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Accuracy, Sensitivity, Specificity

REVIEW

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The Accuracy of Fecal Immunochemical Test in Colorectal Cancer Screening: A Meta-Analysis

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Abstract

Objective: To investigate the accuracy of OC-Sensor and colorectal cancer screening in a population-based randomized controlled trial at Khon Kaen province, Thailand. **Methods:** The MOOSE Guidelines for Systematic Reviews and Meta-Analyses of Observational Studies was applied. Eligibility criteria were English language, hand searching was conducted using Medline databases from 2010 to 2021 for identify literatures reviews of OC-Sensor and colorectal cancer screening. The initials screen based on the research titles and abstracts, final screenings based on full-text reports. Synthesis the results with meta-analysis using fixed effect model, random effect model, determined statistically significant with p-value < 0.05. Confirmed the pooled effect sizes of high heterogeneity by meta-regression including tested precision of each estimates by bubble plot using STATA version 14. **Results:** Meta-regression showed sensitivity of OC- sensor = 72.54% (95% CI: 65.82-79.25), and specificity of OC- sensor = 89.59% (95% CI: 87.23-91.95). **Conclusions:** Sample size and cut-off of fecal hemoglobin concentration in each study were differed but sub-group analysis and sensitivity analysis were not considered for this analysis because population, setting and location for detected cancer of included study are not differences.

Keywords: FIT- advance neoplasia- colorectal cancer

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Introduction

In term of measurements, accuracy is a set of the measurements to a specific value which low accuracy causes a difference between a result and a true value. As more than 80% of colorectal cancers arise from adenomatous polyps, screening for this cancer is effective not only for early detection but also for prevention. Diagnosis of cases of colorectal cancer through screening tends to occur 2-3 years before diagnosis of cases with symptoms (Cunningham et al., 2010). American Cancer Society (2018) recommended methods for colorectal cancer screening such as Flexible sigmoidoscopy, Colonoscopy, Double-contrast barium enema (DCBE), CT colonography (virtual colonoscopy), Guaiac-based fecal occult blood test (gFOBT), Stool DNA test including Fecal immunochemical test (FIT). Fecal immunochemical test or FIT for colorectal cancer screening were used to measure human hemoglobin in stool. However, most of FITs are qualitative tests can indicate when hemoglobin is detected in the sample that is higher than a specific reference standard. A few FITs are quantitative tests, the amount of hemoglobin is measured numerical and then reported as positive if greater than a reference count (Songster et al., 1980, Robertson et al., 2017) moreover, immunochemical tests are accurate and do not require dietary or medication changes before testing (Lee et al., 2014). However, the study of Silva-Illanes and Espinoza (2018) were conducted a systematic review to critical analysis of Markov models used for the economic evaluation of colorectal cancer screening, found that parameterization of adenoma dwell time, sojourn time, and surveillance differed between studies, and there was a lack of validation and statistical calibration against local epidemiological data. Colorectal cancer screening using FIT in a population-based randomized controlled trial at Khon Kaen province, Thailand, procedures for collecting FIT, all participants in study arm receive a sampling bottle and instructions for collecting a stool sample, and sending to the laboratory at hospital. The quantitative human hemoglobin content of each the collected stool specimens is measured in the laboratory using OC-Sensor (Sarakarn et al., 2017). The authors conducted a systematic reviews and meta-analysis to investigate the accuracy which refer to sensitivity and specificity of OC-Sensor and colorectal cancer screening (Table1)

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Materials and Methods

Sources

The procedures followed the MOOSE Guidelines for Systematic Reviews and Meta-Analyses of Observational Studies. The eligibility criteria for the studies were English language, hand searching was conducted using the Medline databases, from 2010 to 2021 from wording "sensitivity" and or "specificity" "fecal immunochemical test" or FIT and colorectal cancer screening or "CRC" for identify literatures reviews of OC-Sensor and colorectal cancer screening. Colorectal cancer defined as advance neoplasia and colorectal cancer in adults. The selection of each study in the initials screening were based on the research titles and abstracts. Final screenings based on full-text reports excepted results from systematic reviews and meta-analysis double checked from abstracts.

Study Selection

The authors considered selected articles for investigate the accuracy of FIT such as cohort study, observation study including excluded results from systematic reviews and articles from meta-analysis. Each studies presents percentage and 95%CI of sensitivity and specificity of clinical testing for OC-Sensor and advance neoplasia or colorectal cancer. Assessment study quality and estimates precision of each study by considerate sample size and 95%CI in the studies including comparable characteristic of participants in each studies between FIT and colonoscopy.

