

Systematic review and meta-analysis of the evidence for flexible sigmoidoscopy as a screening method for the prevention of colorectal cancer

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Background: Colorectal cancer is a significant cause of death. Removal of precancerous adenomas, and early detection and treatment of cancer, has been shown to reduce the risk of death. The aim of this review and meta-analysis was to determine whether flexible sigmoidoscopy (FS) is an effective population screening method for reducing mortality from colorectal cancer.

Methods: MEDLINE (1946 to December 2012) and Embase (1980–2012, week 15) were searched for randomized clinical trials in which FS was used to screen non-symptomatic adults from a general population, and FS was compared with either no screening or any other alternative screening methods. Meta-analysis was carried out using a random-effects Mantel–Haenszel model.

Results: Twenty-four papers met the inclusion criteria, reporting results from 14 trials. Uptake of FS was usually lower than that for stool-based tests, although FS was more effective at detecting advanced adenoma and carcinoma. FS reduced the incidence of colorectal cancer after screening, and long-term mortality from colorectal cancer, compared with no screening in a selected population. Compared with stool-based tests in a general population, FS was associated with fewer interval cancers.

Conclusion: FS is efficacious at reducing colorectal cancer mortality compared with no screening. It is more effective at detecting advanced adenoma and carcinoma than stool-based tests. FS may be compromised by poorer uptake. Introduction of FS as a screening method should be done on a pilot basis in populations in which it is not currently used, and close attention should be paid to maximizing uptake. The relative risk of adverse events with FS compared with stool-based tests should be quantified, and its real-world effectiveness evaluated against the most effective stool-based tests.

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Introduction

Colorectal cancer is the third most common cancer in the UK and USA, and the third leading cause of cancer death in women (after lung and breast cancer) and men (after lung and prostate cancer)^{1,2}. It develops as a result of changes in the epithelium of the colon^{3,4}. Initially adenomatous polyps develop, which can progress to adenocarcinoma (and other rarer forms of cancer). Population screening for, and removal of, these polyps can reduce colorectal cancer mortality^{5,6}. A number of different screening modalities have been investigated, including varieties of faecal occult blood test (FOBT), colonoscopy and flexible sigmoidoscopy (FS)⁷.

The decision to implement a screening programme usually requires evidence of a significant reduction in mortality from randomized clinical trials⁸. Although FS has been suggested as a potential screening method for colorectal cancer for some time⁹, its effectiveness in reducing mortality compared with existing methods of colorectal cancer screening is unknown.

The primary objective of this review was to determine whether FS is an effective method for population screening to reduce mortality from colorectal cancer. Secondary objectives were to quantify FS screening uptake, and to determine the advanced adenoma, colorectal cancer and postscreening colorectal cancer incidence rates.

Methods

Eligibility

Databases of peer-reviewed journals were searched for randomized clinical trials in which FS was used to screen a healthy adult population for colorectal cancer. Eligible studies used a randomized design to allocate participants to FS or to no screening or any other screening method.

Information sources

Using OVID, a search was made of MEDLINE (1946 to December 2012) and Embase (1980 to April week 15 2012) by a single author. Medical subject heading (MeSH) terms used in the search were 'colorectal cancer', 'colon cancer', 'bowel cancer', 'rectal cancer', 'neoplas*', 'sigmoid*' and 'screen*' (Table S1, supporting information). No language restrictions were made during searches. No search of the grey literature was made, and authors were not contacted. The final search was conducted on 16 April 2012.

Study selection

Titles and abstracts were initially screened by one author, and potentially relevant studies were obtained in full text.

Data extraction

A standard table was designed for data extraction purposes, and data were extracted independently by two authors and then compared. Data extracted included: uptake of screening method; method of bowel preparation; screen-detected rates of advanced adenoma, defined as any adenoma of 1 cm or larger, tubulovillous or villous histology, or severe dysplasia; screen-detected rates of colorectal cancer; postscreening follow-up incidence of colorectal cancer; and postscreening mortality from colorectal cancer.

Risk of bias assessment

All included studies were assessed using the Scottish Intercollegiate Guidelines Network methodology checklist for randomized trials¹⁰.

Summary measures

Uptake by screening procedure was calculated as a percentage of those invited to participate. Detection rates for advanced adenoma and carcinoma (per 1000 screened) were calculated using the number of participants actually screened as the denominator; 95 per cent

confidence intervals (c.i.) were calculated using Fisher's exact test. Owing to the presence of clinical heterogeneity, meta-analysis was undertaken using the Mantel–Haenszel random-effects method, even when statistical heterogeneity was low¹¹. Data analysis was undertaken using Review Manager version 5.1 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

The results of the search strategy are summarized in Fig. 1. Searching the databases produced 625 records, of which 523 remained after removal of duplicate records. Among these were five reviews^{12–16}. Citations in these reviews were searched using ISI Web of Science, which identified an additional four reviews and guidelines^{7,17–19}. The reference lists of the nine reviews and guidelines were checked, and a further nine records were identified as being eligible for screening. This produced a total of 536 papers for screening, initially by consideration of titles and abstracts. Of these, 506 were excluded and 30 were obtained in full text. The reference lists of these papers were also searched. Of the 30 papers, six were excluded and 24 that met the eligibility criteria were appraised critically^{20–43}.

