Evidence Summary 15-14

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Colorectal Cancer Screening in Average Risk Populations: Evidence Summary

J. Tinmouth, E. Vella, N.N. Baxter, C. Dubé, M. Gould, A. Hey, N. Ismaila, B.R. McCurdy, L. Paszat

Report Date: November 11, 2015

An assessment conducted in January 2022 deferred the review of Evidence Summary (ES) 15-14. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

ES 15-14 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2101

Section 1:	**Executive Summary and Conclusions**
Section 2:	**Evidentiary Base**
Section 3:	**Internal Review**

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Evidence Summary 15-14: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Colorectal Cancer Screening in Average Risk Populations: Conclusions

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EXECUTIVE SUMMARY

Cancer Care Ontario's Prevention and Cancer Control portfolio and the Program in Evidence-Based Care (PEBC) developed this evidentiary base to help inform program policy and the quality assurance program for colorectal cancer (CRC) screening in Ontario.

The purpose of this systematic review was to evaluate the existing evidence concerning screening of adults at average risk for CRC in the context of an organized, population-based screening program. The main objectives were to identify the benefits and harms of screening in this population, the optimal primary CRC screening test(s) for this population, the appropriate ages for screening initiation and cessation in this population, and the intervals at which people at average risk should be recalled for CRC screening.

A systematic review of the evidence was performed and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method was used to evaluate the quality of the evidence for each of the outcomes. There was strong agreement among the members of the Working Group that CRC-related mortality and complications from screening tests were critical outcomes for recommendation development. All-cause mortality, CRC incidence, participation rate and diagnostic outcomes were considered important outcomes of interest.

CONCLUSIONS

The following were the conclusions developed by the working group. When discussing the effects of various screening tests, the outcomes vary by test. Please see Section 2 of the evidence summary for more details.

Fecal Tests for Occult Blood

There was strong evidence to support the use of fecal tests for occult blood to screen people at average risk for CRC.

Guaiac Fecal Occult Blood Test (gFOBT) Versus No Screening

- The overall certainty of the evidence was high, suggesting a definite reduction in CRC-related mortality. The magnitude of the effect was small (relative risk [RR], 0.87; 95% confidence interval [CI], 0.82 to 0.92); it was comparable to the disease-specific reduction in mortality from mammography for breast cancer screening (RR, 0.79; 95% CI, 0.68 to 0.90) [1], but was less than that from the human papillomavirus (HPV) test for cervical cancer screening (hazard ratio [HR], 0.52; 95% CI, 0.33 to 0.83) [2]. The

anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.

Fecal Immunochemical Test (FIT) Versus gFOBT

- The overall certainty of the evidence was moderate. The magnitude of the desirable anticipated effects was at least equivalent to gFOBT, and it is likely that the desirable effects of FIT are greater than for gFOBT. The anticipated undesirable effects associated with FIT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.
- While there were well-designed randomized controlled trials (RCTs) comparing FIT with gFOBT, the outcomes of these trials (participation, detection rates) were considered to be of lesser importance than CRC-related mortality. However, it was anticipated that the reduction in CRC-related mortality and the complications resulting from screening with FIT would be at least equivalent to those observed from screening with gFOBT. FIT's greater sensitivity for detection of CRC and advanced adenomas compared with gFOBT suggest that the reduction in CRC incidence with FIT could be greater than for gFOBT; however, the magnitude and significance of any additional benefit of FIT over gFOBT is unknown. It is important to highlight that the FIT positivity threshold selected would be an important determinant of the magnitude of the benefits and harms of FIT relative to gFOBT.

Lower Bowel Endoscopy

There was strong evidence to support the use of flexible sigmoidoscopy (FS) to screen people at average risk for CRC. There was no direct evidence to support the use of colonoscopy to screen people at average risk for CRC, but evidence from FS informed the assessment of the benefits and harms of colonoscopy in screening people at average risk for CRC.

FS Versus No Screening

- The overall certainty of the evidence was high, suggesting that FS has a definite effect on CRC-related mortality and incidence when compared with no screening. The magnitude of the effect on CRC mortality was modest (RR, 0.72; 95% CI, 0.65 to 0.80); it exceeds the anticipated disease-specific reduction in mortality from gFOBT for CRC screening (RR, 0.87; 95% CI, 0.82 to 0.92), and is similar to the effects of mammography on breast cancer mortality (RR, 0.79; 95% CI, 0.68 to 0.90) [1] and of the HPV test on cervical cancer mortality (HR, 0.52; 95% CI, 0.33 to 0.83) [2]. The effect on survival with FS was also comparable to the benefit achieved with the current standard of care for patients with completely resected stage III CRC (5-fluorouracil/leucovorin plus oxaliplatin [FOLFOX or FLOX] versus 5-fluorouracil/leucovorin alone, HR for overall survival at six years, 0.80; 95% CI, 0.65 to 0.97) [3]. The anticipated harms associated with FS (including follow-up colonoscopy for people with positive tests) were small and outweighed by the benefits.

Colonoscopy versus no screening

- The overall certainty of direct evidence supporting the use of colonoscopy to screen people at average risk for CRC was very low when compared with no screening. The desirable and undesirable anticipated effects were uncertain.
- It is anticipated that the benefit of screening with colonoscopy would be at least equivalent to that observed for screening with FS; however, the magnitude of

additional benefit over FS, if any, is unknown. The magnitude of additional undesirable effects of colonoscopy relative to FS is also unknown.

Fecal Tests for Occult Blood Versus Lower Bowel Endoscopy

There was insufficient evidence to determine how fecal tests for occult blood perform compared with lower bowel endoscopy to screen people at average risk for CRC.

- The studies that compared one-time fecal tests for occult blood to lower bowel endoscopy were heterogeneous, with few comparisons where data could be pooled. However, in general, the evidence suggested that participation was higher and detection rate was lower with fecal-based tests compared with endoscopic tests.
- The overall certainty of the evidence was low. CRC-related mortality was not evaluated and the design of the studies favoured endoscopic tests because the comparison was to one-time fecal-based testing (rather than repeated testing over time, which is how these tests are used in usual practice). There was significant heterogeneity in participation. The undesirable anticipated effects of endoscopy (including follow-up endoscopy for people with positive fecal tests) are probably small. It is uncertain whether the desirable effects are large relative to the undesirable effects.

Radiological Tests

Computed Tomography Colonography Versus Colonoscopy

There was insufficient evidence to determine how computed tomography colonography performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was low. The desirable and undesirable anticipated effects were uncertain.

Capsule Colonoscopy Versus Colonoscopy

There was insufficient evidence to determine how capsule colonoscopy performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Double-Contrast Barium Enema (DCBE)

There was no evidence to support the use of DCBE to screen people at average risk for CRC.

- Since 2006, there has been no new published evidence on this topic. Most recent CRC guidelines except for a 2008 guideline by the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology [4] have not endorsed the use of DCBE for screening [5-9].

DNA Tests

Stool DNA versus fecal occult blood tests (gFOBT or FIT)

There was insufficient evidence to determine how stool DNA performs compared with gFOBT or FIT to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other DNA Tests

There was insufficient evidence to support the use of mSEPT9 to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Metabolomic Tests

Fecal M2-PK

There was insufficient evidence to support the use of fecal M2-PK to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other Metabolomic Tests

There was no evidence to support the use of other metabolomic tests (e.g., low levels of hydroxylated polyunsaturated long chain fatty acids [Cologic®]) to screen people at average risk for CRC.

Age of Initiation/Cessation

Age of Initiation/Cessation With gFOBT

Currently, the Ontario CRC screening program recommends that average-risk individuals initiate screening with gFOBT beginning at 50 years of age and ending at age 74. There was insufficient evidence to support changing the ages of initiation and cessation for CRC screening with gFOBT in Ontario.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality using gFOBT across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.

Age of initiation/cessation with FS

There was insufficient evidence to recommend ages of initiation or cessation when screening with FS in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality or incidence using FS across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Of the four large FS RCTs, three examined “once in a lifetime” FS between the ages of 55 and 64, while the fourth RCT examined baseline FS between the ages of 55 and 74 with a second FS after three or five years.

Age of Initiation/Cessation with Colonoscopy

There was insufficient evidence to recommend an age of initiation or cessation to screen with colonoscopy in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in CRC detection using colonoscopy across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Currently, the Ontario CRC screening program does not recommend colonoscopy to screen persons at average risk for CRC. The program does recommend colonoscopy in people at increased risk (one or more first-degree relatives with CRC) starting at 50 years of age or 10 years younger than the age at which the relative was diagnosed, whichever occurred first.

Age of Initiation/Cessation with FIT

There were no studies that met our inclusion criteria for age of initiation/cessation for FIT.

Screening Intervals

gFOBT Intervals

There was evidence to suggest that either annual or biennial screening using gFOBT in people at average risk for CRC reduces CRC-related mortality.

- The overall certainty of the evidence was moderate. The desirable anticipated effects on CRC mortality were small and similar for annual or biennial screening. The undesirable anticipated effects were not reported for each interval group. Anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) were small for biennial screening and were likely to be greater for annual screening. In addition, annual screening is anticipated to increase burden to the participant.

FIT Intervals

There was insufficient evidence to recommend an interval to screen people at average risk for CRC using FIT.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

FS and Colonoscopy Intervals

There were no studies that met our inclusion criteria for screening intervals for FS or colonoscopy.

NEXT STEPS

This evidence summary reports what is known about the clinical effectiveness and safety of CRC tests and is central to the ongoing development of Ontario's colorectal cancer screening program. However, the evidence summary is necessary but not sufficient to guide program development as other context-specific criteria such as cost-effectiveness, existing program design, public acceptability and feasibility (from an organizational and economic perspective) must be considered. In addition, the program must also consider the balance between choice and informed decision making and issues not well addressed by the evidence such as how best to implement colorectal cancer screening when there is more than one colorectal cancer screening test supported by high-quality evidence. An expert panel which included members from national and international screening programs, primary care physicians, general surgeons, gastroenterologists, pathologists and laboratory medicine professionals, nurse endoscopists and members of the public was convened to provide guidance on how to incorporate the evidence in light of the other issues listed above. Their level of agreement with the conclusions and their comments are reflected in Section Three. The CCC program will use findings from the evidence summary as well as expert panel recommendations to guide its ongoing development.

Evidence Summary 15-14: Section 2

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Colorectal Cancer Screening in Average Risk Populations: Evidence Summary

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INTRODUCTION

Ontario has one of the highest rates of colorectal cancer (CRC) in the world, with an estimated 9200 cases in 2015 [10]. CRC is also one of the leading causes of cancer-related death for men and women combined in Ontario, with an estimated 3350 deaths in Ontario in 2015. However, if CRC is found in its early stages, there is a 90% chance that it can be cured [10]. Cancers detected through screening tend to be earlier stage compared with cancers detected outside of screening [11-14]. In 2008, Ontario launched its CRC screening program, which offers screening to Ontarians aged 50 to 74 years. People at average risk are offered the guaiac fecal occult blood test (gFOBT) once every two years, while people at increased risk, defined as having one or more first-degree relatives with CRC, are offered colonoscopy. In 2012, approximately 58% of Ontarians were up-to-date with CRC screening tests [15].

In light of emerging evidence, the provincial CRC screening program is seeking guidance for CRC screening in Ontario. Cancer Care Ontario's Prevention and Cancer Control portfolio and the PEBC developed this evidentiary base to help inform program policy and the quality assurance program for CRC screening in Ontario. This systematic review will evaluate the evidence supporting primary screening tests for CRC, ages of initiation and cessation for CRC screening, and screening intervals for selected CRC screening tests in people at average risk for CRC.

SYSTEMATIC REVIEW OBJECTIVES

The purpose of this systematic review is to evaluate the existing evidence concerning screening of adults at average risk for CRC in the context of an organized, population-based screening program. The main objectives are to identify:

- The benefits and harms of screening in this population;
- The optimal primary CRC screening test(s) for this population;
- The appropriate ages of initiation and cessation for screening in this population; and
- The intervals at which people at average risk should be recalled for CRC screening.

INTENDED USERS

The intended users include primary care providers, endoscopists, policy-makers, and program planners in Ontario.

RESEARCH QUESTIONS

Primary Research Question:

1. How do different screening tests, individually or in combination, perform in average-risk people in preventing CRC-related mortality or all-cause mortality or in decreasing the incidence of CRC? Secondary outcomes include the detection of cancer or its precursors, screening participation rate, adverse effects of tests, and test characteristics, such as sensitivity, specificity, positive predictive value, negative predictive value, and proportion of false-positives or of false-negatives.

Secondary Research Questions:

1. What are the appropriate ages of initiation and cessation for screening in people at average risk for CRC? Is there a relationship between age and the effectiveness of CRC screening?
2. What are the appropriate intervals between CRC screening tests (by test)? Is there a relationship between screening intervals and the effectiveness and risks of screening?

METHODS

This evidentiary base was developed by a working group consisting of one primary care physician, one colorectal surgeon, one expert in public health screening, one policy analyst from the Ontario CRC screening program, two methodologists and three gastroenterologists (Appendix 1). The PEBC, a provincial program of Cancer Care Ontario, is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated programs is editorially independent from the ministry.

A planned two-stage method was used. It is summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then they were included as a part of the evidentiary base.
2. Original systematic review of the primary literature: This review focused on areas not covered by existing and accepted reviews.

Literature Search Strategy

A systematic search was conducted in OVID MEDLINE (2006 to September 3, 2014), EMBASE (2006 to September 3, 2014), the Cochrane library (Issue 2-4, October 2013) and the American Society of Clinical Oncology (ASCO) conference proceedings (2009 to 2013). Details of the literature search strategy are included in Appendix 2.

Study Selection Criteria and Protocol

Systematic reviews were included if:

- They addressed at least one of the research questions;
- They evaluated randomized or non-randomized control trials of asymptomatic average-risk subjects undergoing CRC screening;
- The literature search strategy for the existing systematic review was reproducible (i.e., reported) and appropriate; and
- The existing systematic review reported the sources searched, as well as the dates that were searched.

Identified systematic reviews were assessed using the Assessing of Methodological Quality of Systematic Reviews (AMSTAR) tool [16]. In cases where multiple systematic reviews were identified for a particular outcome, only evidence from the most recent systematic review with the highest quality was used in the evidence base. The literature was searched for new primary studies published after the end search date of included systematic reviews.

Individual study quality from the studies included in the systematic reviews as well as any new primary studies was assessed in order to complete the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tables for risk of bias.

If no existing systematic review was identified for a given test or question, or if identified reviews were incomplete, a systematic review of the primary literature was performed. Articles in reference lists from included studies were also searched. The scope of the primary literature review was tailored to address the gaps in the incorporated existing systematic reviews (e.g., subject areas covered, time frames covered). The criteria for the primary literature are described below.

Inclusion Criteria:

1. Randomized controlled trials (RCTs) (primary research question, secondary research questions 1 and 2) that could be identified directly from the search or from reference sections of systematic reviews;
2. Cohort/case-control studies, minimum study size n=30 (secondary research questions 1 and 2);
3. Evidence from non-randomized prospective comparative studies with historical or contemporaneous controls, with the consensus of the working group, when there were gaps in available evidence from RCTs;
4. Studies with asymptomatic average risk subjects were preferred. Population-based studies that did not oversample adults with symptoms of CRC or a family history of CRC were also considered acceptable;
5. For conference abstracts: RCTs (all questions); and
6. The following screening tests were considered for inclusion:
   - Fecal-based tests including gFOBT, fecal immunochemical test (FIT), stool DNA panel (stool DNA) and fecal M2-PK,
   - Blood tests (Cologic®, ColonSentry®, mSEPT9, metabolomics, hydroxylated polyunsaturated long chain fatty acids),
   - Endoscopic tests including flexible sigmoidoscopy (FS), colonoscopy, capsule colonoscopy,
   - Radiological tests including double-contrast barium enema (DCBE) and computed tomography colonography (CT colonography).

Exclusion Criteria:

1. Letters, comments or editorials;
2. Studies that included a population enriched with subjects with symptoms of CRC or a family history of CRC;
3. Non-systematic reviews; and
4. Non-English-language publications.

One of two reviewers (NI and EV) independently reviewed the titles and abstracts resulting from the search. For items that warranted full-text review, NI or EV reviewed each item independently. However, in uncertain cases, a second reviewer (JT) was asked to review them.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies were independently extracted by NI and EV. If there was more than one publication for the same study, only the most updated or recent versions of the data were reported in the result. All extracted data and information were audited by an independent auditor.

Important quality features, such as randomization details, sample size and power, intention-to-screen (ITS) analysis, length of follow-up and funding, for each RCT were extracted. The quality of observational studies was assessed using a modified Newcastle-Ottawa Scale [17]. The quality of diagnostic studies was assessed using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [18]. The GRADE method for assessing the quality of aggregate evidence was used for each comparison using the GRADEpro Guideline Development Tool [19,20]. The working group used the GRADE system for ranking outcomes and scored each outcome from the evidence review on a scale from 1 to 9. Outcomes with a score from 1 to 3 were considered of limited importance, from 4 to 6 were important, and from 7 to 9 were critical in the development of recommendations for the CRC screening program. Only outcomes that were considered critical or important were included in the GRADE evidence tables.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was conducted using review manager software (RevMan 5.3) provided by the Cochrane Collaboration [21]. For all outcomes, the dichotomous model with random effects was used. The number of person-years, rather than the total number of subjects, was used, if available. The number of person-years takes into account the fact that different people in the study may have been followed up for different lengths of time. The number needed to screen was calculated with the following formula:

$1/((1-e^{(-\text{control outcome/person-years*time})})-(1-e^{(-\text{experimental outcome/person-years*time})}))$ [22]

For the GRADE tables, the control rates for the no screening groups in the gFOBT and FS trials were combined and calculated from the total number of cases across all gFOBT and FS trials over the total number of person-years across all gFOBT and FS trials.

Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

Process for Developing Conclusions

The working group members met in-person on four occasions to develop evidence-based conclusions through consensus. For each comparison (e.g., gFOBT versus no screening) the working group assessed the quality of the body of evidence for each outcome using the GRADE process [19]. Five factors were assessed for each outcome in each comparison, including the risk of bias, inconsistency, indirectness, imprecision and publication bias. Observational studies began as low quality and RCTs as high quality; the quality of the evidence was downgraded when serious threats were identified to one or more factors. At the in-person meetings, the working group discussed each comparison and agreed on the overall certainty of the evidence across outcomes (Table 1), whether the desirable anticipated effects were large, whether the undesirable anticipated effects were small, and whether the desirable effects were large relative to the undesirable effects. Conclusions were developed that reflected these working group discussions for each comparison.

Table 1. Quality of evidence grades.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

RESULTS

Literature Search Results

A total of 7538 studies were identified and 378 were selected for full-text review. Of those, 48 met the pre-defined eligibility criteria for this systematic review. An additional 27 articles were found from the reference lists. After our literature search, we became aware of and included an updated publication for one of the FS screening RCTs that had already been identified [23]. A total of 76 articles were included of which eight were systematic reviews [24-31], 39 [14,23,32-68] were from 30 RCTs, 19 were prospective studies [69-87], five were retrospective studies [88-92], and five of which were case-control studies [93-97]. The quality of the systematic reviews is described in Table 2. Evidence from five of the eight systematic reviews was included either because the reviews were the most recent systematic review with the highest quality evidence for a particular outcome or because they included an outcome of interest not covered by other high-quality reviews [24,26,28,29,31]. The included systematic reviews are described for each comparison below. After the search process and quality assessment, a total of 73 articles in this systematic review. The search flow diagram is available in Appendix 3. Table 3 provides a summary of the number and type of studies used for each comparison. The quality of the primary studies is reported by comparison and can be found in the relevant section below.

Table 2. AMSTAR evaluation of included systematic reviews.

ITEM	Brenner et al. 2014[24]	Elmunzer et al. 2012[25]	Hewitson et al. 2011[27]	Hassan et al. 2012[26]	Holme et al. 2013[28]	Littlejohn et al. 2012[29]	Massat et al. 2013[30]	Niv et al. 2008[31]
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	Y	N	N	N
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	Y	Y	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	Y	Y	Y	N	Y	Y
5. Was a list of studies (included and excluded) provided?	Y	Y	Y	Y	Y	Y	N	N
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	Y	Y	Y	N	N
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	Y	Y	Y	N	N
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	Y	Y	Y	Y	Y	N
10. Was the likelihood of publication bias assessed?	Y	Y	N	N	Y	N	N	N
11. Was the conflict of interest stated?	Y	Y	Y	Y	Y	Y	Y	N
TOTAL AMSTAR POINTS	11	11	10	10	11	8	6	4

Abbreviations: AMSTAR = A Measurement Tool to Assess Systematic Reviews; N = no; Y = yes

Table 3. Summary of included studies by research question.

Research question and references*	Systematic reviews	Outcomes	RCTs	Prospective studies	Retrospective studies	Case-control studies
PRIMARY QUESTION: CRC SCREENING TESTS**						
gFOBT vs no screening [28,44,45,47,49-51,53,56,58,62]	1	CRC mortality	4			
		Complications from tests	3			
		All-cause mortality	4			
		CRC incidence	5			
FS vs no screening [14,23,28,32,33,40,41,57,60,64]	1	CRC mortality	4			
		Complications from tests	5			
		All-cause mortality	4			
		CRC incidence	4			
Colonoscopy vs no screening [24,31,70,72,77-95]	2	CRC mortality		2	1	
		Complications from tests		11	4	
		CRC incidence		2		3
mSEPT9 alone [71]		Diagnostic test accuracy outcomes		1		
Fecal M2-PK alone [74,97]		Diagnostic test accuracy outcomes		1		1
Stool DNA vs gFOBT or FIT [69,75,76,96]		Diagnostic test accuracy outcomes		3		1
FIT vs gFOBT [26,36,38,42,43,46,66]	1	Complications from tests	1			
		CRC/Advanced adenoma detection rate (ITS)	5			
		CRC/Advanced adenoma detection rate (PP)	5			
		Participation rate	6			
		Diagnostic test accuracy outcomes - False-positives/total screened	5			
CT colonography vs colonoscopy [63]		Complications from tests	1			
		CRC/Advanced adenoma detection rate (ITS)	1			
		CRC/Advanced adenoma detection rate (PP)	1			
		Participation rate	1			
Capsule colonoscopy vs colonoscopy [73]		Complications from tests		1		
		Adenoma detection rate (PP)		1		
Fecal-based tests vs endoscopy – FIT vs colonoscopy	3	Complications from tests	2			
		CRC/Advanced adenoma detection rate (ITS)	3			
		Participation rate	3			

[26,28,29,34,35,37,39,43,48,52,54,55,59,61,67,68]	FIT vs FS		Complications from tests	1			
			CRC/Advanced adenoma detection rate (ITS)	3			
			Participation rate	3			
	gFOBT vs colonoscopy		Complications from tests	1			
			Participation rate	2			
	gFOBT vs FS		Complications from tests	1			
			CRC/Advanced adenoma detection rate (ITS)	2			
			Participation rate	4			
	gFOBT vs gFOBT + FS		Complications from tests	1			
			CRC/Advanced adenoma detection rate (ITS)	2			
			Participation rate	3			
SECONDARY QUESTION #1: AGE OF INITIATION AND CESSATION BY TEST							
gFOBT vs no screening [58,62]			CRC mortality by age group	2			
FS vs no screening [14,23,33,57]			CRC mortality by age group	2			
			CRC incidence by age group	4			
Colonoscopy vs no screening [94]			CRC risk by age group				1
SECONDARY QUESTION #2: SCREENING INTERVAL BY TEST							
gFOBT [50,51,62]			CRC mortality by interval (annual vs biennial)	1			
			All-cause mortality by interval (annual vs biennial)	1			
			CRC incidence by interval (annual vs biennial)	1			
FIT [65]			CRC/Advanced adenoma detection rate by interval (1 vs 2 vs 3 years)	1			
			Participation rate by interval (1 vs 2 vs 3 years)	1			

Abbreviations: CRC = colorectal cancer; CT = computed tomographic; DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; ITS = intention to screen; PP = per protocol; RCT = randomized controlled trial; vs = versus
*Some RCTs published multiple articles.
**Tests that were included in our search strategy but yielded no results were not included.

