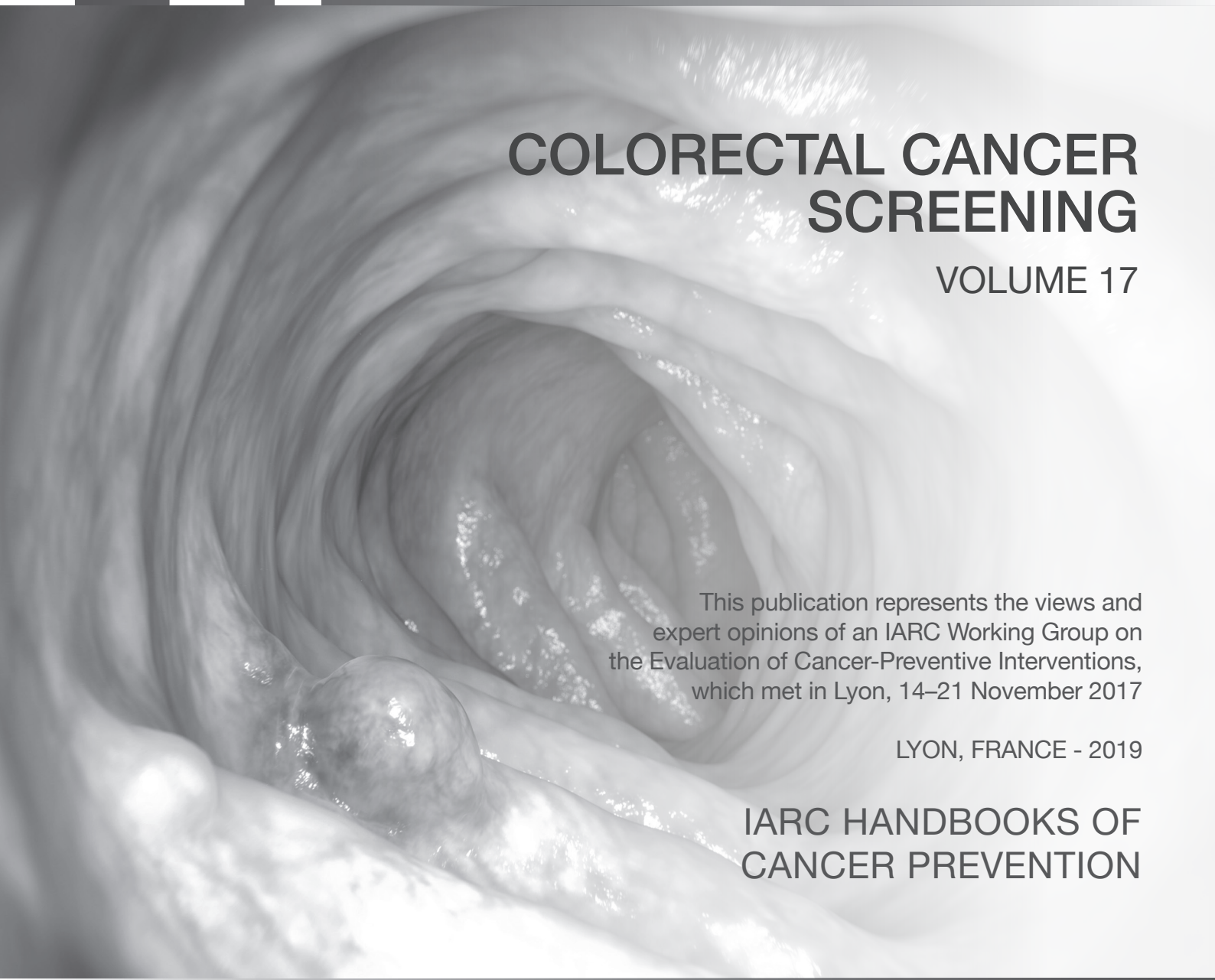
IARC HANDBOOKS



COLORECTAL CANCER SCREENING

VOLUME 17

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, 14–21 November 2017

LYON, FRANCE - 2019

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

3.2 Stool-based tests for blood

3.2.1 Techniques

(a) Introduction

Faecal occult blood tests (FOBTs), used as primary tests for CRC screening, are based on the detection of gastrointestinal occult blood in stool (Young et al., 2015; Schreuders et al., 2016). However, CRC and precancerous lesions are not the only sources of blood in faeces. In addition to other conditions (e.g. inflammatory bowel disease or colitis), other lesions such as haemorrhoids, hyperplastic polyps, and diverticular disease can lead to blood in the stool (Digby et al., 2013). The probability that FOBTs will detect gastrointestinal bleeding depends on the anatomical site of the bleeding, patient characteristics (transit time of faeces, consistency of faeces, degradation of haemoglobin [Hb] in the intestine), and factors that affect the bleeding of gastrointestinal lesions (intermittent bleeding) (Ahlquist et al., 1989); in addition, factors intrinsic to the test, such as its capacity to detect the activity or the presence of the Hb molecule or other blood constituents, will influence the detection of bleeding (Young et al., 2015). Depending on the origin of the bleeding, faeces will contain Hb, haem, or the globin moiety at different degradation stages (Rose et al., 1989; Young et al., 1990; Rockey et al., 1999).

Recently, a stool-based test combining DNA with a faecal immunochemical component has been developed for CRC screening (see Section 3.7.1).

(b) Methods and equipment

(i) gFOBT

The guaiac FOBT (gFOBT) was developed at the beginning of the 20th century by the German gastroenterologist Boas (Boas, 1914). gFOBT was the first test to be widely used for CRC screening and to be evaluated in RCTs (see Section 3.2.2). gFOBT detects blood by the use of paper impregnated with guaiac, which is extracted from the wood resin of *Guaiacum* trees, to which hydroperoxidase is added. When it comes into contact with haem (but not exclusively), the hydroperoxidase oxidizes guaiac, leading to a blue colour that is evaluated as a qualitative result (positive or negative for the presence of blood). The standard gFOBT consists of three paper cards, each with two panels, requiring sampling from three separate faeces samples (Schreuders et al., 2016). gFOBT can be analysed with or without rehydration. gFOBT does not detect Hb concentrations of less than approximately 600 µg Hb/g faeces; when gFOBT is rehydrated, the analytical sensitivity is higher, but more false-positive results are obtained (Tinmouth et al., 2015). One manufacturer has developed a high-sensitivity gFOBT (HSgFOBT) with performance similar to that of rehydrated gFOBT (Allison et al., 1996). Results of gFOBT are read with the naked eye, which leads to a subjective evaluation. Results are not quantifiable using automated instrumentation and are therefore not suited to high-throughput screening programmes.