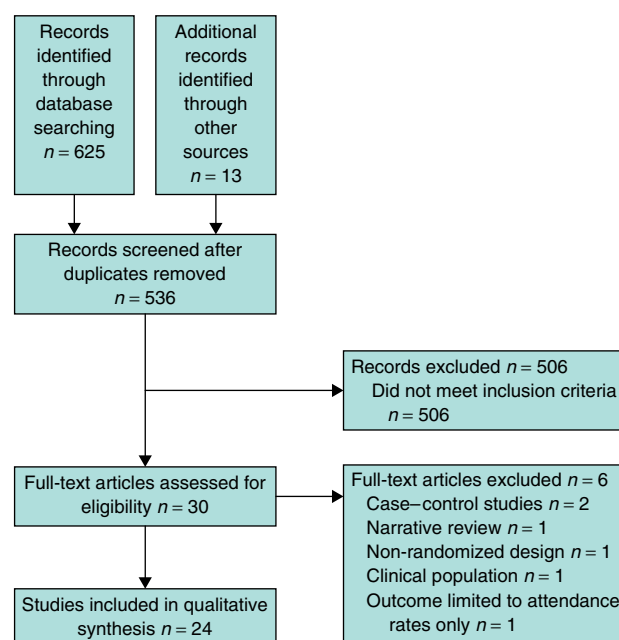


Fig. 1 Flow diagram showing search strategy

Study characteristics and risk of bias within studies

The 24 papers reported data from a total of 14 randomized trials, undertaken in Australia, the USA and Western Europe (Table 1). Four trials (8 papers) used populations whose willingness to accept FS screening was pre-established by questionnaire^{20–27}. The other ten trials (16 papers) used an unselected, general population^{28–43}. Five trials reported use of random number generators or computer algorithms as part of the randomization method^{23,28,37,39,40}, whereas details were lacking in the remainder. One trial reported FS being undertaken blind to the FOBT result³¹; no trial reported that colonoscopy was performed blind to the initial screening method. Five trials did not report whether groups were similar by age and sex at baseline^{20,21,26,32,35}.

The definition of a positive FS screening test showed marked heterogeneity across studies. One trial referred

participants who had a polyp of any size detected³², one referred participants with a polyp greater than 3 mm³¹, one referred participants with a polyp greater than 5 mm²³, six referred participants with a polyp greater than 10 mm^{20,22,35,37,40,42}, three referred participants with adenoma^{29,30,39}, and one referred participants with any neoplasia²⁸; one study did not have formal referral criteria²⁶.

Twelve studies did not describe the quality assurance method used to ensure that the sigmoid–descending colon junction was reached during FS; two papers reported measuring the depth to which the sigmoidoscope was inserted^{26,36}.

In the following text the acronyms FS, FOBT and FIT (faecal immunochemical test) are used to indicate the use of these screening methods in isolation. Combinations (such as FIT + FS) are used to show where participants were

Table 1 Trials included in the review

Reference	Year	Method	Comments	Level of evidence*
Atkin <i>et al.</i> ²⁰	1998	Selected population randomized to either FS or not contacted	Baseline results	1+
UKFSST				
UKFSSTI ²¹	2002	Selected population randomized to either FS or not contacted	Baseline results	1+
Atkin <i>et al.</i> ²²	2010		11-year follow-up (mortality)	1++
SCORE				
Segnan <i>et al.</i> ²³	2002	Selected population randomized to either FS or not contacted	Baseline results	1+
Bonelli <i>et al.</i> ²⁴	2006		Secondary analysis	
Segnan <i>et al.</i> ²⁵	2011		Secondary analysis	
PLCO Cancer Screening Trial				
Weissfeld <i>et al.</i> ²⁶	2005	Population received mailings offering a range of screening tests including FS, and then randomized to either test or no-test condition	Baseline results	1+
Schoen <i>et al.</i> ²⁷	2003		3-year follow-up	
Berry <i>et al.</i> ²⁸	1997	FOBT + FS <i>versus</i> FOBT	Baseline results	1+
Brevinge <i>et al.</i> ²⁹	1997	FS <i>versus</i> FOBT	Baseline results	1+
Verne <i>et al.</i> ³⁰	1998	FS <i>versus</i> FOBT + FS <i>versus</i> FOBT	Baseline results	1+
Rasmussen <i>et al.</i> ³¹	1999	FOBT + FS <i>versus</i> FOBT	Baseline results	1+
Telemark Polyp Study				
Thiis-Evensen <i>et al.</i> ³²	1999	Random sample randomized to either FS or not contacted	Baseline results	1–
Hoff <i>et al.</i> ³³	2001		13-year follow-up (mortality)	1–
Thiis-Evensen <i>et al.</i> ³⁴	2001		13-year follow-up (incidence)	1–
NORCCAP Screening Study				
Gondal <i>et al.</i> ³⁵	2003	FS <i>versus</i> FIT + FS	Baseline results	1–
Hoff <i>et al.</i> ³⁶	2009		6-year follow-up (mortality)	1++
SCORE 2				
Segnan <i>et al.</i> ³⁷	2005	FS <i>versus</i> FS + FIT <i>versus</i> FIT	Baseline results	1+
Senore <i>et al.</i> ³⁸	2010		Secondary analysis	
MACS Group ³⁹	2006	FIT + FS <i>versus</i> FIT	Baseline results	1+
SCORE 3				
Segnan <i>et al.</i> ⁴⁰	2007	FS <i>versus</i> FIT	Baseline results	1+
Fracchia <i>et al.</i> ⁴¹	2010		Secondary analysis	
Dutch trial				
Hol <i>et al.</i> ⁴²	2010	FS <i>versus</i> FOBT <i>versus</i> FIT	Baseline results	1+
Hol <i>et al.</i> ⁴³	2010		Secondary analysis	

*According to the Scottish Intercollegiate Guidelines Network. FS, flexible sigmoidoscopy; UKFSST(I), UK Flexible Sigmoidoscopy Screening Trial (Investigators); PLCO, Prostate, Lung, Colorectal and Ovarian; FOBT, faecal occult blood test; NORCCAP, Norwegian Colorectal Cancer Prevention; FIT, faecal immunochemical test; MACS, Multicentre Australian Colorectal-neoplasia Screening.

randomized to receive both screening methods, with the order of testing implicit in the order of the combined terms (FIT + FS means that FIT was undertaken before FS, whereas FS + FIT means that FS was carried out before FIT).

