Incidence of faecal occult blood test interval cancers in population-based colorectal cancer screening: a systematic review and meta-analysis

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ABSTRACT

Objective

Faecal immunochemical tests (FITs) are replacing guaiac faecal occult blood tests (gFOBTs) for colorectal cancer (CRC) screening. Incidence of interval colorectal cancer (iCRC) following a negative stool test result is not yet known. We aimed to compare incidence of iCRC following a negative FIT or gFOBT.

Design

We searched Ovid Medline, Embase, Cochrane Library, Science Citation Index, PubMed and Google scholar from inception to December 12th, 2017 for citations related to CRC screening based on stool tests. We included studies on FIT or gFOBT iCRC in average-risk screening populations. Main outcome was pooled incidence rate of iCRCs per 100,000 person-years (p-y). Pooled incidence rates were obtained by fitting random effect Poisson regression models.

Results

We identified 7426 records, and included 29 studies. Meta-analyses comprised data of 6,987,825 subjects with a negative test result, in whom 11,932 screen-detected CRCs and 5548 gFOBT or FIT iCRCs were documented. Median faecal haemoglobin (Hb) positivity cut-off used was 20 (range 10-200) microgram Hb/gram faeces in the 17 studies that provided FIT results. Pooled incidence rates of iCRC following FIT and gFOBT were 20 (95%CI 14-29;I^2=99%) and 34 (95%CI 20-57;I^2=99%) per 100,000 p-y, respectively. Pooled incidence rate ratio of FIT versus gFOBT iCRC was 0.58 (95%CI 0.32-1.07;I^2=99%) and 0.36 (95%CI 0.17-0.75;I^2=10%) in sensitivity analysis. For every FIT iCRC, 2.6 screen-detected CRCs were found (ratio 1:2.6), for gFOBT the ratio between iCRC and screen-detected CRC was 1:1.2. Age below 60 years, and the third screening round were significantly associated with a lower iCRC rate.

Conclusion

A negative gFOBT result is associated with a higher iCRC incidence than a negative FIT. This supports the use of FIT over gFOBT as CRC screening tool.

INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most common cancer in men and the second in women.[1] Randomised controlled trials have shown that screening with guaiac faecal occult blood tests (gFOBTs), and subsequent colonoscopy if the result is positive, is associated with a 15%-33% decrease in CRC-related mortality.[2-4] Consequently, these stool tests are widely used for CRC screening.[5]

A cost-effective screening program is inevitably associated with the occurrence of what are known as interval colorectal cancers (iCRCs) – defined as CRCs detected after a negative screening test and before the next recommended test is due.[6, 7] The rate of occurrence is strongly related to the sensitivity of a screening test and reflects the quality of a screening program.[8, 9] Therefore, the International Agency for Research on Cancer (IARC) recommends to collect and report data on iCRCs.[8] In CRC screening programs, iCRCs are cases either missed by stool tests or at colonoscopy.[7] Prevalence and associated risk factors of post-colonoscopy iCRCs in screening programs have been described.[10, 11] However, data on prevalence and associated risk factors of iCRCs following negative occult stool tests are still lacking.

In fecal occult blood test (FOBT)-based CRC screening programs, gFOBTs have been the most commonly used occult stool tests for years. At present, gFOBT is rapidly replaced by fecal immunochemical testing (FIT).[5] FIT detects human-specific globin, whereas gFOBTs react with heme, including consumed non-human heme. FITs are more sensitive for the detection of CRC as well as its precursors than gFOBTs.[12, 13] Moreover, FITs allow single stool testing, are easier to handle, have higher participation rates and provide quantitative test results, which enables to adjust the positivity cut-off to match available resources.[14-16] Despite these advantages of FIT over gFOBT, gFOBT is still being used in several regions.[5] Although interval cancer rate is a key quality indicator in screening programs, data on the incidence rate of FOBT iCRC is limited and no data are available on how these two types of FOBT compare with regard to iCRC.

We therefore performed a systematic literature search and meta-analysis to determine and compare the pooled incidence rates of iCRC following gFOBT and FIT in population-based CRC screening programs. Secondly, we assessed if screening-related or patient-related factors are associated with iCRC incidence rate.

METHODS

Search strategy and selection criteria

We carried out a systematic review and meta-analysis of published trials, including observational and experimental trials or both, according to the preferred reporting items

for systematic reviews and meta-analyses (PRISMA) guidelines.[17] We additionally used a checklist containing specifications for reporting of meta-analysis of observational studies in epidemiology (MOOSE).[18]

Studies were identified through a systematic literature search until the 10th of May 2016 in the following electronic databases: Medline, Embase, Web of Science, the Cochrane Library, PubMed publisher and Google Scholar. A search update was performed on the 12th of December 2017. The search strategy was designed and conducted using controlled vocabulary supplemented with key words and without any restrictions on date or language (supplementary material 1). The titles and abstracts of identified studies were reviewed by at least two of the authors independently (EW, EHS or EJG). Studies were excluded that did not address the research question, based on the inclusion and exclusion criteria mentioned below. The full texts of the remaining publications were carefully and independently examined by the same authors. In case of disagreement, consensus was reached by consulting a fourth author (MCWS). In addition, the reference lists of the included studies were hand-searched to identify additional, potentially relevant studies (published within 5 years preceding our search).

Studies were included if they reported on CRC occurrence within one to five years after a negative gFOBT or FIT in average-risk screening populations. Both prospective and retrospective studies were included. Only studies comprising asymptomatic average-risk individuals aged 40 years and above were included, as these were considered representative for a population-based CRC screening program. Studies were eligible if participants with a positive test were referred for endoscopic confirmation. For the purpose of this systematic review, diagnostic tests accepted as endoscopic confirmation included colonoscopy, or if colonoscopy was not available or contra/-indicated sigmoidoscopy, computed tomography colonoscopy or double contrast barium enema. Only full-text articles were included. We did not restrict studies based on language or publication date. If the same screening cohort was described in more than one publication, the one with the most recently updated and most complete data was included.

