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Effect of Sex, Age and Positivity Threshold on Fecal Immunochemical Test Accuracy: a Systematic Review and Meta-Analysis

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Abstract

Background & Aims: Quantitative fecal immunochemical tests (FITs) for hemoglobin are commonly used for colorectal cancer (CRC) screening. We aimed to quantify the change in CRC and advanced adenoma detection and number of positive test results at different positivity thresholds and by sex and age.

Methods: We searched MEDLINE and EMBASE, selecting articles of FIT for CRC detection in asymptomatic adults undergoing screening. We calculated sensitivity and specificity, as well as detected number of cancers, advanced adenomas, and positive test results at positivity thresholds ≤10 μg hemoglobin/g feces, 10 to ≤20 μg/g, 20 to ≤30 μg/g, and >30 μg/g. We also analyzed results from stratified by patient sex, age, and reference standard.

Results: Our meta-analysis comprised 46 studies with 2.4 million participants and 6478 detected cancers. Sensitivity for detection of CRC increased from 69% (95% CI, 63%–75%) at thresholds >10 μg/g and ≤20 μg/g to 80% (95% CI, 76%–83%) at thresholds ≤10 μg/g. At these threshold values, sensitivity for detection of advanced adenomas increased from 21% (95% CI, 18%–2%5) to 31% (95% CI, 27%–35%), whereas specificity decreased from 94% (95% CI, 93%–96%) to

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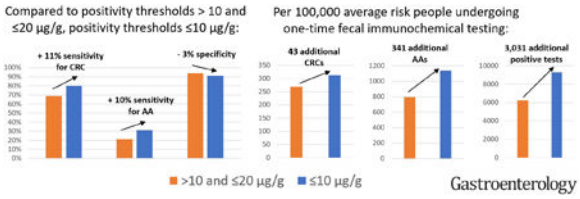
91% (95% CI, 89%–93%). In 3 studies stratified by sex, sensitivity of CRC detection was 77% in men (95% CI, 75%–79%) and 81% in women (95% CI, 60%–100%) (*P*=.68). In 3 studies stratified by age groups, sensitivity of CRC detection was 85% for ages 50–59 years (95% CI, 71%–99%) and 73% for ages 60–69 years (95% CI, 71%–75%) (*P*=.10). All studies with colonoscopy follow up had similar sensitivity levels for detection of CRC to studies that analyzed 2-year registry follow-up data (74%; 95% CI, 68%–78% vs 75%; 95% CI, 73%–77%).

Conclusions: In a meta-analysis of studies that analyzed detection of CRC and advanced adenomas at different FIT positivity thresholds, we found the sensitivity and specificity of detection to vary with positive cut-off value. It might be possible to decrease positive threshold values for centers with sufficient follow-up colonoscopy resources. More research is needed to precisely establish FIT thresholds for each sex and age subgroup.

Graphical Abstract:



Lay summary:

Quantitative fecal immunochemical tests, or FITs, are commonly used for colorectal cancer screening. Screening programs could detect significantly more cancers and polyps by using lower thresholds to define a positive result, provided they have enough specialists to perform the necessary follow-up colonoscopies.

Keywords

colon cancer; advanced neoplasia; fecal occult blood test; diagnostic performance

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.[1] Randomized clinical trials have demonstrated that screening with guaiac fecal occult blood test (gFOBT) can reduce CRC mortality.[2] Fecal immunochemical tests (FITs) are recommended for CRC screening[3, 4] because they obtain better diagnostic performance and higher participation rates than gFOBT.[5]

The optimal positivity threshold of quantitative FIT for screening is unknown and may vary by sex and age; it can be adjusted to optimize CRC detection and be concordant with local colonoscopy resources.[6] Some experts in the United States favor a uniform threshold of ≤20 µg hemoglobin/g feces, but evidence is limited because individual studies included small numbers of patients with CRC; data and consistent definitions for advanced adenoma detection were frequently not included;[3, 7] variable comparison groups between studies;[7] and variability between FIT brands[8] and positivity thresholds.[9, 10] Normal mean fecal hemoglobin concentrations varies significantly by sex and age,[9, 11–13] as does cancer

incidence; combined, these trends could have important impacts on FIT performance. Higher mean stool hemoglobin concentrations in men than in women might generate more positive results, potentially impacting both sensitivity and specificity (because more men would go to colonoscopy). Whether the quantitative abnormal cut-off should vary by sex and age, like peripheral complete blood cell counts, is largely unexplored, due to the difficulty of evaluating these subpopulations in individual studies.[14–16]

In this context, we substantially expanded prior systematic reviews[7, 17] to provide more precise risks and benefits of varying FIT positivity thresholds and to explore the effects of patient (sex and age), test (FIT brand), and study characteristics (reference standard and geographic area) on optimal cut-offs for FIT performance.

Methods

We employed a protocol (PROSPERO CRD42017068760) based on standard guidelines for the systematic review of diagnostic tests. We followed the Standards for the Reporting of Diagnostic Accuracy Studies (STARD)[18] and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) of Diagnostic Test Accuracy Studies[19] statements for reporting our systematic review. All authors had access to the study data and reviewed and approved the final manuscript.

Literature Search:

In addition to articles from a previous review with studies from 1996 to 2013,[7] we searched for eligible articles published between January 1 2012 and May 30 2018, using MEDLINE (via Ovid), EMBASE, and Database of Abstracts of Reviews of Effects (Supplemental Table 1). We also manually searched bibliographies and reference lists of eligible papers and consulted experts in the field.