Statistical analysis

The authors summarizing the effects size of sensitivity, specificity and confidence interval of each selected articles, synthesis the results with meta-analysis using fixed effect model, random effect model, by considered heterogeneity from Tau^2, Chi^2, I^2, and determined statistically significant with p-value < 0.05. However, the selected articles are not differences between population, setting and location for sub-group analysis, finally calculated standard error from 95%CI, and confirmed the pooled effect sizes of high heterogeneity by meta-regression including tested precision of each estimates by bubble plot using STATA program version 14.

Results

Meta regression is useful when there is substantial heterogeneity, a guide for the interpretation of the amount of heterogeneity is considered as I^2 from 0% to 40% might not be important, I^2 from 30% to 60% is represent moderate heterogeneity, I^2 from 50% to 90% is represent substantial heterogeneity, and I^2 from 75% to 100% considered as high heterogeneity (Higgins and Green, 2011). Result from meta-regression showed Knapp-Hartung modification I^2 = 96.80% for sensitivity of OC- sensor effect sized = 72.54 (95% CI: 65.82-79.25), and Knapp-Hartung modification I^2 = 99.10% for specificity of OC- sensor effect sized = 89.59% (95% CI: 87.23-91.95). The way to present the fitted model, sometimes refer to a bubble plot that is a graph for the fitted regression line together with circles representing the estimates from each study, sized according to the precision of each estimate (The Stata Journal Science Citation Index Expanded and CompuMath Citation Index, 2008). (Table 2, Table 3, Figure 1, Table 4, Table 5, Figure 2, Table 6, and Figure 3).

Discussion

This meta-regression showed high accuracy which is sensitivity and specificity of OC-Sensor for detecting fecal hemoglobin concentration and colorectal cancer screening. Interval FIT testing is capable of detecting neoplasia in the high-risk adult population undergoing colonoscopy

Table 1. Quantitative FIT Brand for Using Colorectal Cancer Screening (Robertson et al., 2017)

Authors	Year	FIT brand	FIT samples	Cut-off fHb (μg/g)	Reference standard
Nakama et al.	1999	Monohaem	1	20	Colonoscopy
Morikawa et al.	2005	Magstream	1	67	Colonoscopy
Hundt et al.	2009	ImmoCARE-C	1	30	Colonoscopy
Haug et al	2010	Ridascreen	1	14	Colonoscopy
Brenner and Tao	2013	Ridascreen	1	24.5	Colonoscopy
Itoh	1996	OC-Hemodia	1	10	2-year follow up
Sohn et al.	2005	OC-Hemodia	1	20	Colonoscopy
Nakazato et al.	2006	OC-Hemodia	2	16	Colonoscopy
Levi et al.	2007	OC-Micro	3	15	Colonoscopy
Park et al.	2010	OC-Micro	1	20	Colonoscopy
Parra-Blanco et al.	2010	OC-Ligh	1	10	2-year follow up
Chiang et al.	2011	OC-Light	1	10	Colonoscopy
Levi et al.	2011	OC-Micro	3	14	2-year follow up
Brenner and Tao	2013	OC-Sensor	1	6.1	Colonoscopy
Kapidzic et al.	2014	OC-Sensor	1	10	Colonoscopy
Hernandez et al.	2014	OC-Sensor	1	20	Colonoscopy
Imperiale et al.	2014	OC-FIT CHEK	1	20	Colonoscopy