Accuracy studies in which all participants underwent both the stool test and colonoscopy were excluded. Also excluded were reviews, systematic reviews, editorials and letters to the editor. Lastly, studies in which individuals were referred to endoscopy after two or more consecutive positive tests were excluded.

Outcomes

The primary outcome was the pooled incidence of interval colorectal cancer during gFOBT and FIT screening per 100,000 person-years (p-y) in an average CRC screening population.

Secondary outcomes were the proportional rate between iCRCs en screen-detected CRCs and pooled incidence of iCRCs per subgroup. Subgroups were categorized by means of screening-related and screenee-related factors, including number of screening round, duration of follow-up after a negative stool test, positivity cut-off, gender, age, tumour stage, and tumour location.

Definitions

Screen-detected CRC was defined as a CRC detected by endoscopic conformation after a positive test. Interval colorectal cancers were defined in agreement with the definition of the World Endoscopy Organization as cancers diagnosed after a negative test and before the next test was due.[7] Post-colonoscopy CRCs diagnosed after a negative colonoscopy were not taken into account. If a study did not describe when the next occult blood test was due, we assumed the interval to be 2 years. Proximal CRCs were defined as CRCs located in the cecum, ascending colon, transverse colon, or splenic flexure; and distal CRCs as CRCs located in the descending colon, sigmoid colon, or rectum. Early CRC was defined as Dukes A, or TNM stage 1.[19] In case of quantitative FIT, we converted units for positivity cut-off into micrograms (µg) of haemoglobin (Hb) per gram of stool for each study.[20]

Data extraction

Study characteristics and data were independently extracted by two investigators (EW and EHS) and recorded on a standardized data extraction form. Any discrepancies were resolved by consensus. The types of data extracted are shown in supplementary material 2. If data were incomplete, the corresponding author was asked to provide the missing information. Alternatively, we derived data from other publications on the same study cohort. If applicable, data from multiple screening rounds were included for analysis.

Data analyses

Incidence rates of iCRC were calculated per 100,000 p-y. The follow-up p-y were calculated as the number of participants with a negative test multiplied by the mean years of follow-up or the number of years for which interval cancers were identified, by using data from the cancer registry.

Pooled incidence rates were obtained by fitting random effect Poisson regression models. Heterogeneity was quantified by using the inconsistency index (I^2) test. Heterogeneity values ranged from 0% (no heterogeneity) to 100%.[21, 22] I^2 greater than 25%, 50%, and 75% was defined as indicative of low, moderate, and high heterogeneity.[22] For studies describing both a gFOBT and FIT study arm, we interpreted each arm as a separate study, ignoring the within study correlation. We used prediction intervals to calculate the expected incidence of iCRC for new settings similar to the ones included in the meta-analysis.

An incidence rate ratio was used to compare pooled incidence rates of iCRC after FIT and gFOBT. The sensitivity analysis included only studies in which both a FIT and gFOBT study arm was described. This allowed comparison of incidence rate of iCRC between the two test types in the same study population.

Meta-regression analysis

Meta-regression analyses served to assess if screening-related and patient-related factors were associated with FOBT iCRCs. For these analyses, gFOBT and FIT studies were pooled together as only few studies reported on these factors. Incidence rate ratios or proportions were used to describe categorical variables. Relative risk was used for continuous outcomes.

Quality assessment

A funnel plot was created to assess the presence of publication bias.[23] The study quality of observational studies was assessed using the Ottawa Newcastle criteria of Wells *et al*.[24] Studies were considered as high quality studies in case of a score of eight or nine out of nine stars according to the Ottowa Newcastle criteria, absence of selection bias and adequate cohort follow-up. Selection bias was considered to be present if <90% of the total inception cohort was followed. With respect to study follow-up a minimum of 2 years follow-up was required to define a high-quality study. The study quality of randomised trials was assessed using the Cochrane risk of bias tool.[25] We performed a post hoc subset analysis with high-quality studies only, to assess incidence of iCRC. The quality of evidence was rated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[26]

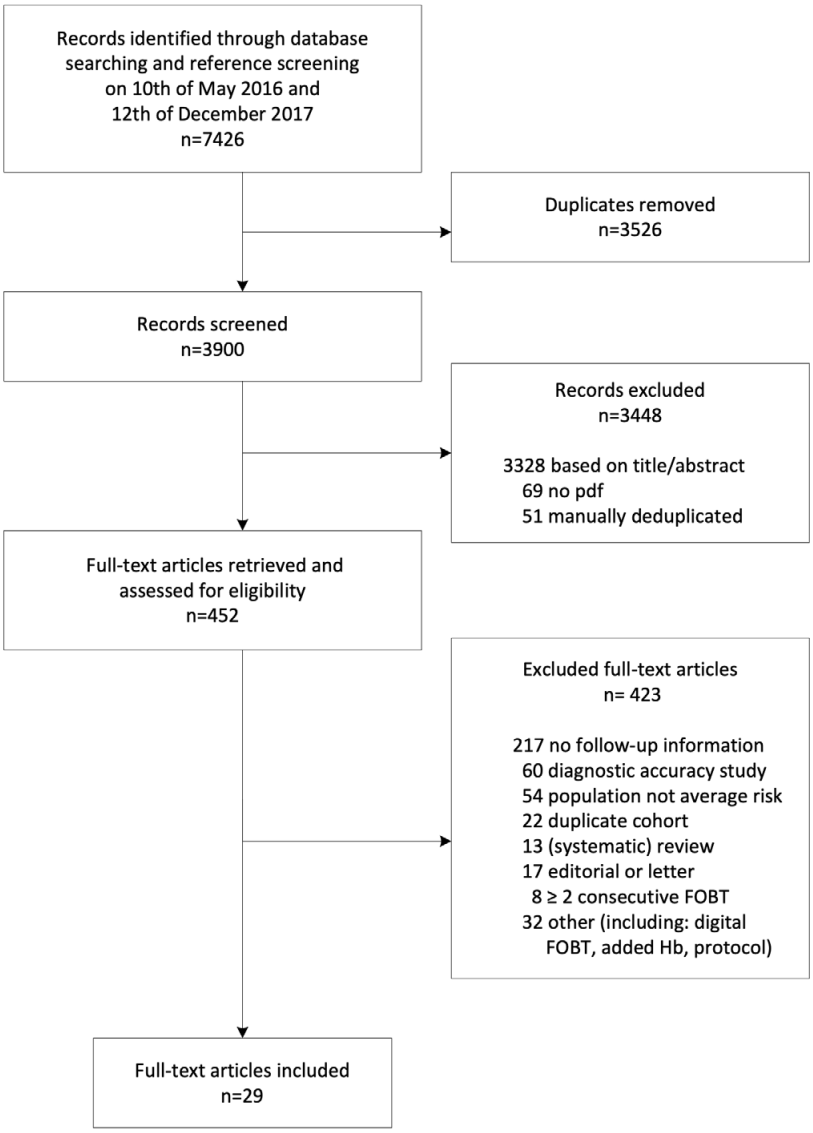
All analyses were done using R version 2.15.1.