Conclusions About Importance of Outcomes

There was complete or near complete agreement among working group members that CRC mortality and complications from a test were critical outcomes (Table 4). There was greater variability in the ranking of the remaining outcomes, all of which were considered important but not critical. Possible reasons for this observed variation were discussed. Although an effect on all-cause mortality would be an important benefit, some members ranked it lower because they believed it was unlikely to be affected by screening. Some members believed that screening could reduce incidence without affecting mortality (i.e., reduction in indolent cancers only). Therefore, incidence should not be considered alone and must be considered in conjunction with mortality. Also, there was concern that regional and cultural factors might significantly affect participation; therefore, the generalizability of the studies using this outcome was questionable. The detection of cancer and its precursors as well as

diagnostic test accuracy outcomes were considered indirect or surrogate evidence for the tests' ability to reduce CRC mortality and therefore ranked lower.

Table 4. Working Group members ranking of outcomes by importance.

Outcomes	# of working group members		
	Critical	Important	Of limited importance
CRC mortality	6	0	0
Complications from a test such as perforations, bleeding	5	1	0
All-cause mortality	4	0	2
CRC incidence	2	1	3
Participation rate	1	3	1
CRC/advanced adenoma detection rate	2	4	0
Diagnostic test accuracy outcomes such as sensitivity, specificity	1	4	1

Abbreviation: CRC = colorectal cancer

Primary Research Question

How do different screening tests, individually or in combination, perform in average-risk people in preventing death from and/or incidence of CRC?

gFOBT Versus No Screening

Systematic review

One Cochrane systematic review by Holme 2013 summarized the adverse outcomes reported for the trials comparing gFOBT with no screening (Table 2) [28]. Holme 2013 reported a 0.03% major complication rate after follow-up among all gFOBT participants, defined as bleeding, perforation, or death within 30 days of screening; however, there was incomplete reporting of death in the trials [28]. In the Goteborg trial, three of the 2108 participants who had follow-up with FS had perforations of the sigmoid colon [44]. For subjects receiving follow-up with colonoscopy in the same trial, three of 190 had complications (two perforations and one bleed) [44]. For patients with a positive gFOBT in the Nottingham trial who went on to receive colonoscopy (n=1474), seven had complications (five perforations and one bleed) [56]. There were no colonoscopy-related deaths. In the Minnesota trial, there were four perforations of the colon and 11 episodes of serious bleeding among 12,246 follow-up colonoscopies performed [49].

Primary Studies

Since the Holme 2013 publication, the Minnesota trial has published updated findings [62]. The characteristics and quality of the four large RCTs, including this most recent publication, can be found in Tables 5 to 7. The quality of the four RCTs is high: subjects were adequately randomized resulting in comparable study groups, the sample sizes were large, and subjects were

followed for an extensive period of time with few lost to follow-up. Three of the studies randomized patients from the general population; only the Minnesota trial randomized volunteers. All of the studies included blinded, standardized assessment for mortality. Also, mortality was assessed using an ITS analysis in all trials, except in the Goteborg trial.

An additional Finnish RCT study by Paimela 2010 reported the results of the first FOBT screening round [53]. They did not have data on mortality outcomes or the incidence ratio; therefore, this study was not included in the meta-analyses.

Meta-analyses using the more recent Minnesota data resulted in similar conclusions to the Holme 2013 review (Tables 8 and 9, Figures 1 to 3). When cases per person-years were included in the meta-analyses, there was no difference in CRC incidence (relative risk [RR], 0.96; 95% confidence interval [CI], 0.90 to 1.02; p=0.15) among those screed with gFOBT vs no screening. There was a 13% relative risk reduction in CRC mortality (RR, 0.87; 95% CI, 0.82 to 0.92; p<0.00001), but no difference in all-cause mortality (RR, 1.00; 95% CI, 0.99 to 1.01; p=0.65). Eight hundred and eighty-seven people would need to be offered screening with gFOBT to prevent one death due to CRC over 10 years.

Table 5: Characteristics of included RCTs – gFOBT versus no screening.

Author/year	Frequency	Kit details	Sample size	Mean age ± SD (range) years	Duration of follow up (years)	Reference standard/ outcomes	Location
Minnesota trial Shaukat 2013[62]	Annual (11 rounds) or biennial (6 rounds)	Hemoccult – diet restricted and rehydrated	46,551	62.3±7.8 (screen group) 62.3±7.7 (control) (50-80)	30 total	Colonoscopy/ mortality	Minnesota, United States
Nottingham trial Scholefield 2012[58]	Biennial (3-6 rounds)	Hemoccult	151,975	(45-74)	19.5 (median)	Colonoscopy/ mortality, incidence	Nottingham, United Kingdom
Goteborg trial Lindholm 2008[47]	1.5 to 2 years (2 rounds)	Hemoccult II – diet restricted and rehydrated	68,308	(60-64)	9 (mean)	Sigmoidoscopy and DCBE/ mortality	Goteborg, Sweden
Funen trial Kronborg 2004[45]	Biennial (9 rounds)	Hemoccult II – diet restricted	61,933	59.8 (45-75)	17 total	Colonoscopy/ mortality, incidence	Funen, Denmark
Paimela 2010[53]	Biennial	Hemoccult – diet restricted	106,000	(60-64)	23 months (mean)	Colonoscopy/ incidence	Finland

Abbreviations: DCBE = double-contrast barium enema; gFOBT = guaiac fecal occult blood test; RCT = randomized controlled trial; SD = standard deviation

Table 6: Quality of included RCTs – gFOBT versus no screening.

Author/year	Randomization details	Sample size and power calculation done	Baseline patient characteristics	ITS analysis	Follow-up (years)	Blinding	Funding
Minnesota trial Shaukat 2013[51,62]	Stratified and randomized by age, sex and place of residence	46,551 Yes	Healthy volunteers from American Cancer Society, and veterans and employee groups in Minnesota	Yes	30: Follow-up for vital status through year 18 complete for 88.8%, 89.1%, and 88.5% and death certificates were obtained for 99.7%, 99.8%, and 99.8% of annual, biennial, and control group participants, respectively.	Blinded, standardized assessment for mortality	Veterans Affairs Merit Review Award Program
Nottingham trial Scholefield 2012[58]	Randomized by household and stratified by size, sex and average age of eligible members	151,975 Yes	Individuals identified through general practice to which they were registered	Yes	28.4: 1.7% (2599) lost to follow-up	Blinded, standardized assessment for mortality	Medical Research Council, United Kingdom
Goteborg trial Lindholm 2008[47]	Random allocation of individuals (3 cohorts born 1918-1922, 1923-1927, 1928-1931)	68,308 Yes	Patients identified through local population register; age similar for both groups	No	19.5: 713 from screening group died before second round and 58 could not be	Blinded, standardized assessment for mortality	Swedish Cancer Society

					located; 593 from control group died before second round and 29 could not be located		
Funen trial Kronborg 2004[45]	Central randomization from population registry. Married couples allocated to same group. Only individuals who took part in first round of screening were invited in future rounds	61,933 Yes	Inhabitants of Funen, Denmark; age and sex similar for both groups	Yes	17: 6 people lost to follow-up	Blinded, standardized assessment for mortality	Danish Cancer Society
Paimela 2010[53]	Individual level randomization	106,000 Yes	Individuals living in municipalities volunteering to implement a screening program	Yes	Mean 23 months	NR	Finnish Ministry of Social Affairs and Health

Abbreviations: gFOBT = guaiac fecal occult blood test; RCT = randomized controlled trial; ITS = intention to screen

Table 7: GRADE evidence profile – gFOBT versus no screening.

Quality assessment							# of patients		Effect		Quality[1]	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gFOBT (cases/person-years)	No screening (cases/person-years)	Relative (95% CI)	Absolute (cases/person-years)		
CRC mortality (follow up: range 17-30 years)												

4	Randomised trials	Not serious	Not serious	Not serious	Not serious	Not serious	2027/2674854 (0.08)%	2326/2669246 (0.09)% Control (gFOBT + FS) = 0.06%	**RR 0.87** (0.82 to 0.92)	113 fewer per 1000000(from 70 fewer to 157 fewer) 78 fewer per 1000000(from48 fewer to 108 fewer)	⊕⊕⊕⊕ HIGH	Critical
Complications from tests (from Holme 2013[28])[2]												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious			N/A[3]		⊕⊕⊕⊕ HIGH	Critical
All-cause mortality (follow-up: range 17-30 years)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious	74,481/2,674,854 (2.8%)	74,174/2,669,246 (2.8%) Control (gFOBT + FS) = 1.85%	**RR 1** (0.99 to 1.01)	0 fewer per 1,000,000 (from 278 fewer to 278 more) 0 fewer per 1000000(from 185 fewer to 185 more)	⊕⊕⊕⊕ HIGH	Important
CRC incidence (follow-up: range 17-30 years)												
5	Randomized trials	Not serious	Not serious	Serious[4]	Not serious	Not serious	4324/2,434,487 (0.2%)	4489/2,431,961 (0.2%) Control (gFOBT + FS) = 0.16%	**RR 0.96** (0.9 to 1.02)	74 fewer per 1,000,000 (from 37 more to 185 fewer) 64 fewer per 1,000,000 (from 32 more to 160 fewer)	⊕⊕⊕◯ MODERATE	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; N/A = not applicable; RR = relative risk

[1]**GRADE working group grades of evidence**

- **High quality** = We are very confident that the true effect lies close to that of the estimate of effect.
- **Moderate quality** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality** = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality** = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[2]Major complication defined as bleeding, perforation, or death within 30 days of screening, follow-up colonoscopy or surgery

[3]See text for absolute rate

[4]Goteborg trial used sigmoidoscopy and double-contrast barium enema as reference standard; other trials used colonoscopy

Table 8: Outcome data of included RCTs in absolute values – gFOBT versus no screening.

	# recruited		CRC mortality		Mortality (all-cause)		Incidence of CRC	
~~Test~~	FOBT	No screening	FOBT	No screening	FOBT	No screening	FOBT	No screening

Author/year								
Minnesota trial Shaukat 2013[50,62]	31,157	15,394	437	295	22,076	10,944	435*	507
Nottingham trial Scholefield 2012[58]	76,056	75,919	1176	1300	40,681	40,550	2279	2354
Goteborg trial Lindholm 2008[47]	34,144	34,164	252	300	10,591	10,432	721	754
Funen trial Kronborg 2004[45]	30,967	30,966	362	431	12,205	12,248	889	874
Paimela 2010[53]	52,998	53,002	NR	NR	NR	NR	128	99

Abbreviations: CRC = colorectal cancer; FOBT = fecal occult blood test; gFOBT = guaiac FOBT; NR = not reported; RCT = randomized controlled trial
*for biennial screening group

Table 9: Outcome data of included RCTs in person-years – gFOBT versus no screening.

	CRC mortality				Mortality (all-cause)				Incidence of CRC			
Test / Author /year	FOBT		No screening		FOBT		No screening		FOBT		No screening	
	Events	Total*	Events	Total*	Events	Total*	Events	Total*	Events	Total*	Events	Total*
Minnesota trial Mandel 2000 Shaukat 2013[50,62]	237	475,880	295	469,897	11,004	475,880	10,944	469,897	435	235,513	507	232,612
Nottingham trial Scholefield 2012[58]	1176	1,296,712	1300	1,296,614	40681	1,296,712	40,550	1,296,614	2279	1,296,712	2354	1,296,614
Goteborg trial Lindholm 2008[47]	252	471,072	300	471,980	10,591	471,072	10,432	471,980	721	471,072	754	471,980
Funen trial Kronborg 2004[45]	362	431,190	431	430,755	12,205	431,190	12,248	430,755	889	431,190	874	430,755

Paimela 2010[53]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CRC = colorectal cancer; FOBT = fecal occult blood test; gFOBT = guaiac FOBT; NR = not reported; RCT = randomized controlled trial
*in person-years

Figure 1: Colorectal cancer mortality – gFOBT versus no screening.

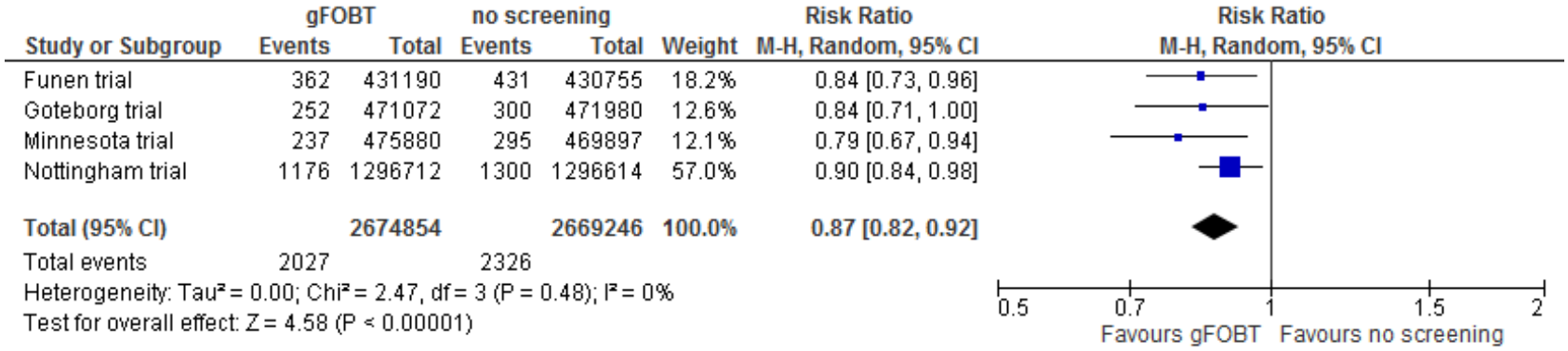


Figure 2: All-cause mortality – Guaiac fecal occult blood test (gFOBT) versus no screening.

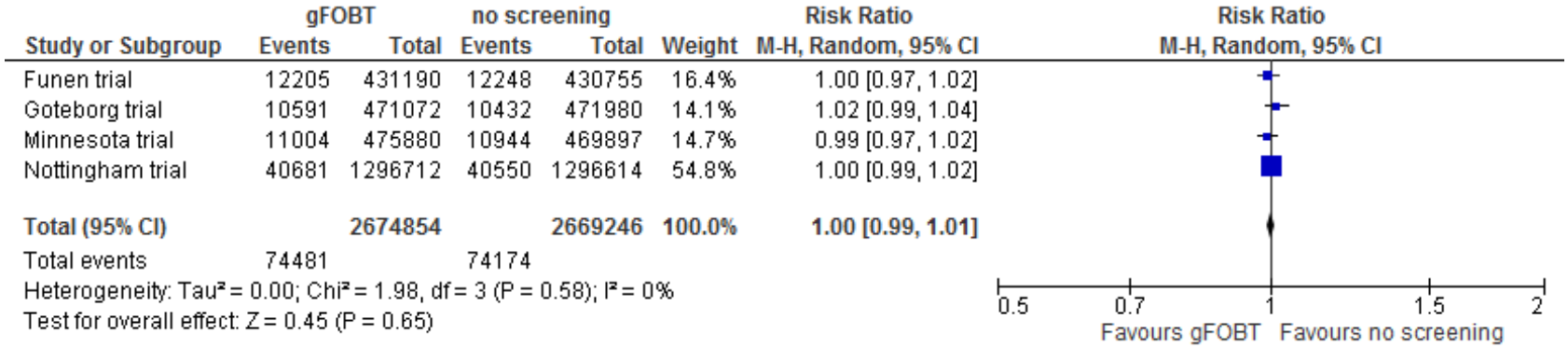
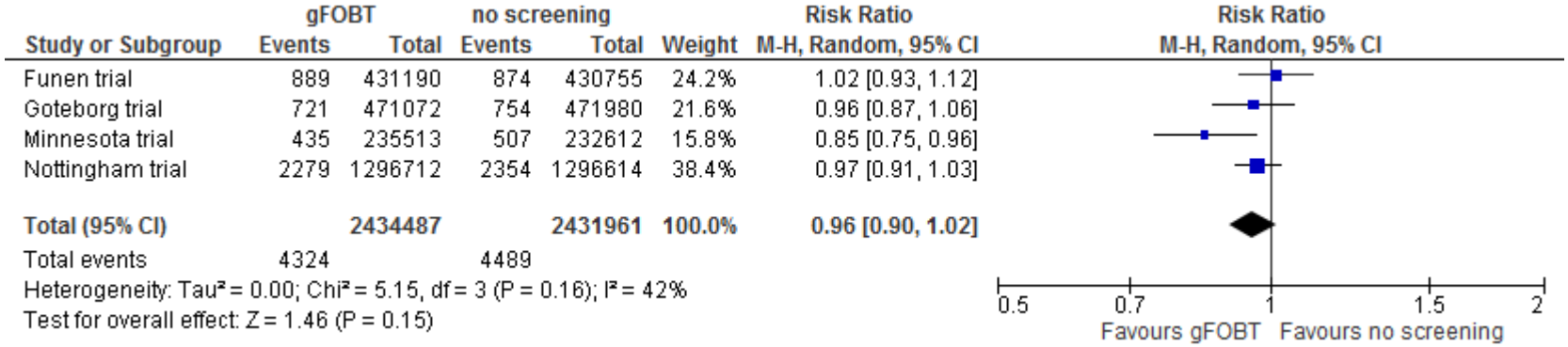


Figure 3: Colorectal cancer incidence - gFOBT versus no screening.



FS Versus No Screening

Systematic Reviews

The Cochrane review by Holme 2013 also compared FS with no screening [28]. Holme 2013 reported a 0.08% complication rate among all people undergoing screening with FS, defined as bleeding, perforation or death within 30 days of FS screening, follow-up colonoscopy or surgery; however, there was incomplete reporting of death in the trials [28]. The number of perforations and bleeds associated with FS or colonoscopy was low. The 2002 trial performed in the UK reported one perforation and 12 bleeds from the initial screening FS (n=40,332) and four perforations and nine bleeds among those having follow-up colonoscopy (n=2377) [32]. Segnan 2002 reported one perforation from the initial screening FS (n=9911), and one perforation and one bleed among those having follow-up colonoscopy (n=775) [60]. Schoen 2012 reported three perforations from the initial screening FS (n=107,236) and 19 perforations among people having follow-up colonoscopy (n=17,672) [57]. The Norwegian Telemark trial by Thiss-Evenson 1999 did not report on bleeding or perforations resulting from the initial screening FS, but reported that there were no complications from endoscopic examinations or polypectomies [64]. A more recent publication of the Norwegian Colorectal Cancer Prevention (NORCCAP) trial, not included in the Holme 2013 review, reported no complications after FS and no screening-associated deaths [23]. They reported six perforations during colonoscopy (n=2816) and four participants were admitted to the hospital for postpolypectomy bleeding [23].

Primary Studies

The characteristics and quality of the five RCTs from the Holme 2013 review can be found in Tables 10 to 12 [14,33,41,57,64]. In the Holme 2013 review, the risk of bias was considered to be low in four of the studies [14,33,41,57] and high for the Thiis-Everson 1999 Norwegian Telemark trial [64]. This difference was due to potential selection bias because participants in the intervention group were selected among those born in January and February, whereas participants in the control group were randomized irrespective of month of birth [64]. The investigators did find a month-of-birth all-cause mortality difference

suggesting selection bias may have occurred [40]. In all the trials, mortality was assessed using an ITS analysis. However, as shown in Table 10, different thresholds were used to define a positive FS resulting in various rates of follow-up colonoscopy.

Meta-analyses using the recent publication from the NORCCAP trial in events per person-years were performed for CRC-related incidence and mortality (Table 13, Figures 4 to 6), which showed a 28% RR reduction in CRC mortality (RR, 0.72; 95% CI, 0.65 to 0.80; p<0.00001) and a 22% reduction in CRC incidence with FS (RR, 0.78; 95% CI, 0.74 to 0.83; p<0.00001). Eight hundred and twenty-seven people would need to be offered screening with FS to prevent one death due to CRC over 10 years. Similarly, Holme 2013 found screening with FS had a 28% reduction in the relative risk of CRC mortality (RR, 0.72; 95% CI, 0.65 to 0.79; p<0.00001) and an 18% reduction in the incidence of CRC associated with FS screening (RR, 0.82; 95% CI, 0.74 to 0.90; p=0.0001) [28]. The meta-analysis using the recent publication from the NORCCAP trial showed a significant reduction in all-cause mortality in the FS group compared with the no screening group (RR, 0.97; 95% CI, 0.96 to 0.99; p=0.003); however, the effect size was small and close to one. This differs from the Holme 2013 analysis, which found a non-significant result (RR, 0.98; 95% CI, 0.95 to 1.01) [28]; this difference can be explained by the inclusion of the 1999 Telemark trial by Thiis-Everson in the Holme 2013 analysis [64]. This small, low-quality trial was excluded from our meta-analysis of all-cause mortality because the number of person-years was not reported separately for each arm [64]. A re-analysis of the Holme 2013 data excluding the Telemark trial reduced the statistical heterogeneity (I^2) from 45% to 0% and showed a significant effect of FS screening on all-cause mortality (RR, 0.97; 95% CI, 0.96 to 0.99; p=0.006). Similar to our findings, this reduction in all-cause mortality was small and close to one.

Table 10: Characteristics of included RCTs – FS versus no screening.

Author/year	Screening test	Frequency	Threshold for positive test / follow-up colonoscopy rate	Sample size	Mean age (range), years	Duration of follow-up (median)	Country
Shoen 2012[57]	FS vs usual care	Twice (2nd was at the 3rd or 5th year)	Polyp or mass detected/21.9%	154,900	(55-74)	11.9 years	United States
Segnan 2011[14]	FS vs no screening	Once	>5 mm distal polyps, inadequate bowel preparation with at least 1 polyp, or CRC/4%	34,292	59.7 (95% CI 55.5 - 64.3) 59.6 (95% CI 55.5 - 64.4)	11.4 years for mortality 10.5 years for Incidence	Italy

Atkin 2010[33]	FS vs no screening	Once	≥1 cm polyps, ≥3 adenomas, polyps with tubulovillous or villous histology, polyps with severe dysplasia or malignant disease or ≥20 hyperplastic polyps above the distal rectum/5%	170,432	60 60 (55-64)	11.2	United Kingdom
Hoff 2009, Holme 2014[23,41] NORCAAP (Norwegian Colorectal Cancer Prevention Trial)	FS or FS+FIT vs no screening	Once	≥10 mm polyp, any histologically verified adenoma irrespective of size, carcinoma, or positive FIT/20%	98,792	56.9 56.1	11.2 years 10.9 years	Norway
Thiis-Evensen 1999[98] Telemark trial	FS vs no screening	Once	Any polyp/NR	799	67.4 67.0 (63-72)	13 years	Norway

Abbreviations: FIT = fecal immunochemical test; NR = not reported; FS = flexible sigmoidoscopy; RCT = randomized controlled trial; vs = versus

Table 11: Quality of RCTs – FS versus no screening.

Author/year	Randomization details	Sample size and power calculation done?	Baseline patient characteristics	ITS analysis	Blinding	Funding

Schoen 2012[57]	Randomization was performed in blocks stratified according to screening centre, age, and sex	154,900 Yes	Characteristics similar between groups	Yes	Deaths that were potentially related to prostate, lung, colorectal, or ovarian cancer were reviewed in a blinded fashion, in an end-point adjudication process	Division of Cancer Prevention, National Cancer Institute
Segnan 2011[14]	Cluster randomization (i.e., by physician) used in 3 centres contributed 17,602 subjects from the rosters of 507 physicians; the remaining 16,690 subjects were randomly assigned individually	34,292 Yes	Age and sex family history of CRC and interest in screening were similar between groups. The proportion of people who had a colorectal endoscopy (colonoscopy or sigmoidoscopy) in the past 3–25 years was higher in the intervention arm than in the control arm (8.6% vs 7.9%)	Yes	Experts assessing CRC cases were blinded to the allocation of the subjects to the intervention or control group at randomization	Associazione Italiana per la Ricerca sul Cancro and the Italian National Research Council
Atkin 2010[33]	Randomization was stratified by trial centre, general practice within centre, and household type. Sequentially numbered randomization was done centrally in blocks of 12, but with the added constraint of no more than 3 consecutive allocations to 1 group within or across blocks	170,432 Yes	There were 29,105 (51%) women in the intervention group and 57,602 (51%) in the control group, and the mean age was 60 years (SD 2.9) in both groups.	Yes	A second analysis was done after blinded verification of assignment of CRC as an underlying cause of death	Medical Research Council, National Health Service R&D, Cancer Research UK, and KeyMed

Hoff 2009, Holme 2014[23,41]	An independent body used a computer algorithm for randomization and equal numbers of men and women were randomly sampled for screening; remaining individuals in the screening areas constituted the control group, which was not offered any screening; participants in the screening group were further randomized (1:1) to receive once-only FS or a combination of once-only FS and FIT (FlexSure OBT, Beckman-Coulter)	98,792 Yes	There were 50% women in both groups; in 2000, sample extended to include individuals aged 50 - 54 years.	Yes	Assessment of both the cause of death and CRC staging for the registries used was blinded to the group status of participants in the study	Norwegian Cancer Society and the Norwegian Ministry of Health
Thiis-Evensen 1999[98]	Four hundred men and women, who were born in January or February, were selected from the population register and offered a FS screening examination. A further 399 subjects were drawn from the same register, irrespective of month of birth, and enrolled as a control group	799 NR	There were no differences between the 2 groups with regard to the number of individuals who complained of loose stools, diarrhoea, flatulence, mucus in the stools, anal pruritus, hemorrhoids, or symptoms consistent with irritable bowel syndrome	Yes	NR	Norwegian Cancer Society

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; ITS = intention to screen; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

Table 12: GRADE evidence profile – FS versus no screening.