(ii) FIT

FIT for Hb was developed in the late 1970s by the clinical pathologist Barrows. The method was based on using goat anti-Hb antibodies and demonstrated improved sensitivity and specificity compared with gFOBT in the detection of small amounts of Hb in faeces (Barrows et al., 1978). FIT detects the globin moiety of human Hb by immunoassay methodology using different methods. Two of the most widely used methods are lateral flow immunochromatography (qualitative) and immunoturbidimetry (quantitative) (Phalguni et al., 2015). FIT can detect human blood with high analytical sensitivity (Rockey, 1999), which ranges from 1 µg to 300 µg Hb/g faeces, depending on the FIT characteristics and the manufacturer. However, FIT does not usually detect small quantities of blood from the upper gastrointestinal tract (i.e. above the stomach),

because it is degraded by digestive proteolytic enzymes (Rockey et al., 1999).

In qualitative FIT, each manufacturer can adjust the conditions of the analysis at a specific concentration of Hb. Quantitative FIT has a detection limit that ranges from 6 µg to 50 µg Hb/g faeces. FIT typically relies on samples in which faeces are collected using specimen sampling devices designed for direct processing on analysers; this allows for high-throughput, standardized methodology and therefore decreases performance variability (Tinmouth et al., 2015).

The concentration of faecal Hb associated with colonic lesions increases along the adenoma–carcinoma sequence, from normal mucosa to hyperplastic polyps through to non-advanced polyps and then from advanced polyps to carcinoma (Carroll et al., 2014). Several studies have shown that there is an association between Hb concentration and the detection of colorectal neoplasia (Liao et al., 2013; Auge et al., 2014; van Doorn et al., 2015; Chen et al., 2016). Therefore, the performance of quantitative FIT depends on the cut-off level used to define a positive test result. If the FIT cut-off level is increased, fewer but more advanced lesions will be detected and fewer colonoscopies will be required (Allison et al., 2014). By using quantitative FIT, screening programmes can choose the faecal Hb cut-off level appropriate to their resources (Halloran et al., 2012; Allison et al., 2014).

(c) Technical factors that affect FOBT results and quality control

(i) gFOBT

In gFOBT, any dietary Hb or myoglobin (e.g. from meat, especially if raw or half-cooked) as well as drugs or foods that have peroxidase properties (e.g. some uncooked fruits and vegetables, such as cabbage and green beans) can potentially lead to a positive test result, although there is no consistent evidence that positivity rates differ substantially between gFOBT participants with or without restrictions of those foods (Rozen et al., 1999; Pignone et al., 2001). In contrast, antioxidants in drugs or foods (e.g. vitamin C or vitamin E) have the potential to lead to a negative test result by interfering with the oxidation of guaiac (Jaffe et al., 1975; Müftügil, 1985; Allison et al., 2014). There is no consistent evidence of medications with anticoagulant properties, such as aspirin, non-steroidal anti-inflammatory drugs, or warfarin, causing positive gFOBT results in individuals without disease (Norfleet, 1983; Greenberg et al., 1996, 1999; Kahi & Imperiale, 2004; Clarke et al., 2006) or altering the positive predictive value of gFOBT (Sawhney et al., 2010; Lee et al., 2012; Gandhi et al., 2013). Finally, the dark-green or black appearance of faeces in patients treated with iron supplements, antacids, or antidiarrhoeal treatments with bismuth can be confounded with the blue colour of a positive gFOBT (Laine et al., 1988; Rockey, 1999).

Factors that can affect gFOBT reading include interobserver variability, reproducibility of reads by laboratory personnel (Niv, 1990; Fleisher et al., 1991; Selinger et al., 2003), temperature, the design of the gFOBT card, the colour of the laboratory walls, and the brightness of the artificial lighting (Halloran et al., 2012).

Professional external quality assessment schemes are unusual, and internal quality control is usually restricted to a performance monitor feature included in the gFOBT cards. Staff training, including double reading of positive results, has a large effect on the reliability and validity of interpretation (Rabeneck et al., 2008).

(ii) FIT

FIT is analytically sensitive to low concentrations of all types of intact human Hb (excluding fetal Hb) and therefore has a significantly improved analytical specificity, avoiding cross-reactivity with dietary Hb as well as other dietary components (Allison et al., 2014).

Table 3.2.1 Comparison of the main characteristics of gFOBT and FIT for colorectal cancer screening

gFOBT	FIT
Chemical reaction	Immunochemical reaction
Nonspecific for human haemoglobin	Specific for human haemoglobin
Larger faecal specimen	Smaller faecal specimen
Cumbersome specimen collection	Less cumbersome specimen collection
Qualitative	Qualitative or quantitative
Subjective interpretation of test results	Objective interpretation of test results
Manual analysis	Automated analysis (high-throughput)
Basic quality control procedures	Advanced quality control procedures
Nonspecific for lower intestinal tract	Higher analytical specificity for lower intestinal tract
Lower sensitivity and detection rate for advanced neoplasia	Higher sensitivity and detection rate for advanced neoplasia

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

Quantitative FIT is becoming the most commonly used stool-based method for CRC screening (Schreuders et al., 2015). Many different quantitative FIT devices are commercially available; they vary in collection method, Hb stability, analytical methodology, polyclonal or monoclonal antibody characteristics, or calibration material. One of the major differences among the FITs from different manufacturers is that they use different faecal sample collection devices, which vary in the amount of faeces collected and the volumes of preservation buffers used (Fraser et al., 2012). The observed/apparent discrepancies in diagnostic performance of quantitative FITs can be largely reduced by adjusting the cut-off level to provide specific positivity rates or defined levels of specificity (Gies et al., 2018).

