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3.4 Comparison of the preventive effects of endoscopic methods and stool-based tests for blood

To date, only two methods have been assessed in RCTs to investigate reductions in CRC incidence or mortality: gFOBT and sigmoidoscopy. This section deals with comparisons between major endoscopic and stool-based CRC screening methods (i.e. sigmoidoscopy or colonoscopy vs gFOBT or FIT) in terms of mortality or incidence outcomes, ADRs, and cost–effectiveness. Comparisons of the established screening methods (colonoscopy, sigmoidoscopy, gFOBT, and FIT) in terms of participation are described in Section 3.6.

3.4.1 Reduction in colorectal cancer incidence or mortality

No RCT is available that directly compares two or more CRC screening tests. Evidence comes from indirect comparisons of observational studies and from indirect meta-analyses, so-called network meta-analyses using Bayesian statistics. Results from network meta-analyses are considered here, in the absence of direct comparison studies. [The Working Group highlighted as weaknesses of network meta-analyses the risk of non-comparability of control groups, the different screening participation rates across trials, and the heterogeneity in study designs available for the different screening methods compared (i.e. no trials available for colonoscopy or FIT). In conclusion, results from these studies were interpreted as lower-quality evidence.]

Of the five network meta-analyses identified, two focused exclusively on RCTs and thus included only gFOBT and sigmoidoscopy (Holme et al., 2013; updated by Emilsson et al., 2017), whereas the remaining three included observational studies as well but acknowledged that comparative estimates may be biased towards

superiority of colonoscopy (Brenner et al., 2014; Elmunzer et al., 2015; Zhang et al., 2017).

The meta-analysis by Emilsson et al. (2017) included nine RCTs with 338 467 individuals randomized to screening and 405 919 individuals randomized to the control groups (Table 3.4.1). An indirect comparison of the primary analyses showed that sigmoidoscopy was superior to gFOBT in reducing CRC incidence (RR, 0.84; 95% predictive interval [PrI], 0.72–0.97). For CRC mortality, the relative risk for sigmoidoscopy versus gFOBT was 0.89 (95% PrI, 0.68–1.17). No heterogeneity was observed among the sigmoidoscopy trials, and moderate heterogeneity was reported among the gFOBT trials ($I^2 = 51.5\%$).

The remaining meta-analyses conducted indirect comparisons including both RCTs and observational studies. [Brenner et al. (2014) and Zhang et al. (2017) did not perform analyses restricted to studies in CRC screening settings as opposed to clinical settings, and therefore these network meta-analyses are not included in this evaluation.] With analyses restricted to studies in a screening setting, Elmunzer et al. (2015) reported improved effectiveness of colonoscopy in reducing CRC mortality compared with both sigmoidoscopy (RR, 0.56; 95% CI, 0.32–0.94) and gFOBT (RR, 0.49; 95% CI, 0.30–0.76). [There was significant heterogeneity among the studies included. However, when outlier studies were removed, the results were strengthened.]

3.4.2 Detection rates of adenoma and colorectal cancer

(a) Meta-analyses

Hassan et al. (2012) assessed participation in screening and compared the detection rates of advanced neoplasia between endoscopic methods and stool-based tests for blood, as well as within stool-based tests for blood (gFOBT vs FIT). Littlejohn et al. (2012) compared sigmoidoscopy either with no screening (not reported

Table 3.4.1 Network meta-analyses comparing incidence and/or mortality reduction from screening with endoscopic methods and stool-based tests for blood

