sensitivities for CRC in the distal colon/rectum than

Table I Characteristics Of Included Studies In This Review

Ref.	Author, Year	Study Period	Country/District	Study Setting[a]	Study Population Total[c]	Study Population Male (%)	Study Population Mean Age (Range)	No. Of Population CRC	No. Of Population AA	No. Of Population Free Of AN	FOBT Brand[b] gFOBT	FOBT Brand[b] iFOBT
15	Thomas, 1992	N.A.	UK	0	332	64	69 (29–86)	50	21[d]	261	3	2
16	Hope, 1996	1991.5–1992.10	Australia	0	160	40	51 (24–89)	3	21[d]	136	12	4
17	Greenberg, 2000	N.A.	US	0	554	44	60	16	39	390		1
18	Lieberman, 2001	1994.2–1997.1	Portland	1	2885	97	63 (50–75)	24	282	1791	4	
19	Nakama, 2001	1990.4–1999.3	Japan	1	9952	59	54	64	70	9569		13
20	Sung, 2003	N.A.	People's Republic of China	1	505	44	57 (50–79)	4	102[d]	399	4	
21	Young, 2003	1999.1–2001.8	Australia	0	398	52	63 (24–90)	36	29	277		1, 6
22	Morikawa, 2005	1983.4–2002.3	Japan	1	21,805	72	48 (20–91)	79	648	17,480		14
23	Nakazato, 2006	1998.7–2002.7	Japan	1	3090	85	53	19	53	2765		N.A.
24	Ahlquist, 2008	2001–2007	US	1	2497	72	64 (50–80)	39	135	1871	3, 5	
25	Shastri, 2008	2003.1–2007.5	Germany	0	640	41	55 (42–88)	55	21	516		11
26	Bjerregaard, 2009	2002.9–2003.12	Denmark	0	256	42	63 (40–94)	8	12	206	5	
27	Graser, 2009	N.A.	Germany	1	285	60	61 (50–81)	1	29	194		17
28	Hundt, 2009	2006.1–2007.12	Germany	1	1319	50	63 (31–86)	0	405[d]	914	3	11,18–22
29	Haug, 2010	2006.1–2007.13	Germany	1	1319	51	63 (31–87)	0	405[d]	914		15
30	Oono, 2010	2007.6–2008.6	Japan	0	1073	52	65 (26–89)	91	224[d]	758		7
31	Park, 2010	2007.12–2008.11	South Korea	1	770	51	59 (50–75)	13	59	479	4	23
32	Haug, 2011	2006.1–2009.11	Germany	1	2310	49	N.A.	14	214	2082[e]		15
33	Khalid-de Bakker, 2011	N.A.	The Netherlands	1	329	42	55 (50–65)	0	38	243		10
34	De Wijkerslooth, 2012	2009.6–2010.7	The Netherlands	1	1256	58	60 (50–75)	8	113	1135[e]		10
35	Wong, 2012	2008.4–2009.10	Canada	1	1075	46	56 (50–75)	2	67	1006[e]	4	14, 16
36	Chiu, 2013	2005.9–2010.9	Taiwan	1	18,296	59	60	28	632	14,252		9

(Continued)

Table I (Continued).

Ref.	Author, Year	Study Period	Country/District	Study Setting[a]	Study Population			No. Of Population			FOBT Brand[b]	
					Total[c]	Male (%)	Mean Age (Range)	CRC	AA	Free Of AN	gFOBT	iFOBT
37	Kaul, 2013	N.A.	UK	0	112	46	66 (34–87)	17	0	96		9
38	Koga, 2013	2009.10–2012.9	Japan	0	224	60	65 (30–84)	117	0	107		8
39	Lee, 2013	2011.3–2012.2	Taiwan	1	3139	61	53 (19–92)	39	106	2965	5	10
40	Kim, 2014	N.A.	South Korea	0	326	N.A.	N.A.	175	0	51		10
41	Imperiale, 2014	2011.6–2012.11	US	1	9989	N.A.	N.A.	65	758	6281		24
42	Castro, 2015	2010.1-2011.12	Spain	1	1292	47	58	8	145	1129[e]		10
43	Kim, 2016	2013.6–2015.5	Korea	1	3990	54	64	79	376	3566[e]		10
44	Brenner, 2017	2008.11–2014.9	Germany	1	3466	50	62 (50–80)	29	354	2397		17
45	Jung, 2018	2010–2014	South Korea	1	12,270	71	N.A.	13	301	9575		10