Manufacturers of automated quantitative FITs provide an internal quality control, and participation in an external quality assessment scheme is particularly important for national screening programmes in which different laboratories are involved (Halloran et al., 2012). Another important issue that must be taken into account is the sample quality. The globin moiety (detected with FIT) is less stable than the haem moiety (detected with gFOBT); therefore, proteolysis of globin should be avoided between sample collection and analysis. Samples show good stability at refrigerator temperatures but marked deterioration with rising temperature. Samples refrigerated at 4 °C showed no significant degradation over a period of 21 days (daily degradation, 0.3% ± 0.4%), whereas with storage at 28 °C a daily degradation of 3.7% ± 1.8% was shown (Vilkin et al., 2005; Rozen et al., 2006; Halloran et al., 2012). A decrease in positivity, a lower detection rate, and a loss of clinical sensitivity have been reported during seasons with high temperatures (van Roon et al., 2012; Doubeni et al., 2016). Manufacturers invest effort in developing new preservation buffers to improve stability, but sample conservation still represents a challenge to the organization of FIT-based screening programmes. Table 3.2.1 summarizes the main characteristics of gFOBT and FIT.

(d) Screening performance

Screening performance refers to the ability of the test to detect cancer and to distinguish cancer from non-cancer conditions. The ultimate effectiveness of CRC screening tests depends on their performance within a screening programme, i.e. across multiple rounds of testing and the complete screening episode in subjects who

Table 3.2.2 Performance of gFOBT for detection of colorectal cancer, advanced adenoma, or advanced neoplasia

Reference	Test used	Sensitivity (%)	Specificity (%)
Colorectal cancer			
Bang et al. (1986)	Hemoccult II (without rehydration)	25.0	97.6
Ahlquist et al. (1993)	Hemoccult II (without rehydration)	25.0	–
Castiglione et al. (1994)	Hemoccult II (with rehydration)	85.7	–
Castiglione et al. (1994)	Hemoccult II SENSA (HSgFOBT)	71.7	–
Allison et al. (1996)	Hemoccult II (without rehydration)	37.1	97.7
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	79.4	86.7
Lieberman et al. (2001)	Hemoccult II (with rehydration)	50.0	94.0
Sung et al. (2003)	Hemoccult II (without rehydration)	25.0	79.0
Imperiale et al. (2004)	Hemoccult II (without rehydration)	12.9	95.2
Allison et al. (2007)	Hemoccult II SENSA (HSgFOBT)	64.0	91.0
Park et al. (2010)	Hemoccult II (without rehydration)	30.8	92.4
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	54.2	96.9
Advanced adenoma			
Allison et al. (1996)	Hemoccult II (without rehydration)	30.8	98.1
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	68.6	87.5
Imperiale et al. (2004)	Hemoccult II (without rehydration)	11.0	–
Allison et al. (2007)	Hemoccult II SENSA (HSgFOBT)	41.0	–
Ahlquist et al. (2008)	Hemoccult II (without rehydration)	11.0	98.0
Ahlquist et al. (2008)	Hemoccult II SENSA (HSgFOBT)	21.0	97.0
Park et al. (2010)	Hemoccult II (without rehydration)	13.6	92.4
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	19.8	97.4
Advanced neoplasia (colorectal cancer + advanced adenoma)			
Allison et al. (1996)	Hemoccult II (without rehydration)	32.4	98.1
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	71.2	87.5
Lieberman et al. (2001)	Hemoccult II (with rehydration)	24.0	–
Sung et al. (2003)	Hemoccult II (without rehydration)	14.0	–
Park et al. (2010)	Hemoccult II (without rehydration)	16.7	92.9
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	23.8	97.7

gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT.

successfully complete diagnostic follow-up of positive test results.

Wide ranges of sensitivities of gFOBT (any type) for the detection of CRC and advanced adenomas have been described (Table 3.2.2). For FIT (any type), the pooled sensitivity and specificity for the detection of CRC (based on a meta-analysis) have been estimated to be 79% (95% confidence interval [CI], 69–86%) and 94% (95% CI, 92–95%), respectively (Lee et al., 2014). However, different sensitivities and specificities have been reported using different FIT strategies (Table 3.2.3). Several studies conducted in average-risk screening populations have shown that the sensitivity of FIT is higher than that of gFOBT in detecting both CRC and advanced neoplasia.

Another important issue for stool-based tests for blood is the cumulative performance over multiple screening rounds. A study conducted in Italy in the context of a FIT-based screening programme in the population aged 50–69 years

Table 3.2.3 Performance of FIT for detection of colorectal cancer

Number of subjects	Number of lesions	Number of studies	FIT procedure	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
111 125	422	19	All (qualitative and quantitative)	79 (69–86)	94 (92–95)
54 275	196	11	Cut-off level < 20 µg Hb/g faeces	86 (75–92)	91 (69–93)
13 796	63	6	Cut-off level 20–50 µg Hb/g faeces	63 (43–79)	96 (94–97)
42 075	156	4	Cut-off level > 50 µg Hb/g faeces	67 (59–74)	96 (94–98)
86 481	317	13	Pooled; 1 sample	78 (65–87)	95 (93–96)
15 892	78	4	Pooled; 2 samples	77 (59–89)	93 (90–95)
19 514	89	6	Pooled; 3 samples	80 (66–89)	93 (89–95)

CI, confidence interval; FIT, faecal immunochemical test.
Based on a meta-analysis by Lee et al. (2014).

showed, after five rounds of biennial screening, cumulative detection rates for CRC (0.85%) and advanced adenoma (5.9%) similar to those reported in one round of primary screening with colonoscopy between screens in a programme in Italy (subjects aged 50–69 years; 0.85% for CRC and 5.9% for advanced adenoma) and in a trial in the USA (subjects aged 50–84 years; 0.7% for CRC and 7.6% for advanced adenoma or sessile serrated lesions ≥ 1 cm) (Zorzi et al., 2018). These data suggest that the efficacy of FIT screening is closely related to the cumulative sensitivity of repeated tests; therefore, comparisons between FIT and other screening strategies should not be based on a single round of FIT. For quantitative FIT, a study showed that, after 5 years of follow-up, participants with a FIT result of between 8 µg and 10 µg Hb/g faeces (below the established cut-off level for positivity) had a significant 8-fold higher cumulative incidence of advanced neoplasia than those with a baseline of undetectable faecal Hb (Grobbee et al., 2017a). A study in Taiwan, China, reported an increase in the risk of interval cancer with increasing concentrations of faecal Hb, with relative risks ranging from 1.6 in those with concentrations of 50–99 µg Hb/g faeces to 2.9 in those with concentrations higher than 149 µg Hb/g faeces (Chiu et al., 2017). Information about the comparison of the performance of gFOBT versus FIT in relation to the detection rate of advanced neoplasia is summarized in Section 3.4.2.