Reference	Study design Population	Screening exposure; age of included subjects	Linkage or use of screening, cancer registry, death databases; data items available	CRC incidence and mortality, absolute effects	Indirect comparison RR (95% CI/95% PrI)	Adjustments/ comments
Elmunzer et al. (2015)	Meta-analysis with indirect comparison of 4 RCTs on FS, 4 RCTs on gFOBT, and 8 observational studies on colonoscopy, 3 on FS, and 13 on gFOBT Average-risk population 1 290 544 individuals in the colonoscopy observational studies, 21 950 in the FS observational studies, 414 966 in the FS RCTs, 900 843 in the gFOBT RCTs, 4 329 642 in the gFOBT observational studies	Colonoscopy: Once-only colonoscopy in all studies Age at inclusion, 50–90 yr FS: Once-only FS in all but one RCT (which used 2 rounds of screening) Age at inclusion, 55–74 yr for RCTs and 69 yr mean for 1 observational study gFOBT: Annual or biennial Age at inclusion, 45–80 yr for RCTs and 40–80 yr for observational study Test intervals not given	End-point ascertainment registries, survey, and end-point committees. No details given per study.	Absolute effects not reported	Colonoscopy vs gFOBT: Mortality: 0.49 (0.30–0.76)	No studies on FIT included Mixtures of ITT analyses from RCTs and observational studies with imbalance for design between the 3 tests
Emilsson et al. (2017)	Meta-analysis with indirect comparison of 5 RCTs on FS and 4 RCTs on gFOBT Average-risk population 338 467 individuals randomized to screening and 405 919 individuals randomized to the control groups	FS: 4 RCTs with 1 round, 1 RCT with 2 rounds Age at inclusion, 50–74 yr gFOBT: 2 RCTs with biennial screening, 1 RCT with biennial or annual screening, and 1 RCT with a mixture of different intervals Age at inclusion, 45–80 yr	End-point ascertainment through national, regional, or local registries, or survey. Some studies had end-point committee, others did not	FS: Mortality: No screening, 8 per 1000 Screening, 6 per 1000 Incidence: No screening, 20 per 1000 Screening, 16 per 1000 gFOBT: Mortality: No screening, 8 per 1000 Screening, 7 per 1000 Incidence: No screening, 20 per 1000 Screening, 19 per 1000	FS vs gFOBT: Mortality: 0.89 (0.68–1.17) Incidence: 0.84 (0.72–0.97)	The study is an update of Holme et al. (2013)

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; ITT, intention-to-treat; PrI, predictive interval; RCTs, randomized controlled trials; RR, relative risk; vs, versus; yr, year or years.

here) or with alternative screening methods. All individual studies included in these meta-analyses are summarized in Table 3.4.2.

Both meta-analyses included RCTs or controlled studies, and they overlapped in seven studies (Berry et al., 1997; Verne et al., 1998; Rasmussen et al., 1999; Segnan et al., 2005, 2007; Multicentre Australian Colorectal-neoplasia Screening (MACS) Group, 2006; Hol et al., 2010).

The meta-analysis by Hassan et al. (2012) included several comparisons of screening methods in relation to detection of advanced neoplasia, advanced adenoma, and CRC. The study found that endoscopic techniques (sigmoidoscopy and colonoscopy) were more likely than stool-based tests for blood (gFOBT or FIT) to detect advanced neoplasia (RR, 3.21; 95% CI, 2.38–4.32) and CRC (RR, 1.58; 95% CI, 0.97–2.56). Separately, the detection rates of advanced neoplasia with both colonoscopy (RR, 3.56; 95% CI, 1.79–7.09) and sigmoidoscopy (RR, 3.2; 95% CI, 1.87–5.19) were significantly higher than those with gFOBT or FIT, whereas no significant differences were observed for the detection rates of CRC.

Littlejohn et al. (2012) included six studies that compared sigmoidoscopy with FOBT for the detection of advanced adenoma. Sigmoidoscopy (alone or in combination with FOBT) was more effective than FOBT alone in detecting advanced adenoma (sigmoidoscopy vs gFOBT: RR, 7.23; 95% CI, 4.86–10.75, comparing 4 studies; sigmoidoscopy vs FIT: RR, 3.74; 95% CI, 3.03–4.62, comparing 3 studies). Similar results were observed for the detection of CRC with sigmoidoscopy (alone or in combination with gFOBT) compared with gFOBT alone (RR, 3.34; 95% CI, 1.70–6.54) and with sigmoidoscopy (alone or in combination with FIT) compared with FIT alone (RR, 1.63; 95% CI, 0.67–3.97). [The Working Group noted that these comparisons were based on a small number of cases, and that the associations were weaker or non-significant for the CRC end-point.]