Uptake of screening programmes

In the 13 trials that reported uptake by screening group, uptake was highly variable (*Table 2*). The four trials that

used a population preidentified as willing to accept FS reported the highest uptake rates^{20,21,23,26}. In the trials that included non-selected populations, six of nine studies reported FS uptake rates to be lower than FOBT or FIT uptake rates^{28,29,31,37,39,42}, and one reported uptake of FS to be the same as that of FIT⁴⁰. Two trials reported uptake of FS alone to be higher than that of FS offered after FOBT or FIT^{30,35}.

Uptake of colorectal cancer screening was increased by a family history of the disease, and reduced in

Table 2 Uptake of screening

Reference	Age (years)	Screening method*	Uptake (%)
FS <i>versus</i> no screening			
Atkin <i>et al.</i> ²⁰	55–64	FS alone	74.7
Segnan <i>et al.</i> ²³	55–64	FS alone	58.3
UKFSSTI ²¹	55–64	FS alone	71.0
Weissfeld <i>et al.</i> ²⁶	55–74	FS alone	83.5
FS <i>versus</i> FOBT			
Brevinge <i>et al.</i> ²⁹	55–56	FS alone	42.5
		FOBT alone	59.5
Hol <i>et al.</i> ⁴²	50–74	FS alone	29.5
		FOBT alone	49.0
FOBT + FS <i>versus</i> FOBT			
Berry <i>et al.</i> ²⁸	50–74	FOBT + FS combined	
		FOBT returned	48.4
		FOBT returned but FS not accepted or did not attend	28.2
		FOBT returned and FS accepted	20.2
Rasmussen <i>et al.</i> ³¹	50–75	FOBT alone	50.0
		FOBT + FS combined	
		FOBT returned but FS not accepted	1.3
		FOBT returned and FS accepted	40.4
Verne <i>et al.</i> ³⁰	50–75	FOBT not returned but FS accepted	0.2
		FOBT alone	55.7
		FS alone	46.7
		FOBT + FS combined	
		Either FOBT returned or FS accepted	39.5
		Both FOBT returned and FS accepted	30.1
		FOBT alone	31.5
FS <i>versus</i> FIT			
Segnan <i>et al.</i> ⁴⁰	55–64	FS alone	32.3
		Biennial FIT	32.3
Hol <i>et al.</i> ⁴²	50–74	FS alone	29.5
		FIT alone	61.4
FIT + FS <i>versus</i> FIT			
MACS Group ³⁹	50–54 and	FIT + FS combined (reported as combined uptake)	13.7
	65–69	FIT alone	27.4
FS <i>versus</i> FS + FIT <i>versus</i> FIT			
Segnan <i>et al.</i> ³⁷	55–64	FS alone	27.8
		FS + biennial FIT combined	27.6
		FIT alone	29.3
FS <i>versus</i> FIT + FS			
Gondal <i>et al.</i> ³⁵	55–64	FS alone	66.9
		FIT + FS combined	
		FIT returned and FS accepted	54.4
		FIT not returned but FS accepted	8.3

*All one-off unless stated otherwise. FS, flexible sigmoidoscopy; UKFSSTI, UK Flexible Sigmoidoscopy Screening Trial Investigators; FOBT, faecal occult blood test; FIT, faecal immunochemical test; MACS, Multicentre Australian Colorectal-neoplasia Screening.