(e) Additional factors that affect performance

The ability of stool-based tests to detect faecal blood is closely related to the characteristics of the colorectal lesions as well as their localization.

Because sessile serrated lesions are typically flat, non-ulcerated, and without haemorrhagic features, FOBTs fail to detect these lesions (Heigh et al., 2014), and because of their low prevalence, they are unlikely to represent a suitable target for FOBT-based screening programmes (Zorzi et al., 2017). In relation to the localization, Brenner et al. (2017) reported a higher sensitivity of FIT in the detection of advanced adenomas in the distal colon (44%; 95% CI, 38–51%) than in the proximal colon (20%; 95% CI, 14–28%).

Faecal Hb concentration varies with sex and age; it is higher in older people and in men (McDonald et al., 2011). Variations are also seen across countries and even between neighbourhoods in the same city; these differences are related to the level of socioeconomic deprivation (Fraser et al., 2014, 2015; Buron et al., 2017). FOBT performance differs between men and women (Brenner et al., 2010a). Using FIT with the same cut-off level for both sexes results in a higher sensitivity and a lower specificity for advanced colorectal neoplasia in men than

in women (Grobbee et al., 2017b). Regardless of these differences, screening programmes currently use the same strategies for both sexes in relation to the cut-off level and the screening intervals. Adjusting cut-off levels on the basis of age and sex could contribute to the efficacy of FIT-based CRC screening programmes and optimize the use of available endoscopy resources.

3.2.2 Randomized controlled trials

(a) Descriptions of RCTs

Five RCTs on screening with gFOBT have been published. The characteristics of these trials are presented in Table 3.2.4.

In the Minnesota trial, which started in 1975, 46 551 participants aged 50–80 years were randomly assigned to CRC screening once a year, to screening every 2 years, or to a control group (Mandel et al., 1993). Participants were recruited from among volunteers for the American Cancer Society and other groups in Minnesota, USA. Participants submitted six guaiac-impregnated paper slides (the Hemoccult test) containing two smears from each of three consecutive stools. The slides were mailed to a central laboratory for testing, and because of the potential for drying (and associated decrease in sensitivity of the test) caused by delays in mail delivery, the slides were rehydrated with a drop of water during processing, beginning in 1977. This procedure was fully implemented in 1982 and was used until the end of trial screening (82.5% of slides rehydrated). Participants with one or more slides that tested positive were advised to undergo diagnostic evaluation. Initially, this was with rigid sigmoidoscopy or single-contrast barium enema, which was replaced with colonoscopy in 1978.

In contrast to the Minnesota trial, the other four RCTs did not have an annual screening arm, and the slides were rehydrated in only one of those trials.

In the Nottingham trial, 152 850 individuals, identified from general practice registers in Nottingham, United Kingdom, were randomly assigned to biennial screening with Hemoccult (two samples from each of three consecutive stools) or to a control group (Hardcastle et al., 1996). Controls were not told about the study. A repeat test was sent to individuals with up to four slides that tested positive. To limit false-positive rates, those individuals were advised to restrict their diets for 2 days before taking two samples from each of three consecutive stools. Only participants with five or more slides that tested positive on the first test and those with one or more slides that tested positive on the repeat test were advised to undergo colonoscopy.

In the Funen trial, 137 485 residents of Funen, Denmark, identified from the population register of Funen County, were randomized to biennial screening with Hemoccult II, to a control group, or to not be enrolled in the study (Kronborg et al., 1996). Controls were not told about the study and continued to use health-care facilities as usual. Participants were asked to provide two samples from each of three consecutive stools. Individuals with one or more slides that tested positive were invited for colonoscopy.

In the Gothenburg trial, 68 308 residents of Gothenburg, Sweden, aged 60–64 years in three cohorts (those born in 1918–1922, 1923–1927, and 1928–1931) were randomized to screening with Hemoccult II or to a control group (Kewenter et al., 1994). A second screening round was offered 16–24 months after the initial round. Participants were asked to provide samples on 3 days. The slides were rehydrated, except those from participants born in 1918–1920. The results from the three cohorts were pooled. Participants in the 1928–1931 cohort with a positive test result on the first or second screening were retested with Hemoccult II, and only those with a positive result on the retest were invited for workup. This included an interview with a physician to determine whether the participant had experienced abdominal symptoms or rectal bleeding in the previous 6 months. A rectal examination,

Table 3.2.4 Descriptions of randomized controlled trials on colorectal cancer screening with gFOBT

Trial Country Reference[a]	Randomization	Number of subjects randomized	Accrual period for screening		Age at entry (years)	Intervention	Screening interval (years)	Number of screening rounds	Attendance at first round (%)
			Invited group	Control group					
Minnesota trial USA Mandel et al. (1993)	Individual	46 551	1975–1977	1975–1977	50–80	R-gFOBT[b]	1 2	11 (annual) 6 (biennial)	NR
Nottingham trial United Kingdom Hardcastle et al. (1996)	Individual	152 850	1981–1991	1981–1991	45–74	gFOBT	2	3–6	53.4
Funen trial Denmark Kronborg et al. (1996)	Individual	137 485	1985	1985	45–75	gFOBT	2	9	66.8
Gothenburg trial Sweden Kewenter et al. (1994)	Individual	68 308	1982–1990	1982–1990	60–64	R-gFOBT[c]	2	2–3	63.0
Finnish screening programme Finland Malila et al. (2008)	Cluster	360 492 [sic][d]	2004–2012	2004–2012	60–69	gFOBT	2	NA	68.8

gFOBT, guaiac faecal occult blood test; NA, not applicable; NR, not reported; R-gFOBT, gFOBT with rehydration.