Study Selection:

Two investigators (KS, EL or CD) independently reviewed each pertinent title/abstract to determine eligibility. We included studies which: 1) evaluated asymptomatic screening participants with a mean age ≥40 years old; 2) evaluated the diagnostic accuracy of quantitative FIT for CRC (studies of qualitative FIT were excluded); 3) reported data for the calculation of the absolute numbers of true-positive, false-negative, true-negative, and false-positive observations at ≥1 FIT positivity thresholds; 4) included adequate follow-up, defined as colonoscopy for all participants or colonoscopy for patients with positive FIT result combined with ≥1-year follow-up with medical records or cancer registry of FIT-negative individuals as reference standard; and, 5) used a randomized trial or cohort study design. Data for advanced adenomas were extracted if available and a definition provided. Except where noted, advanced adenomas were defined as any adenoma ≥10 mm or containing villous histology or high-grade dysplasia (regardless of size). To avoid duplicate reporting of the same population, we manually reviewed papers and used data from the latest publication or studies with data from multiple positivity thresholds (Supplemental Table 2).

Data Extraction and Synthesis:

Two reviewers (KS, EL or CD) independently evaluated and extracted relevant information and assessed study quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument.[20] For studies with incomplete or unavailable information, we contacted the authors; additional data were provided that allowed us to include 5 additional studies.[8, 21–24] Positivity thresholds were converted to micrograms of hemoglobin per gram of stool.[25]

Statistical Analysis:

For each study, we calculated the sensitivity and specificity for CRC detection, including 95% confidence intervals. For studies with colonoscopy follow-up of all participants, we also calculated the sensitivity for advanced adenoma detection and the specificity among those without advanced adenoma and CRC.

We first performed analyses of FIT accuracy for CRC and advanced adenomas stratified by positivity thresholds (≤10 μg hemoglobin/g of stool, >10 and ≤20 μg/g, >20 and ≤30 μg/g, and >30 μg/g) using a bivariate random-effects model.[26] Studies could contribute sensitivity and specificity pairings at multiple positivity thresholds, if available. For this analysis, which included both CRCs and advanced adenomas, we restricted to studies with colonoscopy follow-up of all participants to minimize differential verification bias, as it can make lower positivity thresholds appear disadvantageous,[27] and to provide consistent estimates of both CRC and advanced adenoma detection (which are typically asymptomatic). We then calculated the number of CRCs and advanced adenomas detected and number of positive tests generated at each positivity threshold per 100,000 individuals undergoing screening colonoscopy using the pooled prevalence from all prospective studies with colonoscopy follow-up of all participants (Supplementary Table 3).

For all other analyses, we included studies with both colonoscopy and registry follow-up using the primary positivity threshold from each study (not stratified by positivity threshold) (Table 1).[7] We generated overall hierarchical summary receiver-operating characteristic (ROC) curves and calculated the area under the hierarchical summary ROC curve for CRC and advanced adenoma, respectively.[28] We calculated FIT sensitivity and specificity for CRC stratified by sex and age including only studies that provided stratified results. Sex and age stratified bivariate random effects analyses could not be performed due to the small number of studies, and univariate random effects analyses were conducted instead. This approach does not account for the correlation between sensitivity and specificity across studies. However, in situations where the bivariate random effects model cannot be fit due to a small number of studies or sparse data, valid summary estimates of sensitivity and specificity can be obtained with univariate random effects models.[29]

Sensitivity Analyses and Evaluation of Heterogeneity:

We performed sensitivity analyses for overall sensitivity and specificity for CRC by excluding studies which: used discontinued tests; had >1 FIT sample per patient; had a mean age <50 years; had >70% men; lacked a reported positivity threshold; or that included participants with a family history of CRC (Supplementary Table 4).

The inconsistency index (I^2) test was used to estimate heterogeneity between studies using the sensitivity.[30] We used Stata, version 14.2 (StataCorp, College Station, Texas) for all statistical analyses. All tests were 2-sided, and P-values less than 0.05 were considered statistically significant. We evaluated for causes of between-study heterogeneity using stratified analyses based on the reference standard (colonoscopy vs. clinical follow-up), geographic region of the study (North America, Europe, or Asia), and FIT brand (for brands with 3 or more included studies). OC-Sensor and OC-Micro were considered together.[31] Sensitivity and specificity were compared between subgroups using bivariate, mixed-effects meta-regression.

Results

Study Selection:

The literature search in MEDLINE and EMBASE identified 1775 articles published between 2012 and 2018, of which 131 full-text articles were evaluated and 23 articles met the inclusion criteria (Supplemental Figure 1). These were supplemented by ten articles identified from our previous systematic review[7] and 4 from manual searches, providing a total of 37 articles including 46 studies that met the inclusion criteria (Table 1, Supplement).

Characteristics of Included Studies:

Sample sizes ranged from 80 to 723,113 patients (Table 1), with a total of 2,412,518 participants and 6478 detected cancers. Thirty-four studies with 121,545 participants used colonoscopy as the reference standard (gold standard) in all participants, regardless of FIT result, and, among these, 32 reported sensitivity and specificity for advanced adenomas. The remaining 12 studies used longitudinal follow-up of patients with cancer registries and/or medical records during 1 to 2 years, with colonoscopy for those with positive FIT results. Twenty-two studies evaluated more than one positivity threshold. Only two articles[8, 32] examined more than one FIT brand on the same study participants. The mean age ranged between 42 and 64 years and the proportion of men from 29% to 86%.