Table 3 Screen-detected high-risk adenoma and carcinoma

Reference	Intervention versus comparison	n	Participation*	Outcomes	Advanced adenoma		Colorectal cancer	
					No. detected at screening	Rate per 1000 screened†	No. detected at screening	Rate per 1000 screened†
Berry <i>et al.</i> ²⁸	One-off FOBT versus one-off FOBT + FS	3128 versus 3243	1564 (50.0) from FOBT-only group versus 1571 (48.4) returned FOBT from FS + FOBT group, of whom 656 (20.2) also accepted FS	Detection of adenoma (≥ 1 cm) and carcinoma by screening FS, or by CPY in those FOBT-positive	4 versus 26	2.5 (0.7, 6.5) versus 39.6 (26.1, 57.5)	2 versus 3	1.3 (0.2, 4.6) versus 4.6 (0.9, 13.3)
Brevinge <i>et al.</i> ²⁹	One-off FOBT versus one-off FS	3181 versus 3184	1893 (59.5) versus 1353 (42.5)	Detection of adenoma (≥ 1 cm) and carcinoma by screening FS, or by FS or DCBE in those FOBT-positive	9 versus 26	4.8 (2.2, 9.0) versus 19.2 (12.6, 28.0)	1 versus 5	0.5 (0.01, 2.9) versus 3.7 (1.2, 8.6)
Atkin <i>et al.</i> ²⁰	One-off FS versus no screening	1749	1306 (74.7) attended FS	High-risk adenoma (≥ 1 cm, ≥ 3 adenomas, tubulovillous or villous histology, severe dysplasia or malignancy, ≥ 5 metaplastic polyps) and CRC detected at screening by FS	68	52.1 (40.7, 65.5)	8	6.1 (2.6, 12.0)
Verne <i>et al.</i> ³⁰	One-off FOBT versus one-off FOBT + FS versus one-off FS	1249 versus 1250 versus 1245	393 (31.5) versus 494 (39.5) accepted either; 376 (30.1) accepted both versus 582 (46.7%)	High-risk adenoma (≥ 1 cm, tubulovillous or villous histology, severe dysplasia) and CRC at screening FS or CPY in those FOBT-positive	1 (by CPY following FOBT- positive result, but unclear if in FOBT-alone group or FOBT + FS group) 25 (by FS or CPY; unclear if this includes CPY following FOBT- positive result)	Unclear denominator	1 (by CPY following FOBT- positive result, but unclear if in FOBT- alone group or FOBT + FS group) 4 (by FS or CPY)	Unclear denominator
Rasmussen <i>et al.</i> ³¹	One-off FOBT versus one-off FOBT + FS	5483 versus 5495	3055 (55.7) versus 2222 (40.4) accepted both, 1% returned for FOBT only, 0.2% attended FS only	Adenoma (≥ 1 cm) and CRC detected at screening by FS, or by CPY or DCBE in those who screened FS-, or FOBT-positive; incidence of adenoma and CRC from national registry	14 versus 72	4.6 (2.5, 7.7) versus 32.4 (25.4, 40.6)	4 versus 12	1.3 (0.4, 3.3) versus 5.4 (2.8, 9.4)

Table 3 (Continued)

Reference	Intervention versus comparison	n	Participation*	Outcomes	Advanced adenoma		Colorectal cancer	
					No. detected at screening	Rate per 1000 screened†	No. detected at screening	Rate per 1000 screened†
Segnan <i>et al.</i> ²³	One-off FS versus no screening	17 148	9999 (58.3) attended FS; undertaken in 9911 (99.1)	Advanced adenoma (≥ 1 cm, or villous component > 20%, severe dysplasia, or > 2 adenomas of any type) and CRC at screening FS, or CPY in those FS-positive	120	12.1 (10.1, 14.5)	54	5.4 (4.1, 7.1)
UKFSSTI ²¹	One-off FS versus no screening	57 254	40 674 (71.0) attended FS	Advanced adenomas (≥ 1 cm, ≥ 3 adenomas, tubulovillous or villous histology, severe dysplasia) and CRC at screening FS, or CPY in those FS-positive	1905	46.8 (44.8, 48.9)	140	3.4 (2.9, 4.18)
Gondal <i>et al.</i> ³⁵	One-off FIT + FS versus one-off FS versus no screening	9990 versus 10 013	5435 (54.4) returned FIT and attended FS; 831 (8.3) did not return FIT but attended FS versus 6694 (66.9) attended FS	High-risk adenoma (≥ 1 cm or villous components or severe dysplasia) and CRC at screening FS or CPY in those FS- or FIT-positive	258 versus 287	41.2 (36.4, 46.4) versus 42.9 (38.2, 48.0)	20 versus 21	3.2 (1.9, 4.9) versus 3.1 (1.9, 4.8)
Segnan <i>et al.</i> ³⁷	1 × FIT by mail versus 1 × FIT by GP/ screening centre versus one-off FS versus one-off FS + biennial FIT versus choice of FIT or one-off FS	2326 versus 5985 versus 3695 versus 11 045 versus 3631	682 (29.3) versus 1654 (27.6) versus 1026 (27.8) versus 3049 (27.6) versus 970 (26.7)	Advanced adenoma (≥ 1 cm, > 20% villous or high-grade dysplasia) and CRC at screening FS, or CPY or DCBE in those FS- or FIT-positive	35 (FIT by mail, GP, screen- ing centre) versus 213 (FS or FS + FIT) versus 4 (FIT by choice) versus 16 (FS by choice)	14.9 (10.5, 20.1) (FIT) versus 52.3 (45.6, 59.6) (FS or FS + FIT)	8 (FIT by mail, GP, screening centre) versus 14 (FS or FS + FIT) versus 2 (FIT by choice) versus 4 (FS by choice)	3.4 (1.5, 6.7) (FIT) versus 3.4 (1.9, 5.8) (FS or FS + FIT)
Weissfeld <i>et al.</i> ²⁶	One-off FS (as part of multiple- screen intervention group) versus usual care group	77 465	64 658 (83.5) received FS	Advanced adenoma (≥ 1 cm, > 20% villous or tubulovillous, severe or high-grade dysplasia) and CRC at screening FS, or recorded in medical notes within 365 days of screening	Positive screen in 15 150; clinical follow- up in 11 241 (74.2); 2147 high-risk adeno- mas detected	33.2 (31.8, 34.6)	180	2.8 (2.4, 3.2)

Table 3 (Continued)