[a] Reference of the first publication, in which the design of the trial is presented.

[b] 82.5% of the slides were rehydrated.

[c] [91.7%] of the slides were rehydrated.

[d] This value should probably be 362 492, as the sum of 181 210 and 181 282 (see text).

proctoscopy, sigmoidoscopy, and double-contrast barium enema were performed. Those with a negative workup were retested again with three Hemoccult II slides. Then those with one or more slides that tested positive underwent colonoscopy (Kewenter et al., 1988).

In Finland in 2004–2012, while the national CRC screening programme was being implemented, men and women aged 60–69 years were randomized to be invited or not to biennial CRC screening with gFOBT without rehydration. A total of 181 210 subjects were allocated to the screening arm and 181 282 to the control arm, covering 43.5% of the target population in Finland aged 60–69 years at the end of 2012 (Malila et al., 2008; Pitkäniemi et al., 2015).

(b) Results of RCTs

The published results on CRC mortality and incidence of the most recent follow-ups of the five RCTs are shown in Table 3.2.5.

For the Minnesota trial (Shaukat et al., 2013), after a mean follow-up of 30 years, the cumulative CRC mortality rate was 42 per 100 000 person-years in the annual screening group (200 deaths; 1.8%) and 50 per 100 000 person-years in the biennial screening group (237 deaths; 2.2%), compared with 63 per 100 000 person-years in the control group (295 deaths; 2.7%). Screening reduced CRC mortality (relative risk [RR], 0.68; 95% CI, 0.56–0.82 with annual screening; RR, 0.78; 95% CI, 0.65–0.93 with biennial screening). In stratified analyses, reductions in CRC mortality in the biennial screening group were significantly larger in men than in women (RR, 0.63; 95% CI, 0.48–0.82 in men; RR, 0.92; 95% CI, 0.72–1.18 in women). In addition, reductions in CRC mortality were largest in men aged 60–69 years compared with men younger than 60 years or older than 70 years ($P_{\text{interaction}} < 0.04$). An earlier publication from the Minnesota trial, on CRC incidence after 18 years of follow-up, reported cumulative CRC incidence ratios of 0.80 (95% CI, 0.70–0.90) in the annual screening group and 0.83 (95% CI, 0.73–0.94) in the biennial screening group (Mandel et al., 2000). [The Working Group noted that the reduction in CRC incidence in this RCT could be attributed to greater referral to colonoscopy among the participants because of a higher positivity rate for gFOBT with rehydration.]

For the Nottingham trial (Scholefield et al., 2012), after a median follow-up of 19.5 years, the cumulative CRC mortality rate was 91 per 100 000 person-years (1176 deaths) in the biennial screening group, compared with 100 per 100 000 person-years (1300 deaths) in the control group. Screening reduced CRC mortality (RR, 0.91; 95% CI, 0.84–0.98). There was no significant difference in the reductions in CRC mortality in men and women separately or in those younger than 60 years compared with those 60 years or older. There was no significant difference in CRC incidence between the screening group and the control group (RR, 0.97; 95% CI, 0.91–1.03).

For the Funen trial (Kronborg et al., 2004), after 17 years of follow-up (1985–2002), the cumulative CRC mortality rate was 84 per 100 000 person-years in the biennial screening group (362 deaths), compared with 100 per 100 000 person-years in the control group (431 deaths). Screening reduced CRC mortality (RR, 0.84; 95% CI, 0.73–0.96). CRC incidence was similar in the screening group and the control group (RR, 1.02; 95% CI, 0.93–1.12).

For the Gothenburg trial (Lindholm et al., 2008), after 9 years of follow-up, the cumulative CRC mortality rate was 53 per 100 000 person-years in the biennial screening group (252 deaths), compared with 64 per 100 000 person-years in the control group (300 deaths). Screening reduced CRC mortality (RR, 0.84; 95% CI, 0.71–0.99). There was no difference in CRC incidence between the screening group and the control group (RR, 0.96; 95% CI, 0.86–1.06).

In the Finnish screening programme (Pitkäniemi et al., 2015), after a median follow-up of 4.5 years, the cumulative CRC mortality rate

Table 3.2.5 Results of randomized controlled trials on colorectal cancer screening with gFOBT

Trial Country Reference	Age at enrolment/ screening (years)	Duration of follow-up (years)	Number of subjects	CRC mortality		CRC incidence	
				RR	95% CI	RR	95% CI
Minnesota trial USA Shaukat et al., (2013)	50–80	Mean, 30[a]	46 551	0.68 0.78	(0.56–0.82) (annual) (0.65–0.93) (biennial)	0.80 0.83	(0.70–0.90) (annual) (0.73–0.94) (biennial)
Nottingham trial United Kingdom Scholefield et al. (2012)	45–74	Median, 19.5	152 850	0.91	(0.84–0.98)	0.97	(0.91–1.03)
Funen trial Denmark Kronborg et al. (2004)	45–75	Mean, 17	137 485	0.84	(0.73–0.96)	1.02	(0.93–1.12)
Gothenburg trial Sweden Lindholm et al. (2008)	60–64	Mean, 9	68 308	0.84	(0.71–0.99)	0.96	(0.86–1.06)
Finnish screening programme Finland Pitkäniemi et al. (2015)	60–69	Median, 4.5	360 492 [sic][b]	1.04	(0.84–1.28)	1.11	(1.01–1.23)

CI, confidence interval; CRC, colorectal cancer; gFOBT, guaiac faecal occult blood test; RR, relative risk.

[a] Incidence ratios based on 18 years of follow-up (Mandel et al., 2000).

[b] This value should probably be 362 492 (see Table 3.2.4).