The sensitivities for CRC and advanced adenoma ranged from 0% to 100% and from 4% to 54%, respectively; specificities ranged from 80% to 99% and from 84% to 98% (Table 1). Thirteen quantitative FIT brands from 10 manufacturers were evaluated. OC-Sensor/OC-Micro was tested in 21 studies, OC-Hemodia (now discontinued) in 6, and FOB-Gold and Magstream in 3 studies; the remaining brands in 1 or 2 studies. Six studies analyzed the performance characteristics of 2 to 4 FIT samples, with 1 or more positive samples defined as a positive result.[33–38] The positivity threshold values varied widely, ranging from 2 to 251 μg hemoglobin/g of stool; however, 30 included positivity thresholds between 10 and 20 μg/g, inclusive. Funding sources varied: 10 articles reported government funding only, 9 non-industry funding except for provision of the FIT kits by the manufacturer, 5 other forms of partial industry funding, 3 industry funding only,[36, 39, 40] and 10 did not report a funding source.

Quality Assessment:

Overall results of the QUADAS-2 assessment from the 37 articles are shown in Supplemental Figure 2 and Supplemental Table 5. All 12 articles with registry follow-up were at high-risk of bias because of lack of blinding of endoscopists to FIT results and differential follow-up depending on FIT results. Six were at high risk because they used frozen stool samples.[8, 32, 36, 41–43] Numerous articles had 'patient selection' applicability concerns, with 10 articles explicitly including patients with a family history of CRC[22, 24, 35, 38, 42, 44–48] and 6 articles patients either younger than 40 years or older than 80 years[38, 44, 46, 49–51]. Three articles were rated as low risk in all risk of bias and applicability domains.[39, 40, 52]

Stratification of Studies with Colonoscopy Follow-Up by Positivity Threshold:

Sensitivity for CRC increased from 69% (95%CI 63–75) for studies with a threshold of >10 and ≤20 μg/g to 80% (95%CI 76–83) for studies with a threshold ≤10 μg/g, and specificity among those without CRC or an advanced adenoma decreased from 94% (95%CI 93–96) to 91% (95%CI 89–93) (Table 2). Statistical heterogeneity was moderate for these estimates, with I^2 values between 30% and 52%.[30] Sensitivity for advanced adenoma increased from 21% (95%CI 18–25) at >10 and ≤20 μg/g to 31% (95%CI 27–35) at ≤10 μg/g, and specificity decreased from 96% (95%CI 95–97) to 93% (95%CI 91–95). Differences of sensitivity and specificity between studies with thresholds >10 and ≤20 μg/g and higher were smaller.

Among the studies using the OC-Sensor/OC-Micro FIT, the sensitivity for CRC increased from 64% (95%CI 26–90) at >20 μg/g, to 71% (95%CI 64–78) at 10 to 20 μg/g, and 74% (95%CI 65–81) at ≤10 μg/g (Supplemental Figure 10). Specificity decreased from 96% (95%CI 95–97), to 94% (95%CI 92–96) and 90% (95%CI 85–93), respectively. Sensitivity for advanced adenomas increased from 23% (95%CI 18–29) at 10 to 20 μg/g to 33% (95%CI 28–39) at ≤10 μg/g (Supplementary Figure 11).

CRC and advanced adenomas detected at varying positivity thresholds in a theoretical screening population:

We calculated the effect of sensitivity and specificity values on a theoretical cohort of 100,000 participants (Figure 2 and Supplemental Table 3). The number of detected CRCs increased by 16%, from 269 (95%CI 245–292) at >10 and ≤20 μg/g to 312 (95% CI 296–323) at <10 μg/g (Figure 2). Advanced adenoma detection increased by 43%, from 794 (95% CI 681–946) at >10 and ≤20 μg/g to 1135 (95% CI 983–1286) at <10 μg/g. The number of positive tests increased by 49% from 6246 (95% CI 4230–7265) at >10 and ≤20 μg/g to 9277 (95% CI 7269–11,281) at <10 μg/g.

Overall Accuracy of FIT:

The sensitivity and specificity for CRC using the primary threshold of all included studies (i.e., colonoscopy and registry follow-up) were 76% (95% CI 72–80) and 94% (95% CI 92–95), respectively, with high heterogeneity (I^2 = 91% [95%CI 89–93]). The exclusion of 4 registry studies with less than 2-year follow-up for all participants[44, 53–55] resulted in similar estimates of sensitivity and specificity (76% [95%CI 72–79]) and 93% [95%CI 92–94]

respectively) and decreased (moderate) heterogeneity (I^2 = 53% [95%CI 36–69]). Registry studies with less than 2-years follow-up were therefore excluded from subsequent analyses. Summary receiver operator characteristic curves are in Supplemental Figures 6 and 9.

Stratified results by sex and age:

Three studies with 1,459,185 participants provided results stratified by sex.[9, 15, 56] Pooled sensitivity by sex was 77% (95%CI 75–79) in men and 81% (95%CI 60–100) in women (Figure 2, *P*=0.68), with high heterogeneity (overall I^2=99%). Specificity was 92% (95%CI 89–95) and 94% (95%CI 91–97), respectively (*P*=0.28). Four studies with 1,393,499 participants stratified by age;[9, 15, 46, 56] pooled sensitivity for 3 studies was 85% for ages 50 to 59 (95%CI 71–99) and 73% for ages 60 to 69 (95%CI 71–75, *P*=0.10), with high heterogeneity (overall I^2=80%).[9, 15, 56] Specificity was 94% (95%CI 92–97) and 93% (95%CI 90–96) respectively (*P*=0.39). No studies reported FIT accuracy by race or ethnicity.