Reference	Intervention versus comparison	n	Participation*	Outcomes	Advanced adenoma		Colorectal cancer	
					No. detected at screening	Rate per 1000 screened†	No. detected at screening	Rate per 1000 screened†
MACS Group ³⁹	One-off FIT versus one-off FIT + FS versus one-off CTC versus one-off CPY	1333 (group sizes not given)	125 returned FIT versus 52 FIT + FS versus 38 accepted CTC versus 63 accepted CPY	Advanced colorectal neoplasia (adenoma > 1 cm, villous histology, high-grade dysplasia or carcinoma) at screening	1 (FIT) versus 0 (FIT + FS) versus 1 (CTC) versus 5 (CPY)	Unclear denominator	0	Unclear denominator
Segnan <i>et al.</i> ⁴⁰	Biennial FIT versus one-off FS versus one-off CPY	6075 versus 6018 versus 6021	1965 (32.3) versus 1944 (32.3) versus 1597 (26.5)	Advanced adenoma (any adenoma > 1 cm, villous histology, high-grade dysplasia or carcinoma <i>in situ</i>) and CRC at screening FS or CPY, or CPY in those FIT-positive	21 (FIT) versus 88 (FS) versus 100 (CPY)	10.7 (6.6, 16.3) versus 45.3 (36.5, 55.5) versus 62.6 (51.2, 75.6)	2 (FIT) versus 12 (FS) versus 13 (CPY)	1.0 (0.1, 3.7) versus 6.2 (3.2, 10.8) versus 8.1 (4.3, 13.9)
Hol <i>et al.</i> ⁴²	One-off FOBT versus one-off FIT versus one-off FS	4798 versus 4843 versus 4700	2351 (49.0) versus 2975 (61.4) versus 1386 (29.5)	Advanced adenoma (≥ 1 cm, ≥ 25% villous or high-grade dysplasia) and CRC detected by screening FS, and CPY in those FOBT-, FIT- or FS-positive	22 (FOBT) versus 59 (FIT) versus 103 (FS)	9.4 (5.9, 14.1) versus 19.8 (15.1, 25.5) versus 74.3 (61.1, 89.4)	6 (FOBT) versus 14 (FIT) versus 8 (FS)	2.6 (0.9, 5.5) versus 4.7 (2.6, 7.9) versus 5.8 (2.5, 11.3)

Values in parentheses are *percentages and †95 per cent confidence intervals. FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; CPY, colonoscopy; DCBE, double-contrast barium enema; CRC, colorectal cancer; UKFSSTI, UK Flexible Sigmoidoscopy Screening Trial Investigators; FIT, faecal immunochemical test; GP, general practitioner; MACS, Multicentre Australian Colorectal-neoplasia Screening; CTC, computed tomography colonography.

those with self-reported anxiety or knowledge of previous colorectal cancer test results³⁸. Significantly more participants screened by FS described it as 'burdensome' compared with those screened by FOBT/FIT (13 per cent *versus* less than 3 per cent; $P < 0.001$)⁴³. Those screened by FS were significantly less likely to be willing to attend successive screening rounds than those screened by FOBT/FIT (84 *versus* 94 per cent; $P < 0.001$)⁴³.

All the trials invited participants by post, although bowel preparation methods varied. The trials that posted participants an oral laxative (with or without an enema) reported uptake rates of 46.7 per cent³⁰ and 42.5 per cent²⁹. The trial that mailed an enema to participants (or offered nurse administration on attendance as an alternative) reported one of the lowest uptake rates (29.5 per cent)⁴². The trials that required participants to collect an enema from their general practitioner or the screening centre reported uptakes of 27.8 and 32.3 per cent^{37,40}. The trials that provided an enema administered on site before FS reported uptakes of 20.2 and 66.9 per cent^{28,35}.

Detection of advanced adenoma and colorectal cancer at screening

Thirteen papers reported on detection rates at screening of advanced adenoma and colorectal cancer (Table 3).

Detection of advanced adenoma by flexible sigmoidoscopy

Four trials reported the detection rate for advanced adenoma for FS, where this was being compared with a no-screen control group. The c.i. around the rate per 1000 detected in the UK population overlapped: 52.1 (95 per cent c.i. 40.7 to 65.5) and 46.8 (44.8 to 48.9)^{20,21}. The rates from Italy (12.1, 95 per cent c.i. 10.1 to 14.5) and the USA (33.2, 31.8 to 34.6) were both lower^{23,26}.

Detection of advanced adenoma by flexible sigmoidoscopy versus faecal occult blood test

Meta-analysis showed that, on average, screening involving FS was over seven times more effective at detecting advanced adenomas than FOBT screening that did not involve FS (risk ratio (RR) 7.23, 95 per cent c.i. 4.86 to 10.75) (Fig. 2).

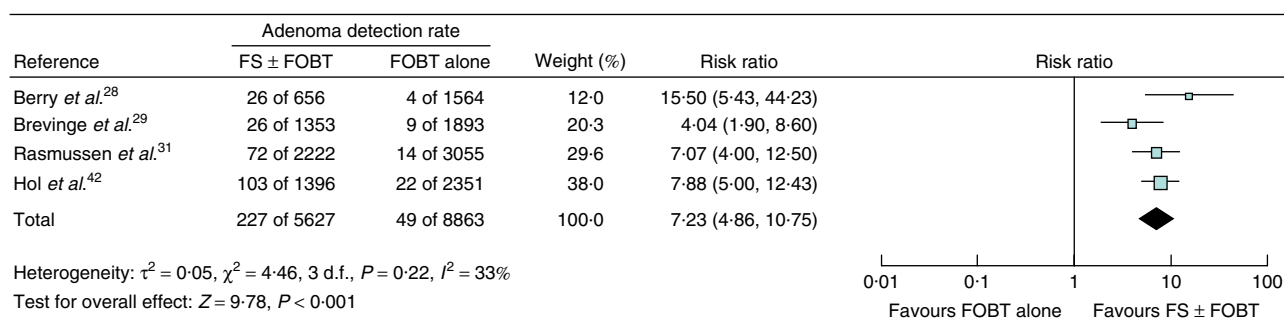


Fig. 2 Forest plot showing comparison of effectiveness of flexible sigmoidoscopy (FS) with or without faecal occult blood test (FOBT) *versus* FOBT alone for detection of advanced adenoma. A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