Table 3.2.6 Results of meta-analyses of randomized controlled trials on the efficacy of colorectal cancer screening with gFOBT

Reference	Maximum duration of follow-up (years) of all RCTs included	Population		Number of CRC deaths		CRC mortality	
		Screened	Control	Screened	Control	RR	95% CI
Towler et al. (1998)[a,b]	10	172 734	156 908	885	928	0.84	0.77–0.93
Moayyedi & Achkar (2006)[c]	18	122 778	122 439	1002	1146	0.87	0.80–0.95
Hewitson et al. (2008)[a,b]	17	172 734	156 908	1477	1592	0.84	0.78–0.90
Fitzpatrick-Lewis et al. (2016)[a,d]	30	156 737	156 443	1990	2326	0.82	0.73–0.92

CI, confidence interval; CRC, colorectal cancer; gFOBT, guaiac faecal occult blood test; RCT, randomized controlled trial; RR, relative risk.

[a] Towler et al. (1998), Hewitson et al. (2008), and Fitzpatrick-Lewis et al. (2016) included all of the RCTs described in Table 3.2.4 except the Finnish screening programme.

[b] Towler et al. (1998) and Hewitson et al. (2008) included both the annual screening arm and the biennial screening arm of the Minnesota trial.

[c] Moayyedi & Achkar (2006) did not include the Gothenburg trial and included only the biennial screening arm of the Minnesota trial.

[d] Fitzpatrick-Lewis et al. (2016) included only the annual screening arm of the Minnesota trial and excluded 875 subjects whose records were not traceable in the Office for National Statistics database at the time of the analysis.

was 21.1 per 100 000 person-years in the biennial screening group (170 deaths), compared with 20.4 per 100 000 person-years in the control group (164 deaths). There was no reduction in CRC mortality (RR, 1.04; 95% CI, 0.84–1.28) or in CRC incidence (RR, 1.11; 95% CI, 1.01–1.23) as a result of screening.

(c) Results of meta-analyses of RCTs

The results of the four published meta-analyses of RCTs on the efficacy of CRC screening with gFOBT are shown in Table 3.2.6. The first meta-analysis was published in 1998 (Towler et al., 1998), and the most recent was published in 2016 (Fitzpatrick-Lewis et al., 2016). Three of the meta-analyses (Towler et al., 1998; Hewitson et al., 2008; Fitzpatrick-Lewis et al., 2016) included the results from the Minnesota, Nottingham, Funen, and Gothenburg trials described in Table 3.2.4, although Fitzpatrick-Lewis et al. (2016) included only the annual screening arm of the Minnesota trial. The other meta-analysis (Moayyedi & Achkar, 2006) did not include the Gothenburg trial and excluded the results from the annual screening arm of the Minnesota trial. The findings across the different meta-analyses are remarkably consistent, showing a modest significant reduction in CRC mortality. The relative risks for CRC mortality ranged from 0.82 to 0.87. Screening with gFOBT reduced the incidence of late-stage CRC by 8% (RR, 0.92; 95% CI, 0.85–0.99), based on a pooled estimate of results from the Minnesota trial and the Nottingham trial with a combined sample of 220 284 individuals and a median follow-up of 14.25 years (Fitzpatrick-Lewis et al., 2016).

(d) FIT

There is only one cluster randomized trial that evaluated FIT screening and CRC mortality in rural China (Zheng et al., 2003; Fitzpatrick-Lewis et al., 2016). In 1989, residents aged 30 years and older from 21 townships in Jiashan County were enrolled in the trial. The residents were randomized to a screening group (10 townships) or to a control group (11 townships), which did not undergo screening. The screening and control townships were matched by age and population size into 10 pairs. Participants in the screening group completed a single FIT based on reverse passive haemagglutination. Participants with a positive FIT result underwent sigmoidoscopy

or colonoscopy. There were 94 423 participants in the screening group and 97 838 individuals in the control group. Duration of follow-up was 5–6 years, and causes of death in 1989–1996 were certified by qualified physicians. At the end of the study period, 361 deaths from CRC had occurred in the screened group and 357 in the control group. There was no significant difference in CRC mortality between the screened group and the control group (RR, 0.88; 95% CI, 0.72–1.07). [The Working Group noted that the limitations of this trial included enrolment of younger people and short follow-up.]

3.2.3 Observational studies on preventive effects

This section summarizes the observational studies assessing the preventive effects of screening with gFOBT or FIT versus no screening, with CRC mortality and/or CRC incidence as an outcome. Studies that compare gFOBT with FIT in terms of the detection rates of adenoma, neoplasia, or CRC are summarized in Section 3.4.2.

(a) Cohort studies

A total of nine cohort studies (including a nested case–control study) conducted in China, Denmark, Finland, France, Italy, Japan, Scotland, and Taiwan, China, have reported on CRC mortality and/or CRC incidence after screening with gFOBT or FIT, mostly in the age group 50–69 years (Table 3.2.7).

(i) gFOBT

A nested case–control study with annual gFOBT screening after age 40 years and matched for age, sex, and family history of both CRC and adenomas was conducted in Italy in 1978–1995. A large but non-significant reduction in CRC mortality was reported (odds ratio [OR], 0.64; 95% CI, 0.36–1.15) for attenders (ever screened) versus non-attenders (never screened). Also, the reduction in CRC mortality increased with the number of screening tests: having two or three tests reduced the risk by 29%, whereas having four or more tests reduced the risk by up to 66% (Bertario et al., 1999).

In a pilot study conducted in Finland, the population aged 50–63 years from three municipalities in southern Finland was invited to screening. A total of 1785 individuals were screened only once with a gFOBT developed in Finland (Malila et al., 2007). After 25 years of follow-up, no effects on CRC mortality or CRC incidence were observed compared with the general Finnish population, in terms of standardized mortality and incidence rates. The pilot study was stopped after one screening round, because of costs and low specificity. [The Working Group noted as limitations that this was a small population with only one round of screening, the participation rate was high (69%), and the positivity rate of the gFOBT used was higher than in other studies, i.e. 19%.]