Sensitivity Analyses and Evaluation of Heterogeneity

Sensitivity analyses:

Excluding studies with discontinued FIT, unusually higher numbers of men or older participants, or atypical methods gave similar results (Supplemental Figure 7).

Stratification by reference standard:

Studies using colonoscopy to follow up all participants had a similar sensitivity (74% [95%CI 68–78]) as studies using 2-year registry follow-up (75% [95%CI 73–77]) (Figure 2). Specificity was also similar at 93% (95%CI 92–95) and 94% (95%CI 91–95), respectively.

Stratification by study region:

The pooled sensitivity of studies conducted in Asia (72% [95%CI 63–79]) and North America (sensitivity 70% [95%CI 56–82, *P*=0.06]) were similar, and lower than those in Europe (80% [95%CI 75–83], *P*=0.01 and >0.001 respectively). Pooled specificities for North America (95% [95%CI 93–96]) and Asia (94% [95%CI 92–96]) were similar, while for Europe they were lower (92% [95%CI 90–94], *P*<0.001 for both).

Stratification by FIT brand:

Four FIT brands (OC-Sensor/OC-Micro, OC-Hemodia, FOB Gold and Magstream) had 4 or more studies that could be pooled for subgroup analyses (Figure 2). OC-Sensor/OC-Micro was evaluated in 21 studies and had the most precise estimates for sensitivity and specificity, 75% (95%CI 73–76, I^2 47% [95%CI 20–84]) and 93% (95%CI 91–95) respectively. When compared with OC-Sensor/OC-Micro, OC-Hemodia (discontinued) had lower sensitivity at 68% (95%CI 47–83, *P*=0.02) and a higher specificity (96% [95%CI 93–98, *P*<0.01]). The other two test (FOB Gold and Magstream) did not have statistically significantly higher sensitivities (*P*=0.86 and *P*=0.25, respectively).

Discussion

This meta-analysis found that the use of a positivity threshold ≤10 μg/g rather than between >10 and ≤20 μg/g increased sensitivity for CRCs from 69% to 80% and for advanced adenomas from 21% to 31%, with a corresponding decrease in specificity for CRC from 94% to 91%. Contrary to expectations, given lower mean fecal hemoglobin concentrations among women and younger participants,[9, 11] we did not find statistically significant lower FIT sensitivity for CRC among women or younger patients.

Our results, with a favorable tradeoff of additional cancers and advanced adenomas detected to additional positive tests generated, should be interpreted in the context of three recent studies.[9, 17, 57] First, our sensitivity of 80% from studies with a threshold ≤10 μg/g is consistent with an estimate from a meta-analysis by Imperiale et al that pooled studies with a threshold of <10 μg/g and equal to 10 μg/g separately.[17] They found sensitivities of 78% and 91% respectively, suggesting a higher sensitivity at 10 μg/g than below, a surprising finding not supported by within study comparisons of varying thresholds.[17] Overall, we had a larger number of studies because we included studies with registry follow-up. However, the choice of studies was similar for the comparison between positivity thresholds, because here we excluded studies with registry follow-up. Second, our finding that a threshold of ≤10 μg/g detects 16% more CRCs and 43% more advanced adenomas with 49% more positive tests is more favorable than a recent, community-based cohort with registry follow-up and multiple tests over 2 years.[9] The registry follow-up study found that a decrease from 20 to 10 μg/g would result in 7% more cancers and 75% more positive tests.[9] This is likely because registry follow-up cannot quantify advanced adenoma detection, we included studies with thresholds below 10 μg/g, and the current study primarily includes first-time screening participants undergoing colonoscopy, thus with a higher prevalence of cancers. Third, our findings are more favorable than a large meta-analysis of interval cancer incidence after FIT, which showed no decrease in interval cancers with lower quantitative thresholds.[57] That study had large numbers of participants in later screening rounds who had fewer interval cancers, again suggesting that the advantages of lower thresholds may be lower during repeat screening. We applied our results to a theoretical cohort of 100,000 screening participants and the real-world trade-offs of various positivity thresholds are more complex.

The present study suggests that screening programs with adequate colonoscopy resources may wish to consider positivity thresholds at the lower end of the ≤20 μg/g range currently recommended by the U.S. Multi-Society Task Force on Colorectal Cancer Screening.[3] OC-Sensor, the most commonly used FIT in the US, has been validated at thresholds as low as 4 μg/g and a small number of certified laboratories in the United States already use quantitative results to guide colonoscopy recommendations at thresholds below 20 μg/g (Helen Landicho, personal communication, November 19 2018).

This systematic review is the first to examine the effect of sex and age on CRC detection. Previous studies suggested important differences in FIT performance by sex and age[9, 15, 58, 59] and possible benefits of stratifying FIT-positive patients by sex, age and quantitative result.[60] Some did not have follow-up for all participants[59, 60] or were performed on non-screening populations.[58] Among the limited number of eligible studies

with data by sex and age, we did not identify statistically significant differences in sensitivity or specificity for CRC. Studies of advanced adenomas suggest higher sensitivity in men than women (Supplemental Table 6).[14–16, 61] We observed a trend towards decreasing sensitivity with age that did not reach statistical significance, though this was not seen in two studies of FIT accuracy for advanced neoplasia[15, 61] (Supplemental Table 7). The trend in registry studies could be due to more rapid development of neoplasms in older age groups.