RESULTS

In total, 7426 records were identified. After removal of duplicates, 3526 records were screened for eligibility based on title and/or abstract. In total, 452 full-text records were reviewed for eligibility criteria, of which 423 were excluded for various reasons (Figure 1). Thus, twenty-nine studies were included for qualitative and quantitative analysis.[2, 3, 6, 27-52]

Characteristics of the included studies are shown in Table 1. Nineteen studies were performed in Europe, seven in Asia, and three in North America. Fourteen studies contained data on FIT related iCRCs, twelve on gFOBT related iCRCs, and three on both gFOBT and FIT related iCRCs. The median faecal haemoglobin (Hb) positivity cut-off in the 17 studies that provided FIT results, was 20 (range 10-200) microgram Hb/gram faeces. The study quality score of the twenty-seven observational studies ranged from 4 to 8 stars according to the

Figure 1 Flow chart of literature search and study inclusion



FOBT: faecal occult blood test; Hb: haemoglobin

Ottawa Newcastle criteria (Supplementary Table 1). The two randomised controlled trials were both scored as good quality studies according to the Cochrane risk of bias tool.[32, 39]

Meta-analysis

Meta-analysis comprised data of 6,987,825 screening participants with a negative FOBT result, ranging from 1071 to 2,033,526 participants per study (Table 1). Of all twenty-nine

Table 1 Study and test characteristics of a) FIT studies and b) gFOBT studies included in meta-analysis.

a) FIT studies

Study	Country	Time period	Age range of population screened	Males in population screened	No. of screening rounds included in meta-analyses	No. of stools/ no. of samples per stool	FIT cut-off	Participants with a negative FIT	Person years	Total screen-detected CRCs	Total FIT iCRCs
			years	%			µg Hb/g faeces	n		n	n
Chen[28]	Taiwan	1994-2008	>40	n.a.	1	n.d./1	20	221,874	443,748	298	133
Chiu[29]	Taiwan	2004-2008	50-70	38	3	1/1	20	1,113,932	6,683,592	2728	968
Crotta[30]	Italy	2001-2008	50-74	n.a.	4	1/1	20	1928	16,388	8	5
Denters*[32]	NL	2006-2008	50-74	45	1	1/1	10	2638	5276	21	4
Digby[33]	Scotland	2010-2011	50-74	n.a.	1	n.d./1	80	30,140	60,280	30	31
Giorgi Rossi[50]	Italy	2000-2008	50-79	46	1	1/1	20	805,914	805,914	n.a.	172
Itoh[35]	Japan	1991-1992	≥40	n.a.	1	1/1	10	26,370	52,740	77	12
Jensen[36]	USA	2007-2008	50-69	47	3	n.d./1	20	641,559	2,566,236	830	242
Launoy[38]	France	2001-2003	50-74	43	1	2/1	≥67 in ≥1 FITs	6987	13,974	24	4
Levi*[39]	Israel	2008-2011**	50-75	45	1	3/1[40]	≥14 in ≥1 FITs	1071	2142	6	0
McNamara[41]	Ireland	2008-2012	50-75	42	1	2/1	≥20 in ≥1 FITs	4549	9098	21	1
Nakama[42]	Japan	1991	>40	49	1	1/1	Qualitative	3208	9624	10	4
Parente[44]	Italy	2005-2007	50-69	n.a.	1	1/1	100	36,401	72,802	165	8
Portillo[51]	Spain	2009-2015	50-69	n.a.	3	1/1	17-20	769,124	4,614,744	2518	186
Shin[46]	Korea	2004-2007	>50	54	2	1/1	10 or qualtitative	2,033,526	8,134,104	2961	2047
van der Vlugt[52]	NL	2006-2015	50-74	n.a.	3	1/1	10	15,711	111,705	89	27
Zappa*[48]	Italy	1992-1997	50-70	n.a.	2	n.d./1	200-300	20,120	80,480	73	8
Total	-	-	-	-	-	-	-	**5,725,052**	**23,682,847**	**9859**	**3852**