(b)   Additional RCTs

Several additional RCTs published after 2012 have reported on the detection rates of advanced neoplasia, advanced adenoma, and/or CRC, comparing different screening modalities (see Table 3.4.2; Castells et al., 2014; Holme et al., 2014; Sali et al., 2016).

In a subanalysis of the population-based COLONPREV trial in Spain, which used FIT and colonoscopy in two study arms, the authors used the information from the colonoscopy up to the splenic flexure and interpreted it as sigmoidoscopy, with the aim of assessing how many colonic lesions sigmoidoscopy could detect. [The Working Group noted the possible limitation of simulating sigmoidoscopy by extrapolating from the colonoscopy results.] Simulated sigmoidoscopy was better than one-time FIT in detecting distal neoplasia (OR, 2.61; 95% CI, 2.20–3.10). Also, FIT and sigmoidoscopy did not differ significantly in their performance in detecting advanced proximal neoplasia (OR, 1.17; 95% CI, 0.78–1.76) (Castells et al., 2014).

In a trial in Norway of about 100 000 people, comparing sigmoidoscopy (n = 10 283) and the combination of FIT and sigmoidoscopy (n = 10 289), the detection rates of advanced adenoma and CRC were similar for the two modalities: the detection rates of advanced adenoma increased by 4.6% with sigmoidoscopy versus no screening and by 4.5% with combined FIT and sigmoidoscopy versus no screening, and the detection rate of CRC increased by 0.3% in both groups (Holme et al., 2014).

In a study of 9288 and 1036 residents of Florence, Italy, aged 54–65 years invited to participate in a CRC screening RCT with FIT or colonoscopy, respectively, Sali et al. (2016) reported that the detection rates of advanced neoplasia were 1.7% with first-round FIT and 7.2% with colonoscopy. The same study reported that colonoscopy was almost 5 times as likely as FIT to detect advanced neoplasia, in a model adjusted

Table 3.4.2 Individual studies included in the meta-analyses comparing detection rates of neoplastic lesions with endoscopic methods versus stool-based tests for blood

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Berry et al. (1997)[b,c] United Kingdom	6371 50–74 yr	1. gFOBT 2. gFOBT+FS 2a. Returns the gFOBT test 2b. Goes to FS	1. 50 2a. 48.4 2b. 20.2	gFOBT: 0.1/0.1 gFOBT+FS: 0.8/0.1	
Brevinge et al. (1997)[c] Sweden	6367 55–56 yr	1. FS 2. gFOBT	1. FS: 42.5 2. gFOBT: 59.5	FS: 0.8/0.2 gFOBT: 0.3/0.03	
Verne et al. (1998)[b,c] United Kingdom	3744 50–75 yr	1. FS 2. gFOBT+FS 2a. Either gFOBT returned or FS accepted 2b. Both gFOBT returned and FS accepted 3. gFOBT alone	1. 46.6 2a. 39.5 2b. 30.1 3. 31.6	FS: 2.2/0.2 gFOBT+FS: 0.1/0.1 gFOBT: 0.1/0.1	
Rasmussen et al. (1999)[b,c] Denmark	10 978 50–75 yr	1. gFOBT 2. FS+gFOBT	1. gFOBT: 56 2. FS+gFOBT: 41	gFOBT: 1.3/0.2 FS+gFOBT: 0.3/0.07	
Gondal et al. (2003)[c] Norway	20 780 50–64 yr	1. FS 2. FIT+FS 2a. FIT returned and FS accepted 2b. FIT not returned but FS accepted	1. 66.9 2a. 54.4 2b. 8.3	FS: 2.9/0.2 FIT+FS: 2.6/0.2	
Segnan et al. (2005)[b,c] Italy	28 319 55–64 yr	1. Biennial FIT (delivered by mail) 2. Biennial FIT (delivered by GP or screening facility) 3. Once-only FS 4. FS+biennial FIT 5. Patient's choice of screening test 5a. Once-only FS 5b. FS, then biennial FIT	1. 30 2. 28 3. 28 4. 28 5a. 15 5b. 13	FIT (by mail or by GP): 1.5/0.3 FIT (patient's choice): 0.8/0.4 FS (once-only or FS+FIT): 5.3/0.3 FS (patient's choice): 3.6/0.9	