Quality assessment	# of patients	Effect	Quality	Importance

# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FS (cases/person-years)	No screening (cases/person-years)	Relative (95% CI)	Absolute (cases/person-years)		
CRC mortality (follow-up: 6-12 years)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious	576/1,902,184 (0.03%)	1321/3,114,546 (0.04%) Control (gFOBT + FS) = 0.06%	**RR 0.72** (0.65 - 0.80)	119 fewer per 1,000,000 (from 85 fewer to 148 fewer) 168 fewer per 1,000,000 (from 120 fewer to 210 fewer)	⊕⊕⊕⊕ HIGH	Critical
Complications from tests (from Holme 2013[28])[1]												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious		N/A[2]			⊕⊕⊕⊕ HIGH	Critical
All-cause mortality (follow-up: 6-12 years)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious	19,525/1,902,184 (1.0%)	32,903/3,114,546 (1.1%) Control (gFOBT + FS) = 1.85%	**RR 0.97** (0.96 - 0.99)	317 fewer per 1,000,000 (from 106 fewer to 423 fewer) 555 fewer per 1,000,000 (from 185 fewer to 740 fewer)	⊕⊕⊕⊕ HIGH	Important
CRC incidence (follow-up: 6-12 years)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Not serious	2218/1,860,990 (0.1%)	4579/3,067,081 (0.1%) Control (gFOBT + FS) = 0.16%	**RR 0.78** (0.74 - 0.83)	328 fewer per 1,000,000 (from 254 fewer to 388 fewer) 352 fewer per 1,000,000 (from 272 fewer to 416 fewer)	⊕⊕⊕⊕ HIGH	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; RR = relative risk; N/A = not applicable

[1]Major complication rate included bleeding, perforation or death within 30 days of screening, follow-up colonoscopy or surgery

[2]See text for absolute rate

Table 13: Outcomes data of included RCTs in person-years – FS versus no screening.

	CRC mortality				Mortality (all cause)				Incidence of CRC			
Test / Author /year	FS		No screening		FS		FS		No screening		FS	
	Events	Total*	Events	Events	Total*	Events	Events	Total*	Events	Events	Total*	Events

Schoen 2012**[57]	252	871,930	341	252	871,930	341	252	871,930	341	252	871,930	341
Segnan 2011[14]	65	187,532	83	65	187,532	83	65	187,532	83	65	187,532	83
Atkin 2010[33]	189	620,045	538	189	620,045	538	189	620,045	538	189	620,045	538
Holme 2014[23]***	70	222,677	359	70	222,677	359	70	222,677	359	70	222,677	359
Thiis-Evensen 1999 [98]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CRC = colorectal cancer; FS = flexible sigmoidoscopy; NR = not reported
*in person-years
** For all-cause mortality Schoen 2012 excludes death due to prostate, lung and ovarian cancer
***Number of cases estimated using (age-adjusted cases/100,000 person-years) × person-years of observation

Figure 4: Colorectal cancer mortality – FS versus no screening.

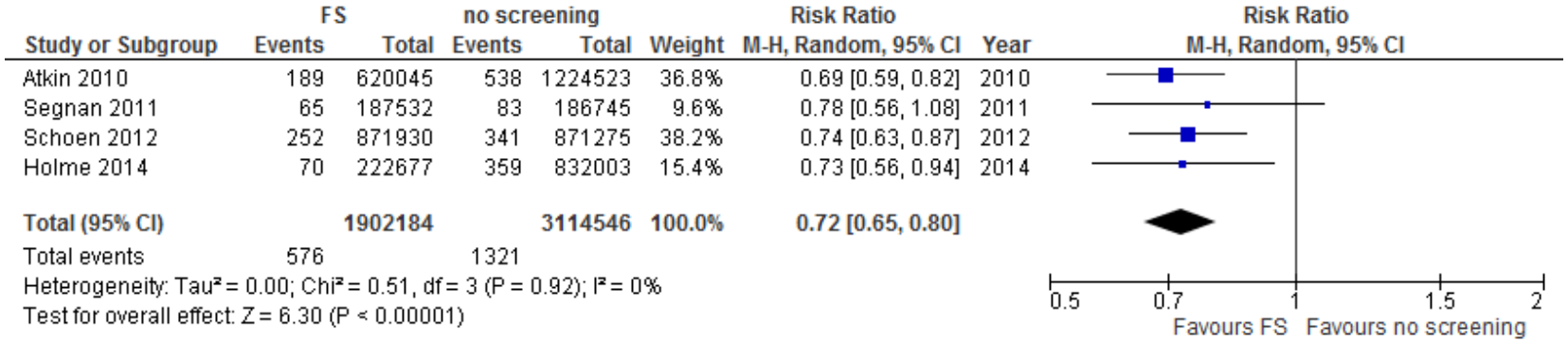


Figure 5: All-cause mortality – FS versus no screening (Schoen 2012 excludes death due to prostate, lung and ovarian cancer).

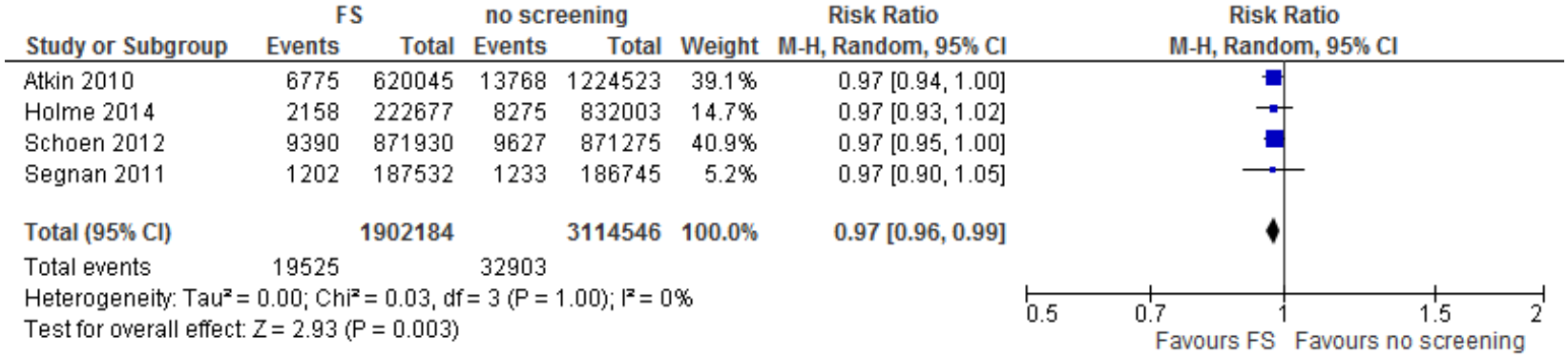
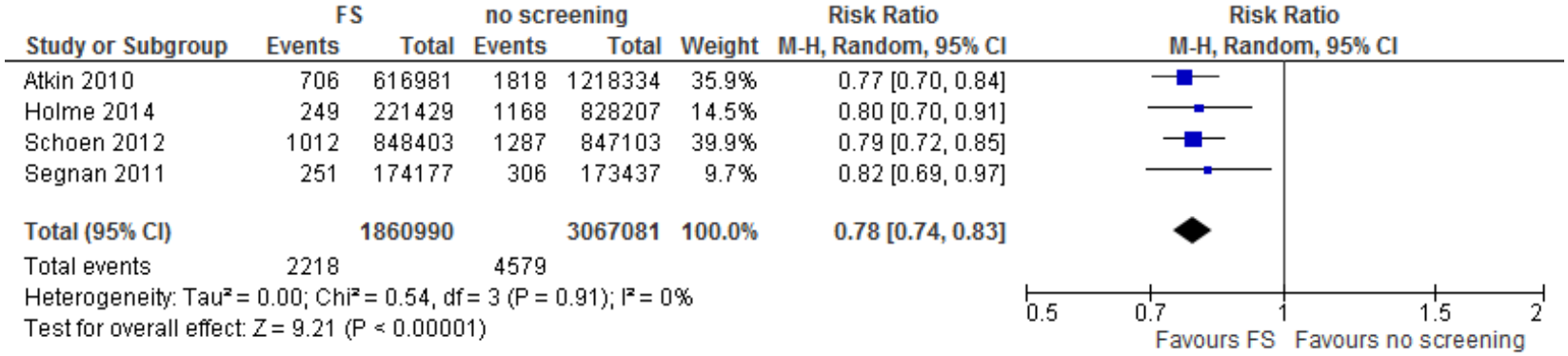


Figure 6: Colorectal cancer incidence – FS versus no screening.



Colonoscopy Versus No Screening

No RCTs were found that compared screening colonoscopy with no screening in average-risk screening populations. Two meta-analyses were found, one high-quality [24] and one low-quality [31] (Table 2). The high-quality meta-analysis included six comparative observational studies that evaluated the outcomes of CRC-related mortality and CRC incidence [24,79,83,90,93-95]. Niv 2008 was considered to be low quality because the quality of the included studies was not assessed and the statistical methods were not described in detail; however, it included information on complications (perforation, bleeding, or death) associated with a screening colonoscopy in asymptomatic people (Table 3) [31]. These two meta-analyses are considered separately below for their different outcomes of interest.

CRC-Related Mortality and Incidence

No other comparative studies were found outside of those reported in the Brenner 2014 review [24]. The quality of the included studies was considered to be very low (Tables 14 to 16, Table 20) [79,83,90,93-95]. Only two studies were prospective [79,83]. However, one prospective study used data from the general population as the comparison group [79] and the other prospective study used subjects who refused to participate in the screening program as the control group [83]. Of the remaining four studies, three were case-control studies [93-95] and one was retrospective [90]. Furthermore, one case-control study investigated only late-stage CRC [95]. Combining the results from these six observational studies, the Brenner 2014 meta-analysis found that screening with colonoscopy reduced the incidence of CRC (RR, 0.31; 95% CI, 0.12 to 0.77), but the heterogeneity was high (94%) [24]. The heterogeneity was reduced when the Cotterchio 2005 and Brenner 2014 studies were removed with only a small change to the estimate of risk reduction for CRC incidence (RR, 0.36; 95% CI, 0.25 to 0.53) [24]. Meta-analysis of three of the studies from the Brenner 2014 review also showed a reduction in CRC mortality (RR, 0.32; 95% CI, 0.23 to 0.43) [24]. In addition, Brenner 2014 performed an indirect comparison between colonoscopy and FS, and found a non-significant reduction in the pooled estimate for incidence of CRC (RR, 0.61; 95% CI, 0.23 to 1.58; p=0.31) and CRC mortality (RR, 0.59; 95% CI, 0.30 to 1.15; p=0.12) [24].

Colonoscopy-Related Complications

The risk of complications associated with a screening colonoscopy was not reported in the six studies in Brenner 2014 [24]. However, this was an outcome in the low-quality systematic review by Niv 2008 [31]. Fifteen observational studies in total, eight studies from the Niv 2008 review [70,77,82,84-87,92], and seven additional studies found in the literature search and from reference lists [72,78,80,81,88,89,91], included information on complications associated with a screening colonoscopy (Tables 17 to 20). Of the six studies of no subjects with family histories of CRC, there were no perforations, bleeds, or deaths reported [70,72,78,88,91,92]. In the remaining nine studies [77,80-82,84-87,89], the risks of perforation or bleeding were less than 1% ranging from 0% to 0.22% for perforations and 0% to 0.19% for bleeding. Four of these studies reported that no deaths occurred [80,82,84,89].

Table 14: Characteristics of included observational studies – colonoscopy and CRC-related mortality and incidence.

Author / year	Study design	Sample size	Mean age (range) years	Men %	Complete colonoscopy	Previously screened?	Family history in first degree relative?	Ascertainment of procedures	Frequency	Duration of follow-up, median (range)	Confounders considered in analysis	Country
Brenner 2014[93]	Case-control	2516 cases with CRC 2284 controls	Median 70 (NR)	59.0 cases 58.6 controls	10.9% cases 1.7% of cases due to screening 38.3% controls	43 cases 275 controls were due to screening	14.7 cases 11.0 controls	Self-report and physicians records of colonoscopy	Multiple and once (sensitivity analysis excluding multiples revealed	At least 10 years	Age, sex, education, family history, body mass index, smoking, acetylsalicylic	Germany

Author / year	Study design	Sample size	Mean age (range) years	Men %	Complete colonoscopy	Previously screened?	Family history in first degree relative?	Ascertainment of procedures	Frequency	Duration of follow-up, median (range)	Confounders considered in analysis	Country
					12.0% of controls due to screening				similar results)		acid or other non-steroidal anti-inflammatory drugs, hormone replacement therapy, participation in a general health screening examination	
Doubeni 2013[95]	Case-control	471 cases with stage IIB or higher CRC 509 controls	71.7 (55-85)	51.4 cases 50.1 controls	2.8 cases and 9.0 controls	Only included cases exposed to definite or probable screening test	0	Information about procedures collected from databases	Multiple and once (sensitivity analysis excluding multiples revealed similar results)	10 years	Age, sex, health plan enrolment, socioeconomic status, comorbidity, family history, other screening exposures	United States
Nishihara 2013[90]	Retrospective cohort	Person years: no screening - 1,182,248; screening colonoscopy - 357,008	NR	37	NA	NA	Yes, numbers not reported per group	Asked whether they had undergone either sigmoidoscopy or colonoscopy and, if so, reason for investigation; confirmed with medical records	Last colonoscopy reported	22 years	Age, sex, family history, body mass index, physical activity, smoking alcohol consumption, nutritional factors, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, hormone replacement therapy, other drugs	United States

Author / year	Study design	Sample size	Mean age (range) years	Men %	Complete colonoscopy	Previously screened?	Family history in first degree relative?	Ascertainment of procedures	Frequency	Duration of follow-up, median (range)	Confounders considered in analysis	Country
Manser 2012[83]	Prospective cohort	2044 screened 20,774 no screening	(50-80)	52	1912 screened	<5 years excluded	12.8% screened 7.3% not screened	Patients who refused to participate in screening program were the control group	Once	5 years	Age, sex, profession, family history, body mass index, physical activity, smoking, nutritional factors, participation in general health screening examinations	Switzerland
Kahi 2009[79]	Prospective cohort	733 screened control group was from the SEER database person-years 10,492	61 (50-86)	59	715	<3 years excluded	0	All subjects underwent fecal occult blood testing using Hemoccult II (Beckman Coulter, Fullerton, CA) during the week before colonoscopy	Once	8 (3-16) years	Age, sex	United States
Cotterchio 2005[94]	Case-control	971 cases with CRC 1944 controls	(20-74)	52 in cases 53 in controls	4% for cases 4% for controls	31% in cases 11% in controls	31% for cases 11% for controls	Subjects selected from database; Information about procedures from self-report	First colonoscopy at least one year prior to diagnosis/referent date	Ever had test	Age, sex, marital status, education, family history, medical conditions, body mass index, weight, physical activity, smoking alcohol consumption, nutritional factors,	Canada

Author / year	Study design	Sample size	Mean age (range) years	Men %	Complete colonoscopy	Previously screened?	Family history in first degree relative?	Ascertainment of procedures	Frequency	Duration of follow-up, median (range)	Confounders considered in analysis	Country
											acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, hormone replacement therapy, other drugs	

Abbreviations: CRC = colorectal cancer; NA = not applicable; NR = not reported

Table 15: Quality of included observational studies – colonoscopy and CRC-related mortality and incidence.

ITEM	Brenner 2014[93]	Doubeni 2013[95]	Nishihara 2013[90]	Manser 2012[83]	Kahi 2009[79]	Cotterchio 2005[94]
1. Representativeness of cohort	N	N	N	N	Y	N
2. Selection of the comparison group	N	N	N	N	Y	N
3. Demonstration that outcome of interest was not present at the start of the study	N	N	Y	Y	Y	N
4. Comparability of cohorts on the basis of design or analysis	Y	Y	Y	N	Y	Y
5. Assessment of outcome	Y	Y	Y	Y	Y	Y
6. Was follow-up long enough for outcomes to occur	Y	Y	Y	N	Y	?
7. Adequacy of follow-up of cohorts	Y	Y	Y	Y	Y	Y

Abbreviations: CRC = colorectal cancer; N = No; Y = Yes; ? = not enough information

Table 16: Outcome table – colonoscopy and CRC-related mortality and incidence.

Author, year	CRC death	Odds ratio in mortality	CRC incidence	Odds ratio in incidence

Brenner 2014[93]	NR	NR	43 cases and 275 controls	0.09 (95% CI, 0.07-0.13)
Doubeni 2013[95]	NR	NR	13 cases and 46 controls	0.29 (95% CI, 0.15-0.58)
Nishihara 2013[90]	52 deaths in screening colonoscopy group; 349 deaths in no screening lower endoscopy group	Age-adjusted HR 0.32 (95% CI, 0.24-0.44) Multivariate HR 0.32 (95% CI, 0.24-0.45)	NR	NR
Manser 2012[83]	1 in the screened group and 51 in the non-screened group	0.12 (95% CI, 0.01-0.93)	12 in screened group and 213 in non-screened group	0.31 (95% CI, 0.16-0.59)
Kahi 2009[79]	3 (95% CI, 0–9). expected number of deaths based on SEER data was 9	(based on SEER data) 0.35 (95% CI, 0.0–1.06)	12 (5 found at baseline and 7 found after a median follow-up period of 8 years) expected number based on SEER data was 23	0.52 (95% CI, 0.22–0.82)
Cotterchio 2005[94]	NR	NR	40 cases and 69 controls	0.69 (95% CI, 0.44-1.07)

Abbreviations: CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; NR = not reported

Table 17: Characteristics of included observational studies – colonoscopy-related complications.

Author/year	Study design	Sample size	Recruitment/program	Country
Chung 2010[89]	Retrospective cross-sectional study	5254	Most self-paid, one-quarter paid by companies	Korea
Choe 2007[88]	Retrospective cross sectional analysis of data	5086	Screening colonoscopy as a part of a routine health check-up	Korea
Kim 2007[80]	Prospective cohort	4491	Voluntarily underwent colonoscopies as a part of a health examination program	Korea
Kim 2007[81]	Prospective cohort	3163	Referred from primary care	United States
Regula 2006[84]	Prospective cohort	Total=50,148; without high-risk=39,705	National screening colonoscopy program	Poland

Author/year	Study design	Sample size	Recruitment/program	Country
Strul 2006[92]	Retrospective cohort	1177	A primary screening colonoscopy was initiated by the patients or their family doctors and conducted in an outpatient clinic.	Israel
Chiu 2005[70]	Prospective cohort	1741	Among patients who participated in the health evaluation program, only ethnic Chinese patients who had a total colonoscopy were included in the study.	Taiwan
Schoenfeld 2005[86]	Prospective cohort	All women 1463=total; without high-risk=1233	Referred for colorectal screening	United States
Soon 2005[87]	Prospective cohort	Taiwan = 1512, USA = 3463	Colonoscopy screening program	Taiwan, United States
Prajapati 2003[91]	Retrospective cohort	1282	Federally funded Medicare program	United States
Imperiale 2000[77]	Prospective cohort	1994	Screening colonoscopy through health insurance	United States
Lieberman 2000[82]	Prospective cohort	3121	Screening colonoscopy in people recruited from Veterans Affairs medical centres by random selection from centre's clinic list on basis of age, or by selection of asymptomatic patients referred for screening sigmoidoscopy, by advertisement for patients with a family history of colorectal cancer	United States
Rogge 1994[85]	Prospective cohort	639	Screening colonoscopy program established as a service for physicians who desired a colorectal cancer screening program for their patients	United States
DiSario 1991[72]	Prospective cohort	119	Referred for sigmoidoscopy screening	United States
Johnson 1990[78]	Prospective cohort	90	Routine healthy maintenance proctosigmoidoscopy examination	United States

Table 18: QUADAS evaluation of included observational studies – colonoscopy-related complications.

ITEM	Representative spectrum	Acceptable reference standard	Acceptable delay between tests	Partial verification avoided	Differential verification avoided	Incorporation avoided	Index test results blinded	Reference test results blinded	Relevant clinical information	Uninterpretable results reported	Withdrawals explained
Chung 2010[89]	N	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Choe 2007[88]	Y	Y	Y	Y	Y	Y	NA	NA	N	N	N
Kim 2007[80]	Y	Y	Y	Y	Y	Y	NA	NA	N	N	N

Kim 2007[81]	Y	Y	Y	Y	Y	Y	NA	NA	N	N	N
Regula 2006[84]	Y	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Strul 2006[92]	Y	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Chiu 2005[70]	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	N
Schoenfled 2005[86]	N	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Soon 2005[87]	N	Y	Y	Y	Y	Y	NA	NA	Y	Y	N
Prajapati 2003[91]	Y	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Imperiale 2000[77]	Y	Y	Y	Y	Y	Y	NA	NA	N	N	N
Lieberman 2000[82]	N	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Rogge 1994[85]	N	Y	Y	Y	Y	Y	NA	NA	N	N	N
DiSario 1991[72]	Y	Y	Y	Y	Y	Y	NA	NA	Y	N	N
Johnson 1990[78]	Y	Y	Y	Y	Y	Y	NA	NA	Y	N	N

Abbreviations: N = No; NA = Not applicable; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; Y = Yes

Table 19: Outcome table – colonoscopy-related complications.

Study	Sample size	Complete colonoscopy	Previously screened?	Family history	Men %	Mean age (years)	Perforation	Bleeding	Death
Chung 2010[89]	5254	5254	NR	348	66	NR	1	5	0
Choe 2007[88]	5099	5086	<10 years excluded	0	70.5	49.3	0	0	0
Kim 2007[80]	4629	4491	NR	NR	53	48.4	0	0	NR
Kim 2007[81]	3163	NR	NR	265	44.4	58.1	7	0	0
Regula 2006[84]	Total=50,148 without high-risk=39,705	91.1% for total	NR	10,442	36.3	55.2 for total	5 for total	13 for total	0
Strul 2006[92]	1177	1177	<5 years excluded	0	47.2	NR	0	0	0
Chiu 2005[70]	1741	1708	<5 years excluded	0	59.8	52.5	NR	NR	0
Schoenfeld 2005[86]	1483	1463=total; without high-risk=1233	<5 years excluded	230	0	58.9 for total	0	0	NR
Soon 2005 Taiwan cohort[87]	1512	1456	NR	NR	62	53.5	0	0	NR
Soon 2005 Seattle cohort[87]	3463	3403	NR	NR	49	58.7	1	1	NR
Prajapati 2003[91]	1282	NR	Never	0	41	62	0	0	0
Imperiale 2000[77]	1994	97%	NR	NR	58.9	59.8	1	3	NR
Lieberman 2000[82]	3196	3121	<10 years excluded	434	96.8	62.9	0	6	0
Rogge 1994[85]	639	627	NR	NR	56	56	0	1	NR

Study	Sample size	Complete colonoscopy	Previously screened?	Family history	Men %	Mean age (years)	Perforation	Bleeding	Death
DiSario 1991[72]	119	119	Never	0	100	NR	0	0	0
Johnson 1990[78]	90	88	<3 years excluded	0	68	65	0	0	0

Abbreviations: NR = not reported

Table 20: GRADE evidence profile – colonoscopy and CRC-related mortality and incidence.