Notes: [a]0=clinical setting; 1=screening setting. [b]1=FlexSure OBT; 2=HemeSelect; 3=Hemoccult blood; 4=Hemoccult blood II; 5=Hemoccult blood Sensa; 6=InSure; 7=Hemo Techt NS-Plus; 8=OC-Hemocatch; 9=OC-Light; 10=OC-Sensor; 11=PreventID-CC; 12=Monohaem; 13=Imdia-HemSp; 14=Magstream 1000/Hem SP automated system; 15=RIDASCREEN haemoglobin; 16=Hemoccult blood ICT; 17=Sentinel Diagnostics; 18=Bionexia FOBplus; 19=Bionexia Hb/Hp Complex; 20=ImmoCARE-C; 21=FOB advanced; 22=QuickVue iFOB; 23=OC-SENSA MICRO; 24=OC FIT-CHEK. [c]Numbers of participates who actually completed both FOBT and colonoscopy. [d]Patients with all kind of adenomas were included. [e]Patients with non-advanced adenomas were also included.
Abbreviations: AA, advanced adenomas; CRC, colorectal cancer; AN, advanced neoplasia, including colorectal cancer and advanced adenoma.
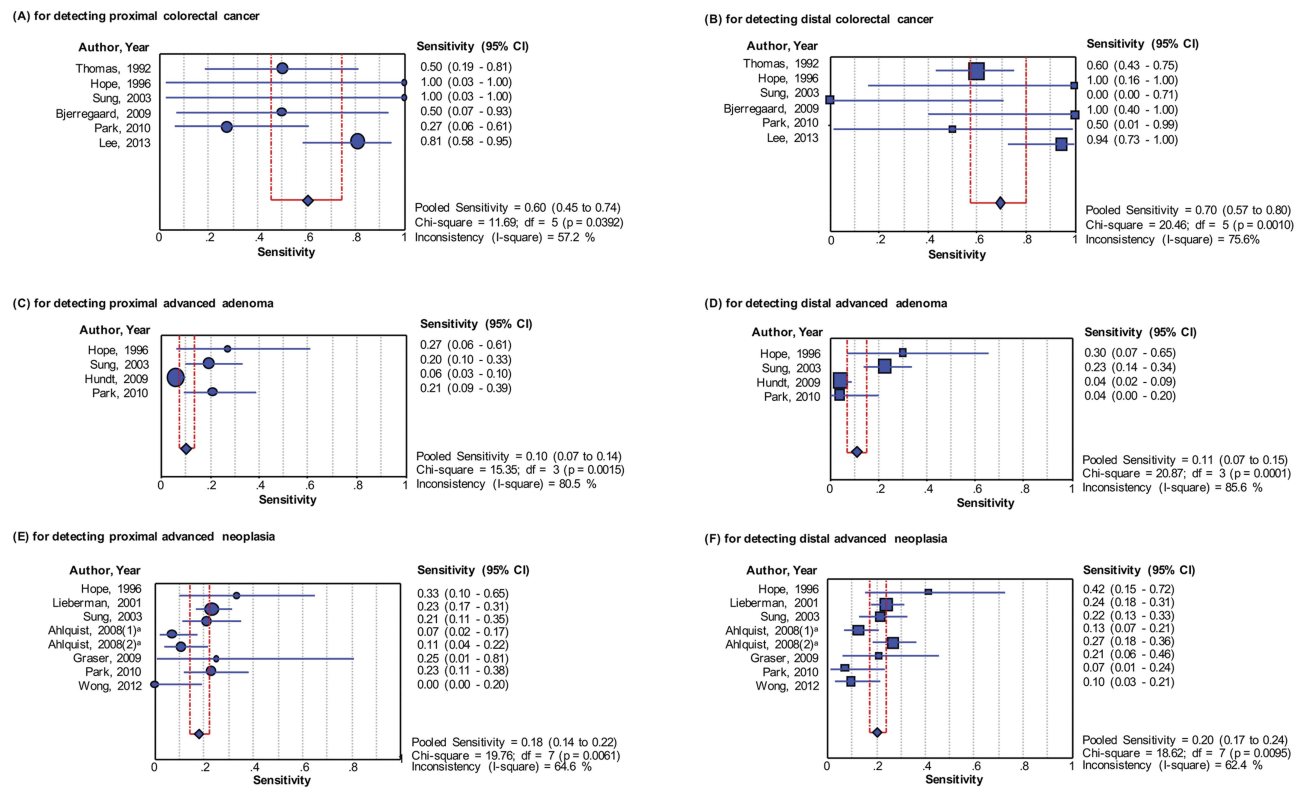
Figure 2 Forest plots for the pooled sensitivities of guaiac-fecal occult blood test on the detection of colorectal neoplasms, (**A**) for detecting proximal colorectal cancer; (**B**) for detecting distal colorectal cancer; (**C**) for detecting proximal advanced adenoma; d) for detecting distal advanced adenoma; (**E**) for detecting proximal advanced neoplasia; (**F**) for detecting distal advanced neoplasia.
Note: [a]Ordinal numbers were applied to mark the studies which contain variable FOBT brands.