Table 2. Summarizing Sensitivity of OC-Sensor and CRC Screening

No.	Authors	Years	Population	n	Location	Cut-off fHb (µg/g)	Sensitivity (%)	95%CI (%)
1	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 50	92	84 - 97
2	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 75	91	83 - 96
3	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 100	90	81 - 96
4	Gimeno-Garcia	2011	Spain	346	AN	≥ 50	64	48 - 78
5	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 50	88	47 - 99
6	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 75	75	36 - 96
7	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 100	75	36 - 96
8	Terhaar sive Droste	2012	Netherlands	1,041	CRC	50	80	28 - 99
9	Castro et al.	2014	Spain	595	CRC	50	71	52 - 98
10	Castro et al.	2014	Spain	595	CRC	100	71	52 - 98
11	Chiang et al.	2014	Taiwan	747,076	CRC	20	80	76 - 84
12	Hernandez et al.	2014	Spain	779	CRC	50	95	90 - 100
13	Hernandez et al.	2014	Spain	779	CRC	75	95	90 - 100
14	Hernandez et al.	2014	Spain	779	CRC	100	95	90 - 100
15	Cubiella	2014	Spain	787	AN	≥ 20	31	21 - 41
16	Quintero et al.	2014	Spain	638	AN + CRC	≥ 10	75	19 - 99
17	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 10	97	83 - 99
18	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 15	97	83 - 99
19	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 20	93	77 - 99
20	Otero-Estevez et al.	2015	Spain	516	AN	≥ 100	37	24 - 51
21	Vleugels et al.	2015	Netherlands	173	AN	20	40	21 - 61
22	Aniwan et al.	2017	Thailand	1,580	CRC	25	79	49 -95
23	Aniwan et al.	2017	Thailand	1,580	CRC	50	79	52 - 96
24	Aniwan et al.	2017	Thailand	1,580	CRC	100	79	49 - 95
25	Digby et al.	2020	Scotland	593	CRC+HRA	<2 LoD	76	60-88
26	Digby et al.	2020	Scotland	593	CRC+HRA	<4 LoQ	71	55-84
27	Digby et al.	2020	Scotland	593	CRC+HRA	<10	51	35-67
28	Mattar et al.	2020	Brazil	289	CRC, FIT1	10	83	37-99
29	Mattar et al.	2020	Brazil	289	CRC, FIT2	10	75	36-96
30	Ykema et al.	2020	Netherlands	73	AN	10	37	16-62
31	Ykema et al.	2020	Netherlands	73	AN	15	32	13-57
32	Ykema et al.	2020	Netherlands	73	AN	20	26	Sep-51
33	Young	2020	Australia	626	AN, FIT1	7.4	47	43-51
34	Young	2020	Australia	626	AN, FIT2	12.8	57	53-61
35	Vieito et al.	2021	Spain	38,675	CRC, FIT1	≥ 10	91	88-93
36	Vieito et al.	2021	Spain	38,675	CRC, FIT2	≥ 20	88	85-90
37	Lu et al	2021	China	3144	CRC, FIT1	8	58	40-75
38	Lu et al	2021	China	3144	CRC, FIT2	14.4	58	40-75
39	Lu et al	2021	China	3144	CRC, FIT3	20.8	58	40-75

surveillance and a first time FIT can detected significant neoplasia in 1.8% of subjects who were enrolled in a colonoscopy-based surveillance program for either a personal or family history of colonic neoplasia (Robertson et al., 2017, Bampton et al., 2005) including interval FIT in patients who had at least 2 prior colonoscopy

Table 3. Summarizing the Sensitivity and 95% CI of OC-Sensor and CRC Screening

Model	Heterogeneity test			Sensitivity (%)	95%CI (%)
	Tau^2	I^2	Chi^2		
Fixed effect	-	95.80%	$p < 0.0001$	81.33	80.21-82.44
Random effect weight with inverse variance	319.48	95.80%	$p < 0.0001$	71.94	65.69-78.19