b) gFOBT studies

Study	Country	Time period	Age range of population screened	Males in population screened	No. of screening rounds included in meta-analyses	N. of stool / n. of samples per stool	Participants with a negative gFOBT	Person years	Total screen-detected CRCs	Total gFOBT iCRCs
			years	%			n		n	n
Blom[49]	Sweden	2008-2014	60-69	n.a.	3	3/1	193,690	1,162,140	219	301
Bouvier[27]	France	1991-1994	45-74	n.a.	1	n.d.	69,287	207,861	152	100
Cummings[31]	USA	1984	>40	40	1	3/2	11,233	22,466	13	1
Denters*[32]	NL	2006-2008	50-74	42	1	3/2	2059	4118	8	4
Faivre[34]	France	1988-1998	45-74	n.a.	6	3/2	131,680	263,360	196	219
Hardcastle[2]	UK	1981-1991	50-74	48	6	3/1 or 2	43,748	341,234	236	147
Kewenter[37]	Sweden	1982-1985	60-64	n.a.	1	3/2	8700	14,503	35	16
Kronborg[3]	Denmark	1985-1995	45-75	47	5	3/2	85,794	171,588	120	146
Levi*[39]	Israel	2008-2011**	50-75	43	1	3/2	2178	4356	8	5
Mandel[40]	USA	1957-1982	50-80	n.a.	5	3/2	91,332	456,660	183	22
Paimela[43]	Finland	2004-2006	60-64	31	1	3/2	36,708	70,357	95	35
Rennert[45]	Israel	1992	50-74	n.a.	1	3/2	21,158	60,124	58	10
Souques[47]	France	1980-1995	40-70	n.a.	7	3/2	24,504	171,528	15	10
Steele[6]	Scotland	2000-2007	50-69	45	3	3/2	498,724	2,992,344	698	635
Zappa*[48]	Italy	1992-1997	50-70	n.a.	2	n.d.	31,978	127,912	66	45
Total	-	-	-	-	-	-	**1,252,773**	**6,070,551**	**2073**	**1696**

*Studies that described both a FIT and gFOBT study arm

**Exact study time period not described. However, this study was approved in 2008 and published in 2011.

n.a.: not applicable; NL: Netherlands; USA: United states of America; FOBT: faecal occult blood test; Hb: haemoglobin; CRC: colorectal cancer; iCRC: interval colorectal cancer; n.d.: not described; FIT: faecal immunochemical test; gFOBT guaiac faecal occult blood test

included studies, total follow-up for participants with a negative screening test was 32 million p-y, with a mean follow-up of 4.0 years. In these studies, 11,932 screen-detected CRCs (range 6 to 2961) and 5548 iCRCs (range 0 to 2047) were documented. For every iCRC, 2.6 screen-detected CRC were found with FIT. In gFOBT-based studies the ratio between iCRC and screen-detected CRC was 1:1.2. The Forest plot of the ratio of iCRC following a negative stool test compared to screen-detected CRC is shown in Supplementary Figure 1. This ratio was 0.19 (95%CI 0.13 to 0.27) for FIT studies compared to 0.36 (95%CI 0.28 to 0.45) for gFOBT studies, p=0.005, I^2=99%.

The overall pooled incidence rate of iCRC following a negative stool test was 26 (95%CI 19 to 36; I^2=99%, n=29 studies) per 100,000 p-y (Figure 2). Pooled incidence rates of iCRC for FIT and gFOBT were 20 (95%CI 14 to 29; I^2=99%) and 34 (95%CI 20 to 57; I^2=99%) per 100,000 p-y, respectively (Figure 2). The pooled incidence rate ratio between FIT iCRC and gFOBT iCRC was 0.58 (95%CI 0.32-1.07, n=29 studies). The GRADE level of evidence was very low (Supplementary Table 2). The funnel plot provided no evidence for the presence of publication bias, (Supplementary Figure 2). The prediction intervals of the incidence rate of FIT and gFOBT iCRC are shown in Figure 2.

Subgroup analysis of the studies with high quality established with the Ottawa Newcastle criteria and Cochrane risk of bias tool yielded an incidence rate of iCRC after FIT of 15 (95%CI 8 to 30, n=7 studies) and after gFOBT of 55 (95%CI 35 to 87, n=8 studies) per 100,000 p-y.

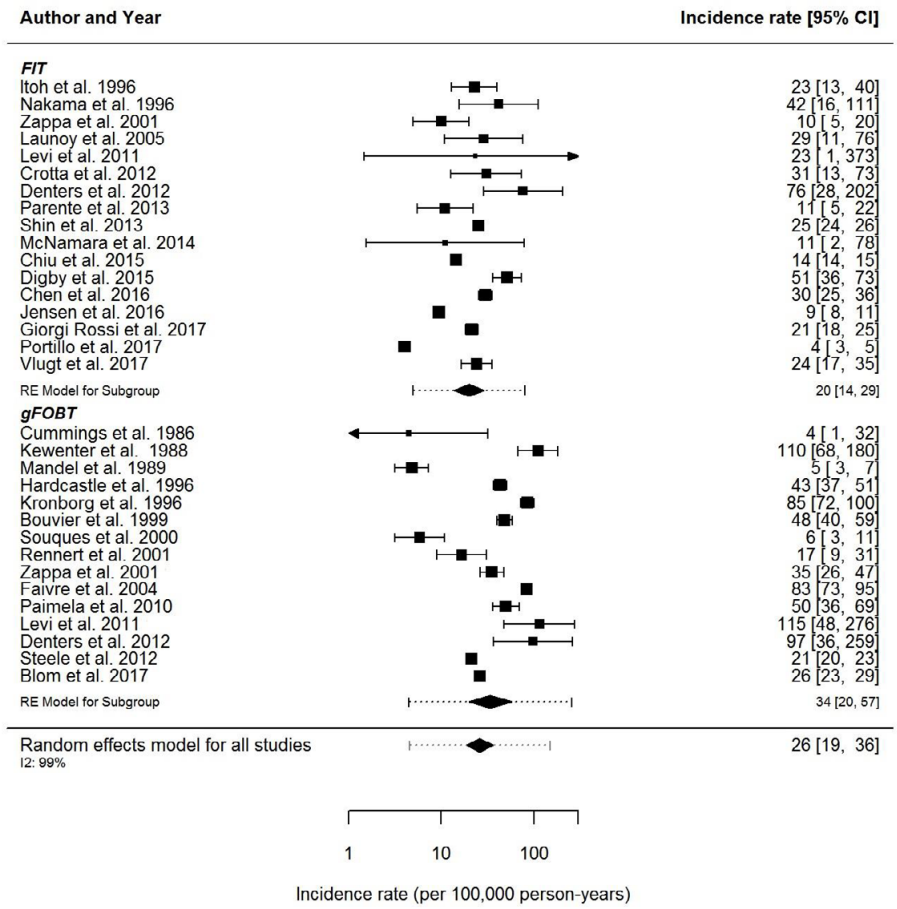
Three studies that described both a FIT and gFOBT arm were included in a sensitivity analysis to compare incidence rate of iCRC between FIT and gFOBT.[32, 39, 48] The pooled incidence rate ratio between FIT iCRC and gFOBT iCRC was 0.36 (95% CI 0.17-0.75, I^2=10%). This ratio was classified as high-quality evidence according to the GRADE score (Supplementary Table 2).