Contrary to a previous systematic review showing higher sensitivity in registry studies,[7] studies with 2-year follow-up in this updated review had a similar pooled sensitivity as those with colonoscopy follow-up for all (Figure 2). Other reviews have excluded registry studies because of incomplete ascertainment of CRCs and advanced adenomas among those who do not undergo colonoscopy.[10, 17] Nonetheless, they have larger sample sizes to allow subgroup analyses and represent real-world use of FIT that are less susceptible to overdiagnosis (i.e. detection of lesions that would never progress to symptomatic cancer). The finding of similar pooled sensitivity and specificity in studies with 2-year follow-up supports their utility, even if they are reporting on interval cancers rather than missed cancers at the time of a negative result.

Similar to previous reviews[7, 10, 17] and a study directly comparing 9 different FITs,[8] we did not find significant differences between currently available FIT brands in accuracy for CRC and AA detection (OC Hemodia is no longer sold). By far the largest number of studies examined the performance of the OC-Sensor FIT (Figure 2).

Despite the large number of studies conducted since our previous review, gaps remain for further research. Few studies have reported results stratified by sex and age and none have stratified by race/ethnicity in the same population. In addition, FIT has not been widely used at lower positivity thresholds (e.g., ≤10 μg/g) with annual screening or over multiple rounds of screening. Finally, methods used to define sensitivity and specificity varied widely in the 12 studies with registry follow-up.

Strengths of the current meta-analysis include the addition of several recent large studies, strict adherence to the PRISMA guidelines and comprehensive assessment of study quality. There are several potential limitations. First, there was moderate to high heterogeneity for several summary estimates. However, stratified estimates by quantitative threshold had lower heterogeneity (Table 2) and several subgroup analyses and sensitivity analyses gave similar results (Figures 2 and Supplemental Figure 7). Second, meta-analyses are subject to the detection, verification, and spectrum biases of the original studies. Third, results are dominated by one test (OC-Sensor/Micro) and may not be transferable to other FIT brands. Finally, greater than expected heterogeneity among studies with 1-y registry follow-up led to modification of the study protocol to evaluate more homogeneous strata.

The study provides important information on the diagnostic performance of FIT at varying positivity thresholds. Lower positivity thresholds (e.g. ≤10μg) may be preferable as the threshold value in settings with sufficient follow-up colonoscopy resources. Additional data are needed regarding the influence of sex and age on test performance. Future research

should determine the impact of quantitative thresholds of ≤10 μg/g with multiple rounds of annual testing and provide better estimates of FIT performance in important subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BACKGROUND AND CONTEXT:

We performed a meta-analysis to determine whether quantitative fecal immunochemical test performance varies with test positivity threshold and among patient subgroups (by sex and age).

NEW FINDINGS:

Sensitivity and specificity for colorectal cancers and advanced adenomas is substantially improved at thresholds ≤10 μg/g. We did not find statistically significant differences in FIT accuracy by sex or age.

LIMITATIONS:

Estimates were based on 1-time FITs and not annual or biennial screening. Few studies compared subgroups, limiting comparisons by sex and age.

IMPACT:

Colorectal cancer screening programs with sufficient colonoscopy resources should consider using lower FIT positive thresholds.

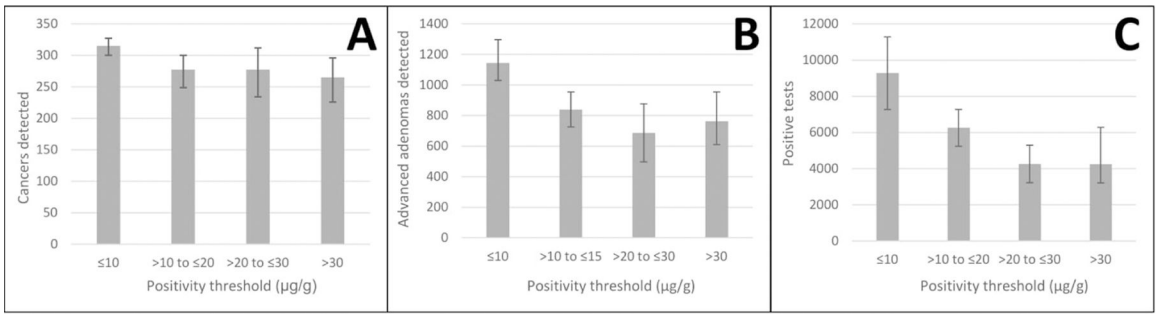

Figure 1: Quantitative fecal immunochemical test performance at varying positivity thresholds in a theoretical cohort of 100,000 average risk adults.

Panel A: Number of colorectal cancers detected. Panel B: Number of advanced adenomas[a] detected. Panel C: Number of positive tests requiring colonoscopy follow-up. Cancer and advanced adenoma prevalence calculated based on pooled prevalence of included cohort studies.[b] Error bars represent 95% confidence intervals generated from pooled estimates of sensitivity and specificity in Table 3.

µg/g: micrograms of stool per gram of buffer

[a]Advanced adenomas defined as adenomas ≥10 mm, containing villous histology, and/or with any high-grade dysplasia.