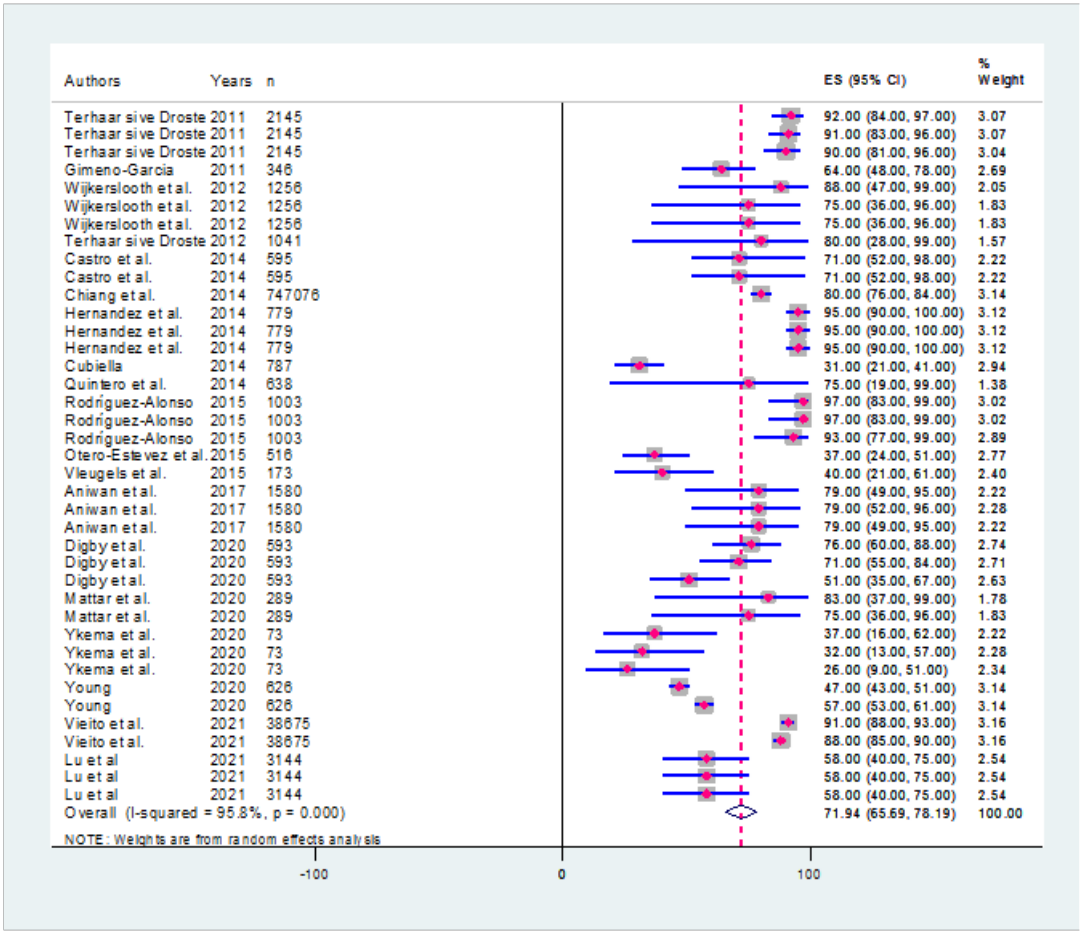

Figure 1. Forest Plot Showed Random Effect of Sensitivity, 95% CI of OC-Sensor and CRC Screening

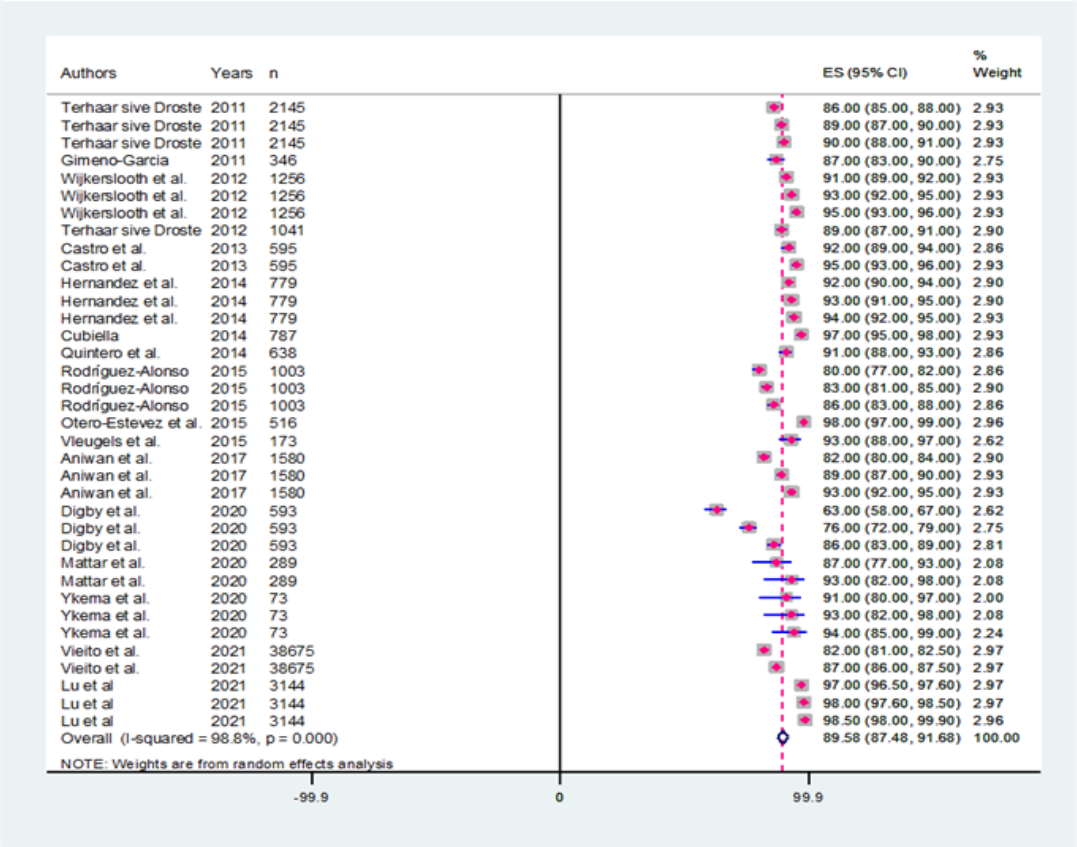

Figure 2. Forest Plot Showed Random Effect of Specificity, 95% CI of OC-Sensor and CRC Screening