Quality assessment							Effect		
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Quality	Importance
CRC mortality (from Brenner 2014)[24]									
3	Observational studies	Serious[1]	Not serious	Not serious	Not serious	Not serious	RR 0.32 (0.23 - 0.43)	⊕◯◯◯ VERY LOW	Critical
Complications from tests (perforations, bleeding, deaths)									
15	Observational studies	Not serious	Not serious	Not serious	Not serious	Not serious	N/A[2]	⊕⊕◯◯ LOW	Critical
CRC incidence (from Brenner 2014)[24]									
5	Observational studies	Serious[1]	Serious[3]	Not serious	Not serious	Not serious	RR 0.31 (0.12 to 0.77)	⊕◯◯◯ VERY LOW	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; N/A = not applicable
[1] Mixed study designs included case-control and retrospective
[2]See text for absolute rate
[3] Heterogeneity: $Tau^2 = 1.0$; ($p<0.0001$); $I^2 = 94\%$

mSEPT9

One prospective study evaluated mSEPT9 in patients undergoing screening colonoscopy in the United States and Germany (Tables 21 to 23) [71]. All patients with CRC and a random sample of the remaining subjects were analyzed. The sensitivity was found to be 48.2% (95% CI, 32.4% to 63.6%) and the specificity was 91.5% (95% CI, 89.7% to 93.1%) [71].

Table 21: Characteristics of included study – mSEPT9.

Author/year	Study design	Patient population	Country of study	Outcomes	Summary of findings
Church 2013[71]	Blinded prospective nested case-control cross-sectional	Asymptomatic individuals ≥50 years old scheduled for screening colonoscopy (n=7941)	United States and Germany	Sensitivity, Specificity for detection of CRC	• Included all cancer cases but randomly selected from the non-cancer cases • Results from 53 CRC cases and from 1457 subjects without CRC yielded a standardized sensitivity of 48.2% (95% CI, 32.4% to 63.6%; crude rate 50.9%) • For CRC stages I–IV, sensitivities were 35.0%, 63.0%, 46.0%, and 77.4%, respectively. • Specificity was 91.5% (95% CI 89.7% to 93.1%; crude rate 91.4%). • Sensitivity for advanced adenomas was low (11.2%).

Abbreviation: CRC = colorectal cancer

Table 22: QUADAS evaluation of the quality of included study – mSEPT9.

ITEM	Church 2013[71]
1. Representative spectrum	Y
2. Acceptable reference standard	Y
3. Acceptable delay between tests	Y
4. Partial verification avoided	Y
5. Differential verification avoided	Y
6. Incorporation avoided	Y
7. Index test results blinded	Y
8. Reference test results blinded	Y
9. Relevant clinical information	N
10. Uninterpretable results reported	Y
11. Withdrawals explained	Y

Abbreviations: N = no; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; Y = yes

Table 23: GRADE evidence profile – mSEPT9.

Quality assessment	# of patients	Effect	Quality	Importance

# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Sensitivity/specificity										
1	Observational study	Not serious	Not serious	Serious[1]	Serious[2]	Not serious	See table 21	See table 21	⊕◯◯◯ VERY LOW	Important

Abbreviation: GRADE = Grading of Recommendations, Assessment, Development and Evaluations
[1] surrogate outcome for CRC mortality
[2] only 53 CRC cases, only 1 study

Fecal M2-PK

Two prospective studies reported the sensitivity and specificity of fecal M2-PK tests in subjects undergoing screening colonoscopy (Tables 24 to 26) [74,97]. Tonus 2006 was a case-control diagnostic study of the test characteristics for the detection of CRC, whereas Haug 2008 was a cohort diagnostic study that excluded patients with CRC and only examined adenomas [74,97]. In the Tonus 2006 study, the sensitivity was 78% for CRC in the cases and the specificity was 93% in the controls at a cut-off level of 4.0 kU/L [97]. At the same cut-off level, the sensitivity for advanced adenoma was 22% (95% CI, 14% to 31%) and the specificity was 82% (95% CI, 78% to 84%) in the Haug 2008 study [74].

Table 24: Characteristics of included studies – fecal M2-PK.

Author/year	Comparison/ # recruited	Patient population	Country of study	Outcomes	Summary of findings
Tonus 2006[97]	M2-PK – 42 controls, 54 cases	Participated in national screening program	Germany	Sensitivity, specificity for detection of CRC	• Colorectal tumours were accompanied by a highly significant increase (P<0.001) in fecal tumour M2-PK levels (median: colon carcinoma, 23.1 kU/L; rectal carcinoma, 6.9 kU/L; colorectal carcinoma, 14.7 kU/L) • At a cut-off level of 4.0 kU/L, the sensitivity was 91% for colon carcinoma, 57% for rectal carcinoma and 78% when both groups were combined; control group: 93% specificity • Strong correlation between fecal tumour M2-PK levels and staging
Haug 2008[74]	M2-PK – 1082	Participants in screening	Germany	Sensitivity, specificity for	• Thirty percent of the participants had any adenoma and 10% had an advanced adenoma • The median (interquartile range) tumour M2-PK level in the whole study population was 1.3 UmL^{-1} (0.3–3.3).

		colonoscopy program that is offered to average-risk subjects aged 55 years or older		detection of adenomas	• At a cut-off value of 4 UmL^{-1}, sensitivity was 22% (14-31) and 23% (17-29) for detection of advanced and other adenomas, respectively, whereas specificity was 82% (78-84). • The area under the receiver-operating characteristics curve (95% confidence interval) was 0.54 (0.51–0.58) and 0.56 (0.52–0.59) for advanced and other adenomas, respectively.

Abbreviation: CRC = colorectal cancer

Table 25: QUADAS evaluation of quality of included studies – fecal M2-PK.

ITEM	Tonus 2006[97]	Haug 2008[74]
1. Representative spectrum	N	N
2. Acceptable reference standard	Y	Y
3. Acceptable delay between tests	Y	Y
4. Partial verification avoided	Y	Y
5. Differential verification avoided	Y	Y
6. Incorporation avoided	Y	Y
7. Index test results blinded	N	Y
8. Reference test results blinded	N	Y
9. Relevant clinical information	N	Y
10. Uninterpretable results reported	N	N
11. Withdrawals explained	N	N

Abbreviations: N = no; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; Y = yes

Table 26: GRADE evidence profile – fecal M2-PK.

Quality assessment							# of patients	Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				

Sensitivity/specificity										
2	Observational studies	Serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	See Table 24	See Table 24	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; GRADE = Grading of Recommendations, Assessment, Development and Evaluations;
[1]Mixed study designs – case-control and cohort
[2]Haug 2008 excluded patients with CRC; surrogate outcome for CRC mortality
[3]Only 54 with CRC and 106 with advanced adenomas

Stool DNA Versus gFOBT or FIT

Three high-quality cross-sectional studies [69,75,76] compared stool DNA (sDNA) with fecal occult blood tests against the gold standard of colonoscopy, and one small case-control study [96] compared sDNA with FIT against a screening colonoscopy (Tables 27 to 29). Imperiale 2014 compared sDNA with FIT, and Ahlquist 2008 and Imperiale 2004 compared sDNA with gFOBT [69,75,76]. Imperiale 2004 used the Hemoccult II gFOBT and Ahlquist 2008 used either Hemoccult or Hemoccult Sensa [69,76]. Imperiale 2004 used an sDNA test that targeted the same markers as Alquist 2008 (Table 27) [69,76]. Ahlquist 2008 also used a second sDNA test (called sDNA test 2), which used a more broadly informative marker panel [69]. Imperiale 2014 used a newer, more sensitive version of the sDNA test than the test used in the Ahlquist 2008 and Imperiale 2004 studies [69,75,76]. The DNA marker panel evaluated in Koga 2014 six gene markers [96] that were different from the panels evaluated in the others studies. In all four studies, sDNA tests were found to have a higher sensitivity for detecting CRC or other screen-relevant features compared with fecal occult blood tests. The Imperiale 2014 and Koga 2014 studies both found that the sDNA test had higher sensitivity but lower specificity for the detection of CRC compared with FIT [75,96]. When compared to gFOBT, the sDNA tests also had higher sensitivity for CRC and advanced adenomas with comparable specificities.

Table 27: Characteristics of included studies – sDNA versus gFOBT or FIT.

Author/year	Comparison/ # Recruited	Study design	Patient population	Country of study	sDNA tests markers	Summary of findings
Imperiale 2014[75]	sDNA vs FIT (OC FIT-CHEK, Polymedco)	Blinded multicentre cross-sectional study	11,016 asymptomatic, average-risk people between 50 and 84 years who were undergoing screening colonoscopy	USA and Canada	Aberrantly methylated BMP3 and NDRG4 promoter regions, KRAS mutations, ß-actin	• sDNA – detected 60/65 CRCs, sensitivity 92.3% (95% CI, 83.0 to 97.5) and 321/757 advanced precancerous lesions, sensitivity 42.4% (95% CI, 38.9 - 46.0); FIT – detected 48/65 CRCs, sensitivity 73.8% (95% CI, 61.5 - 84.0) (p=0.002) and 180/757 advanced precancerous lesions, sensitivity 23.8% (95% CI, 20.8 - 27.0) (p<0.001)

						• sDNA - specificity for no CRC or advanced precancerous lesions was 86.6% (95% CI, 85.9 - 87.2); FIT - specificity for no CRC or advanced precancerous lesions was 94.9% (95% CI, 94.4 - 95.3) (p<0.001) • sDNA detected 13/60 screen-relevant cancers that were undetected by FIT; FIT detected 1 cancer that was undetected by sDNA
Koga 2014[96]	sDNA (*3D*-Gene) vs FIT (Hemo-Plus)	Case-control (blinding not reported)	Training set: 41 with CRC, 54 healthy controls from screening colonoscopy; validation set: 12 with CRC, 7 healthy controls from screening colonoscopy	Japan	CCAAT/enhancer binding protein, beta; Pc fragment of IgG, low-affinity IIIa, receptor; 6-phosphfructo-2-kinase/fructose-2, 6-biphophatase 3; interleukin 8; superoxide dismutase 2; regulator of G-protein signalling 2	• Training set: sDNA – sensitivity for CRC 35/41 (85.4%), specificity for CRC 46/54 (85.2%); FIT – sensitivity for CRC 22/41 (53.7%), specificity for CRC 53/54 (98.1%) • Validation set: sDNA – sensitivity for CRC 10/12 (83.3%), specificity for CRC 6/7 (85.7%); FIT – sensitivity for CRC 8/12 (66.7%), specificity for CRC 7/7 (100%)
Ahlquist 2008[69]	sDNA (SDT-1 or 2) vs gFOBT (Hemoccult and Hemoccult SENSA)	Blinded multicentre cross-sectional study	Average risk adults (n=4482) 39 patients had cancer + high-grade dysplasia	USA	SDT-1 – 21 mutations (3 on *K-ras* gene, 10 on *APC* gene, 8 on *p53* gene), BAT-26, long DNA SDT-2 – K-ras mutations, APC mutations, vimentin gene methylation	• Sensitivity for screen-relevant neoplasms (included CRC) was 20% by SDT-1, 11% by Hemoccult (p=0.020), 21% by Hemoccult SENSA (p=0.80) • Sensitivity for cancer plus high-grade dysplasia did not differ among tests. • Specificity for cancer, high-grade dysplasia and adenomas ≥1 cm was 96% by SDT-1, compared with 98% by Hemoccult (p<0.001) and 97% by Hemoccult SENSA (p=0.20).

						• SDT-2 detected 46% of screen-relevant neoplasms, compared with 16% by Hemoccult (p<0.001) and 24% by Hemoccult SENSA (p<0.001). • SDT-2 detected 46% of adenomas 1 cm or larger, compared with 10% by Hemoccult (p<0.001) and 17% by Hemoccult SENSA (p<0.001). • Among colonoscopically normal patients, the positivity rate was 16% with SDT-2, compared with 4% with Hemoccult (p=0.010) and 5% with Hemoccult SENSA (p=0.030).
Imperiale 2004[76]	sDNA vs gFOBT (Hemoccult II)	Blinded cross-sectional study	4404 average risk, all received screening colonoscopy At least 50 years of age Stratified according to age, with a minimum of ¾ subjects 65 years of age or older	USA	21 mutations (3 on *K-ras* gene, 10 on *APC* gene, 8 on *p53* gene), BAT-26, long DNA	• Sensitivity - sDNA - detected 16/31 CRC (sensitivity 51.6%), gFOBT detected 4/31 CRC (sensitivity 12.9%) (p<0.003); sDNA - detected 29/71 CRC plus adenomas with high-grade dysplasia (sensitivity 40.8%), gFOBT detected 10/71 CRC (sensitivity 14.1%) (p<0.001) • Specificity for no polyp detection was 94.4% for fecal DNA and 95.2% for gFOBT

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; IgG = immunoglobulin G; sDNA = stool DNA; SDT-1 = stool DNA test 1; SDT-2 = stool DNA test 2; vs = versus

Table 28: QUADAS evaluation of quality of included studies – sDNA versus gFOBT or FIT.

ITEM	Imperiale 2014[75]	Koga 2014[96]	Ahlquist 2008[69]	Imperiale 2004[76]
1. Representative spectrum	Y	N	Y	Y
2. Acceptable reference standard	Y	Y	Y	Y
3. Acceptable delay between tests	Y	Y	Y	Y

4. Partial verification avoided	Y	Y	Y	Y
5. Differential verification avoided	Y	Y	Y	Y
6. Incorporation avoided	Y	Y	Y	Y
7. Index test results blinded	Y	N	Y	Y
8. Reference test results blinded	Y	N	Y	Y
9. Relevant clinical information	Y	Y	Y	Y
10. Uninterpretable results reported	Y	N	Y	Y
11. Withdrawals explained	Y	N	Y	Y

Abbreviations: FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; N = no; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; sDNA = stool DNA; Y = yes

Table 29: GRADE evidence profile – stool DNA versus gFOBT or FIT.

Quality assessment							# of patients		Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stool DNA	gFOBT			
Sensitivity/specificity (FIT)											
2	Observational studies	Not serious[1]	Not serious	Serious[2]	Not serious	Not serious	See Table 27	See Table 27	See Table 27	⊕◯◯◯ VERY LOW	Important
Sensitivity/specificity (gFOBT)											
2	Observational studies	Not serious	Not serious	Serious[2]	Not serious	Not serious	See Table 27	See Table 27	See Table 27	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; sDNA = stool DNA

[1]Even though there are mixed study designs (case-control & cohort), Imperiale 2014 is a large multicentre high-quality observational study and both studies had similar conclusions

[2]Surrogate outcome for CRC mortality

FIT Versus gFOBT

Systematic Review

One high-quality meta-analysis by Hassan 2012 included five RCTs comparing FIT with gFOBT for detection of colorectal neoplasia and participation to screening (Table 2) [26,38,42,43,46,66]. The main findings were that the detection rate for advanced neoplasia and cancer with FIT was superior to gFOBT in both per protocol (RR, 1.94; 95% CI, 1.37 to 2.76; I^2 = 56%) and ITS analysis (RR, 2.28; 95% CI, 1.68, 3.10; I^2 = 43%) [26]. FIT also resulted in greater participation compared with gFOBT (RR, 1.16; 95% CI, 1.03, 1.3) [26]. The inter-study heterogeneity (I^2) was high at 96%, but decreased to 0% with the removal of the Levi 2011 study [46].

Primary Studies

An additional RCT was found beyond those included in the Hassan 2012 review [36]. Randomization methods were described in detail for all six RCTs and for the most part were regarded as adequate (Tables 30 to 32) [36,38,42,43,46,66]. All studies randomized before consent, except for Chubak 2013 [36]. Colonoscopy was recommended for all people who had a positive fecal test. People with a negative fecal test were not offered follow-up colonoscopy. Meta-analyses that included Chubak 2013 study resulted in similar conclusions to those reported by Hassan 2012 (Table 33, Figures 7 to 9) [26,36]. The detection rate for advanced neoplasia and cancer with FIT was superior to gFOBT in both per protocol (RR, 1.83; 95% CI, 1.30, 2.57; I^2 = 53%) and ITS analyses (RR, 2.15; 95% CI, 1.58 to 2.94; I^2 = 44%). FIT also resulted in a higher uptake compared with gFOBT (RR, 1.16; 95% CI, 1.05 to 1.28). The inter-study heterogeneity (I^2) was high at 95%, but this was decreased to 58% with the removal of the Levi 2011 study, while still maintaining a significant result [46].

Complications due to follow-up colonoscopy were reported in only one study [36]. Within one month of colonoscopy, Chubak 2013 reported that there were no colonoscopy-related deaths or [36]. Across all included studies, there were more false-positive test results with FIT compared with gFOBT (RR, 2.12; 95% CI, 1.02 to 4.39) (Figure 10). As a result, more unnecessary colonoscopies were performed with FIT than gFOBT, although as noted above, the detection rate was higher with FIT.

Two studies reported on technical problems with the fecal-based tests [38,46]. Levi 2011 found technical performance problems in 13 of 4657 FIT kits but none were reported in the gFOBT kits [46]. Federici 2005 found no difference in the proportion of inadequate samples between the FIT and gFOBT groups (RR, 1.91; 95% CI, 0.80 to 4.71) [38].

Table 30. Characteristics of included RCTs – FIT versus gFOBT.

Author/ year	Exclusion	Sample size	# of samples taken	Kit used - restrictions	Cut-off	Age range and follow-up (years)	Ref std	Summary of findings	Country
Chubak 2013[36]	History of CRC, ulcerative colitis, Crohn disease, colostomy, hereditary polyposis; family history of CRC in first-degree	2263 (consent before randomization)	FIT – 1 sample (OC-Auto) or 2 samples (InSure)	OC-Auto FIT (not during menstruation) InSure FIT (not during menstruation)	OC-Auto – 100 ng/cm^3 InSure – 75 ng/cm^3 gFOBT – not reported	50-74; 1	OC-Auto – colonoscopy 15/19 (79%) InSure – colonoscopy 100%	Return of any kit within 6 months of randomization was different between OC-Auto FIT group proportion=0.69	United States

	relative younger than age 60, or serious chronic disease		gFOBT – 3 samples	gFOBT Hemoccult SENSA (diet and medicine restrictions)			gFOBT – colonoscopy 100%	(95% CI, 0.66-0.72) and other 2 group (P<0.001) but not different between InSure FIT proportion=0.64 (95% CI, 0.61-0.68) and Hemoccult SENSA proportion=0.61 (95% CI, 0.58-0.65)	
Levi 2011[46]	(i) Patients who underwent colonoscopy or sigmoidoscopy in the last 5 years. (ii) patients who participated in the gFOBT general screening program in the last 2 years. (iii) patients who had an established CRC or inflammatory bowel disease	FIT n = 4657 vs gFOBT n = 7880	FIT – 3 samples gFOBT – 6 samples	FIT (OC-MICRO) No diet or medicine restrictions gFOBT (Hemoccult SENSA) diet and medicine restrictions	FIT - 70 ng/mL (highest of 3 tubes) gFOBT – 1+ of 6 positive	50–75; 2	Colonoscopy for 70.6% of FIT positives and 71.6% of gFOBT positives or 2-year follow-up	Overall compliance (test performed per invited population) was 25.9% for FIT and 28.8% for gFOBT (p<0.001) Adjusting for age, ses, SES and tax-paying status revealed that FIT detected more neoplasia (included CRC) better than gFOBT (ITS analysis: OR 2.69; 95% CI, 1.59-4.57; p=0.001; per protocol analysis: OR 3.16; 95% CI, 1.8-5.4; p<0.001)	Israel

Hoffman 2010[42]	With previous adenomatous polyps, CRC, or inflammatory bowel disease	FIT n = 202 vs gFOBT n = 202	FIT – 3 samples gFOBT – 2 samples	FIT (OC-Auto fecal immunochemical test), no diet or medicine restrictions; gFOBT (Hemoccult II), diet and medicine restrictions	FIT – 100 ng/mL gFOBT – visually interpreted, number not reported	50-80	Colonoscopy for positives gFOBT for FIT negatives	Overall screening adherence higher for FIT (137/202, 68%) versus gFOBT (112/202, 55%) p=0.01; however, 12 FIT subjects and 13 gFOBT subjects completed non-protocol gFOBT	United States
Hol 2010[43]	History of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years, major health problems, or those who moved away or died	FIT n = 5007 vs gFOBT n = 5004	FIT – 1 sample gFOBT – 3 samples	FIT (OC-Sensor micro) gFOBT (Hemoccult II); no diet or medicine restrictions for either test	FIT – 100 ng/mL gFOBT – 1+ of 6 positive	50–74	Colonoscopy for 96% of FIT positives and 95% of gFOBT positives	After adjusting for age and sex, FIT detected significantly more advanced neoplasia (included CRC) than gFOBT (OR 2.0; 95% CI, 1.3-3.2)	Netherlands
Van Rossum 2008[66]	Institutionalized and symptomatic patients	FIT n = 10,322 vs gFOBT n = 10,301	FIT – 1 sample gFOBT – 6 samples	FIT (OC-Sensor) gFOBT (Hemoccult II); no diet instructions for either test	FIT – 100 ng/mL gFOBT – 1+ of 6 positive	50–75	Colonoscopy for 82.6% of FIT positives and 88% of gFOBT positives	Tests returned by 4836 in gFOBT group and 6157 in FIT group, difference was significant 12.7% (95% CI, 11.3-14.1; p<0.01) Difference in detection rates for advanced neoplasia (included CRC) was higher for	Amsterdam

								FIT than gFOBT ITS analysis: 0.9% (95% CI 0.6-1.1; p<0.01); per protocol analysis 1.2% (95% CI 0.7-1.7)	
Federici 2005[38]	NR	FIT n=3716; gFOBT n=3604	FIT – 1 sample gFOBT – 3 samples	FIT (OC-Hemodia); no diet or medicine restrictions gFOBT (guaiac Hemo-Fec), diet and medicine restrictions	NR	50-74	Colonoscopy for 70.1% of positives	Higher probability of returning FIT test than gFOBT test (RR 1.06; 95% CI 1.02-1.10) Number of cancers and high-grade adenomas was similar between tests FIT=17, gFOBT=15	Italy

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; ITS = intention to screen; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; Ref std = reference standard; RR = relative risk; SES = socioeconomic status; vs = versus

Table 31. Quality of RCTs – FIT versus gFOBT.

Author/year	Randomization details	Sample size and power calculation done	Baseline patient characteristics	ITS analysis	Blinding	Follow-up (years)	Funding
Chubak 2013[36]	Randomization occurred after consent and was stratified by clinic, age, and sex	2263 Yes	Patients in group health plan given survey before randomization	Yes	Yes	1	National Cancer Institute; Polymedco Cancer Diagnostic Products, LLC provided OC-Auto instrument

Levi 2011[46]	Randomization by clinic was based on SES of the primary care clinic (based on proportion of patients who did not have to pay taxes) 1/3 using FIT (one clinic from each SES) and 2/3 using gFOBT (2 clinics from each SES)	12,537 No	Patients from 9 primary care clinics FIT group was younger and had more males than gFOBT group	Yes	Not reported	2	Eiken Chemical Company Japan provided instrument, reagents and partial financial support for administration
Hoffman 2010[42]	A random digit generator was used to assign patients to groups	404 Yes	Primary care patients from the Veterans Affairs electronic health records who were due for CRC screening	No	NR	NR	Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service
Hol 2010[43]	Computer generated algorithm and 1:1:1 randomization; individuals were randomized by postal address after stratifying by age, sex and social economic status	15,011 Yes	Individuals identified from database of 8 municipality offices	No	Second reviewer blinded to initial test results	NR	Dutch Cancer Society, Dutch Ministry of Health, Olympus Medical Systems Europe and Eiken Chemical Company, Japan
Van Rossum 2008[66]	Randomization was by postal address	20,623 Yes	Individuals identified from municipal registries	Yes	Individuals in same household received same test	NR	Netherlands Organization for Health Research and Development
Federici 2005[38]	Four-armed factorial design: 2 test providers (GP/hospital) and 2 tests (FIT/gFOBT)	7320 Yes	Recruited from 130 GP offices near 13 hospitals that were sampled to represent different gastroenterology units and geographic areas Patients screened at GPs office or hospital	No	Individuals in same household received same test	NR	Agency for Public Health, Lazio Region, Rome, Italy and Campus Biomedico, University Hospital, Rome, Italy GPs and patients were paid incentives

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; GP = general practitioner; ITS = intention to screen; NR = not reported; RCT = randomized controlled trial; SES = socioeconomic status

Table 32: GRADE evidence profile – gFOBT versus FIT.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIT	gFOBT	Relative (95% CI)	Absolute		
Complications from tests												
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious			Not pooled		⊕⊕⊕◯ MODERATE	Critical
CRC/advanced adenoma detection rate (ITS)												
5	Randomized trials	Not serious	Not serious	Serious[2]	Not serious	Not serious	278/24,288 (1.1%)	129/27,346 (0.5%)	**RR 2.15** (1.58 - 2.94)	5 more per 1000 (from 3 more - 9 more)	⊕⊕⊕◯ MODERATE	Important
CRC/advanced adenoma detection rate (PP)												
5	Randomized trials	Not serious	Not serious	Serious[2]	Not serious	Not serious	278/12,146 (2.3%)	129/10,976 (1.2%)	**RR 1.83** (1.30 - 2.57)	10 more per 1000 (from 4 more - 18 more)	⊕⊕⊕◯ MODERATE	Important
False-positive screening test results												
5	Randomized trials	Not serious	Serious[3]	Not serious	Not serious	Not serious	385/24,288 (1.6%)	188/27,346 (0.7%)	**RR 2.12** (1.02 - 4.39)	8 more per 1000 (from 0 fewer - 23 more)	⊕⊕⊕◯ MODERATE	Important
Participation rate												
6	Randomized trials	Not serious	Serious [4]	Not serious	Not serious	Not serious	12,271/24,490 (50.1%)	11075/27,548 (40.2%)	**RR 1.16** (1.05 - 1.28)	64 more per 1000 (from 20 more - 113 more)	⊕⊕⊕◯ MODERATE	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; PP = per protocol; RR = relative risk

[1]Only one study

[2]Surrogate outcome for CRC mortality

[3]Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 56.96$, df = 3 ($p<0.00001$); $I^2 = 93\%$

[4]Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 107.18$, df = 5 ($p<0.00001$); $I^2 = 95\%$

Figure 7: Colorectal cancer/advanced adenoma detection rate (intention to screen) – FIT versus gFOBT.