[b]Cohort studies for follow-up limited to prospective cohorts with colonoscopy follow-up of all participants (Supplementary Table 5)

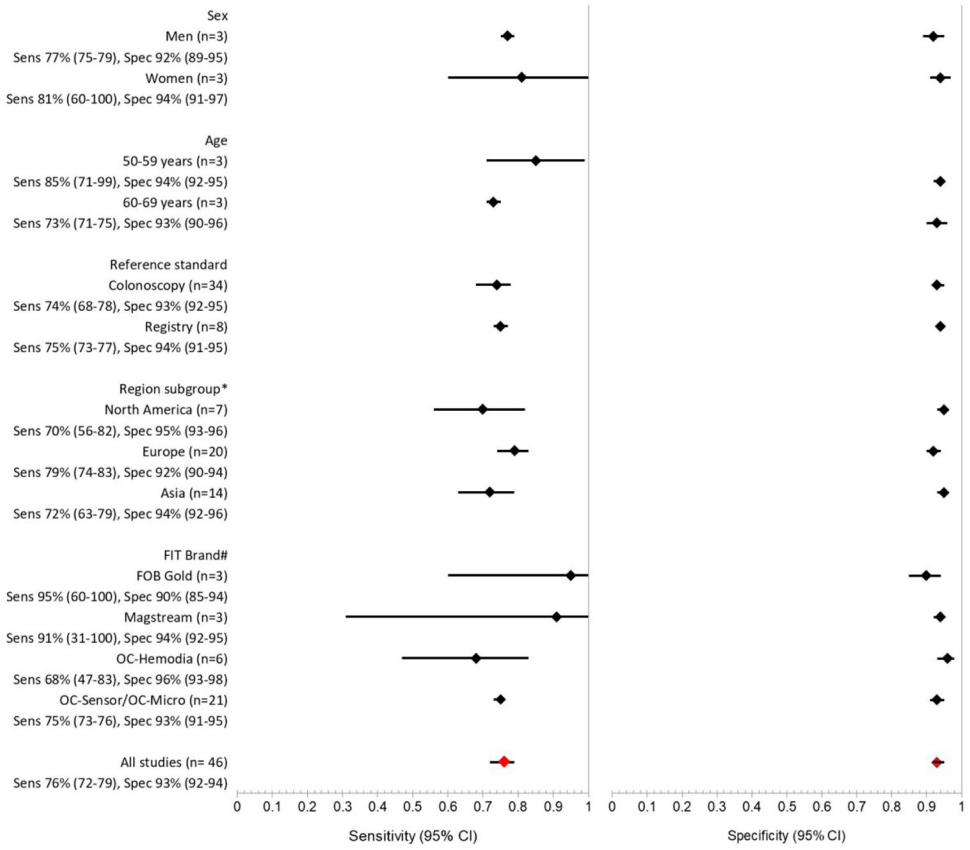

Figure 2: Pooled sensitivity and specificity for colorectal cancer, stratified by study characteristics

*One study from Australia excluded

#Only includes brands with 3 or more available studies to allow pooled estimates

Table 1:

Characteristics of included studies, listed by year. Some articles contributed more than one study. Additional information available in supplementary material.

Author	Year	Country	FIT brand	Primary positivity threshold (μg/g)	Other thresholds	Reference standard	Total Cohort	Cancers detected	CRC Sensitivity (95%CI)	CRC Specificity (95%CI)	Advanced adenomas detected[a]	AA sensitivity (95%CI)	AA specificity (95%CI)
Itoh[62]	1996	Japan	OC-Hemodia	10	-	2-year follow-up	27860	89	87% (78–93)	95% (95–95)	-	-	-
Nakama[38]	2001	Japan	OC-Hemodia	30	10, 60	Colonoscopy	4260	27	81% (62–94)	96% (96–97)	56[b]	54% (40–67)	97% (96–97)
Liu[51]	2003	Taiwan	OC-Hemodia	Not specified	-	Colonoscopy	1387	6	50% (12–88)	98% (97–99)	37[b]	16% (6–32)	98% (98–99)
Morikawa[45]	2005	Japan	Magstream	67	-	Colonoscopy	21805	79	66% (54–76)	95% (94–95)	648[c]	22% (19–26)	95% (95–95)
Launoy[33]	2005	France	Magstream	67	168, 251	2-year registry	7421	28	86% (67–96)	94% (94–95)	-	-	-
Sohn[41]	2005	Korea	OC-Hemodia	20	-	Colonoscopy	3794	12	25% (5–57)	99% (98–99)	67	6% (2–15)	99% (98–99)
Nakazato[34]	2006	Japan	OC-Hemodia	16	-	Colonoscopy	3090	19	53% (29–76)	87% (86–87)	53[b]	25% (14–38)	87% (86–89)
Levi[35]	2007	Israel	OC-Micro	15	-	Colonoscopy	80	3	67% (9–99)	83% (73–91)	15	53% (27–79)	92% (82–97)
Castiglione[63]	2007	Italy	OC-Hemodia	20	-	2-year registry	27503	83	81% (71–89)	96% (96–96)	-	-	-
Graser[36]	2009	Germany	FOB-Gold	2.38	-	Colonoscopy	285	1	100% (3–100)	84% (79–88)	24	29% (13–51)	86% (81–90)
Park[39]	2010	Korea	OC-Micro	20	15	Colonoscopy	770	13	77% (46–95)	94% (92–95)	59	24% (14–37)	94% (92–96)
Levi[37]	2011	Israel	OC-Micro	14	-	2-year registry	1204	6	100% (54–100)	88% (86–90)	-	-	-
Chen[44]	2011	Taiwan	OC-Sensor	20	-	1-year registry	46355	115	61% (51–70)	96% (96–96)	-	-	-
De Wijkerslooth[64]	2012	Netherlands	OC-Sensor	20	10, 15	Colonoscopy	1256	8	75% (35–97)	95% (93–96)	113	29% (21–39)	97% (96–98)
Wong[22]	2012	Canada	Magstream	67	-	Colonoscopy	1075	2	100% (16–100)	91% (90–93)	67	36% (24–48)	93% (92–95)
Brenner[32]	2013	German	RIDASCREE	24.5	-	Colonoscopy	2235	15	60%	95%	207	21%	97%