The large matched cohort study by Libby et al. (2012) included the Scottish arm of the United Kingdom pilot of gFOBT screening, which covered individuals resident in three Scottish National Health Service Boards (Steele et al., 2009). The pilot consisted of three rounds of biennial gFOBT screening carried out in more than 379 655 individuals aged 50–69 years. Follow-up was up to 10 years, and the overall screening participation was 60.6%. A 10% relative reduction in CRC mortality was reported with an intention-to-screen analysis comparing those invited versus those not invited to screening (RR, 0.90; 95% CI, 0.83–0.99), and a 17% relative reduction was reported after adjusting for participation (RR, 0.83; 95% CI, 0.79–0.87). [The Working Group noted that the reported 95% confidence interval of the mortality relative risk adjusted for participation appeared to be too narrow and recalculated it to be 0.74–0.92. Although the effect appeared to be stronger in men and in younger age groups, the Working Group attributed this to

Table 3.2.7 Cohort studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
gFOBT							
Bertario et al. (1999) Milan, Italy	1978–1995 ≥ 40 Median, 7 (follow-up from 1996)	Nested case–control from a larger population-based cohort of 21 879 who participated in an organized CRC screening programme Study (cases): 95 deaths, ascertained by death certificates from municipality archives Reference (controls): 475 controls (5 per case, randomly sampled), same source as cases Matched by age, sex, area of birth; alive at the time of the case's diagnosis	1 or more (1–3, 80%) 1	Same period Same population	Age, sex, family history of CRC, personal history of adenomatous polyps	Mortality Ever vs never screened: OR: 0.64 (0.36–1.15) Time from index date (yr): ≤ 1: 2.32 (0.85–6.35) ≤ 2: 1.09 (0.48–2.44) ≤ 3: 0.88 (0.42–1.85) ≤ 4: 0.80 (0.39–1.61) ≤ 5: 0.78 (0.40–1.52) ≤ 6: 0.81 (0.43–1.52) Number of gFOBT tests: 1: 1.00 2 or 3: 0.71 (0.44–1.14) ≥ 4: 0.34 (0.16–0.75)	"Attenders" defined as those who underwent a second gFOBT within 2 yr of study admission; gFOBT without rehydration used in 1978–1983, and gFOBT with rehydration used in 1984–1995
Malila et al. (2007) Southern Finland, 3 municipalities	1979–1980 50–63 25	Study (invited and screened): 1785 Reference: the entire Finnish population	1 Once only	Same period Same counties	Age and sex	Mortality SMR: 1.17 (0.75–1.73) Incidence SIR: 1.09 (0.80–1.44)	A second test was used to classify the population into screen-negatives and screen-positives. If still positive, colonography or endoscopy was offered at the central hospital A gFOBT without rehydration, developed in Finland, was used

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
Libby et al. (2012) Scotland, 3 counties	2000–2007 50–69 Maximum, 10 (follow-up from 2000)	Study (invited and screened): 379 655 Reference: 379 655 matched controls from non-pilot health boards	3 2	Same period Different counties	Age, sex, and socioeconomic deprivation	Rate ratio Mortality 0.90 (0.83–0.99) 0.83 (0.79–0.87), adjusted for participation Men: 0.89 (0.79–0.99) Women: 0.94 (0.82–1.09) 50–59 yr: 0.86 (0.74–0.99) 60–69 yr: 0.94 (0.84–1.05)	Non-participants had increased CRC mortality vs controls, RR, 1.21 (1.06–1.38); gFOBT without rehydration was used
Hamza et al. (2014) Burgundy, France	1988–2009 45–74 Maximum, 21 (followed up until December 2009)	Study: 45 642 residents of 12 districts were invited to screening, 2409 had first screen Reference: population in 17 non-screened districts with the same CRC incidence as the screened population at the start	11 2	Same period Other districts in Burgundy	Age, sex, and socioeconomic status	Mortality SMR: 0.87 (0.80–0.94) Incidence SIR: 1.01 (0.96–1.06) Men: 0.85 (0.77–0.94) Women: 0.90 (0.80–1.02)	No differences by duration of follow-up or age group (> 65 vs < 65) Larger proportion of stage I CRC in those invited to screening vs non-respondents (44.1% vs 17.4%) Lack of strict randomization of controls gFOBT without rehydration was used
Bjerrum et al. (2016) Denmark, 2 counties	2005–2006 50–74 10 (follow-up from 2005); median, 8.9	Incidence-based mortality cohort study Study (invited and screened):166 277 Reference: 1 240 348 remaining Danes of the same age	1 Once only	Same period Different counties	Age and sex	Mortality (incidence-based) HR: 0.92 (0.86–0.99) Incidence HR: 0.94 (0.90–0.97) All-cause mortality HR: 0.95 (0.94–0.96)	Non-responders had higher CRC mortality and all-cause mortality vs controls [Probably gFOBT without rehydration was used (because of relatively low positivity), but not stated in the publication]

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
FIT							
Ventura el al. (2014) Florence, Italy	1993–1999 50–70 15 (followed up until 2008)	Study (invited and screened): 6961 Reference (invited but unscreened): 26 285	5 (average, 3.5) 2	Same period Same population	Age and sex	Mortality SMR: 0.59 (0.37–0.93) Incidence HR (overall): 0.78 (0.65–0.93) HR (first 6 yr): 1.06 (0.82–1.37) HR (after 6th yr): 0.60 (0.46–0.79)	Women had lower incidence, HR, 0.55 (0.48–0.63), with men as reference No differences in incidence by cancer location (distal vs proximal) SMR computed using the European standard population and SIR using the invited but unscreened population
Giorgi Rossi et al. (2015) Reggio Emilia Province, Italy	2005 (screened cohort) 1997 (non-screened cohort) 50–69 8	Incidence-based mortality cohort study Study (invited and screened): 171 785 (70% of invitees) Reference: population from the non-screened cohort with a similar age and sex structure	4 2	Different period Same counties	Age and sex	Mortality (incidence-based) IRR: 0.64 (0.52–0.78) Cumulative incidence IRR: 0.90 (0.83–0.97) All-cause mortality IRR: 0.73 (0.63–0.85)	Screened and non-screened cohorts were followed up at different time periods; showed no secular trends in CRC mortality/incidence between 1997 and 2005
Chiu et al. (2015) Taiwan, China	2004–2009 50–69 Average, 3; maximum, 6 (followed up until 2009)	Study (invited and screened): 1 160 895 References: Invited but unscreened: 4 256 804 Uninvited: not clear	1–3 2	Same period Same population	Increase in annual CRC incidence rate in Taiwan, China (1.97%) and self-selection bias (in invited vs uninvited analyses)	Cumulative mortality Screened vs unscreened: RR: 0.38 (0.35–0.42) Invited vs uninvited: RR: 0.90 (0.84–0.95)	