Table 3.4.2 (continued)

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Federici et al. (2006)[b] Italy	2987 50–74 yr	1. FS (with further investigation with a colonoscopy if positive) 2. FIT (with further investigation with a colonoscopy if positive)	1. 7.0 2. 17.2	FIT: 0.0/0.8 FS: 0.0/2.8	There was a significant effect of socioeconomic status on the probability of participation; participation was too low to enable effects of FS to be evaluated
Multicentre Australian Colorectal-neoplasia Screening (MACS) Group (2006)[b,c] Australia	1679 50–54 yr and 65–59 yr	1. FIT 2. FIT+FS 3. Colonoscopy 4. Choice of screening test 4a. "FIT kit with letter" 4b. "FIT kit requested by phone"	1. 27 2. 14 3. 18 4a. 19 4b. 23	FIT: 0.4/0 FIT+FS: 0/0 OC: 2.3/0	The study group was rather small, and thus the results were statistically uncertain
Segnan et al. (2007)[b,c] Italy	18 116 55–64 yr	1. Biennial FIT 2. FS once 3. Colonoscopy once	1. FIT: 32.3 2. FS: 32.3 3. OC: 26.5	FIT: 0.3/0.03 FS: 1.5/0.2 OC: 1.7/0.2	
Hol et al. (2010)[b,c] The Netherlands	15 011 50–74 yr	1. gFOBT 2. FIT 3. FS (with further investigation with a colonoscopy if positive)	1. 49 2. 62 3. 32	gFOBT: 0.5/0.1 FIT: 1.2/0.3 FS: 2.2/0.2	
Lisi et al. (2010)[b] Italy	8378 55–64 yr	1. gFOBT 2. Colonoscopy	1. gFOBT: 27.1 2. OC: 10.0	gFOBT: 0.12/0.02 OC: 0.63/0.05	
Quintero et al. (2012)[b] Spain	40 453 50–69 yr	1. FIT 2 Colonoscopy	1. FIT: 33.8 2. OC: 18.5	FIT: 0.8/0.1 OC: 1.8/0.1	
Castells et al. (2014) Spain	57 404 50–69 yr	1. Colonoscopy 2. FIT	1. 21 2. 35	FS[d]: 5.9/0.4 FIT: 2.4/0.3	FS underperforms for women aged 50–59 yr Both FS and FIT were limited in the detection of advanced proximal neoplasia FS was better in the detection of distal neoplasia

Table 3.4.2 (continued)

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Holme et al. (2014) Norway	100 210 50–64 yr	1. FS 2. FS+FIT (with further investigation with a colonoscopy if positive)	1. 65.1 2. 60.9	FS: 4.6/0.3 FS+FIT: 4.5/0.3	
Sali et al. (2016) Italy	16 087 54–65 yr	1. Biennial FIT 2. Colonoscopy	1. 50.4 2. 14.8	FIT: 1.6/0.1 OC: 7.2/0.0	

CRC, colorectal cancer; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; GP, general practitioner; OC, optical colonoscopy; yr, year or years.

[a] Adjusted for attendance (intention-to-treat analysis).

[b] Included in meta-analysis by Hassan et al. (2012).

[c] Included in meta-analysis by Littlejohn et al. (2012).

[d] FS yield was estimated from the results obtained in the colonoscopy by considering lesions detected in the rectum and sigmoid colon and according to the criteria proposed in the United Kingdom Flexible Sigmoidoscopy Screening Trial.

for sex, age, randomization group, and socioeconomic status (RR, 4.72; 95% CI, 2.44–9.13).