for that in the proximal colon/rectum were observed, in both clinical and screening setting subgroups, and similar results were observed for advanced neoplasms. As for advanced adenomas, higher sensitivities for distal advanced adenomas were only observed in the screening setting because the sample size was too limited in the clinical setting to calculate the corresponding pooled sensitivities.

Publication Bias And Quality Assessment

Publication bias was assessed by Deeks' funnel plots (Figure S4) and we found no strong evidence for publication bias (Egger regression tests with all *p*-values >0.05). The risk of bias assessment for included studies (Figure S5) suggested the greatest risk of bias occurred in the "flow and timing". This is mainly because 5 studies did not use identical reference standard,[15,26,33,37,42] while 3 studies failed to include the whole participant group.[9,21,40] The greatest concern of applicability came from the "patient selection" category, where 12 studies potentially included patients who had a history of CRC, inflammatory bowel disease and were actively bleeding,

or who had a history of colonoscopy in the preceding 5 years.[15–17,19,21,25,30,31,34,37,38,40] A summary of risk of bias and applicability concerns for each study was shown in Figure S6.

Discussion

In this article, we systematically evaluated the site-specific diagnostic performance of both gFOBT and iFOBT with a single test for detecting colorectal neoplasms. For gFOBT, the diagnostic accuracy of detecting colorectal lesions located in the two different colon sites were similar, with comparable pooled sensitivities and areas under the SROC curves. For iFOBT, we found that the diagnostic performance of iFOBT for detecting advanced adenomas and advanced neoplasia varied according to the anatomical sites of the colorectum, with better sensitivities for the detection of these lesions in the distal colon/rectum than in the proximal colon. As the evidences have shown that iFOBT is superior to gFOBT for CRC screening, iFOBT has been one of the most widely used non-invasive tests for CRC screening. However, the different diagnostic accuracy
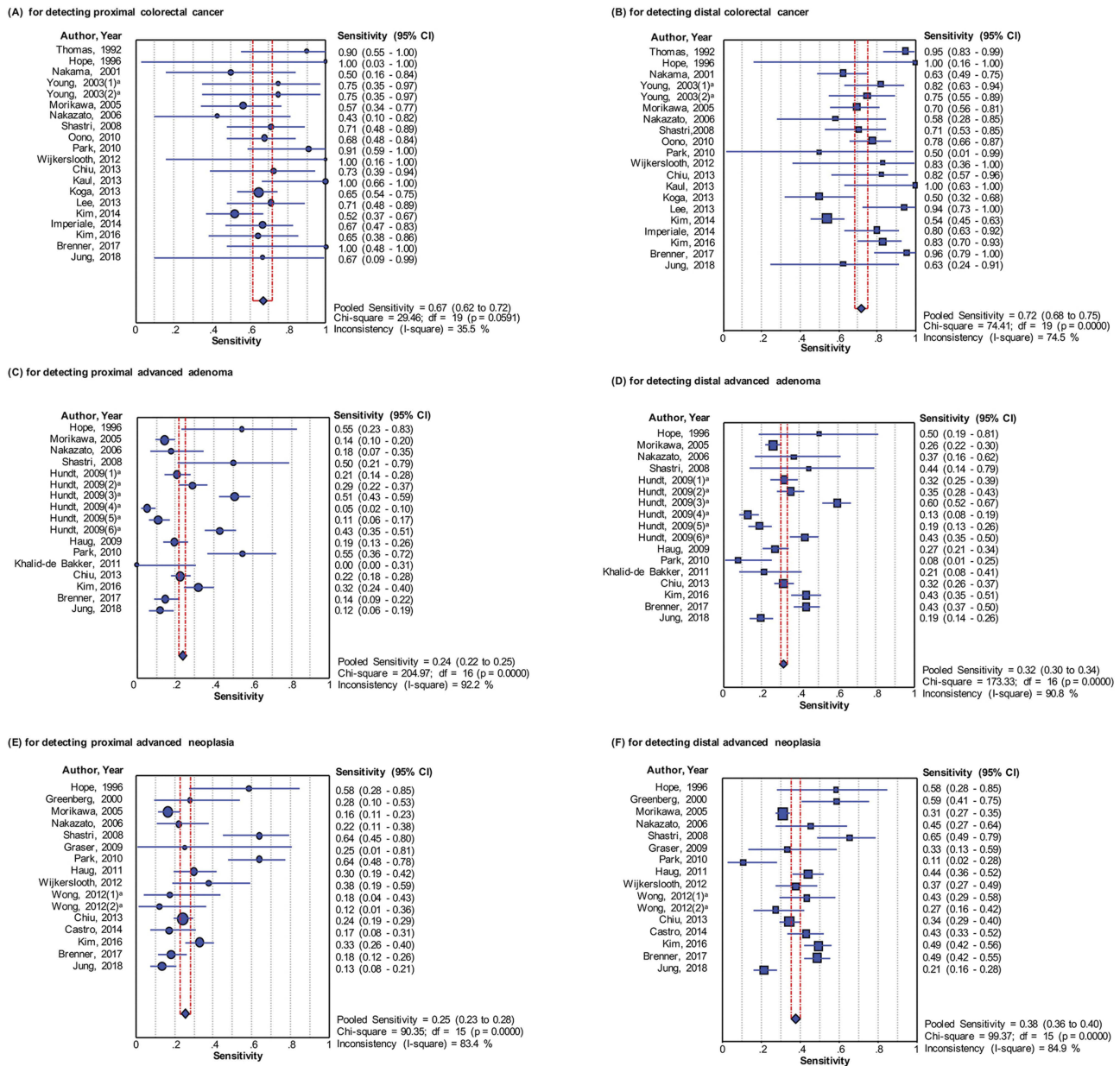
Figure 3 Forest plots for the pooled sensitivities of immunochemical fecal occult blood test on the detection of colorectal neoplasms, (**A**) for detecting proximal colorectal cancer; (**B**) for detecting distal colorectal cancer; (**C**) for detecting proximal advanced adenoma; (**D**) for detecting distal advanced adenoma; (**E**) for detecting proximal advanced neoplasia; (**F**) for detecting distal advanced neoplasia.
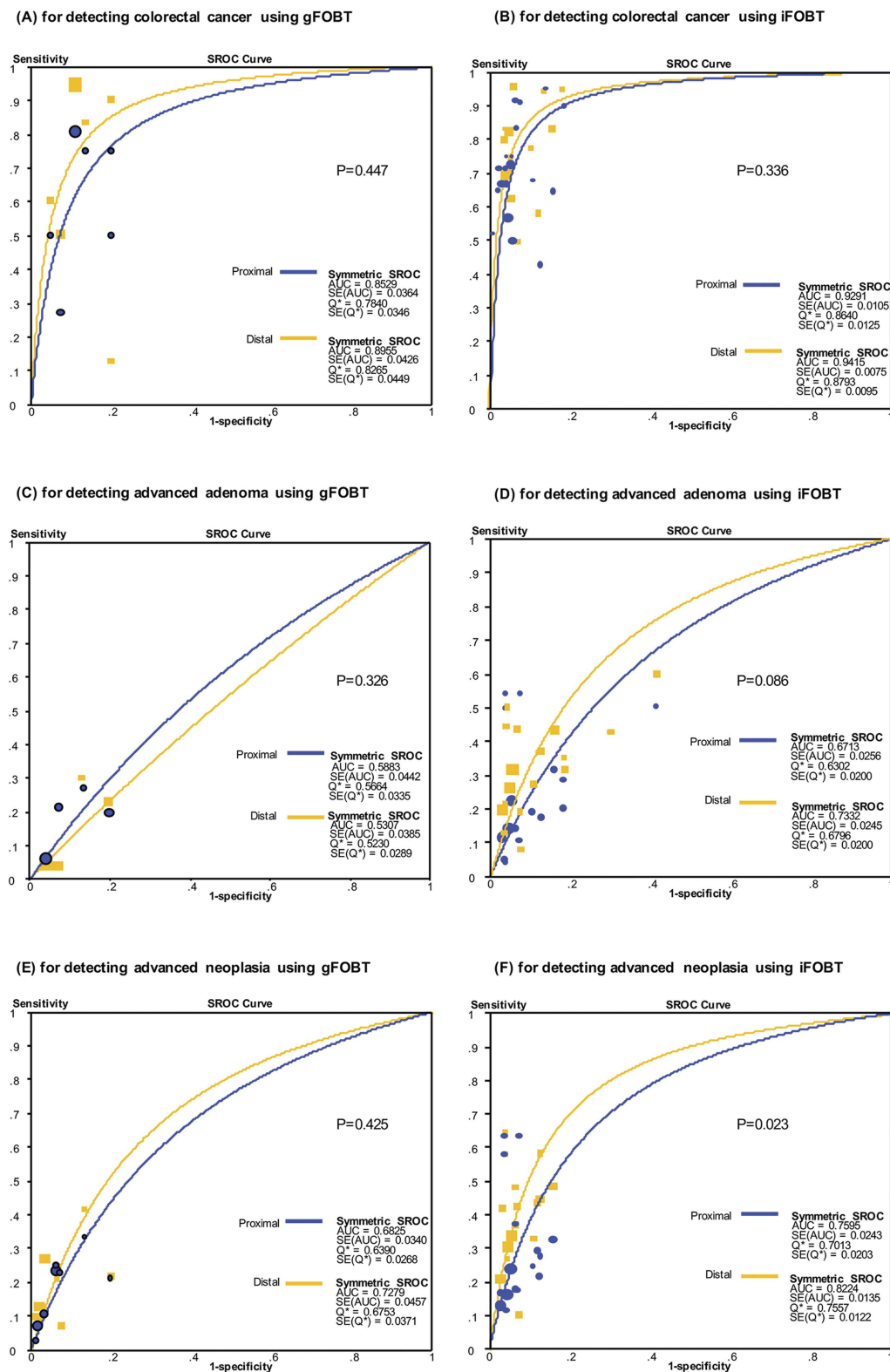**Note:** [a]Ordinal numbers were applied to mark the studies which contain variable FOBT brands.