Meta-regression analyses

For meta-regression analyses, data of FIT and gFOBT studies were pooled.

Fifteen out of twenty-nine studies provided data on test related iCRCs after the first screening round (Table 2). Five studies also provided data on iCRC after the second round, four studies after the third, and one study after four rounds of screening. After the third round there was a significant lower risk of iCRC after a negative test compared to the first round (Table 2).

Figure 2 Forest plot showing the incidence rate of interval colorectal cancers per study and summary estimates for FIT and gFOBT



|·····| Prediction interval

gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test; CI: confidence interval

Eight out of twenty-nine studies provided data on iCRCs one year after a negative test. Six studies provided data on iCRC two years after a negative test and two studies three years after a negative test (Table 2). Compared to one year after a negative FOBT, the relative risk of iCRC was 1.25 (95%CI 1.05-1.49) after two and 1.19 (95%CI 0.89-1.13) after three years.

Thirteen out of seventeen FIT studies used a single quantitative positivity cut-off, ranging from 0-100 µg Hb/g faeces. Association between FIT cut-off and FIT iCRC yielded a relative risk of developing FIT iCRC of 1.00 (0.89-1.13) per 10 µg Hb/g faeces cut-off increase (Table 2).

Table 2 Relative risk to develop FOBT iCRC per screening round, in years since last negative test, and cut-off

Subgroup variable	Studies n	Relative risk (95%CI)	Study references
Screening round			
1	15	*Reference*	6, 27, 28, 31, 32, 36-39, 42, 44-46, 51, 52
2	5	0.93 (0.85-1.02)	6, 36, 45, 46, 52
3	4	0.76 (0.66-0.88)	6, 36, 45, 52
4	1	0.77 (0.54-1.10)	36
Time in years since last negative test			
1	8	*Reference*	2, 27, 28, 38, 42, 45, 50
2	6	1.25 (1.05-1.57)	2, 27, 28, 38, 42, 50
3	2	1.19 (0.76-1.87)	27, 42
Cut-off*			
Per 10 µg Hb/g faeces increase	17	1.00 (0.89-1.13)	28-30, 32, 33, 35, 36, 38, 39, 41, 44, 50, 52

*Based on thirteen studies that used a single fixed cut-off.

Table 3 Incidence rate ratios of FOBT iCRC per gender and age

Subgroup	Studies n	Incidence rate ratio (95%CI)	I^{2}*	Study references
Gender**	3	1.22 (0.94-1.57)	0%	33, 43, 50
Age***	2	0.25 (0.09-0.65)	62%	33, 50

*Heterogeneity was quantified by the heterogeneity variance, using the inconsistency index (I^2) test (range from 0% to 100%). We regarded values greater than 25%, 50%, and 75% for the I^2 as indicative of low, moderate, and high statistical heterogeneity, respectively.
**male versus female
***<60 years versus ≥60

Based on three studies, the iCRC incidence rate ratio between males and females was 1.22 (95%CI 0.94-1.57, I^2= 0%). And based on two out of twenty-nine studies, the iCRC incidence rate ratio of screenees <60 years of age to screenees ≥60 years was 0.25 (95%CI 0.09-0.65, I^2=62%) (Table 3).

Eight out of twenty-nine studies described the location of iCRCs in the colon.[6, 27, 31, 33, 39, 50-52] Based on these studies, iCRCs were located distal from the splenic flexure in 67% (95%CI 64%-70%, I^2=0%) of cases. Six out of twenty-nine studies described tumour stages of iCRCs.[6, 27, 31, 33, 51, 52] These iCRCs were staged as early CRCs in 22% (95%CI 17%-28%, I^2=62%) of cases.

DISCUSSION

This is the first systematic review and meta-analysis to estimate the pooled incidence rates of interval colorectal cancers following negative FOBTs in a CRC screening setting. It showed that iCRCs occur in both FIT-based and gFOBT-based CRC screening. However, the incidence of iCRC is higher after a negative gFOBT than after a negative FIT.

Interval cancer rates reflect the sensitivity of a screening test and quality of a screening program. International guidelines, therefore, designate the interval cancer rate as an important outcome measure.[8, 14] Pooled data on incidence of interval cancers following a negative gFOBT and FIT have been awaited for some time.[14, 53]

The findings of this meta-analysis emphasize that screenees should be adequately informed about the risk of CRC after a negative occult blood test. They may mistakenly feel disease-free and fail to respond to CRC symptoms.[54] A Swedish study indeed reported a significant delay in CRC diagnosis among those with a false-negative FOBT.[55] However, recent evidence showed that both overall and CRC-specific survival rates were better for gFOBT interval cancers than for cancers arising in a non-screened population.[6] We found that iCRC accounted for a significant proportion of CRC found in both gFOBT-based and FIT-based screening programs. In the included gFOBT studies, the total number of CRCs missed by gFOBT almost equalled the number of screen-detected CRCs.