3.4.3 Cost–effectiveness

In recent years, many modelling studies (some of them conducted as part of national or international practice guideline projects) have evaluated the effectiveness of different CRC screening methods. Many of these modelling studies investigated more than one screening method or strategy. For a detailed overview of the studies on cost–effectiveness, see Section 3.2.6 and Section 3.3.6. Of the three systematic reviews of cost–effectiveness analyses of CRC screening, the most recent review by Patel & Kilgore (2015) was the only one to systematically compare all combinations of screening tests. That review included nine simulations that directly compared the costs (in United States dollars) and LYG of 10-yearly colonoscopy with those of annual gFOBT screening (Table 3.4.3). In all of the simulations, colonoscopy was more effective than annual gFOBT, and in most (six of nine simulations) the additional costs were less than US$ 50 000 per LYG. Five simulations compared 10-yearly colonoscopy versus annual HSgFOBT. In all five simulations colonoscopy was more effective than HSgFOBT and the additional costs were less than US$ 50 000 per LYG. For the comparison of 10-yearly colonoscopy versus annual FIT, the results were less consistent. In six of nine simulations, colonoscopy was more effective than FIT and more cost-effective with additional costs of less than US$ 50 000 per LYG, whereas in the other three simulations FIT was more effective and less costly than colonoscopy.

Comparisons of 5-yearly sigmoidoscopy versus annual HSgFOBT and FIT were very consistent, with 10 and 13 simulations, respectively, showing that sigmoidoscopy was less effective and more costly than these types of stool-based tests for blood. 5-Yearly sigmoidoscopy was consistently found to be more effective than

annual gFOBT, and in most of the simulations, its additional costs were less than US$ 50 000 per LYG.

For the purpose of comparing different tests with a high degree of transparency with regard to the model applied, the most comprehensive and up-to-date study is part of the work developed for the latest update of the USPSTF recommendations for CRC screening, published in 2016 (Knudsen et al., 2016). This modelling study involved three microsimulation models – Simulation Model of Colorectal Cancer (SimCRC), Microsimulation Screening Analysis (MISCAN), and Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRC-SPIN) – and used a hypothetical cohort of individuals aged 45, 50, or 55 years at the start of screening and aged 75, 80, or 85 years at the end of screening. A 100% participation rate in screening was assumed for all scenarios.

The following seven screening strategies were compared: HSgFOBT, FIT, the multitarget stool DNA (mt-sDNA) test, sigmoidoscopy (alone or in combination with stool-based testing for blood), computed tomography (CT) colonography, or colonoscopy. Different screening intervals and age ranges were explored. The primary end-point for all modelling analyses was LYG computed with the assumption that all gain from CRC detection would translate into LYG. The average LYG per 1000 people were 175–212 for HSgFOBT, 176–260 for FIT, 193–250 for mt-sDNA, 200–227 for sigmoidoscopy alone, 231–262 for sigmoidoscopy and FOBT, 184–265 for CT colonography, and 264–285 for colonoscopy. Although the ranges in LYG overlap for the different screening strategies, the models consistently found the highest LYG with 10-yearly colonoscopy, followed by the stool-based tests for blood, and the lowest LYG for sigmoidoscopy, which improved when sigmoidoscopy was combined with FOBT (Table 3.4.4).

Table 3.4.3 Systematic comparison of cost–effectiveness of endoscopic methods versus stool-based tests for blood for colorectal cancer screening

Strategy (test 1 vs test 2)	No. of studies	No. of simulations	No. of simulations in which test 1 is more effective and less costly than test 2	No. of simulations in which test 1 is more effective than test 2 and its additional costs are < US$ 50 000 per LYG	No. of simulations in which test 1 is more effective than test 2 and its additional costs are > US$ 50 000 per LYG	No. of simulations in which test 1 is less effective and more costly than test 2
10-yearly colonoscopy vs annual gFOBT	6	9	0	6	3	0
10-yearly colonoscopy vs annual HSgFOBT	2	5	0	5	0	0
10-yearly colonoscopy vs annual FIT	6	9	0	6	0	3
5-yearly FS vs annual gFOBT	5	13	0	9	4	0
5-yearly FS vs annual HSgFOBT	2	10	0	0	0	10
5-yearly FS vs annual FIT	5	13	0	0	0	13

FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT; LYG, life year gained; vs, versus.