Study or Subgroup	FIT Events	FIT Total	gFOBT Events	gFOBT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Federici 2005	17	3716	15	3604	14.2%	1.10 [0.55, 2.20]	2005
Van Rossum 2008	145	10322	57	10301	32.9%	2.54 [1.87, 3.44]	2008
Hol 2010	73	4843	28	4798	24.9%	2.58 [1.67, 3.99]	2010
Hoffman 2010	0	0	0	0		Not estimable	2010
Levi 2011	35	4657	22	7880	20.0%	2.69 [1.58, 4.58]	2011
Chubak 2013	8	750	7	763	8.0%	1.16 [0.42, 3.19]	2013
Total (95% CI)		**24288**		**27346**	**100.0%**	**2.15 [1.58, 2.94]**	
Total events	278		129				

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 7.13$, df = 4 (P = 0.13); $I^2 = 44\%$

Test for overall effect: Z = 4.82 (P < 0.00001)

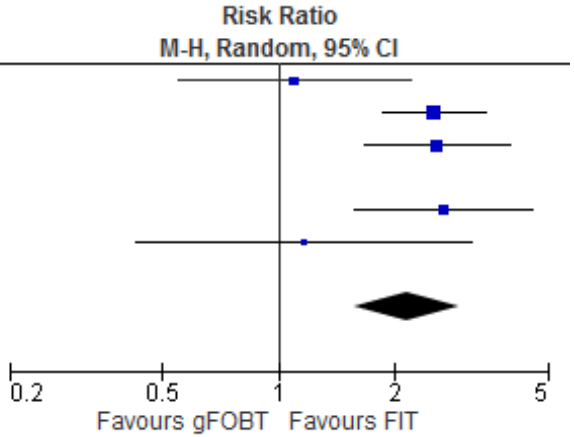


Figure 8: Colorectal cancer/advanced adenoma detection rate (per protocol) – FIT versus gFOBT.

Study or Subgroup	FIT Events	FIT Total	gFOBT Events	gFOBT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Federici 2005	17	1341	15	1096	15.2%	0.93 [0.46, 1.85]	2005
Van Rossum 2008	145	6157	57	4836	30.7%	2.00 [1.47, 2.71]	2008
Hoffman 2010	0	0	0	0		Not estimable	2010
Hol 2010	73	2979	28	2375	24.6%	2.08 [1.35, 3.20]	2010
Levi 2011	35	1224	22	2266	20.5%	2.95 [1.74, 5.00]	2011
Chubak 2013	8	445	7	403	8.9%	1.03 [0.38, 2.83]	2013
Total (95% CI)		**12146**		**10976**	**100.0%**	**1.83 [1.30, 2.57]**	
Total events	278		129				

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.44$, df = 4 (P = 0.08); $I^2 = 53\%$

Test for overall effect: Z = 3.49 (P = 0.0005)

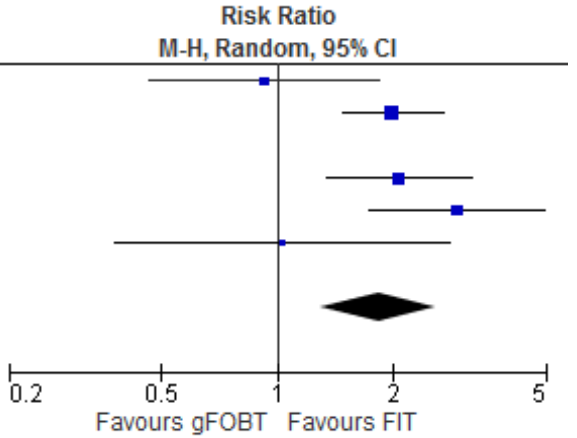


Figure 9: False-positive/total screened test results – FIT versus gFOBT.

Study or Subgroup	FIT Events	FIT Total	gFOBT Events	gFOBT Total	Weight	Risk Ratio M-H, Random, 95% CI
Chubak 2013	13	750	4	763	14.8%	3.31 [1.08, 10.09]
Federici 2005	41	3716	61	3604	21.2%	0.65 [0.44, 0.97]
Hol 2010	64	4843	36	4798	21.1%	1.76 [1.17, 2.64]
Levi 2011	73	4657	41	7880	21.3%	3.01 [2.06, 4.41]
Van Rossum 2008	194	10322	46	10301	21.6%	4.21 [3.06, 5.80]
Total (95% CI)		**24288**		**27346**	**100.0%**	**2.12 [1.02, 4.39]**
Total events	385		188			

Heterogeneity: Tau² = 0.61; Chi² = 56.96, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.02 (P = 0.04)

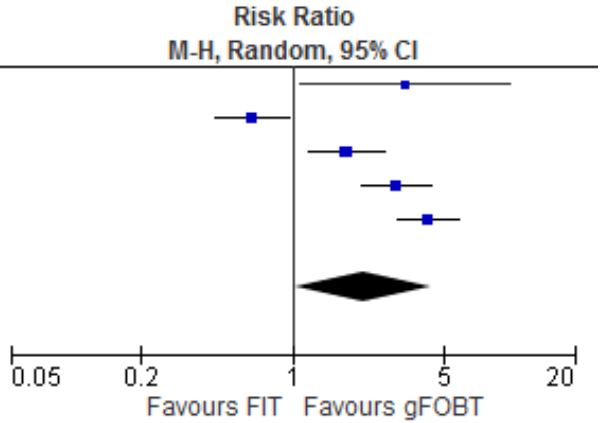
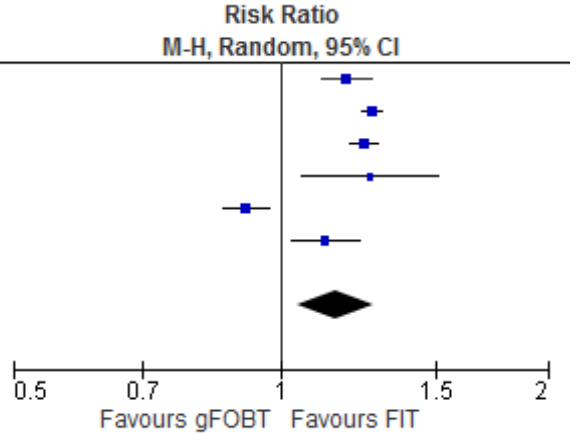


Figure 10: Participation rate –FIT versus gFOBT.

Study or Subgroup	FIT Events	FIT Total	gFOBT Events	gFOBT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Federici 2005	1341	3716	1096	3604	17.4%	1.19 [1.11, 1.27]	2005
Van Rossum 2008	6157	10322	4836	10301	18.5%	1.27 [1.24, 1.30]	2008
Hol 2010	2979	4843	2375	4798	18.3%	1.24 [1.20, 1.29]	2010
Hoffman 2010	125	202	99	202	11.8%	1.26 [1.06, 1.51]	2010
Levi 2011	1224	4657	2266	7880	17.6%	0.91 [0.86, 0.97]	2011
Chubak 2013	445	750	403	763	16.3%	1.12 [1.03, 1.23]	2013
Total (95% CI)		**24490**		**27548**	**100.0%**	**1.16 [1.05, 1.28]**	
Total events	12271		11075				

Heterogeneity: Tau² = 0.01; Chi² = 107.18, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.83 (P = 0.005)



CT Colonograpy Versus Colonoscopy

Only one RCT that randomized patients to screening colonoscopy or CT colonography was found (Tables 33 to 35) [63]. Although the participation rate was significantly better with CT colonography than with colonoscopy (RR, 1.56; 95% CI, 1.46 to 1.68; p<0.0001), colonoscopy detected significantly more advanced neoplasia per 100 subjects than did CT colonography (RR, 1.46; 95% CI, 1.06 to 2.03; p=0·02) [63]. This led to a similar diagnostic yield (number of participants with advanced neoplasia

relative to total number of invitees) (RR, 0.91; 95% CI, 0.66 to 2.03; p=0.56) for both techniques [63]. Serious adverse events included two post-polypectomy bleeds in the colonoscopy group and three in the CT colonography group [63].

Table 33: Characteristics of included RCT – colonoscopy versus CT colonography.

Author/year	Frequency	Sample size	Mean age (range) years	Duration of follow-up (median)	Outcomes	Country	Summary of findings
Stoop 2012[63]	Once	2539	50-75	NR	Participation rate diagnostic yield	Netherlands	• 1276 (22%) of 5924 colonoscopy invitees participated, compared with 982 (34%) of 2920 CT colonography invitees (RR 1.56, 95% CI 1.46–1.68; p<0·0001) • 111 (9%) of participants in the colonoscopy group had advanced neoplasia, of whom 7 (<1%) had a carcinoma. • Of CT colonography participants, 84 (9%) were offered colonoscopy, of whom 60 (6%) had advanced neoplasia and 5 (<1%) had a carcinoma • Diagnostic yield for all advanced neoplasia was 8.7 per 100 participants for colonoscopy vs 6.1 per 100 for CT colonography (RR 1.46, 95% CI 1.06–2.03; p=0.02) and 1.9 per 100 invitees for colonoscopy and 2.1 per 100 invitees for CT colonography (RR 0.91, 95% CI 0.66–2.03; p=0.56) • Diagnostic yield for advanced neoplasia of 10 mm or more was 1.5 per 100 invitees for colonoscopy and 2.0 per 100 invitees for CT colonography, respectively (RR 0.74, 95% CI 0.53–1.03; p=0.07) • Serious adverse events related to the screening procedure were post-polypectomy bleeds: 2 in the colonoscopy group and 3 in the CT colonography group

Abbreviations: CI = confidence interval; CT = computed tomographic; NR = not reported; RCT = randomized controlled trial; RR = relative risk; vs = versus

Table 34: Quality of RCT – colonoscopy versus CT colonography.

Author/year	Randomization details	Sample size and power calculated	Baseline patient characteristics	Intention to screen analysis	Blinding	Follow-up (years)	Funding

Stoop 2012[63]	• Individuals were randomly assigned (2:1) to colonoscopy or CT colonography • Randomization was done before invitation using software • Randomization was done per household • Individuals were stratified for age (50–54, 55–59, 60–64, 65–69, 70–75 years), sex, and socioeconomic status (score 1–5; very low, low, average, high, very high)	Yes	Individuals, not previously invited for screening for colorectal cancer, aged 50-75 years, and of the general Dutch population in the regions of Amsterdam and Rotterdam, were invited for colorectal cancer screening. Individuals were identified with the electronic databases of the regional municipal administration registration.	No	Segmental unblinding of CT colonography findings during colonoscopy for individuals with positive results	NR	Netherlands Organization for Health Research and Development, Centre for Translational Molecular Medicine and the Nuts Ohra Foundation

Abbreviations: CT = computed tomographic; RCT = randomized controlled trial

Table 35: GRADE evidence profile – CT colonography versus colonoscopy.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT colonography	Colonoscopy	Relative (95% CI)	Absolute		
Complications from tests												
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious			Not pooled		⊕⊕⊕◯ MODERATE	Critical
CRC/advanced adenoma detection rate (ITS)												
1	Randomized trial	Not serious	Not serious	Serious[2]	Serious[1]	Not serious	60/2920 (2.1%)	111/5924 (1.9%)	**RR 0.91** (0.66 - 2.03)	2 fewer per 1000 (from 6 fewer to 19 more)	⊕⊕◯◯ LOW	Important

CRC/advanced adenoma detection rate (PP)												
1	Randomized trial	Not serious	Not serious	Serious[2]	Serious[1]	Not serious	60/982 (6.1%)	111/1276 (8.7%)	**RR 1.46** (1.06 - 2.03)	40 more per 1000 (from 5 more to 90 more)	⊕⊕◯◯ LOW	Important
Participation rate												
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious	982/2920 (33.6%)	1276/5924 (21.5%)	**RR 1.56** (1.46 to 1.68)	121 more per 1000 (from 99 more to 146 more)	⊕⊕⊕◯ MODERATE	Important

Abbreviations: CI = confidence interval; CT = computed tomographic; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; PP = per protocol; RR = relative risk
[1]Only 1 study
[2]Surrogate outcome for CRC mortality

Colonoscopy Versus Capsule Colonoscopy

Only one prospective study compared the participation rate of colonoscopy and capsule colonoscopy to the mean annual uptake of colonoscopy in the preceding three years in Germany (Tables 36 to 38) [73].]. The invitation letters used in the study offered both colonoscopy and capsule colonoscopy and found greater uptake when capsule colonoscopy (4.2% versus 1%; p<0.001) was offered than when colonoscopy was (1.6% versus 1%; p=0.075) [73]. The adenoma detection rate was 26.4% (95% CI, 12.9% to 44.4%) for colonoscopy and 9% (95% CI, 4.7% to 18.1%; p=0.013) for capsule colonoscopy [73].

Table 36: Characteristic of included study – Capsule colonoscopy versus colonoscopy.

Author/year	Frequency	Study design	Sample size	Mean age (range) years	Duration of follow- up (median)	Outcomes	Country	Summary of findings
Groth 2012[73]	Once	Prospective cross-sectional ; people older than 55 years of age who have not undergone screening colonoscopy in the preceding 10 years	2150	63.5 (55-70)	NR	Uptake ADR	Germany	• Either capsule or conventional colonoscopy was offered to participants. • Examinations were then performed by 4 local gastroenterologists according to screenees' final choice. • 154 people sought further information, and 34 and 90 underwent conventional and capsule colonoscopy, respectively. • Colonoscopy uptake was increased by invitation

								process by 60% (1.6% vs 1%; p=0.075), while the option of capsule endoscopy led to a fourfold increase of screening uptake (4.2% vs 1%; p<0.001). • The adenoma detection rate with capsule colonoscopy, after verification with colonoscopy for those with positive tests, was 9% (8/90; 95% CI 4.7-18.1) and for the colonoscopy group was (9/34; 26.4%; 95% CI 12.9-44.4) • No adverse events were reported in any of the participants

Abbreviations: ADR = adenoma detection rate; CI = confidence interval; NR = not reported; vs = versus

Table 37: QUADAS evaluation of quality of included study – Capsule colonoscopy versus colonoscopy.

ITEM	Groth 2012[73]
1. Representative spectrum	N
2. Acceptable reference standard	Y
3. Acceptable delay between tests	Y
4. Partial verification avoided	N
5. Differential verification avoided	Y
6. Incorporation avoided	Y
7. Index test results blinded	N
8. Reference test results blinded	N
9. Relevant clinical information	Y
10. Uninterpretable results reported	Y
11. Withdrawals explained	Y

Abbreviations: N = no; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; Y = yes

Table 38: GRADE evidence profile – capsule colonoscopy versus colonoscopy

Quality assessment	# of patients	Effect	Quality	Importance

# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Capsule colonoscopy	Colonoscopy			
Complications from tests											
1	Observation studies	Serious[1]	Not serious	Not serious	Serious[2]	Not serious			See Table 36	⊕◯◯◯ VERY LOW	Important
Adenoma detection rate (PP)											
1	Observation studies	Serious[1]	Not serious	Serious[3]	Serious[2]	Not serious	8/90 (8.9%)	9/34 (26.5%)	See Table 36	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; PP = per protocol
[1]Pathologist not blinded, selection bias, patients given choice between colonoscopy and capsule colonoscopy
[2]Only 1 study
[3]Surrogate outcome for CRC mortality

Stool Versus Endoscopic Test

Systematic Reviews

Three high-quality meta-analyses were found that compared fecal-based tests with endoscopic tests (Table 2) [26,28,29]. The Cochrane review by Holme 2014 used data from trials comparing either gFOBT or FS with no screening in a network meta-analysis [28]. They did not find that one method was better than the other when assessing relative risks comparing FS with gFOBT for CRC mortality (RR, 0.85; 95% CI, 0.72 to 1.01), CRC incidence (RR, 0.85; 95% CI, 0.72 to 1.02) and all-cause mortality (RR, 0.98; 95% CI, 0.95 to 1.00) [28]. The level of evidence was believed to be low because the tests were not directly compared in a trial [28].

The other two meta-analyses combined trials that randomized patients to either fecal-based tests or endoscopic tests. None of the included trials used mortality as an outcome [26,29]. While most of the included studies in these meta-analyses overlapped, some of the studies were included in one review, but not another [35,37,48], and there were important differences in study methodology. Hassan 2012 included trials that compared endoscopy (colonoscopy or FS) with either gFOBT or FIT; CRC was included in the definition of advanced neoplasia when reporting outcomes [26]. Littlejohn 2012 included trials that compared FS (including those combined with fecal occult blood testing) with either gFOBT or FIT; advanced neoplasia was reported separately from CRC [29]. Despite these differences, the two meta-analyses arrived at similar conclusions: 1) screening uptake was higher

with a fecal-based test than with an endoscopic test, and 2) detection of neoplasia was higher with an endoscopic test than a fecal-based test.

Primary Studies

Only one additional RCT was found in addition to the RCTs included in the reviews above; which was available in abstract form only [68]. The risk of bias of the RCTs was summarized in these reviews and included variability in the randomization methods such as cluster randomization and cross-over, or provided insufficient information to assess bias (Tables 39 to 45) [26,28,29,34,35,37,39,43,48,52,54,55,59,61,67,68]. Some studies described methods of blinding the participants, physicians or pathologists, but many did not report details of blinding. There was also variation in the way that a positive FS was defined across studies [29].

Because there are important differences among the evaluated fecal tests and among the evaluated endoscopic tests, studies were re-grouped to separate those evaluating FIT from gFOBT and those evaluating FS from colonoscopy. Where there were two or more similar comparisons, the combined data were analyzed for the outcomes of interest (Table 46, Figures 11 to 19).

Participation: When combining studies that compared FIT with colonoscopy using an ITS analysis, FIT had a higher participation rate than colonoscopy. There was considerable heterogeneity, which was reduced when either the Segnan 2007 or Quintero 2012 studies were removed, while still maintaining significant and similar results [52,61]. It is unclear why removal of these studies reduced the heterogeneity. All other comparisons (gFOBT versus colonoscopy, FIT versus FS, gFOBT versus FS, gFOBT+FS versus FS) were not significant for participation rate.

Detection: Interventions that included endoscopy had higher detection rates for advanced neoplasia (including CRC) compared with interventions that did not include endoscopy (FIT versus colonoscopy; FIT versus FS; gFOBT versus FS; gFOBT versus gFOBT+FS). Again, there was important heterogeneity for the comparison between FIT and colonoscopy, which was reduced when either the Segnan 2007 or Quintero 2012 trials were removed, while still maintaining significant and similar results [52,61]. Similar issues with heterogeneity were observed for FIT versus FS, but this was reduced, while still maintaining a significant and similar result, when both Segnan 2005 and 2007 trials were included and the Hol 2010 trial was removed [43,59,61]. While the results from many of the comparisons were heterogeneous, the direction of the significant results was consistent with the Hassan 2012 and Littlejohn 2012 meta-analyses; in other words, the uptake was higher with fecal-based tests but the detection rate was lower with fecal-based tests compared with endoscopic tests [26,29].

Adverse events: The adverse effects of fecal-based tests or endoscopy tests were reported poorly. Of the 13 primary studies included, eight did not report complication rates for each arm in their study [34,35,37,39,59,61,67,68]. Two RCTs reported that no serious complications occurred [52,55]. Serious complications included bleeding and perforation for the Multicenter Australian Colorectal-Neoplasia Screening (MACS) Group 2006 study, but was not defined in the Rasmussen 1999 study [52,55]. Lisi 2010 reported one vagal reaction in the gFOBT group and one bleed without the need for surgery in the colonoscopy group [48]. Quintero 2012 found the complication rate (including bleeding and perforation) was higher in the colonoscopy group than the FIT group (odds ratio [OR], 4.81; 95% CI, 2.26 to 10.20; $p<0.001$) [54]. Hol 2010 found one complication after 1386 FS and four minimal bleeds among 142 patients referred for colonoscopy [43].

Table 39. Characteristics of included RCTs - stool versus endoscopic tests.