The higher incidence of iCRCs after a negative gFOBT compared to FIT in sensitivity analysis is likely due to the higher sensitivity of FIT for the detection of haemoglobin. Best evidence suggests that the most used gFOBT probably has an effective cut-off of around 150 µg of Hb/g of faeces, whereas the accurate detection level of most FITs lies at 5-10 µg Hb/g of faeces.[13, 56, 57] The incidence of iCRC as primary outcome did not significantly differ between gFOBT and FIT. This may have been due to excessive study bias as shown by subgroup analyses.

We found that older age was associated with a higher iCRC incidence after a negative test. Indeed, the elderly have a higher risk of CRC and its precursors.[58-60] Further, the risk of a FOBT-related iCRC was not significantly different between males versus females. This implies, in view of the fact that FOBT-screening detects more CRCs in males[61], that the ratio of screen-detected colorectal cancers versus interval cancers is less favourable in women than in men. Furthermore, we found lower risks of FOBT-related iCRC with every screening round compared to the first round. A possible explanation for this finding is that with every screening round more CRCs are detected and therefore changes of missing CRC with FIT decline as well. Lastly, use of a higher positivity cut-off resulted in a similar incidence of FIT interval cancers. This finding needs to be confirmed when more data become available.

Moreover, studies included in our analyses used low cut-offs which might be the reason that this association was not found.

For quality assessment of CRC screening, it is recommended to monitor the iCRC incidence.[53] Various measures can be used for this purpose. The incidence of FOBT iCRC can be calculated as the ratio of iCRCs versus i) participants with a negative test; ii) person-years follow-up in those with a negative test; iii) total CRCs (detected and missed); and (iv) CRCs expected without screening. In our study we assessed iCRC per person-years, reflecting the absolute number of iCRC cases in CRC screening populations over time. However, when calculating incidence rates on a program level, participation rates should also be taken into account. Secondary outcome in our study was the relative rate of iCRC versus screen-detected CRC, which is an indirect measure of test sensitivity. Previously published data revealed a higher test sensitivity for FIT compared to gFOBT.[62, 63]

Although this comprehensive meta-analysis is based on a large number of person-years, the point estimates of our calculated pooled incidence rates of iCRC should be interpreted cautiously. First, high statistical heterogeneity among studies was shown. We assessed the robustness of conclusions concerning the effect sizes of real interest in our meta-analysis as substantial statistical heterogeneity was observed in the overall pooled data. Statistical heterogeneity represents the approximate proportion of total variability in point estimates that can be attributed to heterogeneity in underlying incidence rates. To explain the observed heterogeneity of the incidence rates between studies we performed subgroup analyses. A potential important source of heterogeneity are differences between populations screened in terms of gender distribution, age distribution, and number of performed screening rounds. These were all identified in the subgroup analyses as factors that partly explained the observed heterogeneity. Furthermore, we performed sensitivity analyses by only including studies directly comparing gFOBT and FIT, limiting the influence of factors introducing heterogeneity, to directly estimate the difference in incidence rates of both tests. This analysis resulted in a higher gFOBT iCRC incidence compared to FIT. The marked inconsistency among the included trials in incidence rate ratios for iCRC (I^2 = 99%) was substantially reduced (I^2 = 10%) when differences between populations were taken into account. Another important factor potentially introducing heterogeneity between studies was study quality. Additional sensitivity analyses of high quality studies only showed a significant higher gFOBT iCRC incidence than FIT iCRC incidence. Second, test kits may be discrepant in terms of cancer detectability and the resultant future risk of iCRC. Test reliability, stability and the ability to detect invasive cancer or advanced adenoma of different kits have been compared in several previous studies.[64, 65] Further stratifying analysis in our study to correct for differences in test kits was not feasible. Only few studies

have reported on iCRCs within specific subgroups, therefore limited analyses could be done for gFOBT and FIT separately.

In conclusion, interval cancers occur in both gFOBT and FIT-based CRC screening programs. The latter is associated with a significantly lower incidence of iCRC, which further supports the use of FIT over gFOBT.

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Supplementary Material 1 Search strategy

Embase

('large intestine tumor'/exp OR ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) NEAR/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)):de,ab,ti) AND ((((('occult blood'/exp OR 'occult blood':de,ab,ti) AND (faecal or fecal or feces or faeces or stool*):de,ab,ti) OR (FOBT* or FIT* or gFOBT*):de,ab,ti) AND ((immunohistochem* or immunochem* or immunol* or guaiac*):de,ab,ti OR immunochemistry/exp OR guaiac/exp) OR (('fecal immunochemical' NEXT/1 test* or 'faecal immunochemical' NEXT/1 test* or 'fecal immunochemistry' NEXT/1 test* or 'faecal immunochemistry' NEXT/1 test* or ColoScreen or Hema-Screen or Hemdetect or Hemoccult or SENSA or Hema-Check or HemaCheck or hemoCARE or Peroheme or ColoCare or Lifeguard or Fecatwin or HemaWipe or Instaccult or Monohaem or Okokit or Seracult or Dencoccult or Early-detector or Earlydetector or Fe-Cult or Fecult or Feca-EIA or FecaEIA or Hemo-FEC or HemoFEC or Hexagon or SureScreen or Hemaprompt or Hemdetect or Camco-PAK or CamcoPAK or Colocheck or Cecogenics or Hematest or Dencocult or Fecatest or Hemofecia or Quick-CULT or QuickCULT)):de,ab,ti)