for advanced neoplasms in terms of anatomic locations may strongly affect the efficacy of CRC screening, and the effect of this technique on long-term reduction of incidence and mortality would be expected to be stronger for distal than for proximal CRC, which should be given attention in population-based CRC screening programs.

Our results were not completely consistent with that of the two published systematic reviews. A systematic literature review performed by Haug et al suggested a lower sensitivity of FOBT for advanced neoplasia in the right

versus left colon.[10] However, the results may be prone to be bias due to a lack of rigid statistical analyses. Moreover, the conclusion from a meta-analysis by Hirai et al mentioned a worse diagnostic performance of FOBT for CRC in the proximal bowel than in the distal bowel,[11] but this may not be convincing because of the largely overlapping confidence intervals of the site-specific sensitivities. For our study, we conducted an updated systematic review with quantitative analysis to evaluate the site-specific diagnostic accuracy of FOBT not only for CRC, but

(A) for detecting colorectal cancer using gFOBT

(B) for detecting colorectal cancer using iFOBT

(C) for detecting advanced adenoma using gFOBT

(D) for detecting advanced adenoma using iFOBT

(E) for detecting advanced neoplasia using gFOBT

(F) for detecting advanced neoplasia using iFOBT

Figure 4 Comparison of SROCs for detecting colorectal neoplasms located in the proximal and distal colon/rectum, (**A**) for detecting colorectal cancer using guaiac-fecal occult blood test; (**B**) for detecting colorectal cancer using immunochemical fecal occult blood test; (**C**) for detecting advanced adenoma using guaiac-fecal occult blood test; (**D**) for detecting advanced adenoma using immunochemical fecal occult blood test; (**E**) for detecting advanced neoplasia using guaiac-fecal occult blood test; (**F**) for detecting advanced neoplasia using immunochemical fecal occult blood test.