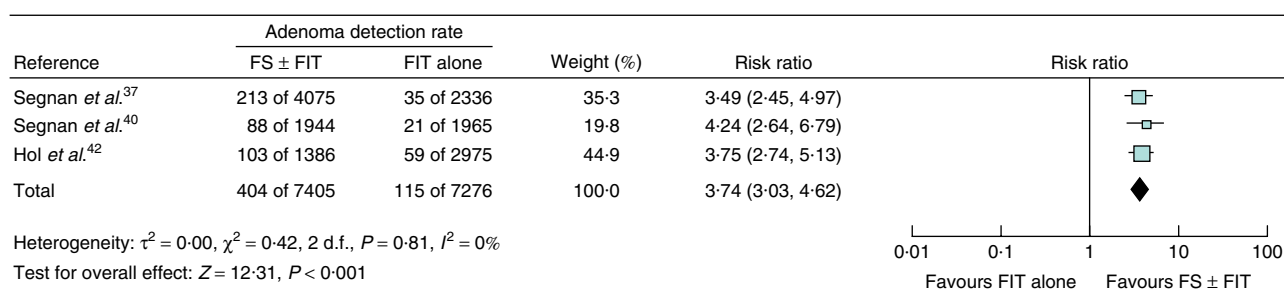


Fig. 3 Forest plot showing comparison of effectiveness of flexible sigmoidoscopy (FS) with or without faecal immunochemical test (FIT) *versus* FIT alone for detection of advanced adenoma. A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

Detection of advanced adenoma by flexible sigmoidoscopy *versus* faecal immunochemical test

In meta-analysis, screening involving FS was shown to be over three times more effective at detecting advanced adenomas than FIT screening that did not involve FS (RR 3.74, 3.03 to 4.62) (Fig. 3).

Subanalyses

Separate subanalyses comparing FOBT *versus* FS, FOBT *versus* FOBT + FS, FIT *versus* FS, FIT *versus* FS + FIT and FIT + FS *versus* FS provided similar evidence of effectiveness (data not shown).

Detection of colorectal cancer by flexible sigmoidoscopy

Four trials reported the FS detection rate for carcinoma, compared with a no-screen control group^{20,21,23,26}. Detection rates ranged from 2.8 to 6.1 per 1000.

Detection of colorectal cancer by flexible sigmoidoscopy *versus* faecal occult blood test

Meta-analysis showed that, on average, screening involving FS was over three times as effective at detecting colorectal

cancer as FOBT screening that did not involve FS (RR 3.34, 1.70 to 6.54) (Fig. 4).

Detection of colorectal cancer by flexible sigmoidoscopy *versus* faecal immunochemical test

In meta-analysis, screening involving FS was not significantly more likely to detect colorectal cancer than FIT screening that did not involve FS (RR 1.63, 0.67 to 3.97) (Fig. 5).

Subanalyses

Separate subanalyses comparing FOBT *versus* FS, FOBT *versus* FOBT + FS, FIT *versus* FS, FIT *versus* FS + FIT and FIT + FS *versus* FS provided similar evidence of effectiveness (data not shown).

Incidence of colorectal cancer following flexible sigmoidoscopy screening

Incidence following flexible sigmoidoscopy versus no screening
 An initial prospective study found no significant difference in the incidence of colorectal cancer between those screened with FS and those in a no-screen control group

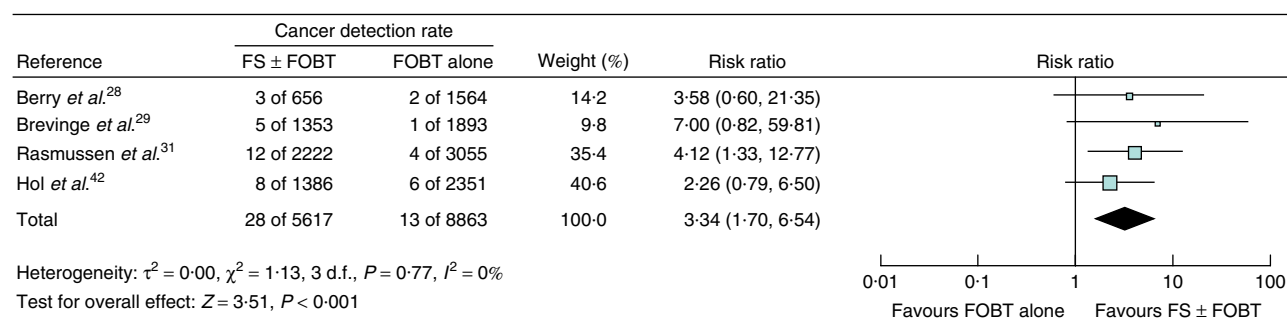


Fig. 4 Forest plot showing comparison of effectiveness of flexible sigmoidoscopy (FS) with or without faecal occult blood test (FOBT) *versus* FOBT alone for detection of colorectal cancer. A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