Medline Ovid

(exp Colorectal Neoplasms/ OR ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)).mp.) AND ((((exp Occult Blood/ OR occult blood.mp.) AND (faecal or fecal or feces or faeces or stool*).mp.) OR (FOBT* or FIT* or gFOBT*).mp.) AND ((immunohistochem* or immunochem* or immunol* or guaiac*).mp. OR exp Immunochemistry/ OR exp Guaiac/) OR ((fecal immunochemical test* or faecal immunochemical test* or fecal immunochemistry test* or faecal immunochemistry test* or ColoScreen or Hema-Screen or HemaScreen or Hemdetect or Hemoccult or SENSA or Hema-Check or HemaCheck or hemoCARE or Peroheme or ColoCare or Lifeguard or Fecatwin or HemaWipe or Instaccult or Monohaem or Okokit or Seracult or Dencoccult or Early detector or Earlydetector or Fe Cult or Fecult or Feca EIA or FecaEIA or Hemo FEC or HemoFEC or Hexagon or SureScreen or Hemaprompt or Hemdetect or Camco PAK or CamcoPAK or Colocheck or Cecogenics or Hematest or Dencocult or Fecatest or Hemofecia or Quick-CULT or QuickCULT)).mp.)

Cochrane Library

(((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) NEAR/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*)):kw,ab,ti) AND (((('occult blood':kw,ab,ti) AND (faecal or fecal or feces or faeces or stool*):kw,ab,ti) OR (FOBT* or FIT* or gFOBT*):kw,ab,ti) AND ((immunohistochem* or immunochem* or immunol* or guaiac*):kw,ab,ti) OR (('fecal immunochemical' NEAR/1

test* or 'faecal immunochemical' NEAR/1 test* or 'fecal immunochemistry' NEAR/1 test* or 'faecal immunochemistry' NEAR/1 test* or ColoScreen or Hema-Screen or Hemdetect or Hemoccult or SENSA or Hema-Check or HemaCheck or hemoCARE or Peroheme or ColoCare or Lifeguard or Fecatwin or HemaWipe or Instaccult or Monohaem or Okokit or Seracult or Dencoccult or Early-detector or Earlydetector or Fe-Cult or Fecult or Feca-EIA or FecaEIA or Hemo-FEC or HemoFEC or Hexagon or SureScreen or Hemaprompt or Hemdetect or Camco-PAK or CamcoPAK or Colocheck or Cecogenics or Hematest or Dencocult or Fecatest or Hemofecia or Quick-CULT or QuickCULT)):kw,ab,ti)

Science Citation Index

TS=(((((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) NEAR/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or polyp* or adenom*))) AND ((((“occult blood”) AND (faecal or fecal or feces or faeces or stool*)) OR (FOBT* or FIT* or gFOBT*)) AND ((immunohistochem* or immunochem* or immunol* or guaiac*)) OR ((“fecal immunochemical” NEAR/1 test* or “faecal immunochemical” NEAR/1 test* or “fecal immunochemistry” NEAR/1 test* or “faecal immunochemistry” NEAR/1 test* or ColoScreen or Hema-Screen or Hemdetect or Hemoccult or SENSA or Hema-Check or HemaCheck or hemoCARE or Peroheme or ColoCare or Lifeguard or Fecatwin or HemaWipe or Instaccult or Monohaem or Okokit or Seracult or Dencoccult or Early-detector or Earlydetector or Fe-Cult or Fecult or Feca-EIA or FecaEIA or Hemo-FEC or HemoFEC or Hexagon or SureScreen or Hemaprompt or Hemdetect or Camco-PAK or CamcoPAK or Colocheck or Cecogenics or Hematest or Dencocult or Fecatest or Hemofecia or Quick-CULT or QuickCULT))))

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“colorectal|colon|colonic|rectal|anal|anus carcinoma|neoplasm|neoplasms|adenocarcinoma|cancer|tumor|tumors” “occult blood” faecal|fecal|feces|faeces|stool|FOBT|FIT|gFOBT

Supplementary Material 2 Variables for which data were extracted

The following data were abstracted when applicable: (i) study characteristics - primary author, journal of publication, year of publication, geographic location of study population, study design (prospective/retrospective), time period of study enrollment, patient selection (inclusion- and exclusion criteria); (ii) FOBT characteristics - type of FOBT used (FIT or gFOBT), brand of FOBT, referral criteria for positive test (i.e. cut-off or number of positive panels), diagnostic test used, diet restrictions; (iii) study cohort characteristics - cohort size, total number of eligible invitees, total number of participants, total tests analyzed, total participants with a positive test, participants demographics (mean age and range, percentage male), reference standard uptake (percentage); (iv) CRC characteristics - total number diagnosed with CRC after negative FOBT, total number diagnosed with CRC after positive FOBT, location of CRC (proximal/distal), CRC stage (I/>I); (v) patient characteristics - gender, age <59 /≥60 years, time of follow-up in years/months (mean, median, min, max), completeness of follow-up (percentage), findings at index diagnostic test.

Supplementary Table 1 Quality assessment of included studies

a) FIT observational studies*

Study	Selection	Comparability	Outcome
Chen[28]	****	*	***
Chiu[29]	****	*	***
Crotta[30]	***	*	**
Digby[33]	****	*	**
Giorgi Rossi[50]	***	*	**
Itoh[35]	***	*	**
Jensen[36]	***	*	***
Launoy[38]	***	*	**
McNamara[41]	***	*	*
Nakama[42]	***	*	***
Parente[44]	***	*	*
Portillo[51]	****	*	***
Shin[46]	***	*	***
van der Vlugt[52]	****	*	***
Zappa[48]	****	*	***

b) gFOBT observational studies*

Study	Selection	Comparability	Outcome
Blom[49]	****	*	***
Bouvier[27]	***	*	***
Cummings[31]	***	*	**
Faivre[34]	****	*	***
Hardcastle[2]	***	*	***
Kewenter[37]	****	*	***
Kronborg[3]	****	*	***
Mandel[4]	****	*	*
Paimela[43]	****	*	**
Rennert[45]	***	*	***
Souques[47]	***	*	*
Steele[6]	****	*	***
Zappa[48]	****	*	***

c) Randomised controlled trials**

Study	Selection bias		Performance bias	Reporting bias	Detection bias	Attrition bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Selective reporting	Blinding of outcome assessment	Incomplete outcome data	Anything else, ideally prespecified
Denters[32]	+	+	+	+	+	?	+
Levi[39]	+	+	+	+	+	?	+