Author	Year	Country	FIT brand	Primary positivity threshold (μg/g)	Other thresholds	Reference standard	Total Cohort	Cancers detected	CRC Sensitivity (95%CI)	CRC Specificity (95%CI)	Advanced adenomas detected[a]	AA sensitivity (95%CI)	AA specificity (95%CI)
		y	N Hb						(32–84)	(94–96)		(15–27)	(96–98)
Brenner[32]			OC-Sensor	6.1					73% (45–92)	96% (95–96)	207	22% (17–29)	97% (97–98)
Shin[53]	2013	Korea	n/a	n/a	-	1-year registry	354014	839	52% (48–55)	97% (97–97)	-	-	-
Imperiale[40]	2014	USA	OC-Sensor	20	-	Colonoscopy	9989	65	74% (61–84)	94% (93–94)	757	24% (21–27)	95% (94–95)
Hernandez[45]	2014	Spain	OC-Sensor	20	10, 15, 25, 30, 40	Colonoscopy	779	5	100% (48–100)	94% (92–95)	92	28% (19–39)	96% (94–97)
Johnson[21]	2014	USA	OC-Sensor	20	-	Colonoscopy	193	2	100% (16–100)	98% (95–99)	25	4% (0–20)	98% (95–100)
Symonds[65]	2015	Australia	OC-Sensor	10	10	Colonoscopy	1381	66	79% (67–88)	80% (78–83)	189	42% (35–50)	84% (82–86)
Stegeman[23]	2015	Netherlands	OC-Sensor	10	-	2-year registry	2871	20	75% (51–91)	92% (91–93)	-	-	-
Lee[52]	2015	Korea	HemoTecht	19	6.3	Colonoscopy	1397	14	71% (42–92)	96% (94–97)	7	43% (10–82)	96% (95–97)
Jensen[54]	2016	USA	OC-Sensor	20	-	1-year registry	323349	645	84% (81–87)	95% (95–95)	-	-	-
Chen[55]	2016	Taiwan	OC-Sensor	20	-	1-year registry	141045	763	93% (91–95)	94% (94–95)	-	-	-
Kim[66]	2016	Korea	OC-Sensor	20	10, 15	Colonoscopy	3990	79	73% (62–83)	83% (81–84)	376	38% (33–43)	84% (82–86)
Chen[43]	2016	Germany	FOB-Gold	17	15, 28, 42, 82	Colonoscopy	3466	29	97% (82–100)	90% (89–91)	354	33% (28–38)	93% (92–94)
Redwood[50]	2016	USA	OC-Sensor	20	20	Colonoscopy	424	4	75% (19–99)	93% (90–95)	56	29% (17–42)	96% (93–98)
Kim[46]	2017	Korea	OC-Sensor	20	-	Colonoscopy	26316	16	69% (41–89)	97% (97–97)	154	19% (16–23)	97% (97–97)
Aniwan[47]	2017	Thailand	OC-Sensor	20	5, 10, 30, 40	Colonoscopy	1479	14	79% (49–95)	93% (92–95)	123	16% (10–24)	94% (93–96)
Van der Vlugt[67]	2017	Netherlands	OC-Sensor	10	-	2-year registry	18716	116	77% (68–84)	89% (89–89)	-	-	-
Haug[68]	2017	Netherlands	OC-Sensor	10	-	2-year registry	4523	25	88% (69–97)	92% (91–93)	-	-	-

Author	Year	Country	FIT brand	Primary positivity threshold (μg/g)	Other thresholds	Reference standard	Total Cohort	Cancers detected	CRC Sensitivity (95%CI)	CRC Specificity (95%CI)	Advanced adenomas detected[a]	AA sensitivity (95%CI)	AA specificity (95%CI)
Shapiro[48]	2017	USA	OC-Sensor	20	-	Colonoscopy	947	2	0% (0–84)	97% (96–98)	53	15% (7–28)	98% (97–99)
Gies[8]	2018	Germany	CAREprime	6.3	7, 12, 15, 26	Colonoscopy	516	16	81% (54–96)	88% (85–91)	200	31% (25–38)	91% (88–94)
Gies[8]			Hb Elisa	2	5, 15, 29				81% (54–96)	82% (78–85)	200	44% (37–51)	86% (81–89)
Gies[8]			OC Sensor	10	4, 7, 15, 18				69% (41–89)	96% (93–97)	200	18% (13–24)	98% (95–99)
Gies[8]			RIDASCREEN Hb	8	12, 15, 30				81% (54–96)	87% (84–90)	200	36% (29–43)	91% (87–94)
Gies[8]			FOB-Gold	17	2, 15, 18, 53				69% (41–89)	95% (92–96)	200	18% (13–24)	96% (94–98)
Gies[8]			Eurolyser FOB test	8.04	2, 6, 15, 21				63% (35–85)	95% (93–97)	200	19% (14–26)	97% (94–99)
Gies[8]			ImmoCare C	6.25	9, 15, 17, 37				81% (54–96)	87% (84–90)	200	35% (28–42)	90% 86–93)
Gies[8]			QuantOn Hem	3.7	10, 15, 18, 30				81% (54–96)	82% (79–85)	200	41% (35–49)	86% (81–89)
Gies[8]			QuikRead go iFOBT	15	23				63% 35–85)	95% (92–97)	200	19% (13–25)	97% (94–98)
Chen[56]	2018	Taiwan	OC-Sensor	20	-	2-year registry	723113	2005	75% (73–77)	96% (96–96)	-	-	-
Selby[9]	2018	USA	OC-Sensor	20	10, 15, 25, 30	2-year programmatic	640859	1245	74% (72–77)	93% (92–93)	-	-	-
Liles[24]	2018	USA	OC-Micro	20	10, 15, 25, 30	Colonoscopy	2771	2	100% (16–1)	96% (95–97)	209	13% (9–19)	97% (96–97)