Author/year	Comparison	Frequency		Patient population	Country of study	Summary of findings
Quintero 2012[54]	FIT (OC-Sensor) vs colonoscopy	FIT – Biennial (but only first round reported) Colonoscopy-once		Asymptomatic adults 50 - 69 years	Spain	• This is an interim report • The rate of participation was higher in the FIT group than in the colonoscopy group (34.2% vs 24.6%; p<0.001) – this included all those who completed FIT or colonoscopy in either group • Colorectal cancer was found in 30 subjects (0.1%) in the colonoscopy group and 33 subjects (0.1%) in the FIT group (OR, 0.99; 95% CI, 0.61 to 1.64; p=0.99). • Advanced adenomas were detected in 514 subjects (1.9%) in the colonoscopy group and 231 subjects (0.9%) in the FIT group (OR, 2.30; 95% CI, 1.97 - 2.69; p<0.001). • Nonadvanced adenomas were detected in 1109 subjects (4.2%) in the colonoscopy group and 119 subjects (0.4%) in the FIT group (OR, 9.80; 95% CI, 8.10 - 11.85; p<0.001).
Zauber 2012[68] (abstract)	gFOBT vs colonoscopy	gFOBT -3 rounds (annual) colonoscopy - once		Asymptomatic men and women age 50-69	United States	• Those in the gFOBT arm that crossed over to screening colonoscopy with either negative gFOBTs or no gFOBTS were considered non-adherent to the program of gFOBT. • Of 1761 randomized to a single screening colonoscopy, 1516 (86%) were adherent, which was significantly higher than that obtained in the program of gFOBT (RR, 2.1; 95% CI 2.0-2.2; p<0.0001). • Crossover to colonoscopy occurred in 388 (22%) without a positive gFOBT.
Lisi 2010[48]	gFOBT (Hemoccult SENSA) vs colonoscopy	Once		Average-risk people, aged 55–64 years	Italy	• Participation rate was higher in the gFOBT (1149/4245 subjects, 27.1%) than in the colonoscopy (414/4133 subjects, 10%) group (p<0.0001) • Participation in colonoscopy screening arm was extremely low in South Italy

						(2.8%), while it was higher in North-Central Italy (12.4%; p<0.0001). • Compliance to colonoscopy in those with a positive gFOBT was only 58%. • Advanced neoplasia (included CRC) was detected in 28 (6.8%) patients in the colonoscopy arm and in 6 (18%) in those with a positive gFOBT submitted to colonoscopy.
Hol 2010[43]	FIT (OC-Sensor Micro) vs gFOBT (Hemoccult II) vs FS (Olympus Europe)	Once		Average-risk people, aged 50–74 years	Netherlands	• The participation rate was o FIT: 61.5% (95% CI, 60.1 - 62.9%) o gFOBT: 49.5% (95% CI, 48.1 - 50.9%) o FS: 32.4% (95% CI, 31.1 - 33.7%) • gFOBT was positive in 2.8%, FIT in 4.8% and FS in 10.2%. • The detection rate for advanced neoplasia was significantly higher in the FIT (2.4%; OR, 2.0; 95% CI, 1.3 - 3.1) and the FS arm (8.0%; OR, 7.0; 95% CI, 4.6 - 10.7) than the gFOBT arm (1.1%). • FS demonstrated a higher diagnostic yield of advanced neoplasia per 100 invitees (2.4; 95% CI, 2.0 - 2.8) than gFOBT (0.6; 95% CI, 0.4 - 0.8) or FIT (1.5; 95% CI, 1.2 - 1.9) screening.
Segnan 2007[61]	FIT (Immudia-HemSp) vs FS vs colonoscopy	FIT – biennial (but only 1 round reported) FS- once colonoscopy-once		Average-risk people, aged 55–64 years	Italy	• The attendance rate was 32.3% (1965/6075) for FIT, 32.3% (1944/6018) for FS, 26.5% (1597/6021) for colonoscopy. • After adjusting for screening centre, age, and sex, proportion of attendees in colonoscopy arm was lower compared with FS arm (OR, 0.74; 95% CI, 0.68 - 0.80) P<0.05, but similar between FIT can FS arms (OR, 1.01; 95% CI, 0.94 - 1.09) • FIT detected 2 patients with CRC (0.1%) and 21 with an advanced adenoma (1.1%). FS detected 12 patients with CRC (0.6%) and 86 (4.5%) patients an advanced adenoma, colonoscopy detected 13 patients with CRC (0.8%)

						and 100 (6.3%) patients an advanced adenoma • After adjusting by age, sex, and screening centre, screening with colonoscopy resulted in a 42% increase (OR, 1.42; 95% CI, 1.08 - 1.88) in the detection rate of advanced neoplasia (included CRC) compared with FS, P<0.05. FIT resulted in a lower detection rate of advanced neoplasia compared with FS (OR, 0.22; 95% CI, 0.14 to 0.35)
Federici 2006[37]	gFOBT (NR) vs FS	Once		Healthy 50–74-year-old subjects	Italy	• Higher participation for gFOBT than FS (RR, 2.5; 95% CI, 1.8 - 3.6) • The fecal occult blood test obtained higher compliance: 17.2% (95% CI, 12.5 - 25.7) vs 7.0% (95% CI, 5.7 - 9.0). • The detection rate for combined high-grade adenoma and CRC was 0.8% and 1.9% for gFOBT and FS, respectively
Multicenter Australian Colorectal-Neoplasia Screening (MACS) Group 2006[52]	FIT (!nform, Enterix, Sydney NSW) vs FIT + FS vs CTC vs colonoscopy	Once		People aged 50-54 or 65-69 years, randomly selected from the electoral roll	Australia	• Participation was similar by age and sex, but lower in Perth than Adelaide (17.1% vs 24.2%; p=0.01). • Participation by screening group was: FIT, 27.4%; FIT/FS, 13.7% (p<0.001 compared with FIT); CTC, 16.3% (p=0.005); colonoscopy, 17.8% (p=0.02); or a choice of test 18.6% ("with FIT kit"; p=0.03) or 22.7% ("without FIT kit"; p=0.3). • Yield of advanced colorectal neoplasia was higher in participants screened by colonoscopy than FIT (7.9% vs 0.8%; p=0.02).
Segnan 2005[59]	FIT (Immudia-HemSp without dietary restrictions) vs FS	Only 1 round reported in all biennial groups 1) biennial FIT sent by mail; 2) biennial FIT delivered by general practitioner or		Aged 55 – 64 years from general practices from 5 Italian study centres	Italy	• The participation rates for groups 1, 2, 3, 4, and 5 were 30.1% (682/2266), 28.1% (1654/5893), 27.1% (970/3579), 28.1% (1026/3650), and 28.1% (3049/10,867), respectively. • The difference in participation rate between FIT (2336/8159, 28.6%) and FS (4075/14517, 28.1%) was not significant

		screening facility (primary care or outpatient clinics); 3) patient's choice of FIT or "once-only" sigmoidoscopy; 4) "once-only" sigmoidoscopy; or 5) sigmoidoscopy followed by biennial FIT beginning 2 years after a sigmoidoscopy with negative findings (only sigmoidoscopy results reported)				• Detection rate for advanced adenomas (excluding CRC and adjusted by age, sex, and screening centre) was higher for FS than FIT (OR, 3.58; 95% CI, 2.49 - 5.14) • Adjusted CRC detection rate was similar for FS as it was for FIT (OR, 0.99; 95% CI, 0.41 - 2.36)
Gondal 2003[39]	FIT (FlexSure OBT) vs FS + FIT	Once		Aged 50-64 years	Norway	• Attendance rate higher in FS group (67%) than in FS+FIT group (63%, p<0.01) • Detection of high-risk adenomas or CRC was not different between FS (2.8%, 0.2%) and FIT (2.6%, 0.2%)
Rasmussen 1999[55]	gFOBT (Hemoccult-II without dietary restrictions or rehydration) vs FS+gFOBT	Once		Aged 50–75 years	Denmark	• Despite lower compliance (40% versus 56%) for the combined procedure (P<0.0001), the diagnostic yield of colorectal neoplasia was higher for combined than for gFOBT alone (12 CRC versus 4 CRC, and 72 large adenomas versus 14)
Verne 1998[67]	gFOBT (Haemoccult without rehydration) vs FS vs gFOBT+FS	Once		Age range (50-75 years) subjects ineligible for the study because of a previous	United Kingdom	• Uptake was significantly higher in the FS group (46.6%) than in the fecal blood test group (31.6%; p<0.001) or than in the group having both tests (30.1%; p<0.001). • The fecal blood test yielded positive results in 0.8% (0.2% to 1.4%) but missed at least 1 cancer and 30 cases of

				diagnosis of colorectal neoplasia, investigation of the colon and rectum within the previous 2 years, and physical or mental disease contraindicating screening		adenoma that were found by sigmoidoscopy in the combined group.
Berry 1997[34]	gFOBT (Haemoccult without dietary restrictions or rehydration) vs FS + gFOBT	Once		Asymptomatic individuals aged 50-74 years from 2 general practices	United Kingdom	• Compliance with gFOBT testing alone was 50%. • In the gFOBT/FS group, 48% returned the gFOBT test but only 20% went on to FS. • The neoplasia yield was 4 times greater in the gFOBT/FS group, gFOBT detected 2.0 patients with significant neoplasia (included CRC) per 1000 screened and gFOBT/FS detected 8.9 patients with significant neoplasia (included CRC) per 1000 screened
Brevinge 1997[35]	gFOBT (Hemoccult II) vs FS	Once		Aged 55-56 years	Sweden	• Participation rate higher in gFOBT group compared with FS for cohorts born in 1938 (61% vs 39%, p<0.001) and in 1941 (55% vs 49%, p<0.01)

Abbreviations: CI = confidence interval; CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; vs = versus

Table 40. Quality of RCTs - stool versus endoscopic test.

Author/year	Randomization details	Sample size and power calculated	Baseline patient characteristics	ITS analysis	Blinding	Follow-up (years)	Funding
Quintero 2012[54]	• Subjects sorted according to household, and stratified according to age and sex.	57,404 Yes (non-inferiority)	Asymptomatic men and women between the ages of 50 and 69 years No difference in age or sex between groups	Yes	NR	NR	• Grants from Asociación Española contra el Cáncer, Instituto de Salud Carlos III, FEDER funds, and Agència de Gestió d'Ajuts Universitaris i de Recerca. Centro de

	• Households were randomly assigned in a 1:1 ratio to undergo either colonoscopy or FIT. • Randomization was performed before invitation with the use of a computer-generated algorithm on the basis of a randomized blocks method. • The study design allowed for crossover between the 2 study groups.						Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas is funded by Instituto de Salud Carlos III. • Additional grants from Obra Social de Kutxa, Diputación Foral de Gipuzkoa, Departamento de Sanidad del Gobierno Vasco, EITB-Maratoia, and Acción Transversal contra el Cáncer del CIBERehd. • Supported by Dirección Xeral de Innovación e Xestión da Saúde Pública, Conselleria de Sanidade, and Xunta de Galicia. Eiken Chemical of Japan and its Spanish representatives, Palex Medical and Biogen Diagnóstica, donated supplies and automated analyzers used for FIT.
Zauber 2012[68] (Abstract)	The study design allowed for crossover between the 2 study groups.	3526 NR	Asymptomatic men and women aged 50-69; groups had equivalent facilitation, including coverage of costs, navigation and available medical resources	NR	NR	NR	NR
Lisi 2010[48]	In each centre, GPs were cluster randomized in a 1:1 ratio between the 2 screening options (gFOBT vs colonoscopy); all eligible subjects within the list of each GP were offered only 1 of the 2 tests (colonoscopy or	9339 Yes	Population-based multicentre, cluster RCT involving 14 reference GI centres located throughout Italy	NR	NR	NR	The Italian League against Cancer and by PROMESAN for providing Hemoccult SENSA

	gFOBT) according to the cluster randomization arm of their GP						
Hol 2010[43]	Computer-generated algorithm and 1:1:1 randomization; individuals were randomized by postal address after stratifying by age, sex, and SES	15,011 Yes	Individuals identified from databases of 8 municipality offices	No	Second reviewer blinded to initial test results	NR	Dutch Cancer Society, Dutch Ministry of Health, Olympus Medical Systems Europe and Eiken Chemical Company, Japan
Segnan 2007[61]	Eligible people were randomized within GP to the 3 screening protocols (ratio 1:1:1) using a computer-generated algorithm based on randomized blocks scheme; patients were randomized on an individual basis, but the algorithm assigned spouses to the same arm.	18,447 Yes	Men and women, aged 55 - 64 years	NR	NR	NR	Italian League against Cancer and by the Istituto Oncologico Romagnolo, the Fondo "E Tempia," the University of Milan, the ULSS 20, and the Piedmont Regional Health Authority for implementation of the study; SOFAR s.p.a. provided the enemas for the bowel preparation.
Federici 2006[37]	Each doctor's practice was centrally randomized to 1 of the 2 tests offered by random number generator.	2987 Yes	Healthy 50–74-year-old subjects	NR	NR	NR	Ravizza Farmaceutici
Multicenter Australian Colorectal-neoplasia Screening (MACS) Group 2006[52]	Used random number generation after stratifying by sex, age group, and SES	1679 yes	Two age groups (50-54 years, 65-69 years), asymptomatic, average risk for CRC	NR	Participants blinded to knowledge of other potential screening groups	NR	Cancer Councils of Western Australia and South Australia, and Melbourne Health

Segnan 2005[59]	• Randomization was performed in each centre, which used a computer-generated algorithm, with an allocation ratio of 2 subjects (arm 1): 5 subjects (arm 2): 3 subjects (arm 3): 3 subjects (arm 4): 9 subjects (arm 5) • The allocation ratios were based on 2 criteria: the expected detection rates of advanced adenomas and cancers among people undergoing a FIT after negative results of an FS (arm 5) or among people allocated to FS or FIT arms; the magnitude of differences in screening participation among different arms • Algorithm assigned spouses to the same arm	22,676 yes	Aged 55 – 64 years; excluded patients who were unable to give informed consent, who had been diagnosed with a terminal illness or inflammatory bowel disease, who had a history of polyps or colorectal cancer or 2 first-degree relatives with colorectal cancer, or who had undergone a colorectal endoscopy or an FIT within the previous 2 years	NR	All colorectal cancer samples and an equal-sized sample of adenomas with high-grade dysplasia were reviewed by 1 pathologist in a blinded fashion	6 years for patients with high-risk adenomas	Italian Association for Cancer Research; the Istituto Oncologico Romagnolo, the Fondo " E Tempia, " the University of Milan and the Piedmont Regional Health Authority
Gondal 2003[39]	Randomized (1:1) to once-only FS or a combination of FS and FIT	20,780 No	Excluded patients with previous open colorectal surgery, ongoing cytotoxic or radiation therapy for malignant disease, severe chronic cardiopulmonary disease, life-long	Yes	NR	NA	Norwegian Cancer Society and the Ministry of Health and Social Affairs

			anticoagulant therapy, a coronary episode or cerebrovascular accident during the previous 3 months, disabled, inability to give written informed consent, resident abroad, unknown address or deceased				
Rasmussen 1999[55]	Central randomization adjusting for married couples, who were always allocated to the same group; the sample was chosen at random but represented the age and sex distribution of the county	10,978 Yes	Aged 50–75 years Excluding individuals with known CRC and adenoma and distant spread from any type of malignant disorder	NR	Physician performing the FS was unaware of the gFOBT results	24-62 months	Danish Cancer Society, the county of Funen and the University of Odense
Verne 1998[67]	Households were randomized by using the random number generator and invited by post to undergo FS, gFOBT or gFOBT+FS	3744 Yes	Subjects from 1 general practice	NR	NR	NR	Smith-Kline-Beecham donated the flexible sigmoidoscopes
Berry 1997[34]	Randomized by household using standard random number tables into 2 groups	6371 No	Asymptomatic individuals aged 50-74 years from 2 general practices excluding unsuitable subjects, e.g., people with proven colorectal neoplasia, patients under investigation for abdominal symptoms, people with other advanced disease	NR	NR	NR	NR
Brevinge 1997[35]	NR	3183 gFOBT and 1071 (without gFOBT) FS no	All subjects of Goteborg born in 1938 and first half of 1941	NR	NR	NR	Swedish foundations

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GI = gastroenterology; GP = general practitioner; ITS = intention to screen; NR = not reported; RCT = randomized controlled trial; SES = socioeconomic status; vs = versus

Table 41: GRADE evidence profile – one-time FIT versus colonoscopy.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIT	Colonoscopy	Relative (95% CI)	Absolute		
Complications with tests												
2	Randomized trials	Not serious	Serious[1]	Serious[2]	Not serious	Not serious			Not pooled		⊕⊕◯◯ LOW	Critical
CRC/advanced adenoma detection rate (ITS)												
3	Randomized trials	Not serious	Serious[3]	Serious[4]	Not serious	Not serious	288/32,908 (0.9%)	662/32,938 (2.0%)	**RR 0.30** (0.14 to 0.67)	14 fewer per 1000 (from 7 fewer to 17 fewer)	⊕⊕◯◯ LOW	Important
Participation rate												
3	Randomized trials	Not serious	Serious[5]	Serious[2]	Not serious	Not serious	11,012/32,908 (33.5%)	6588/32,938 (20.0%)	**RR 1.50** (1.08 to 2.10)	100 more per 1000 (from 16 more to 220 more)	⊕⊕◯◯ LOW	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; RR = relative risk
[1]Different results across studies
[2]Compared only one-time FIT
[3]Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 14.28$, df = 2 (p=0.0008); $I^2 = 86\%$
[4]Compared only one-time FIT; surrogate outcome for CRC mortality
[5]Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 154.54$, df = 2 (p<0.00001); $I^2 = 99\%$

Table 42: GRADE evidence profile – one-time FIT versus FS.

Quality assessment	# of patients	Effect	Quality	Importance

# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIT	FS	Relative (95% CI)	Absolute		
Complications from tests												
1	Randomized trials	Not serious	Not serious	Serious[1]	Serious[2]	Not serious			Not pooled		⊕⊕◯◯ LOW	Critical
CRC/advanced adenoma detection rate (ITS)												
3	Randomized trials	Not serious	Serious[3]	Serious[4]	Not serious	Not serious	139/19077 (0.7%)	438/25235 (1.7%)	**RR 0.37** (0.21 to 0.67)	11 fewer per 1000 (from 6 fewer to 14 fewer)	⊕⊕◯◯ LOW	Important
Participation rate												
3	Randomized trials	Not serious	Serious[5]	Serious[1]	Not serious	Not serious	7280/19077 (38.2%)	7541/25245 (29.9%)	**RR 1.25** (0.82 to 1.89)	75 more per 1000 (from 54 fewer to 266 more)	⊕⊕◯◯ LOW	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; RR = relative risk
[1]Compared only one-time FIT
[2]Only 1 study
[3]Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 16.87$, df = 2 (p=0.0002); $I^2 = 88\%$
[4]Compared only one-time FIT; surrogate outcome for CRC mortality
[5]Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 463.75$, df = 2 (p<0.00001); $I^2 = 100\%$

Table 43: GRADE evidence profile – one-time gFOBT versus colonoscopy.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gFOBT	Colonoscopy	Relative (95% CI)	Absolute		
Complications from tests												

1	Randomized trial	Not serious	Not serious	Serious[1]	Serious[2]	Not serious			Not pooled		⊕⊕◯◯ LOW	Critical
Participation rate												
2	Randomized trials	Not serious	Serious[3]	Serious[1]	Not serious	Not serious	1871/6010 (31.1%)	1930/5894 (32.7%)	**RR 1.13** (0.18 to 6.96)	43 more per 1000 (from 269 fewer to 1952 more)	⊕⊕◯◯ LOW	Important

Abbreviations: CI = confidence interval; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; RR = relative risk
[1]Compared only one-time gFOBT
[2]Only one study
[3]Heterogeneity: $Tau^2 = 1.71$; $Chi^2 = 922.55$, df = 1 ($p<0.00001$); $I^2 = 100\%$

Table 44: GRADE evidence profile – one-time gFOBT versus FS.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gFOBT	FS	Relative (95% CI)	Absolute		
Complications from tests												
1	Randomized trials	Not serious	Not serious	Serious[1]	Serious[2]	Not serious			Not pooled		⊕⊕◯◯ LOW	Critical
CRC/Advanced adenoma detection rate (ITS)												
2	Randomized trials	Not serious	Not serious	Serious[3]	Serious[4]	Not serious	30/6247 (0.5%)	114/6238 (1.8%)	**RR 0.29** (0.14 to 0.59)	13 fewer per 1000 (from 7 fewer to 16 fewer)	⊕⊕◯◯ LOW	Important
Participation rate												
4	Randomized trials	Not serious	Serious[5]	Serious[1]	Not serious	Not serious	4910/10,675 (34.2%)	2740/8558 (31.9%)	**RR 1.31** (0.91 to 1.89)	99 more per 1000 (from 29 fewer to 285 more)	⊕⊕◯◯ LOW	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; RR = relative risk
[1]Compared only one-time gFOBT
[2]Only one study
[3]Compared only one-time gFOBT; surrogate outcome for CRC mortality
[4]Few events
[5]Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 238.42$, df = 3 ($p<0.00001$); $I^2 = 99\%$

Table 45: GRADE evidence profile – one-time gFOBT versus gFOBT+FS.

Quality assessment							# of patients		Effect		Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gFOBT	gFOBT+FS	Relative (95% CI)	Absolute		
Complications from tests												
1	Randomized trials	Not serious	Not serious	Serious[1]	Serious[2]	Not serious			Not pooled		⊕⊕◯◯ LOW	Critical
CRC/advanced adenoma detection rate (ITS)												
2	Randomized trials	Not serious	Not serious	Serious[3]	Serious[4]	Not serious	24/8611 (0.3%)	113/8738 (1.3%)	**RR 0.21** (0.14 to 0.33)	10 fewer per 1000 (from 9 fewer to 11 fewer)	⊕⊕◯◯ LOW	Important
Participation rate												
3	Randomized trials	Not serious	Serious[5]	Serious[1]	Not serious	Not serious	5012/9856 (50.9)%	3247/9988 (32.5)%	**RR 1.54** (0.98 to 2.40)	176 more per 1000 (from 7 fewer to 455 more)	⊕⊕◯◯ LOW	Important

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ITS = intention to screen; RR = relative risk
[1]Compared only one-time gFOBT
[2]Only 1 study
[3]Compared only one-time gFOBT; surrogate outcome for CRC mortality
[4]Few events
[5]Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 223.97$, df = 2 ($p<0.00001$); $I^2 = 99\%$

Table 46. Outcome data from included RCTs - stool versus endoscopic tests.

	# recruited		# of advanced adenoma/cancer detected		# participated	
Test / Author/year	FIT	Colonoscopy	FIT	Colonoscopy	FIT	Colonoscopy
Quintero 2012[54]	26,599	26,703	264	544	8983	4953
Segnan 2007[61]	6075	6021	23	113	1965	1597
MACS 2006[52]	234	214	1	5	64	38
	gFOBT	Colonoscopy	gFOBT	Colonoscopy	gFOBT	Colonoscopy
Zauber 2012[68] (Abstract)	1765	1761	NR	NR	722	1516
Lisi 2010[48]	4245	4133	6	28	1149	414
	FIT	FS	FIT	FS	FIT	FS
Hol 2010[43]	4843	4700	73	111	2979	1522
Segnan 2007[61]	6075	6018	23	100	1965	1944
Segnan 2005[59]	8159	14,517	43	227	2336	4075
	gFOBT	FS	gFOBT	FS	gFOBT	FS
Hol 2010[43]	4798	4700	28	111	2375	1522
Federici 2006[37]	1449	1538	2	3	249	108
Verne 1998[67]	1245	1249	NA	NA	393	582
Brevinge 1997[35]	3183	1071	NR	NR	1893	528
	FIT	CTC	FIT	CTC	FIT	CTC
MACS 2006[52]	234	215	1	1	64	35
	gFOBT	gFOBT + FS	gFOBT	gFOBT + FS	gFOBT	gFOBT + FS
Rasmussen 1999[55]	5483	5495	18	84	3055	2222
Verne 1998[67]	1245	1250	NA	NA	393	376
Berry 1997[34]	3128	3243	6	29	1564	649
	FIT	FIT + FS	FIT	FIT + FS	FIT	FIT + FS
MACS 2006[52]	234	224	1	0	64	31
	FS	gFOBT + FS	FS	gFOBT + FS	FS	gFOBT + FS
Verne 1998[67]	1249	1250	NA	NA	582	376
	FS	FIT + FS	FS	FIT + FS	FS	FIT + FS
Gondal 2003[39]	10013	9990	308	278	6694	6266
	CTC	FIT + FS	CTC	FIT + FS	CTC	FIT + FS
MACS 2006[52]	215	224	1	0	35	31

	Colonoscopy	FIT + FS	Colonoscopy	FIT + FS	Colonoscopy	FIT + FS
MACS 2006[52]	214	224	5	0	38	31
	FS	Colonoscopy	FS	Colonoscopy	FS	Colonoscopy
Segnan 2007[61]	6018	6021	100	113	1944	1597
	CTC	Colonoscopy	CTC	Colonoscopy	CTC	Colonoscopy
MACS 2006[52]	215	214	1	5	35	38

Abbreviations: CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; MACS = Multicenter Australian Colorectal-neoplasia Screening Group; RCT = randomized controlled trial

Figure 11. FIT versus colonoscopy – advanced neoplasia (intention to screen).

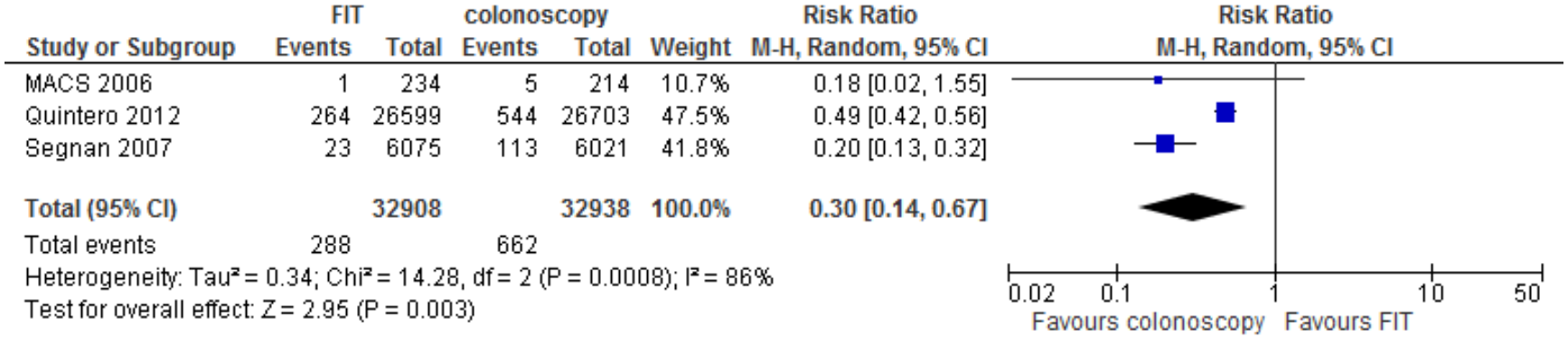


Figure 12. FIT versus colonoscopy – participation rate.