* using the Ottawa Newcastle criteria of Wells *et al*.[24]

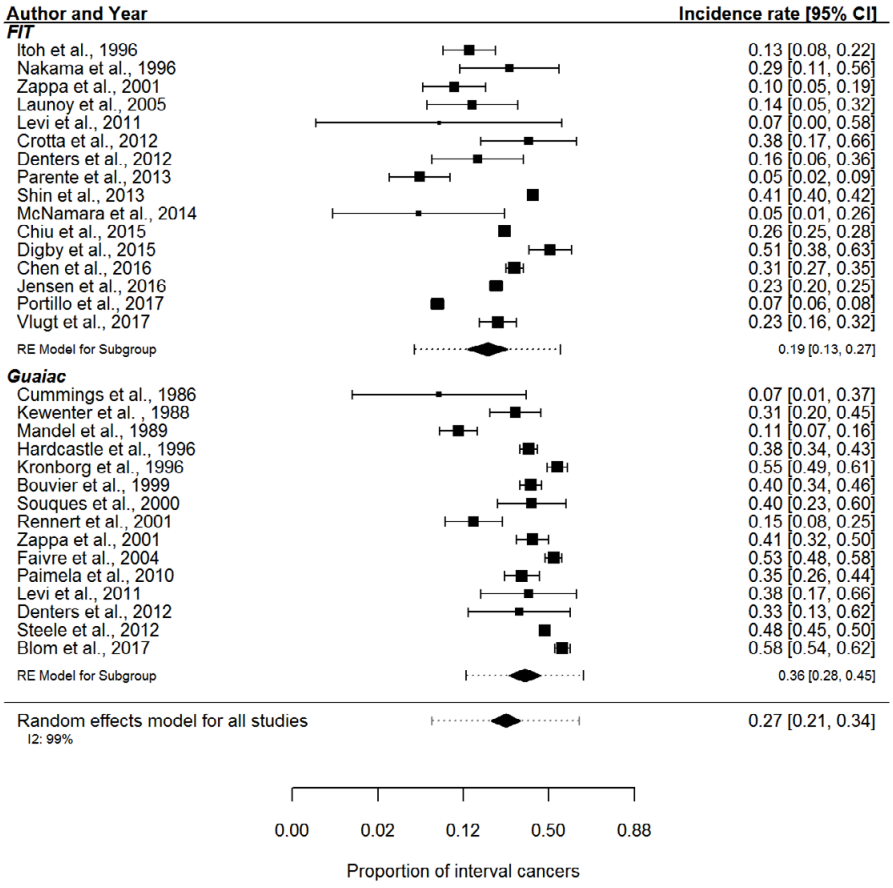
** Both randomised trials were scored as good quality by the Cochrane risk of bias tool.[25] Both studies did not describe handling of incomplete outcome data such as screenees loss to follow-up or missing data when cross-linking the screening pilot database with the cancer registry, therefore, this item was scored as 'unclear risk'. However, this was unlikely to have biased the outcome.

Supplementary Table 2 Quality assessment of the standard and sensitivity analysis of the pooled IRR of FIT iCRC relative to gFOBT iCRC[25]

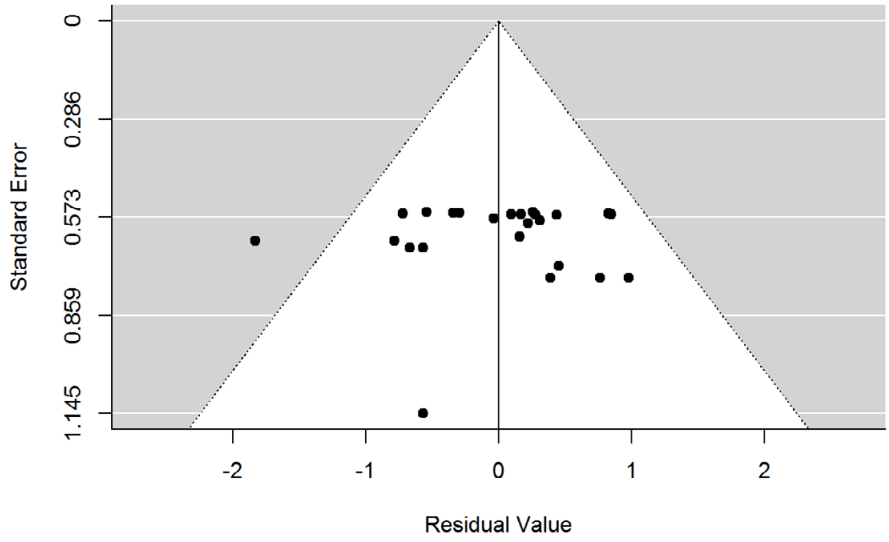
Comparison	**Standard pooled IRR**		**Sensitivity analysis**	
	IRR (95% CI)	Quality of evidence	IRR (95% CI)	Quality of evidence
FIT iCRC versus gFOBT iCRC	0.58 (0.32-1.07)	Very low	0.36 (0·17-0·75)	High

IRR: incidence rate ratio; FIT: faecal immunochemical test; gFOBT guaiac faecal occult blood test; iCRC: interval colorectal cancer

Supplementary Figure 1 Forest plot of FOBT iCRC to screen-detected CRC ratio



Supplementary Figure 2 Funnel plot



Visual inspection of the funnel plot did not show asymmetry and the rank correlation test for asymmetry was not significant (Kendall's tau = -0.0768, p=0.6018).