Abbreviations: gFOBT, guaiac-fecal occult blood testing; iFOBT, immunochemical fecal occult blood testing.

also for advanced adenomas. In addition, we performed subgroup analyses to assess the consistency of the results.

Our findings showed that both gFOBT and iFOBT had comparable sensitivities for detecting CRC located in the proximal or distal colorectum, indicating the overall good performance of FOBT in CRC screening. However, for advanced adenoma, iFOBT showed inferior sensitivity for detecting lesions located in the proximal colon than that for lesions in the distal colon/rectum. Advanced adenoma is the most important precursor of CRC. In population-based CRC screening programs, timely detection of advanced adenoma and adoption of appropriate clinical intervention would strongly improve the overall survival of patients and even reduce the likelihood to develop CRC.[46,47] Therefore, the relative lower sensitivity of iFOBT for detecting proximal advanced adenoma might affect the detection rate of advanced adenoma and limit its overall effectiveness in population-based CRC screening programs. Such an issue should be investigated and resolved in further studies.

To address the lower sensitivity for detecting colorectal neoplasms located in the proximal colon, further measures to optimize the scheme of FOBT-based CRC screening need to be explored. First, tests can be repeatedly performed. Our results were focused on a one-time application of iFOBT. Nevertheless, in a real-world setting, iFOBT-based screening programs are implemented with serial application of iFOBT over time (ie, every 1–2 years),[48,49] and a better detection of colorectal neoplasms is expected to be achieved in such a setting.[49,50] Second, lower cut-off values for quantitative iFOBT could be applied. Previous studies have suggested that the sensitivity of iFOBT for advanced adenomas could be improved when the positivity threshold was lowered. It was shown that quantitative iFOBT, if using a low cut-off value less than 20 µg hb/g feces, may offer improved sensitivity for the detection of CRC compared with a cut-off range from 20 to 50 µg hb/g feces.[9] Third, multiple fecal samples could be used for testing. Bleeding in advanced neoplasia cases may be missed with single-stool sampling due to the characteristic of intermittent bleeding. Therefore, multiple separate samples collected on several consecutive days could probably increase the sensitivity of the test.[4,6] A study from the Netherlands found that 2-sample iFOBT screening using at least 1 positive test as a cut-off was associated with a higher detection rate for advanced neoplasia compared to 1-sample iFOBT screening.[51] However, concerns may be raised regarding the compliance, colonoscopy capacity, and over-screening after

implementation of this screening scheme wherein improvements are made based on the mentioned suggestions. Hence, more studies on cost-effectiveness need to be performed to explore the balance between expense, medical resources, and yield of screening.

There are several strengths and limitations that need to be taken into consideration when interpreting our results. Strengths of our study include the adoption of rigorous inclusion and exclusion criteria in four widely used medical databases to ensure that all potential studies were included in this review. In addition, we compared the site-specific diagnostic accuracy of FOBT in detecting multiple outcomes, including CRC and advanced adenoma, which has not been done in previous review articles. Limitations of our studies include modest heterogeneity among the studies under review, due to different study designs, different study populations, and numerous FOBTs with different cut-off values. Therefore, we conducted subgroup analyses, which showed overall consistency with our main results that indicated to be reliable enough not to be influenced by the heterogeneity. Second, the sensitivity for detecting advanced neoplasms may be under- or overestimated because such an indicator is strongly affected by the proportion of CRC and advanced adenoma cases in the study population. Third, participants younger than 40 years old were enrolled into some studies, which may introduce spectrum bias into our analysis. Fourth, given the limited data on advanced adenoma, its scope was unrestricted and extended to include any colorectal adenoma in 2 studies.[28,32]

Altogether, our study showed that iFOBT had higher sensitivity for detecting advanced colorectal neoplasms, especially advanced adenomas, located in the distal colon/rectum than that for those in the proximal colon. Further efforts should be made to develop customized schemes of CRC screening according to local program needs with enhanced detection of precursors to CRC in the proximal colon and enhanced potential of proximal CRC prevention, while maintaining or even increasing the cost-effectiveness yielded by present screening strategies.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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