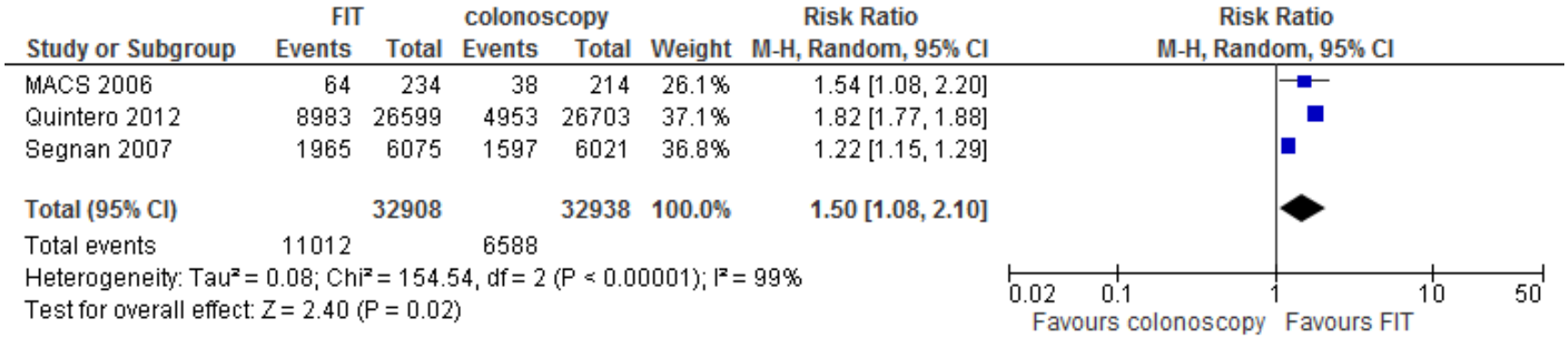


Figure 13. FIT versus FS – advanced neoplasia (intention to screen).

Study or Subgroup	FIT Events	FIT Total	FS Events	FS Total	Weight	Risk Ratio M-H, Random, 95% CI
Hol 2010	73	4843	111	4700	34.8%	0.64 [0.48, 0.86]
Segnan 2005	43	8159	227	14517	34.1%	0.34 [0.24, 0.47]
Segnan 2007	23	6075	100	6018	31.1%	0.23 [0.15, 0.36]
Total (95% CI)		**19077**		**25235**	**100.0%**	**0.37 [0.21, 0.67]**
Total events	139		438			

Heterogeneity: Tau² = 0.24; Chi² = 16.87, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 3.30 (P = 0.0010)

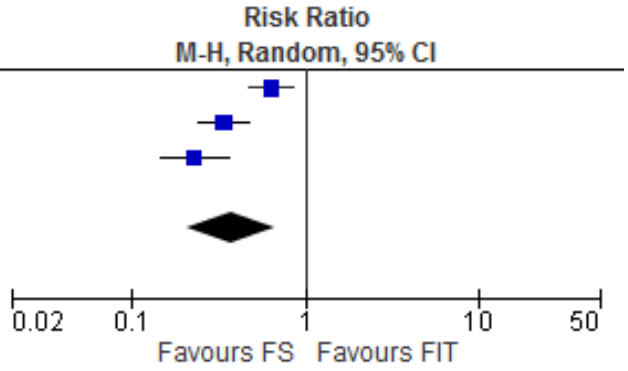


Figure 14. FIT versus FS – participation rate.

Study or Subgroup	FIT Events	FIT Total	FS Events	FS Total	Weight	Risk Ratio M-H, Random, 95% CI
Hol 2010	2979	4843	1522	4700	33.3%	1.90 [1.81, 1.99]
Segnan 2005	2336	8159	4075	14517	33.4%	1.02 [0.98, 1.06]
Segnan 2007	1965	6075	1944	6018	33.3%	1.00 [0.95, 1.05]
Total (95% CI)		**19077**		**25235**	**100.0%**	**1.25 [0.82, 1.89]**
Total events	7280		7541			

Heterogeneity: Tau² = 0.13; Chi² = 463.75, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.05 (P = 0.30)

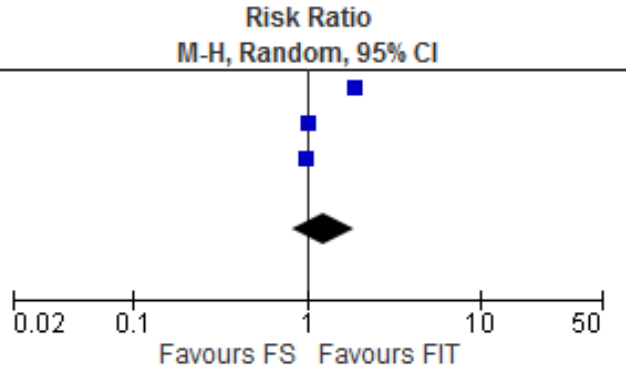


Figure 15. gFOBT versus colonoscopy – participation rate.

Study or Subgroup	gFOBT Events	gFOBT Total	colonoscopy Events	colonoscopy Total	Weight	Risk Ratio M-H, Random, 95% CI
Lisi 2010	1149	4245	414	4133	50.0%	2.70 [2.44, 3.00]
Zauber 2012	722	1765	1516	1761	50.0%	0.48 [0.45, 0.50]
Total (95% CI)		**6010**		**5894**	**100.0%**	**1.13 [0.18, 6.96]**
Total events	1871		1930			

Heterogeneity: Tau² = 1.71; Chi² = 922.55, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.13 (P = 0.89)

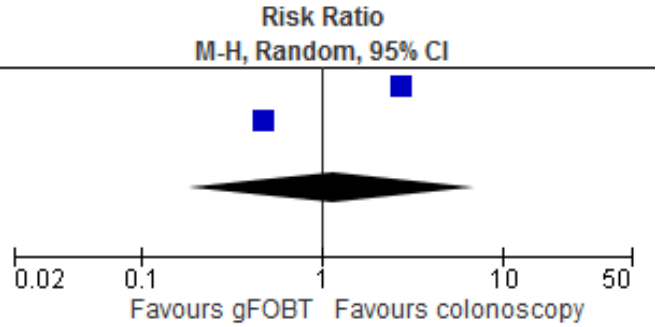


Figure 16. gFOBT versus FS – advanced neoplasia (intention to screen).

Study or Subgroup	gFOBT Events	gFOBT Total	FS Events	FS Total	Weight	Risk Ratio M-H, Random, 95% CI
Federici 2006	2	1449	3	1538	14.5%	0.71 [0.12, 4.23]
Hol 2010	28	4798	111	4700	85.5%	0.25 [0.16, 0.37]
Total (95% CI)		**6247**		**6238**	**100.0%**	**0.29 [0.14, 0.59]**
Total events	30		114			

Heterogeneity: Tau² = 0.12; Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 3.37 (P = 0.0008)

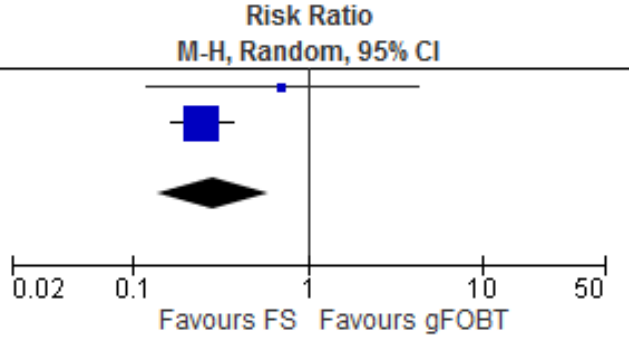


Figure 17. gFOBT versus FS – participation rate.

Study or Subgroup	gFOBT Events	gFOBT Total	FS Events	FS Total	Weight	Risk Ratio M-H, Random, 95% CI
Brevinge 1997	1893	3183	528	1071	25.5%	1.21 [1.13, 1.29]
Federici 2006	249	1449	108	1538	23.7%	2.45 [1.98, 3.03]
Hol 2010	2375	4798	1522	4700	25.6%	1.53 [1.45, 1.61]
Verne 1998	393	1245	582	1249	25.2%	0.68 [0.61, 0.75]
Total (95% CI)		**10675**		**8558**	**100.0%**	**1.31 [0.91, 1.89]**
Total events	4910		2740			

Heterogeneity: Tau² = 0.14; Chi² = 238.42, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.43 (P = 0.15)

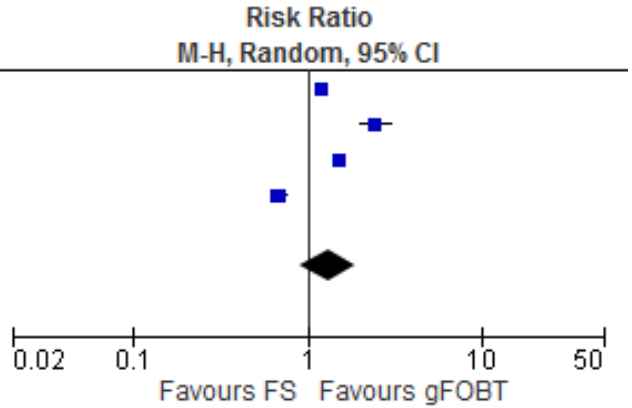


Figure 18. gFOBT versus gFOBT + FS – advanced neoplasia (intention to screen).

Study or Subgroup	gFOBT Events	gFOBT Total	gFOBT+FS Events	gFOBT+FS Total	Weight	Risk Ratio M-H, Random, 95% CI
Berry 1997	6	3128	29	3243	25.1%	0.21 [0.09, 0.52]
Rasmussen 1999	18	5483	84	5495	74.9%	0.21 [0.13, 0.36]
Total (95% CI)		**8611**		**8738**	**100.0%**	**0.21 [0.14, 0.33]**
Total events	24		113			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 6.86 (P < 0.00001)

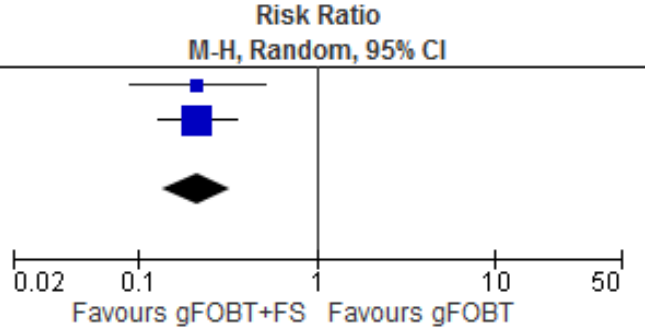
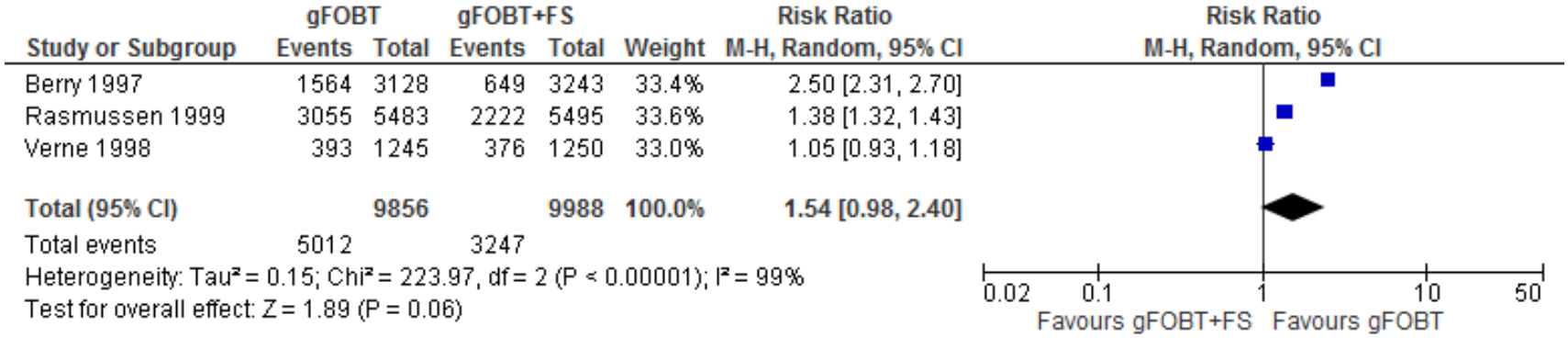


Figure 19. gFOBT versus gFOBT + FS – participation rate.



Secondary Research Question

1. What are the appropriate ages of initiation and cessation for screening in people at average risk for CRC? Is there a relationship between age and the effectiveness of CRC screening?

gFOBT Versus No Screening And Age

There were two RCTs that included subgroup analyses on the effect of gFOBT screening with no screening by age (Table 47) [58,62]. The quality of these data was rated very low because the Nottingham trial stratified by average age of eligible members from a household (Table 48). Also, only one trial found an interaction when subgroup analyses included both age and sex [62].

Because the trials were not powered for these subgroup analyses, it is difficult to draw conclusions regarding the most appropriate age of initiation or cessation for gFOBT screening. The older-than-60 subgroups tended to have a larger magnitude of benefit in terms of reduction in CRC-related mortality. However, Scholefield 2012 found no difference in CRC mortality reduction in people younger than 60 years of age and those 60 years of age and over [58]. Shaukat 2013 found a significant interaction between age and screening in men for CRC-related mortality in the biennial screening group (p=0.04) and the combined screening groups (p=0.04), but not for the annual screening group (p=0.26) [62]. No interaction between age and screening for CRC mortality was found in women [62].

Table 47. Characteristics of included RCTs – gFOBT and age.

Author/year	Sample size	Mean age (range) years	Age	# of deaths/total screened	# of deaths/total in control group	Relative risk of CRC death (95% CI)	CRC mortality ratio (95% CI)	Country

Minnesota trial Shaukat 2013[62]	46,551	62.3±7.8 (biennial screening group) 62.3±7.7 (50-80) (control group)	<60 and male (biennial)	36/3171	50/3211	0.75 (0.48-1.15)		Minnesota, United States
			60-69 and male (biennial)	42/3051	82/3027	0.42 (0.27-0.66)		
			≥70 and male (biennial)	27/1222	22/1196	0.82 (0.40-1.64)		
			<60 and male (combined)	70/6401	50/3211	0.72 (0.50-1.05)		
			60-69 and male (combined)	82/6062	82/3027	0.44 (0.30-0.64)		
			≥70 and male (combined)	48/2470	22/1196	0.79 (0.41-1.52)		
Nottingham trial Scholefield 2012[58]	151,975	(45-74)	<60	457	472		0.96 (0.85-1.10)	Nottingham, United Kingdom
			60+	719	828		0.87 (0.79-0.97)	

Abbreviations: CI = confidence interval; CRC = colorectal cancer; gFOBT = guaiac fecal occult blood test; RCT = randomized controlled trial

Table 48. GRADE evidence profile – gFOBT and age.

Quality assessment							Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRC mortality by age group		
CRC mortality by age group									
2	Randomized trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	See Table 47	⨁◯◯◯ VERY LOW	Critical

Abbreviations: CRC = colorectal cancer; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations;

[1]Nottingham trial stratified by average age of eligible members from a household; neither trial was powered for subgroup analyses

[2]Only the Minnesota trial included subgroup analyses by age and sex

FS Versus No Screening and Age

One RCT reported a subgroup analysis on the effect of FS screening with no screening on mortality by age (Table 49) and found that there was no interaction between age and study group assignment (p=0.11) for the relative risk of CRC mortality [57]. One RCT reported no significant CRC mortality benefit with FS screening for participants screened between 50 and 54 years of age (hazard ratio [HR], 0.74; 95% CI, 0.40 to 1.35; p=0.32 but did find benefit for those screened between 55 to 64 years of age (HR, 0.73; 95% CI, 0.55 to 0.97; p=0.03) [23]. Four RCTs reported incidence data for different age groups [14,23,33,57]. All four studies found similar relative risks or hazard ratios in the incidence of CRC between different age groups with overlapping confidence intervals [14,23,33,57]. Again, these were considered to be very low-quality data because the trials were not powered to detect subgroup differences and only one study, which investigated the interaction of age and FS screening on mortality, was stratified by age (Table 50). Therefore, no strong conclusions can be made.

Table 49. Characteristics of included RCTs – FS and age.

Author/year	Frequency	Sample size	Mean age range (years)	Age	Cases/person-years for screened group	Cases/person-years for control group	Risk ratio (cases of CRC/person-years) (95% CI)	Risk ratio (CRC deaths/person-years) (95% CI)	Country
Shoen 2012[57]	Twice (second was at the third or fifth year)	154,900	55-74	55-64	518	662	0.78 (0.69-0.87)	0.84 (0.67-1.06) (133 cases in screened, 157 cases in control)	United States
				65-74	494	625	0.79 (0.71-0.89)	0.65 (0.52-0.82) (119 cases in screened, 184 cases in control)	
Holme 2014[23]	Once	98,792	FS: 56.9 Control: 56.1	50-54 55-64			Age-adjusted HR: 0.68 (0.49-0.94) Age-adjusted HR: 0.83 (0.71-0.96)	Age-adjusted HR: 0.74 (0.40-1.35) Age-adjusted HR: 0.73 (0.55-0.97)	Norway
Segnan 2011[14]	Once	34,292	55-64 FS: 59.7 (55.5 to 64.3)	55-59	131/97,980	157/98,773	0.84 (0.67-1.06)		Italy
				>60	120/76,197	149/74,664	0.79 (0.62-1.00)		

			Control: 59.6 (55.5-64.4)						
Atkin 2010[33]	Once	170,432	55-64 60 (SD 2.9)	55-59	181/226,033	766/621,428	0.65 (0.55-0.76)		United Kingdom
				60-64	264/218687	1052/596907	0.68 (0.60-0.78)		

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy; HR = hazard ratio; RCT = randomized controlled trial

Table 50. GRADE evidence profile – FS and age.

Quality assessment							Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	by age group		
CRC mortality by age group									
2	Randomized trials	Very serious[1]	Not serious	Serious[2]	Not serious	Not serious	See Table 49	⊕◯◯◯ VERY LOW	Critical
CRC incidence by age group									
4	Randomized trials	Very serious[1]	Not serious	Serious[3]	Not serious	Not serious	See Table 49	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; FS = flexible sigmoidoscopy; GRADE = Grading of Recommendations, Assessment, Development and Evaluations;
[1]Trials were not powered to detect subgroup interactions
[2]Holme 2014 did not stratify by age
[3]Segnan 2011, Atkin 2010 and Holme 2014 did not stratify by age

Colonoscopy Versus No Screening and Age

Only one of the six comparative observational studies investigated the age of initiation for screening [94]. Cotterchio 2005 appeared to find no difference for CRC risk if the first colonoscopy was after the age of 50 years (adjusted OR, 0.68; 95% CI, 0.47 to 1.00) compared with having the first colonoscopy prior to age 50 years (adjusted OR, 0.96; 95% CI, 0.62 to 1.49) [94]. This result needs to be interpreted with caution due to the large amount of missing data (20%) and the data are considered very low-

quality data because they are from a case-control study using retrospective self-report information (Table 51). There were no studies that randomized the age of initiation or cessation for a screening colonoscopy.

Table 51. GRADE evidence profile – colonoscopy and age.

Quality assessment							Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Detection by age group		
CRC risk by age group									
1	Observational study	Serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	Not pooled	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; GRADE = Grading of Recommendations, Assessment, Development and Evaluations;
[1]Case-control design
[2]Surrogate outcome for CRC mortality
[3]Only 1 study

Secondary Research Question

2. What are the appropriate intervals between CRC screening tests (by test)? Is there a relationship between screening intervals and the effectiveness and risks of screening?

There were only two trials examining fecal tests that randomized subjects to different screening intervals (Table 52) [50,51,62,65]. For gFOBT, the high-quality Minnesota RCT allocated subjects to annual or biennial rounds of gFOBT screening (Tables 53 and 54) [50,51,62]. Both annual (RR, 0.80; 95% CI, 0.70 to 0.90) and biennial (RR, 0.83; 95% CI, 0.73 to 0.94) screening resulted in a significant reduction in the incidence of CRC [50], as well as a statistically lower CRC mortality rate (annual RR, 0.67; 95% CI, 0.51 to 0.83; biennial RR, 0.79; 95% CI, 0.62 to 0.97) compared with the control group [51]. This suggests that either annual or biennial gFOBT screening is beneficial in reducing CRC-related mortality.

The randomized controlled trial that evaluated FIT was of low quality because there was a significant difference in age between randomized groups (suggesting failure of randomization), the blinding procedure was not reported and the randomization method was not described in detail (Tables 55 and 56) [65]. Subjects were assigned to FIT screening intervals of one, two or three years. Using multivariate analysis adjusting for participation in the first screening round, interval length was associated with second-round participation. More subjects participated in the second round of biennial screening (OR, 1.18; 95% CI, 0.98 to 1.43) and triennial screening (OR, 1.26; 95% CI, 1.04 to 1.52) compared with annual screening [65]. However, there was no significant difference among the three interval groups in the detection rate of advanced neoplasia (Table 57)

[65]. This suggests that intervals of one, two, or three years may be reasonable options for screening with FIT; however, the quality of the evidence was very low.

Table 52. Characteristics of included studies – intervals.

Study	Type	Sample size age	Test	Country	Interval outcome
gFOBT					
Minnesota trial Shaukat 2013[62] Mandel 2000[50] Mandel 1999[51]	RCT	Annual: 15,570 biennial: 15,587 50-80	Annual (11 rounds) or biennial (6 rounds) Hemoccult – diet restricted and rehydrated	USA	• Incidence, CRC mortality, and all-cause mortality
FIT					
Van Roon 2013[65]	RCT	10,698 50-74	FIT (OC-Sensor Micro) randomized to intervals of 1, 2, or 3 years	Netherlands	• Rescreening participation and ADR rates • Interval cancers

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; RCT = randomized controlled trial

Table 53. Outcome from RCT – interval and mortality – biennial versus annual intervals for gFOBT.

Minnesota trial for gFOBT	Annual screening RR (95% CI)	Biennial screening RR (95% CI)
Cumulative CRC mortality ratio (18 years follow-up) [51]	0.67 (0.51-0.83)	0.79 (0.62-0.97)
Cumulative all-cause mortality (30 years follow-up) [62]	0.71 (0.70-0.72)	0.71 (0.70-0.71)
Cumulative incidence ratio (18 years follow-up) [50]	0.80 (0.70-0.90)	0.83 (0.73-0.94)

Abbreviations: CI = confidence interval; CRC = colorectal cancer; gFOBT = guaiac fecal occult blood test; RCT = randomized controlled trial; RR = relative risk

Table 54. GRADE evidence profile – biennial versus annual intervals for gFOBT.

Quality assessment	# of patients	Effect	Quality	Importance

# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biennial (cases/person-years)	Annual (cases/person-years)			
CRC mortality											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious	237/475,880 (0.0%)	200/475,167 (0.0%)	See Table 53	⊕⊕⊕◯ MODERATE	Critical
All-cause mortality											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious	11,004/475,880 (2.3%)	11072/475,167 (2.3%)	See Table 53	⊕⊕⊕◯ MODERATE	Important
CRC incidence											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[1]	Not serious	435/235,513 (0.2%)	417/235,584 (0.2%)	See Table 53	⊕⊕⊕◯ MODERATE	Important

Abbreviations: CRC = colorectal cancer; gFOBT = guaiac fecal occult blood test; GRADE = Grading of Recommendations, Assessment, Development and Evaluations
[1]Only 1 study

Table 55. Quality of RCT – interval: one- versus two- versus three-year intervals for FIT.

Author/year	Randomization details	Sample size and power calculation done	Baseline patient characteristics	ITS analysis	Blinding	Follow-up (years)	Funding
Van Roon 2013[65]	Random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, The Netherlands); selection was performed per household and occurred before invitation	10,698 Yes	Significant difference in age between groups; used multivariate analysis to control for age, sex, and SES	No	NR	At least 3 years	Dutch Cancer Society, the Dutch Ministry of Health, Health Care Prevention Program-Implementation, Olympus Medical Systems Europe GmbH, Hamburg, Germany, the

							Jacoba Foundation and Eiken Chemical Co, Tokyo, Japan

Abbreviations: FIT = fecal immunochemical test; ITS = intention to screen; NR = not reported; RCT = randomized controlled trial; SES = socioeconomic status

Table 56. GRADE evidence profile: one- versus two- versus three-year intervals for FIT.

Quality assessment							# of patients	Effect	Quality	Importance
# of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Adenoma detection rate										
1	Randomized trial	Serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	See Table 52	Not pooled	⊕◯◯◯ VERY LOW	Important

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test;
[1]Significant difference in age between groups, blinding not reported, randomization method not described in detail
[2] Surrogate outcome for CRC mortality
[3]Only 1 study

Table 57. Participation and detection rates of included study – interval: one- versus two- versus three-year intervals for FIT.