FIT: fecal immunochemical test, CRC: colorectal cancer, AA: advanced adenomas (adenomas ≥ 1 cm,

[a] All authors defined advanced adenomas as: ≥10mm, with villous histology, and/or with any high-grade dysplasia, unless specified

[b] Launoy, Liu and Nakama defined advanced adenomas as ≥10 mm only

[c] Morikawa et al defined advanced adenomas as ≥10 mm or with any high-grade dysplasia only

Table 2:

Pooled sensitivity and specificity of quantitative fecal immunochemical tests for colorectal cancers and advanced adenomas, stratified by positivity threshold, limited to cohorts with colonoscopy follow-up. One study could contribute to more than one pooled analysis if additional positivity thresholds were available

Positivity threshold (μg/g)	Number of studies	Number of CRC	Sensitivity for CRC (95% CI)	Specificity for CRC (95% CI)	I^2	Number of AA	Sensitivity for AA (95% CI)	Specificity for AA +CRC (95% CI)
≤10	18	447	80% (76–83)	91% (89–93)	30%	2,972	31% (27–35)	93% (91–95)
>10 and ≤20	26	432	69% (63–75)	94% (93–96)	52%	4,337	21% (18–25)	96% (95–97)
>20 and ≤30	12	188	73% (62–81)	96% (95–97)	46%	2,241	18% (13–23)	98% (97–98)
>30	8	188	66% (55–75)	96% (94–97)	38%	1,770	19% (14–25)	97% (96–98)

μg/g: micrograms of stool per gram of buffer; CRC: colorectal cancer; 95% CI: 95% confidence interval; I^2: Inconsistency index; AA: advanced adenomas

Table 3:

Studies reporting stratified results of fecal immunochemical test performance for colorectal cancer detection by sex and age[a]

Author, Year	Reference standard	FIT brand, positivity threshold	Sensitivity for CRC among men (95% CI)	Sensitivity for CRC among women (95% CI)	*P*-value	Specificity among men (95% CI)	Specificity among women (95% CI)	*P*-value
Brenner,[15] 2018[b]	Colonoscopy	FOB Gold, 17 μg/g	12/14 86% (57–98)	11/11 100% (72–100)	0.191	1,376/1,545 89% (87–91)	1,518/1,641 93% (91–94)	0.001
Chen,[56] 2018	2-year registry	OC-Sensor, 20 μg/g	813/1,065 76% (74–79)	683/940 73% (70–75)	0.059	262,840/275,977 95% (95–95)	430,834/445,131 97% (97–97)	<0.001
Selby,[9] 2018	2-year programmatic	OC-Sensor, 20 μg/g	552/717 77% (74–80)	373/528 71% (67–75)	0.011	277,174/302,554 92% (92–92)	314,804/337,060 93% (93–93)	<0.001

Author, Year	Reference standard	FIT brand, positivity threshold	Sensitivity for CRC, age group 1 (95% CI)	Sensitivity for CRC, age group 2 (95% CI)	Sensitivity for CRC, age group 3 (95% CI)	*P*-value	Specificity, age group 1 (95% CI)	Specificity, age group 2 (95% CI)	Specificity, age group 3 (95% CI)	*p*-value
Kim,[46] 2017	Colonoscopy	OC-Sensor, 20 μg/g	30–39 years: 1/1 100% (3–100)	40–49 years: 3/4 75% (19–99)	≥50 years: 7/11 64% (31–89)	0.719	30–39 years: 11,072/11,403 97% (97–98)	40–49 years: 10,218/10,534 97% (97–97)	≥50 years: 4,203/4,365 96% (96–97)	0.075
Brenner,[15] 2018[b]	Colonoscopy	FOB Gold, 17 μg/g	50–59 years: 5/5 100% (48–100)	60–69 years: 8/10 80% (44–98)	70–79 years: 10/10 100% (69–100)	0.196	50–59 years: 1,382/1,491 93% (91–94)	60–69 years: 1,034/1,144 90% (89–92)	70–79 years: 478/551 87% (84–90)	<0.001
Chen,[56] 2018	2-year registry	OC-Sensor, 20 μg/g	50–59 years: 673/879 77% (74–79)	60–69 years: 823/1,126 73% (70–76)		0.076	50–59 years: 420,743/435,105 97% (97–97)	60–69 years: 272,931/286,003 95% (95–96)		<0.001
Selby,[9] 2018	2-year programmatic	OC-Sensor, 20 μg/g	50–59 years: 338/428 79% (75–83)	60–69 years: 392/534 73% (69–77)	70–75years: 195/283 69% (63–74)	0.009	50–59 years: 302,444/323,427 94% (93–94)	60–69 years: 215,168/ 234,131 92% (92–92)	70–75 years: 74,366/82,056 91% (90–91)	<0.001

FIT: fecal immunochemical test; CRC: colorectal cancer

[a]Only showing results for those aged 50 years or above

[b]Study not included in overall pooled analyses because of overlap with Chen 2016[43]