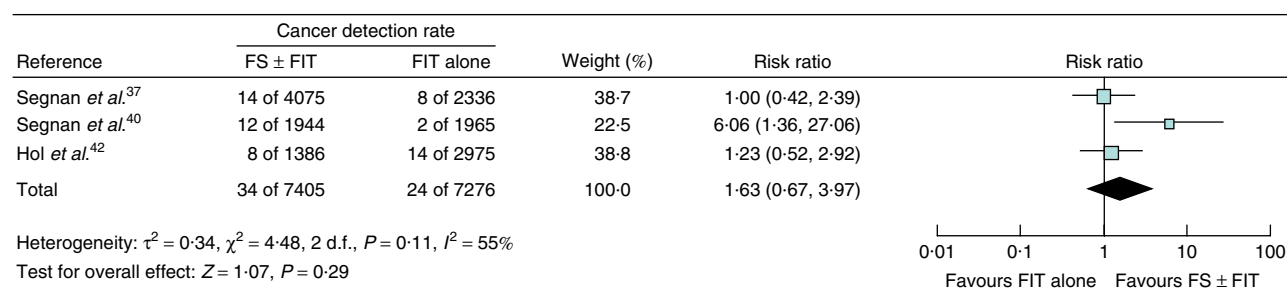


Fig. 5 Forest plot showing comparison of effectiveness of flexible sigmoidoscopy (FS) with or without faecal immunochemical test (FIT) *versus* FIT alone for detection of colorectal cancer. A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

at 7-year follow-up³⁶. Two trials have since reported a 23 per cent risk reduction (hazard ratio 0.77, 95 per cent c.i. 0.7 to 0.84), and an overall 18 per cent risk reduction (RR 0.82, 0.69 to 0.96), for subsequent incidence of colorectal cancer in those screened by FS compared with those not screened, at 11 and 10.5 years' follow-up^{22,25}.

Incidence following faecal occult blood test plus flexible sigmoidoscopy versus faecal occult blood test

One trial reported that there were eight interval cancers following negative FOBT + FS and 18 following negative FOBT, at 2–5 years' follow-up³¹.

Mortality following flexible sigmoidoscopy screening

Colorectal cancer-specific mortality following flexible sigmoidoscopy versus no screening

Four trials reported follow-up colorectal cancer mortality at 6 years³⁶, 11 years^{22,25} and 13 years³³. There was an overall reduction in colorectal cancer mortality of 29 per cent (RR 0.71, 0.61 to 0.81) in those receiving FS, compared with those randomized to receive no screening (Fig. 6).

All-cause mortality following flexible sigmoidoscopy screening

Four trials reported follow-up all-cause mortality at 6 years³⁶, 11 years^{22,25} and 13 years³³. Meta-analysis including three trials^{22,25,33} showed no difference in all-cause mortality in those receiving FS (RR 0.99, 0.91 to 1.07) (Fig. 7). One trial did not provide the absolute number of deaths and therefore could not be included in the meta-analysis, although the reported hazard ratio was consistent with result of the meta-analysis (1.02, 0.98 to 1.07)³⁶.

Adverse effects following flexible sigmoidoscopy screening

Seven trials reported the number of adverse incidents following FS screening^{20,21,23,29,35,37,39}. The most common adverse event associated with FS was bleeding (reported rates 8–306 per 10 000 screened), which was usually self-limiting^{20,29}. Nausea, faintness or dizziness at the time of the examination was reported in 7–50 per 10 000 screened^{20,23}. Bleeding and inflammation requiring admission to hospital was reported in 3–8 per 10 000 screened^{20,23}. The single death reported followed complicated surgery and probably represents an extremely rare outcome²⁰.

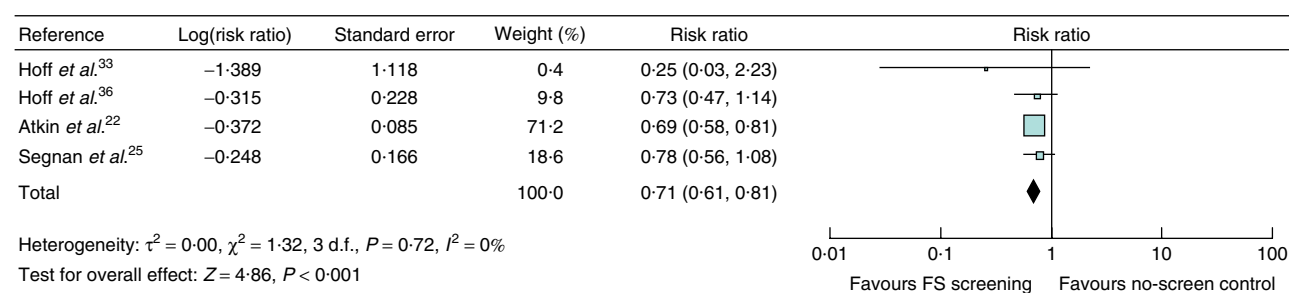


Fig. 6 Forest plot showing relative risk of death from colorectal cancer following screening with flexible sigmoidoscopy (FS) *versus* no screening. An inverse variance random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