Table 4. Summarizing Specificity of OC-Sensor and CRC Screening

No.	Authors	Years	Population	n	Location	Cut-off fHb (µg/g)	Specificity (%)	95%CI (%)
1	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 50	86	85 - 88
2	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 75	89	87 - 90
3	Terhaar sive Droste	2011	Netherlands	2,145	CRC	≥ 100	90	88 - 91
4	Gimeno-Garcia	2011	Spain	346	AN	≥ 50	87	83 - 90
5	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 50	91	89 - 92
6	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 75	93	92 - 95
7	Wijkerslooth et al.	2012	Netherlands	1,256	CRC	≥ 100	95	93 - 96
8	Terhaar sive Droste	2012	Netherlands	1,041	CRC	50	89	87 - 91
9	Castro et al.	2013	Spain	595	CRC	50	92	89 - 94
10	Castro et al.	2013	Spain	595	CRC	100	95	93 - 96
11	Hernandez et al.	2014	Spain	779	CRC	50	92	90 - 94
12	Hernandez et al.	2014	Spain	779	CRC	75	93	91 - 95
13	Hernandez et al.	2014	Spain	779	CRC	100	94	92 - 95
14	Cubiella	2014	Spain	787	AN	≥ 20	97	95 - 98
15	Quintero et al.	2014	Spain	638	AN + CRC	≥ 10	91	88 - 93
16	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 10	80	77 - 82
17	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 15	83	81 - 85
18	Rodríguez-Alonso	2015	Spain	1,003	CRC	≥ 20	86	83 - 88
19	Otero-Estevez et al.	2015	Spain	516	AN	≥ 100	98	97 - 99
20	Vleugels et al.	2015	Netherlands	173	AN	20	93	88 - 97
21	Aniwan et al.	2017	Thailand	1,580	CRC	25	82	80 - 84
22	Aniwan et al.	2017	Thailand	1,580	CRC	50	89	87 - 90
23	Aniwan et al.	2017	Thailand	1,580	CRC	100	93	92 - 95
24	Digby et al.	2020	Scotland	593	CRC+HRA	<2 LoD	63	58-67
25	Digby et al.	2020	Scotland	593	CRC+HRA	<4 LoQ	76	72-79
26	Digby et al.	2020	Scotland	593	CRC+HRA	<10	86	83-89
27	Mattar et al.	2020	Brazil	289	CRC, FIT1	10	87	77-93
28	Mattar et al.	2020	Brazil	289	CRC, FIT2	10	93	82-98
29	Ykema et al.	2020	Netherlands	73	AN	10	91	80-97
30	Ykema et al.	2020	Netherlands	73	AN	15	93	82-98
31	Ykema et al.	2020	Netherlands	73	AN	20	94	85-99
32	Vieito et al.	2021	Spain	38,675	CRC, FIT1	≥ 10	82	81-82
33	Vieito et al.	2021	Spain	38,675	CRC, FIT2	≥ 20	87	86-87
34	Lu et al	2021	China	3144	CRC, FIT1	8	97	96.5-97.6
35	Lu et al	2021	China	3144	CRC, FIT2	14.4	98	97.6-98.5
36	Lu et al	2021	China	3144	CRC, FIT3	20.8	98	98-99

examinations and with personal or family history of colonic neoplasia that detected 86% sensitivity and 63% sensitivity for advanced adenomas during follow-up evaluation (Robertson et al., 2017, Lane et al., 2010). In addition few data are available to guide the development of quality benchmarks for FIT processes given the similarities to FOBT-based programs, examining results from these programs may be informative (Robertson et al., 2017) and 29.8% of those eligible participated in screening, and when FOBT was positive, 74.6% proceeded to colonoscopy in 6 months (Rabeneck et al., 2014). Higher participation rates were reported from England

Table 5. Summarizing the Specificity and 95% CI of OC-Sensor and CRC Screening

Model	Heterogeneity test			Specificity (%)	95%CI (%)
	Tau^2	I^2	Chi^2		
Fixed effect	-	98.80%	$p < 0.0001$	92.98	92.76-93.19
Random effect weight with inverse variance	38.54	98.80%	$p < 0.0001$	89.58	87.48-91.68