Adapted from Patel SS, Kilgore ML, *Cancer Control* (Volume 22, Issue 2) pp. 248–258, copyright © 2015 by SAGE Publications. Reprinted by permission of SAGE Publications, Inc. (Patel & Kilgore, 2015).

Table 3.4.4 Modelling studies comparing colorectal cancer incidence or mortality reduction or quality-adjusted life years gained for different screening strategies

Reference Country	Model type Validation	Screening strategies considered	Population (age, gender, risk factors), screening intervals, and time frame of effect	Assumed compliance with screening interventions and follow-up	Background risk of disease	Outcome
Telford et al. (2010) Canada	Probabilistic Markov model No validation	10 strategies; all included in Knudsen et al. (2016), and at different intervals and combinations	Population aged 50 yr at average risk for CRC	Not known	Not known	**Relative reductions in CRC incidence and mortality vs no screening:** annual gFOBT: 44%, 55% annual FIT: 65%, 74% 10-yearly colonoscopy: 81%, 83%
Knudsen et al. (2016) USA	3 microsimulation models: SimCRC, MISCAN, and CRC-SPIN Validated against UKFSST (2010 data)	HSgFOBT FIT with cut-off of 100 ng (Hb) per mL (20 µg Hb/g faeces) mt-sDNA Sigmoidoscopy alone Sigmoidoscopy with HSgFOBT or FIT CTC Colonoscopy	Previously unscreened people aged 40 yr with no known CRC For each screening modality, evaluated multiple ages to start screening (45, 50, 55 yr) and end screening (75, 80, 85 yr) and multiple screening intervals Lifetime risk	Assumed 100% adherence to all procedures for all scenarios	CRC incidence: lifetime risk for people aged 40 yr, 67–72 per 1000 CRC mortality: lifetime risk for people aged 40 yr, 27–28 per 1000	**Life years gained from CRC diagnosis per 1000[a]:** HSgFOBT: 175–212 FIT: 176–260 mt-sDNA: 193–250 Sigmoidoscopy alone: 200–227 Sigmoidoscopy with HSgFOBT or FIT: 231–262 CTC: 184–265 Colonoscopy: 264–285
Sekiguchi et al. (2016) Japan	Markov model No validation	Strategy 1: annual FIT Strategy 2: colonoscopy Strategy 3: colonoscopy+annual FIT	Population at average risk aged 40 yr at start of screening	60% for all strategies	Not given	**Incremental cost per QALY gained:** Strategy 1 was dominated by strategy 3 For strategy 2 vs strategies 1 and 3, ¥293 616 and ¥781 342, respectively
Aronsson et al. (2017) Sweden	Markov decision analysis model No validation	FIT, 2 rounds Colonoscopy once Biennial FIT 10-yearly colonoscopy	Swedish population, based on scenario in screening of CRC (age 60 yr at start of screening)	Colonoscopy: 38% FIT: 50%	Not given	**Life years gained from CRC diagnosis per 1000[a]:** FIT, 2 rounds: 28 Colonoscopy once: 52 Biennial FIT: 54 10-yearly colonoscopy: 59

CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; CTC, computed tomography colonography; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; Hb, haemoglobin; HSgFOBT, high-sensitivity gFOBT; MISCAN, Microsimulation Screening Analysis; mt-sDNA, multitarget stool DNA; QALY, quality-adjusted life year; RCT, randomized controlled trial; SimCRC, Simulation Model of Colorectal Cancer; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial; yr, year or years.

[a] All-cause mortality or life years gained for all causes not assessed for each study.

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