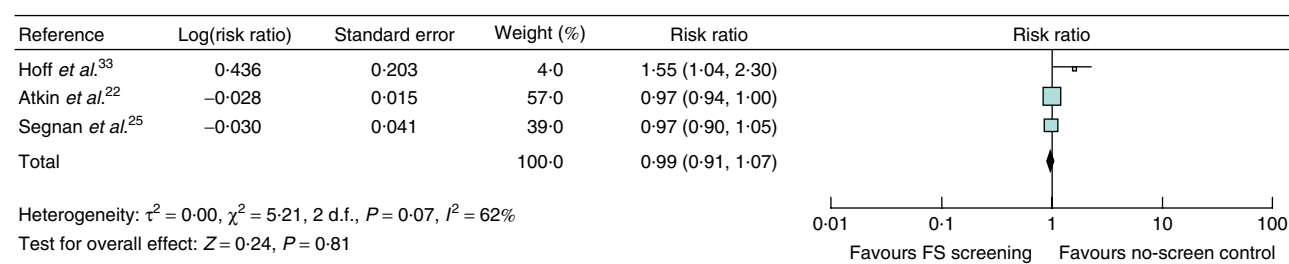


Fig. 7 Forest plot showing relative risk of death from any cause following screening with flexible sigmoidoscopy (FS) *versus* no screening. An inverse variance random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

Discussion

The present analysis suggests that FS is more effective at detecting advanced adenomas and colorectal cancers than stool-based tests. The variation in detection rates reported across trials may be explained partly by the finding that the detection rate is associated with the volume of screening activity by the endoscopist⁴¹. The increased effectiveness of FS at detecting carcinoma compared with FIT was not statistically significant, but the small number of carcinomas may mean that the sample was underpowered to detect a real difference. The incidence of colorectal cancer appears to be reduced after FS screening (compared with no screening) around a decade later, but not before. The colorectal cancer mortality rate is apparently reduced after FS screening, compared with no screening. However, these results were obtained in populations preidentified as being willing to accept FS screening^{22,25}. Thus, although the efficacy of FS screening has been demonstrated, the external validity of claiming evidence of effectiveness in unselected populations remains undemonstrated. There is also no direct evidence of superior effectiveness of FS in reducing mortality compared with stool-based tests. However, the better advanced adenoma and colorectal cancer detection rates, and the suggestion of a lower interval cancer rate³¹, point towards

a claim of FS superiority. An initial finding of increased all-cause mortality following FS screening compared with no screening³³ was not repeated in subsequent, much larger, studies^{22,25}.

However, the effectiveness of FS screening in practice risks being undermined by a tendency to achieve lower uptake rates. High uptake was generally achieved in trials that selected populations preidentified as willing to accept FS screening^{21,23}, or where the study design was known to have biased selection toward more educated and affluent participants²⁷. In unselected populations, uptake of FS screening is highly variable. One variable associated with poorer FS uptake is the prior provision of stool-based testing. It may be that an initial negative stool-based test result can reduce subsequent uptake by providing reassurance that 'all is well'. Offering FS screening as the first test may be preferable to offering it as a second test. Practical measures, such as bowel preparation involving an enema administered on site (rather than mailed or collected), may also increase uptake.

A review of cost-effectiveness studies reported that FOBT and FS colorectal cancer screening programmes were both cost-effective compared with providing no screening, but that an optimal strategy had not been identified⁴⁴. A more recent economic model has shown that the most cost-effective screening strategy when FS,

FOBT and FIT are compared is a one-off FS screening between age 55 and 60 years, followed by biennial FIT⁴⁵. However, the age of initial FS screening is highly relevant, as FS screening before the age of 59 years might be too early to detect most advanced adenomas that could develop⁴⁰.

FS is not without risk of adverse events, although deaths are rare. However, neither is FOBT/FIT screening risk-free, as participants with positive results are invited to undergo colonoscopy, with its attendant risks. The comparative risk profiles of FS *versus* FIT are unknown, and warrant further modelling before FS is used to screen whole populations.

A strength of this systematic review is its adherence to the guidance contained within the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^{46,47}. The systematic search strategy increases confidence that all relevant published randomized trials of FS screening for the prevention of colorectal cancer in general populations were found. The main limitation is that titles were selected by a single author, although the data were extracted by a second author and compared.

Colorectal cancer is a significant cause of mortality. Removal of precancerous adenomas, and early detection and treatment of cancer, has been shown to reduce this mortality risk. FS has proven efficacy in reducing colorectal cancer mortality compared with no screening, and is more effective at detecting advanced adenoma and carcinoma than stool-based tests. However, its effectiveness may be compromised in general population screening by poorer uptake. Introduction of FS as a screening method should be done on a pilot basis in populations in which it is not currently used, and close attention should be paid to maximizing uptake. The relative risk of adverse events associated with FS screening compared with stool-based tests should be quantified, and its real-world effectiveness evaluated against the most effective stool-based tests.

Disclosure

The authors declare no conflict of interest.

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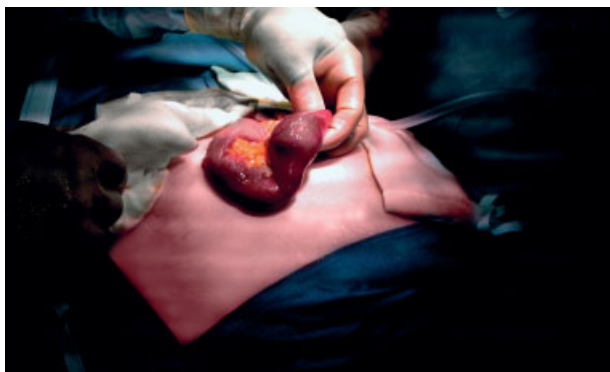
Table S1 Search terms and strategy (Word document)

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Snapshot Quiz

Snapshot Quiz 12/18

Question: This patient had a laparotomy for bowel obstruction. What is obstructing the small bowel?



The answer to the above question is found on page 1600 of this issue of *BJS*.

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