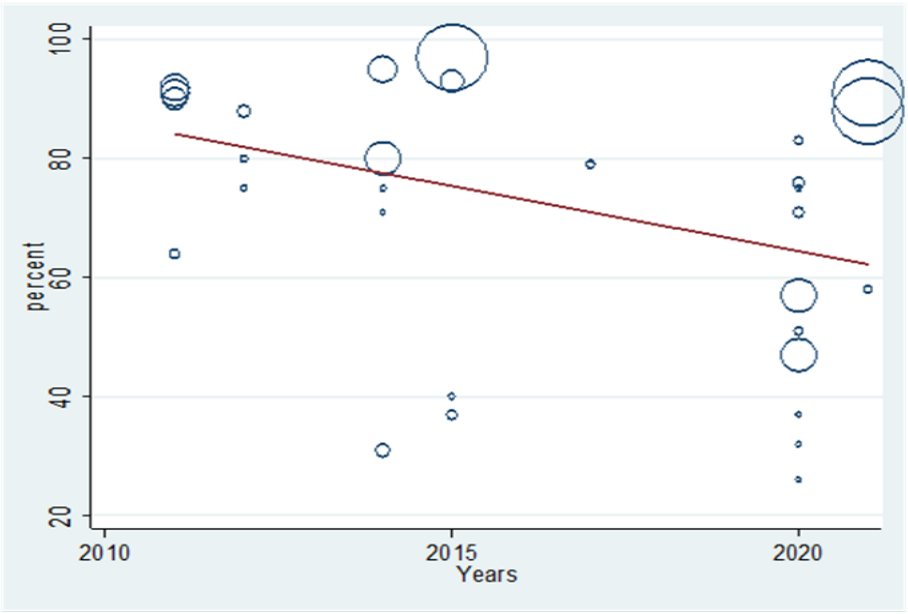

Figure 3. Bubble Plot of Sensitivity of OC-Sensor and CRC Screening

Table 6. Meta-Regression of OC-Sensor and CRC Screening

Accuracy	I^2	Percentage	SE	95%CI
Heterogeneity with Knapp-Hartung modification	96.80%			
Over-all effect of sensitivity from 39 result		72.54	3.32	65.82-79.25
Heterogeneity with Knapp-Hartung modification	99.10%			
Over-all effect of specificity from 36 result		89.59	1.16	87.23-91.95

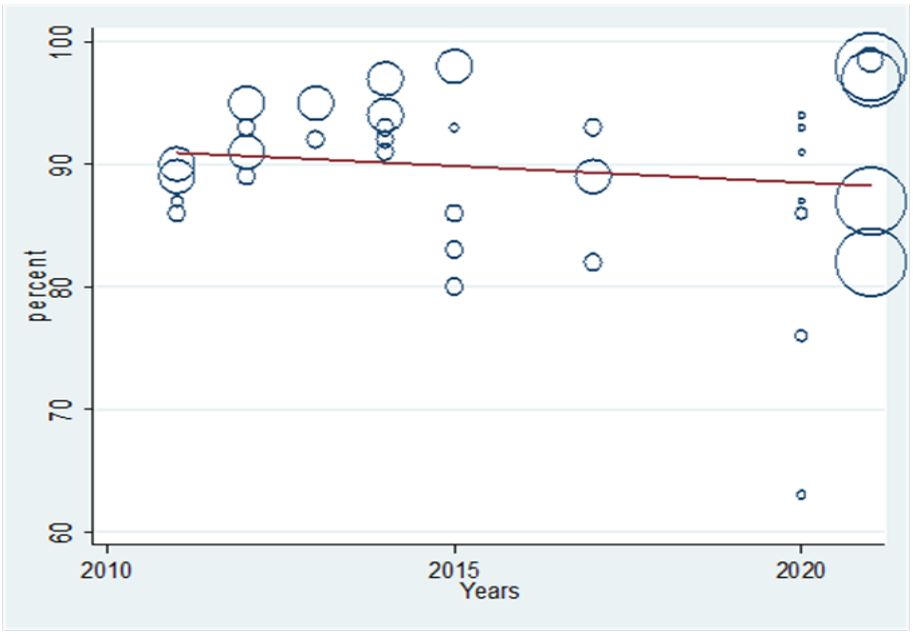

Figure 4. Bubble Plot of Specificity of OC-Sensor and CRC Screening

52% (Logan et al., 2012) and Finland 70% (Malila et al., 2008). The follow-up colonoscopy rate in Ontario also was lower than that reported in England 83% (Logan et al., 2012). Yen, et al., (2014) assessed how much of the variation in incidence of colorectal neoplasia is explained by baseline fecal hemoglobin concentration (FHbC) and also to assess the additional predictive value of conventional risk factors. The result showed the predictive model between FHbC and risk of developing colorectal neoplasia area under curve (AUC) = 83.5% (95% CI: 82.1%–84.9%). Liao Chao - Sheng, et al. (2013) evaluate fecal hemoglobin concentration, in the prediction of histological grade and risk of colorectal tumors. The results showed a significant log-linear relationship