Study		# recruited Round 1	# participated Round 1	# of advanced adenoma/cancer detected (% per protocol) Round 1	# recruited Round 2	# participated Round 2	# of advanced adenoma/cancer detected (% per protocol) Round 2
Van Roon 2013[65]	1 year	2493	1543	55 (3.6)	2057	1286	25 (1.9)
	2 years	2503	1481	43 (3.4)	2096	1280	27 (2.1)
	3 years	2505	1499	50 (3.3)	2055	1298	22 (1.7)
	Reference (2 days)	3197	1876	77 (4.1)			
	6-10 years		332	3 (0.9)			
	>10 years		222	3 (1.4)			

Abbreviation: FIT = fecal immunochemical test

Ongoing, Unpublished or Incomplete Studies

Table 58. Ongoing studies.

Name	Phase	Type	Age	Protocol IDs
Cap Assisted Colonoscopy for the Detection of Colon Polyps	No phase specified	Screening	21 - 85	AR0006 NCT01211132
Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer (CONFIRM)	No phase specified	Screening	50 - 75	577 NCT01239082
PillCam Colon Capsule 2® (PCC2) in the Setting of Colorectal Cancer Screening Program	No phase specified	Screening	50 - 85	25-2011 NCT01744509
Augmentation of Screening Colonoscopy with Fecal Immunochemical Testing	No phase specified	Screening	18 and over	ASC-FIT NCT00892593
Screening for CRC using a Mixed Strategy of Sigmoidoscopy and Colonoscopy in Average-Risk Population According to Age	No phase specified	Screening	50 and over	9561700610 NCT00173277
Screening for Colorectal Cancer with FOBT, Virtual Colonoscopy and Optical Colonoscopy. A Randomized Clinical Trial in the Florence District	No phase specified	Screening, Tissue collection/Repository	55 - 65	D65C09002710007 432/10 NCT01651624
The Northern-European Initiative on Colorectal Cancer	Phase III	Screening	55 - 64	NordICC NCT00883792
Computed Tomography (CT) Colonography versus Optical Colonoscopy	No phase specified	Diagnostic, Screening	19 - 65	H08-00776 NCT01181739

CONCLUSIONS ABOUT THE SCREENING TESTS

Fecal Tests for Occult Blood

There was strong evidence to support the use of fecal tests for occult blood to screen people at average risk for CRC.

Guaiac Fecal Occult Blood Test (gFOBT) Versus No Screening

- The overall certainty of the evidence was high, suggesting a definite reduction in CRC-related mortality. The magnitude of the effect was small (relative risk [RR], 0.87; 95% confidence interval [CI], 0.82 to 0.92); it was comparable to the disease-specific reduction in mortality from mammography for breast cancer screening (RR, 0.79; 95% CI, 0.68 to 0.90) [1], but was less than that from the human papillomavirus (HPV) test for cervical cancer screening (hazard ratio [HR], 0.52; 95% CI, 0.33 to 0.83) [2]. The anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.

Fecal Immunochemical Test (FIT) Versus gFOBT

- The overall certainty of the evidence was moderate. The magnitude of the desirable anticipated effects was at least equivalent to gFOBT, and it is likely that the desirable effects of FIT are greater than for gFOBT. The anticipated undesirable effects associated with FIT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.
- While there were well-designed randomized controlled trials (RCTs) comparing FIT with gFOBT, the outcomes of these trials (participation, detection rates) were considered to be of lesser importance than CRC-related mortality. However, it was anticipated that the reduction in CRC-related mortality and the complications resulting from screening with FIT would be at least equivalent to those observed from screening with gFOBT. FIT's greater sensitivity for detection of CRC and advanced adenomas compared with gFOBT suggest that the reduction in CRC incidence with FIT could be greater than for gFOBT; however, the magnitude and significance of any additional benefit of FIT over gFOBT is unknown. It is important to highlight that the FIT positivity threshold selected would be an important determinant of the magnitude of the benefits and harms of FIT relative to gFOBT.

Lower Bowel Endoscopy

There was strong evidence to support the use of flexible sigmoidoscopy (FS) to screen people at average risk for CRC. There was no direct evidence to support the use of colonoscopy to screen people at average risk for CRC, but evidence from FS informed the assessment of the benefits and harms of colonoscopy in screening people at average risk for CRC.

FS Versus No Screening

- The overall certainty of the evidence was high, suggesting that FS has a definite effect on CRC-related mortality and incidence when compared with no screening. The magnitude of the effect on CRC mortality was modest (RR, 0.72; 95% CI, 0.65 to 0.80); it exceeds the anticipated disease-specific reduction in mortality from gFOBT for CRC screening (RR, 0.87; 95% CI, 0.82 to 0.92), and is similar to the effects of mammography on breast cancer mortality (RR, 0.79; 95% CI, 0.68 to 0.90) [1] and of the HPV test on cervical cancer mortality (HR, 0.52; 95% CI, 0.33 to 0.83) [2]. The effect on survival with FS was also comparable to the benefit achieved with the

current standard of care for patients with completely resected stage III CRC (5-fluorouracil/leucovorin plus oxaliplatin [FOLFOX or FLOX] versus 5-fluorouracil/leucovorin alone, HR for overall survival at six years, 0.80; 95% CI, 0.65 to 0.97) [3]. The anticipated harms associated with FS (including follow-up colonoscopy for people with positive tests) were small and outweighed by the benefits.

Colonoscopy versus no screening

- The overall certainty of direct evidence supporting the use of colonoscopy to screen people at average risk for CRC was very low when compared with no screening. The desirable and undesirable anticipated effects were uncertain.
- It is anticipated that the benefit of screening with colonoscopy would be at least equivalent to that observed for screening with FS; however, the magnitude of additional benefit over FS, if any, is unknown. The magnitude of additional undesirable effects of colonoscopy relative to FS is also unknown.

Fecal Tests for Occult Blood Versus Lower Bowel Endoscopy

There was insufficient evidence to determine how fecal tests for occult blood perform compared with lower bowel endoscopy to screen people at average risk for CRC.

- The studies that compared one-time fecal tests for occult blood to lower bowel endoscopy were heterogeneous, with few comparisons where data could be pooled. However, in general, the evidence suggested that participation was higher and detection rate was lower with fecal-based tests compared with endoscopic tests.
- The overall certainty of the evidence was low. CRC-related mortality was not evaluated and the design of the studies favoured endoscopic tests because the comparison was to one-time fecal-based testing (rather than repeated testing over time, which is how these tests are used in usual practice). There was significant heterogeneity in participation. The undesirable anticipated effects of endoscopy (including follow-up endoscopy for people with positive fecal tests) are probably small. It is uncertain whether the desirable effects are large relative to the undesirable effects.

Radiological Tests

Computed Tomography Colonography Versus Colonoscopy

There was insufficient evidence to determine how computed tomography colonography performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was low. The desirable and undesirable anticipated effects were uncertain.

Capsule Colonoscopy Versus Colonoscopy

There was insufficient evidence to determine how capsule colonoscopy performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Double-Contrast Barium Enema (DCBE)

There was no evidence to support the use of DCBE to screen people at average risk for CRC.

- Since 2006, there has been no new published evidence on this topic. Most recent CRC guidelines except for a 2008 guideline by the American Cancer Society, the US Multi-

Society Task Force on Colorectal Cancer and the American College of Radiology [4] have not endorsed the use of DCBE for screening [5-9].

DNA Tests

Stool DNA versus fecal occult blood tests (gFOBT or FIT)

There was insufficient evidence to determine how stool DNA performs compared with gFOBT or FIT to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other DNA Tests

There was insufficient evidence to support the use of mSEPT9 to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Metabolomic Tests

Fecal M2-PK

There was insufficient evidence to support the use of fecal M2-PK to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other Metabolomic Tests

There was no evidence to support the use of other metabolomic tests (e.g., low levels of hydroxylated polyunsaturated long chain fatty acids [Cologic®]) to screen people at average risk for CRC.

Age of Initiation/Cessation

Age of Initiation/Cessation With gFOBT

Currently, the Ontario CRC screening program recommends that average-risk individuals initiate screening with gFOBT beginning at 50 years of age and ending at age 74. There was insufficient evidence to support changing the ages of initiation and cessation for CRC screening with gFOBT in Ontario.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality using gFOBT across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.

Age of initiation/cessation with FS

There was insufficient evidence to recommend ages of initiation or cessation when screening with FS in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality or incidence using FS across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Of the four large FS RCTs, three examined “once in a lifetime” FS between the ages of 55 and 64, while the fourth RCT examined baseline FS between the ages of 55 and 74 with a second FS after three or five years.

Age of Initiation/Cessation with Colonoscopy

There was insufficient evidence to recommend an age of initiation or cessation to screen with colonoscopy in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in CRC detection using colonoscopy across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Currently, the Ontario CRC screening program does not recommend colonoscopy to screen persons at average risk for CRC. The program does recommend colonoscopy in people at increased risk (one or more first-degree relatives with CRC) starting at 50 years of age or 10 years younger than the age at which the relative was diagnosed, whichever occurred first.

Age of Initiation/Cessation with FIT

There were no studies that met our inclusion criteria for age of initiation/cessation for FIT.

Screening Intervals

gFOBT Intervals

There was evidence to suggest that either annual or biennial screening using gFOBT in people at average risk for CRC reduces CRC-related mortality.

- The overall certainty of the evidence was moderate. The desirable anticipated effects on CRC mortality were small and similar for annual or biennial screening. The undesirable anticipated effects were not reported for each interval group. Anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) were small for biennial screening and were likely to be greater for annual screening. In addition, annual screening is anticipated to increase burden to the participant.

FIT Intervals

There was insufficient evidence to recommend an interval to screen people at average risk for CRC using FIT.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

FS and Colonoscopy Intervals

There were no studies that met our inclusion criteria for screening intervals for FS or colonoscopy.

NEXT STEPS

This evidence summary reports what is known about the clinical effectiveness and safety of CRC tests and is central to the ongoing development of Ontario's colorectal cancer screening program. However, the evidence summary is necessary but not sufficient to guide program development as other context-specific criteria such as cost-effectiveness, existing program design, public acceptability and feasibility (from an organizational and economic perspective) must be considered. In addition, the program must also consider the balance between choice and informed decision making and issues not well addressed by the evidence such as how best to implement colorectal cancer screening when there is more than one colorectal cancer screening test supported by high-quality evidence. An expert panel which included members from national and international screening programs, primary care physicians, general surgeons, gastroenterologists, pathologists and laboratory medicine professionals, nurse endoscopists and

members of the public was convened to provide guidance on how to incorporate the evidence in light of the other issues listed above. Their level of agreement with the conclusions and their comments are reflected in Section Three. The CCC program will use findings from the evidence summary as well as expert panel recommendations to guide its ongoing development.

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Colorectal Cancer Screening in Average Risk Populations: Internal Review

J. Tinmouth, E. Vella, N.N. Baxter, C. Dubé, M. Gould, A. Hey, N. Ismaila, B.R. McCurdy, L. Paszat

Report Date: November 11, 2015

INTERVAL REVIEW

Almost all PEBC documents undergo internal review. As with all evidence summaries, approval for this review was obtained from the Director of the PEBC. This evidence summary was also reviewed by an Expert Panel whose members were asked to vote on their level of agreement with the Working Group's conclusions.

Report Review by the Director of the PEBC

The purpose of the review by the director of the PEBC was to ensure this evidence summary's methodological rigour and quality. The working group was responsible for ensuring the necessary changes were made. If those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval.

The director of the PEBC reviewed and approved the document on February 4, 2015. The summary of main comments from the Director of the PEBC and the working group's modifications/actions/responses are shown in Table 59.

Table 59. Modifications/actions/responses regarding main comments from the director of the PEBC.

Main comments	Modifications, actions, or responses
1. Use of existing systematic reviews and then looking at primary studies – a lot of care is going to be required so that readers and users do not perceive a more robust evidence base than what there is. Most of the meta-analyses done were small variants to the ones done earlier. You may be able to drop the large descriptions of the original meta-analyses since my read was they provided the randomized controlled trials for the ones done by your group.	We have included only the most recent meta-analyses with the highest quality evidence and have reduced their description in the text.
2. Please check to make sure that you can argue that grade levels (really low, low, medium, high) were applied consistently.	We have reviewed our grading scheme to make sure it has been applied consistently.

Report Review by the Expert Panel

After review by the director of the PEBC, the Colorectal Cancer (CRC) Screening Expert Panel was asked to vote on their level of agreement with the working group's conclusions during an in-person meeting on April 29, 2015. Thirty expert panel members attended the in-person meeting and votes were obtained from 27 members (Appendix 1). None of the members declared any conflicts of interest. Results of the vote are reported in Table 60. There was over 75% agreement (either agreed or strongly agreed) with each of the conclusions.

Table 60. Responses of the expert panel to the working group's conclusions.

	Reviewer ratings (N=27)				
Conclusions	Strongly disagree (%)	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Strongly agree (%)
1. Strong evidence to support use of fecal tests for occult blood to screen people at average risk for CRC	0	0	1 (4)	10 (37)	16 (59)
2. Strong evidence to support the use of FS to screen people at average risk for CRC	0	0	0	7 (26)	20 (74)
3. No direct evidence to support the use of colonoscopy to screen people at average risk for CRC, but evidence from FS informs the assessment of benefits and harms of colonoscopy to screen people at average risk for CRC	0	2 (8)	2 (8)	14 (54)	8 (31)
4. Insufficient evidence to determine how fecal tests for occult blood perform compared with lower bowel endoscopy to screen people at average risk for CRC	0	2 (8)	4 (15)	13 (50)	7 (27)
5. Insufficient evidence to determine how CT colonography performs compared with colonoscopy to screen people at average risk for CRC	0	0	1 (4)	8 (33)	15 (63)
6. Insufficient evidence to determine how capsule endoscopy performs compared with colonoscopy to screen people at average risk for CRC	0	0	0	1 (4)	23 (96)
7. No evidence to support the use of double-contrast barium enema to screen people at average risk for CRC	0	0	2 (8)	0	23 (92)
8. Insufficient evidence to determine how fecal DNA performs compared with guaiac fecal occult blood test (gFOBT) or fecal immunochemical test (FIT) to screen people at average risk for CRC	0	0	0	8 (33)	16 (67)
9. Insufficient evidence to support the use of mSEPT9 to screen people at average risk for CRC	0	0	0	2 (8)	23 (92)
10. Insufficient evidence to support the use of fecal M2-PK to screen people at average risk for CRC	0	0	0	3 (12)	23 (89)

11. Insufficient evidence to support the use of other metabolomic tests to screen people at average risk for CRC	0	0	1 (4)	2 (9)	20 (87)
12. Insufficient evidence to support changing ages of initiation and cessation for CRC screening with gFOBT in Ontario	0	1 (4)	1 (4)	9 (36)	14 (56)
13. Insufficient evidence to recommend an age of initiation or cessation to screen with FS in people at average risk for CRC	0	0	3 (12)	9 (36)	13 (52)
14. Insufficient evidence to recommend an age of initiation or cessation to screen with colonoscopy in people at average risk for CRC	0	0	4 (16)	10 (40)	11 (44)
15. Evidence suggests annual or biennial screening using gFOBT in people at average risk for CRC reduces CRC mortality	0	0	1 (4)	11 (42)	14 (54)
16. Insufficient evidence to recommend an interval to screen people at average risk for CRC using FIT	0	1 (4)	4 (15)	13 (50)	8 (31)

During the in-person meeting, the CRC Screening expert panel provided the following key feedback on the evidence summary, which will be taken into consideration when Cancer Care Ontario's Prevention and Cancer Control portfolio develops its screening program.

Table 61. Responses to the expert panel feedback on the evidence summary**.**

Main comments	Responses
1. When considering the fecal occult blood tests, we need to consider the sensitivity of the test and what cut-off was used. The type of test and the cut-off would affect the sensitivity and specificity. The gFOBTs were heterogeneous and combining them for the purposes of a meta-analysis may not have been appropriate. Also, another complication to consider was the false-negative rate, which would be impacted by the type of test and cut-off.	Since the heterogeneity across trial was not substantial in the meta-analysis with regards to CRC mortality, a sensitivity analysis was not performed. The confidence intervals overlapped between trials and although the summary estimate may have changed slightly when considering the type of tests used, it would not have changed the conclusion.
2. Although you may not have RCTs for all of your comparisons, you can use interval cancers as a proxy measure for effectiveness and to help determine the best interval. There are observational data that interval cancers may occur less with FIT than gFOBT, which would provide further support for FIT's effectiveness over gFOBT.	Initial literature review did not identify studies using interval cancers as an outcome, therefore, this outcome was not considered in our review. In the future, interval cancers would be an appropriate outcome to include.
3. Furthermore, there are indirect data that suggest one-time FS has a similar protective effect to repeated FS and therefore we may not need to repeat the test for 10 to 12 years.	There were not studies that directly compared once in a lifetime FS vs repeated FS, therefore the evidence was insufficient to make a conclusion on this issue.

4. You can also use epidemiological data about the prevalence of CRC in the population to determine an appropriate age for screening.	These types of studies were not included in our review as they did not meet inclusion criteria. However, existing age criteria for the CCC program do reflect existing prevalence data.
5. We need to keep in mind that lack of evidence does not equate to lack of effect. Just because we do not have RCTs comparing colonoscopy or FIT to no screening does not mean that colonoscopy or FIT would not be effective screening tests.	This issue is reflected in the wording of our conclusions.
6. We have to consider that an endoscopic test is operator dependent, whereas a fecal-based test is a more standardized test.	This important issue will have to be taken into consideration during implementation.
7. The concluding statement comparing fecal-based tests to endoscopy do not include the specification of one-time fecal-based tests or whether multiple tests were used. Also, the concluding statements for intervals should state which comparators were evaluated. Perhaps the concluding statements should have been framed in a population problem or population, intervention, comparison and outcome(s) (PICO) style.	The concluding statement does not mention "one-time," but the evidence to support the statement is explicitly worded to say that the included studies examined one-time fecal testing only.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest Policy, the guideline authors were asked to disclose potential conflicts of interest. The conflict of interest statements of the working group are summarized in Appendix 1.

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Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

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Appendix 1. Members of the working group.

Name and affiliation	Declarations of interest
Jill Tinmouth Lead Scientist, ColonCancerCheck program, Cancer Care Ontario Scientist and Staff Gastroenterologist, Sunnybrook Health Sciences Centre	Lead scientist at Cancer Care Ontario for ColonCancerCheck and paid as a consultant for this work
Emily Vella Health Research Methodologist Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	None declared
Nancy Baxter Endoscopy Lead, Cancer Care Ontario Staff Surgeon and Division Chief, Division of General Surgery, Department of Surgery, St. Michael's Hospital Scientist LiKaShing Knowledge Institute St. Michael's Hospital	None declared
Catherine Dubé Clinical Lead, ColonCancerCheck program, Cancer Care Ontario Associate Professor, Department of Medicine, Division of Gastroenterology, University of Ottawa The Ottawa Hospital Civic Campus	Published editorial Can J Gastro 2012 26 (7) 417-18.
Michael Gould Gastroenterologist, William Osler Health Centre Medical Director, Vaughan Endoscopy Clinic	Has an endoscopy clinic in Toronto, is a consultant for Abbott Laboratories, is on the Board of Directors for the Ontario Association of Gastroenterology and the Canadian Digestive Health Foundation, is the Clinical Lead for ColonCancerCheck
Amanda Hey Primary Care Physician Regional Primary Care Lead - Northeast Cancer Centre Health Sciences North | Horizon Santé-Nord Sudbury Outpatient Centre	None declared
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Lawrence Paszat Senior Scientist, Institute for Clinical Evaluative Sciences Senior Scientist, Sunnybrook Research Institute Associate Professor, University of Toronto	None declared

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Members of the expert panel.

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Jill Tinmouth	Lead Scientist, ColonCancerCheck, Cancer Care Ontario
Jim Allison	Clinical Professor of Medicine Emeritus, University of California, San Francisco
John Day	Regional Primary Care Lead, Erie St. Clair
Judy Ash	Director, Programs & Member Services, Ontario Association of Medical Laboratories
Larry Hershfield	Lecturer, University of Toronto
Lawrence Paszat	Senior Core Scientist, Institute for Clinical Evaluative Sciences
Linda Rabeneck	Vice President, Prevention and Cancer Control, Cancer Care Ontario
Mark Hartman	Regional Vice President, Northeast Cancer Centre, Health Sciences North

Michael Cotterill	Primary Care Physician, Wawa Family Health Team
Michael Gould	Medical Director, Vaughan Endoscopy Clinic; Gastroenterologist, Etobicoke General Hospital
Michelle Cotterchio	Senior Scientist, Cancer Care Ontario
Nancy Baxter	Provincial Clinical GI Endoscopy Lead, Cancer Care Ontario
Ron Myers	Professor and Director, Division of Population Science, Department of Medicine, Thomas Jefferson University
Roslyn Doctorow	Public Representative
Suzanne Strasberg	Provincial Primary Care Lead, Cancer Care Ontario
Tim Feltis	Deputy Ontario Medical Director, LifeLabs
Tracey Corner	RNFS Nurse Endoscopist, Hamilton Health Science Centre

Appendix 2: Literature search strategies.

Embase
1. colorectal neoplasm.mp. or exp Colorectal Neoplasms/
2. exp colonic neoplasms/
3. (Colonic polyps or colonic tumour or colonic cancer or colorectal tumour or colorectal cancer or colonic polyp).tw.
4. ((cancer$ or neoplas$ or tumour$ or tumor$ or adenoma$) adj3 (colorectal$ or colon$ or rectal$ or rectum$ or bowel$ or large intestine)).ti,ab.
5. CRC.ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp Mass Screening/
8. (screen$ or prevent$).ti,ab.
9. (earl$ adj3 detect$).ti,ab.
10. asymptomatic.mp.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. exp Occult Blood/
14. exp guaiac/ or fecal immunochemical.mp.
15. (FOBT or FIT or sDNA).ti,ab.
16. stool DNA.mp.
17. (stool adj2 DNA).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18. hydroxylation/ or long chain fatty acid/ or hydroxylated polyunsaturated ultra long chain fatty acid.mp. or unsaturated fatty acid/
19. (cologic or colonsentry or septin-9 or Sept9 or metabolomics or Phenomenome).ti,ab.
20. exp Serologic Tests/
21. exp sigmoidoscopy/ or exp colonoscopy/ or exp capsule colonoscopy/ or exp proctoscope/
22. exp enema/ or exp computed tomography colonography/
23. (contrast adj3 enema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. (barium adj3 enema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. Animal/
28. Human/
29. 27 not 28
30. 26 not 29
31. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
32. 30 not 31
33. limit 32 to english language
34. limit 33 to yr="2006 -Current"
35. limit 34 to exclude medline journals

Medline
1. colorectal neoplasm.mp. or exp Colorectal Neoplasms/
2. exp colonic neoplasms/

3. (Colonic polyps or colonic tumour or colonic cancer or colorectal tumour or colorectal cancer or colonic polyp).tw.
4. ((cancer$ or neoplas$ or tumour$ or tumor$ or adenoma$) adj3 (colorectal$ or colon$ or rectal$ or rectum$ or bowel$ or large intestine)).ti,ab.
5. CRC.ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp Mass Screening/
8. (screen$ or prevent$).ti,ab.
9. (earl$ adj3 detect$).ti,ab.
10. asymptomatic.mp.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. exp Occult Blood/
14. exp guaiac/ or fecal immunochemical.mp.
15. (FOBT or FIT or sDNA).ti,ab.
16. stool DNA.mp.
17. (stool adj2 DNA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18. hydroxylation/ or long chain fatty acid/ or hydroxylated polyunsaturated ultra long chain fatty acid.mp. or unsaturated fatty acid/
19. (cologic or colonsentry or septin-9 or Sept9 or metabolomics or Phenomenome).ti,ab.
20. exp Serologic Tests/
21. exp sigmoidoscopy/ or exp colonoscopy/ or exp capsule colonoscopy/ or exp proctoscope/
22. exp enema/ or exp computed tomography colonography/
23. (contrast adj3 enema).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
24. (barium adj3 enema).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. Animal/
28. Human/
29. 27 not 28
30. 26 not 29
31. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
32. 30 not 31
33. limit 32 to english language
34. limit 33 to yr="2006 -Current"

Appendix 3: Literature search flow diagram.