between the concentration and positive predictive value of the FIT for predicting colorectal tumors ($R^2 > 0.95$, $P < 0.001$), and conclude that higher FIT concentrations are associated with more advanced histological grades. Risk prediction for colorectal neoplasia based on individual FIT concentrations is significant and may help to improve the performance of screening programs. Although this study found high accuracy which is sensitivity and specificity of OC-Sensor for detecting fecal hemoglobin concentration and colorectal cancer screening but The American Cancer Society (2018) described the benefit of FIT that no direct risk to the colon, no bowel prep, no pre-test diet changes, sampling done at home and fairly inexpensive but the limitation of FIT that can miss many polyps and some cancers, can produce false-positive test results, needs to be done every year including Colonoscopy will be needed if abnormal. However, in this trial participants who receive positive results are contacted by health officers, who work in their village, and are prepared for a confirmatory colonoscopy examination at a subsequent date. Participants who receive negative results will be examined for FIT every two years which is the optimal timing for a subsequent FIT (Sarakarn et al., 2017). The limitation of this meta-analysis found that although sample size and cut-off of fecal hemoglobin concentration of each study were differed but sub-group analysis and sensitivity analysis were not considered for this analysis because population, setting and location for detected cancer of included study are not differences.

Author Contribution Statement

None declared.

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Conflict of interest

The author declares that is no conflict of interest

References

American Cancer Society A, (2018). What are some of the pros and cons of these screening Retrieved https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/screening-tests-used.html.

Aniwan S, Ratanachu Ek T, Pongprasobchai S, et al (2017). The optimal cut-off level of the fecal immunochemical test for colorectal cancer screening in a country with limited colonoscopy resources: A Multi-Center Study from Thailand. *Asian Pac J Cancer Prev*, **18**, 405-12.

Bampton PA, Sandford JJ, Cole SR, et al (2005). Interval faecal occult blood testing in a colonoscopy based screening programme detects additional pathology. *Gut*, **54**, 803-06.

Brenner H, Tao S (2013). Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. *Eur J Cancer*, **49**, 3049-54.

Castro I, Cubiella J, Rivera C, et al (2014). Fecal immunochemical test accuracy in familial risk colorectal cancer screening. *Int J Cancer*, **134**, 367-75.

Chiang TH, Chuang SL, Chen SL, et al (2014). Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. *Gastroenterology*, **147**, 1317-26.

Chiang TH, Lee YC, Tu CH, Chiu HM, Wu MS (2011). Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract. *Cmaj*, **183**, 1474-81

Cubiella J, Castro I, Hernandez V, et al (2014). Diagnostic accuracy of fecal immunochemical test in average- and familial-risk colorectal cancer screening. *United European Gastroenterol J*, **2**, 522-29.

Cunningham D, Atkin W, Lenz HJ, (2010). Colorectal cancer. *Lancet*, **375**, 1030-47.

de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al (2012). Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. *Am J Gastroenterol*, **107**, 1570-78.

Gimeno-García AZ, Carrillo-Palau M, Hernández-Guerra M, et al (2011). Diagnostic yield of the immunochemical fecal occult blood test in asymptomatic first degree relatives of colorectal cancer patients. *Gastroenterology*, 140 S-406.

Haug U, Hundt S, Brenner H (2010). Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests. *Am J Gastroenterol*, **105**, 682-90.

Hernandez V, Cubiella J, Gonzalez-Mao MC, et al (2014). Fecal immunochemical test accuracy in average-risk colorectal cancer screening. *World J Gastroenterol*, **20**, 1038-47.

Hundt S, Haug U, Brenner H (2009). Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. *Ann Intern Med*, **150**, 162-69.

Itoh M, Takahashi K, Nishida H, Sakagami K, Okubo T (1996). Estimation of the optimal cut off point in a new immunological faecal occult blood test in a corporate colorectal cancer screening programme. *J Med Screen*, **3**, 66-71.

Kapidzic A, Grobbee EJ, Hol L, et al (2014). Attendance and yield over three rounds of population-based fecal immunochemical test screening. *Am J Gastroenterol*, **109**, 1257-64.

Katsoula A, Paschos P, Haidich AB, Tsapas A, Giouleme O (2017). Diagnostic accuracy of fecal immunochemical test in patients at increased risk for colorectal cancer: A Meta-analysis. *JAMA Intern Med*, **177**, 1110-18.

Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al (2011). Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. *Cancer Prev Res (Phila)*, **4**, 1563-71.

Lane JM, Chow E, Young GP, et al (2010). Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology*, **139**, 1918-26.

Lee JK, Liles EG, Bent S, Levin TR, Corley DA (2014). Accuracy of fecal immunochemical tests for colorectal cancer: Systematic Review and Meta-analysis. *Ann Intern Med*, **160**, 171-71.

Levi Z, Birkenfeld S, Vilkin A, et al (2011). A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study. *Int J Cancer*, **128**, 2415-24.

Levi Z, Rozen P, Hazazi R, et al (2007). A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med*, **146**, 244-55.

Liao CS, Lin YM, Chang HC, et al (2013). Application of quantitative estimates of fecal hemoglobin concentration for risk prediction of colorectal neoplasia. *World J Gastroenterol*, **19**, 8366-72.

Logan RFA, Patnick J, Nickerson C, et al (2012). Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut*, **61**, 1439.

Lu M, Zhang YH, Lu B, et al (2021). Head-to-head comparison of the test performance of self-administered qualitative vs. laboratory-based quantitative fecal immunochemical tests in detecting colorectal neoplasm. *Chin Med J (Engl)*, **134**, 1335-44.

Malila N, Oivanen T, Malminiemi O, Hakama M (2008). Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. *BMJ*, **337**, a2261.

Mattar R, Marques SB, Minata MK, et al (2020). Diagnostic accuracy of one sample or two samples quantitative fecal immunochemical tests for intestinal neoplasia detection. *Arq Gastroenterol*, **57**, 316-22.

Nakama H, Yamamoto M, Kamijo N, et al (1999). Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. *Hepatogastroenterology*, **46**, 228-31.

Otero-Estévez O, De Chiara L, Rodríguez-Berrocal FJ, et al (2015). Serum sCD26 for colorectal cancer screening in family-risk individuals: comparison with faecal immunochemical test. *Br J Cancer*, **112**, 375-81.

Parente F, Boemo C, Ardizzoia A, et al (2013). Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. *Endoscopy*, **45**, 27-34.

Park DI, Ryu S, Kim YH, et al (2010). Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol*, **105**, 2017-25.

Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al (2010). Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol*, **45**, 703-12.

Pin-Vieito N, García Nimo L, Bujanda L, et al (2021). Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study. *United European Gastroenterol J*, **9**, 256-67.

Quintero E, Carrillo M, Gimeno-Garcia AZ, et al (2014). Equivalency of fecal immunochemical tests and colonoscopy in familial colorectal cancer screening. *Gastroenterology*, **147**, 1021-30.e1021; quiz e1016-27.

Rabeneck L, Tinmouth JM, Paszat LF, et al (2014). Colon Cancer Check: Results from Canada First Province-Wide Colorectal Cancer Screening Program. *Cancer Epidemiol Biomarkers Prev*, **23**, 508.

Robertson DJ, Lee JK, Boland CR, et al (2017). Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*, **152**, 1217-37.e13.

Rodriguez-Alonso L, Rodriguez-Moranta F, Ruiz-Cerulla A, et al (2015). An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test. *Dig Liver Dis*, **47**, 797-04.

Silva-Illanes N, Espinoza M (2018). Critical analysis of Markov models used for the economic evaluation of colorectal cancer screening: A Systematic Review. *Value Health*, **21**, 858-73.

Sohn DK, Jeong SY, Choi HS, et al (2005). Single immunochemical fecal occult blood test for detection of colorectal neoplasia. *Cancer Res Treat*, **37**, 20-3.

Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al (2011). Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. *Cancer Epidemiol Biomarkers Prev*, **20**, 272-80.

Terhaar sive Droste JS, van Turenhout ST, Oort FA, et al (2012). Faecal immunochemical test accuracy in patients referred for surveillance colonoscopy: a multi-centre cohort study. *BMC Gastroenterol*, **12**, 94.

Vleugels J, Kallenberg F, De Wijkerslooth, T, et al (2015). Mo1979 offering colonoscopy to participants with a negative FIT and a first degree relative with CRC increases the detection of advanced neoplasia in a screening program. *Gastroenterology*, **148**, S-757.

Westwood M, Lang S, Armstrong N, et al (2017). Faecal immunochemical tests (FIT) can help to rule out colorectal cancer in patients presenting in primary care with lower abdominal symptoms: a systematic review conducted to inform new NICE DG30 diagnostic guidance. *BMC Med*, **15**, 189.

Yen AM, Chen SL, Chiu SY, et al (2014). A new insight into fecal hemoglobin concentration-dependent predictor for colorectal neoplasia. *Int J Cancer*, **135**, 1203-12.

Ykema B, Rigter L, Spaander M, et al (2020). Diagnostic accuracy of stool tests for colorectal cancer surveillance in hodgkin lymphoma survivors. *J Clin Med*, **9**.

Young GP, Woodman RJ, Symonds E (2020). Detection of advanced colorectal neoplasia and relative colonoscopy workloads using quantitative faecal immunochemical tests: an observational study exploring the effects of simultaneous adjustment of both sample number and test positivity threshold. *BMJ Open Gastroenterol*, **7**.