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
gFOBT/FIT							
Jin et al. (2013) Beijing Military General Hospital, China	1987–2005 > 50 Maximum, 22 (followed up until 2008)	Dynamic cohort of army officers (75% male) Study (invited and agreed to screen): 3863 Reference (invited and did not agree to screen, same cohort): 1241	18 1	Same period Same population	Age, sex, education level, family history of malignant tumours, body mass index, smoking, alcohol consumption, physical exercise, meat intake, and aspirin use	Mortality RR: 0.36 (0.18–0.71) Incidence RR: 0.51 (0.30–0.87)	Study of gFOBT triaged with FIT No differences in age, sex, or other major risk factors for CRC mortality or all-cause mortality observed between the 2 groups gFOBT with rehydration was used

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; vs, versus; yr, year or years.

a possible lack of statistical power.] The reduction in CRC mortality started from approximately 4 years after initial screening.

In a study conducted in 12 districts of Burgundy, France, residents aged 45–74 years were invited to biennial gFOBT screening. The average participation rate in the first round was 52.8%. A significant reduction of 13% in CRC mortality was observed after 11 screening rounds compared with CRC mortality in the population in 17 non-screened districts (standardized mortality ratio [SMR], 0.87; 95% CI, 0.80–0.94) [the Working Group calculated the participation-adjusted SMR (0.74; 95% CI, 0.63–0.86)], whereas no difference in the CRC incidence rate was observed (standardized incidence ratio [SIR], 1.01, 95% CI, 0.96–1.06) (Hamza et al., 2014).

An incidence-based mortality cohort study (Bjerrum et al., 2016) was conducted in Denmark in 2005–2006 (the study design was published in Lindebjerg et al., 2014), to assess whether participation in once-only gFOBT screening has an effect on CRC incidence and mortality. The study included 182 152 citizens aged 50–74 years (166 277 screened), and the participation rate was 48.5%. After a median of 8.9 years of follow-up, CRC mortality was lower in the screened group compared with the reference group of Danes of the same age (hazard ratio [HR], 0.92; 95% CI, 0.86–0.99). [The Working Group calculated the participation-adjusted HR for CRC mortality (0.82; 95% CI, 0.70–0.95).] A negative association with all-cause mortality was also reported (HR, 0.95; 95% CI, 0.94–0.96). Because CRC mortality and all-cause mortality were almost the same, the authors could not conclude that one round of gFOBT screening had an effect on reducing CRC mortality. CRC incidence was also lower in the screened group compared with the population in the rest of Denmark (adjusted HR, 0.94; 95% CI, 0.90–0.97). [The Working Group calculated the participation-adjusted HR for CRC incidence (0.74; 95% CI, 0.63–0.86). The Working Group highlighted as limitations that the study evaluated only one screening round and that it did not adjust for pre-screening differences in health status between the compared groups.]

(ii) FIT

Ventura et al. (2014) compared CRC mortality and incidence between two cohorts in Italy. One cohort was screened biennially with FIT for up to 11 years after the first screening round (average, 3.6 FITs), and the other cohort was unscreened (defined as those who had been invited to screening but did not comply with the first round). The study reported lower CRC mortality (SMR, 0.59, 95% CI, 0.37–0.93) and lower overall incidence (HR, 0.78; 95% CI, 0.65–0.93) in the attenders versus the non-attenders. [Some contamination in the reference group is likely in this study, with individuals who would not have attended the first round but attended the subsequent rounds. However, the direction of this potential bias would be towards the null effect.]

In a screening programme in northern Italy, launched in 2005, residents aged 50–69 years were invited to screening with biennial FIT (Giorgi-Rossi et al., 2015). After four screening rounds, the study reported a reduction of 36% in incidence-based CRC mortality (RR, 0.64; 95% CI, 0.52–0.78) compared with a historical non-screened cohort in the same area. A decrease of 10% in CRC incidence was observed after 8 years in the screened cohort compared with the control cohort (incidence rate ratio, 0.90; 95% CI, 0.83–0.97). [Data needed for the calculation of the participation-adjusted RR were not available in the published literature.]

In a study by Chiu et al. (2015), the first million individuals aged 50–69 years (20% of the target population) in Taiwan, China, were screened with biennial FIT, and the average follow-up was 3 years. The study reported a 62% decrease in CRC mortality (RR, 0.38; 95% CI, 0.35–0.42) in the screened group versus the invited but unscreened group, which resulted

in a 10% decrease (95% CI, 0.84–0.95) when adjusted for self-selection bias and increasing CRC incidence trends in Taiwan, China. [The Working Group noted that follow-up was short, leading to a possible length-time bias, and that the cumulative CRC mortality in the unscreened group could indicate that individuals previously diagnosed with CRC may have been included, leading to an overestimation of the magnitude of the effect.]

(iii) gFOBT/FIT

Jin et al. (2013) performed a study at Beijing Military General Hospital, China, in 1987–2005. A total of 3863 army officers older than 50 years were screened with annual gFOBT. Those with a positive gFOBT result completed FIT, and those with a positive FIT result were referred for colonoscopy. After 21 years of follow-up, the study reported a relative risk of CRC mortality of 0.36 (95% CI, 0.18–0.71) and a relative risk of CRC incidence of 0.51 (95% CI, 0.30–0.87). [The Working Group considered that this was a very small population in which to evaluate CRC mortality.]

(b) Case–control studies

Case–control studies can complement the results from RCTs and help to address questions related to screening efficacy and frequency (Weiss, 2013).

A total of six case–control studies, in France, Italy, Japan, and the USA, have been published that assessed CRC mortality-associated odds ratios in screened versus unscreened individuals. In addition, some reported mortality trends in relation to (i) the number of screening rounds and (ii) the time since the last screen (Table 3.2.8).

(i) gFOBT

Three studies were published in the USA between 1993 and 1999 (Selby et al., 1993; Lazovich et al., 1995; Scheitel et al., 1999). All three reported a decrease in CRC mortality with gFOBT screening (annual or biennial), ranging from 28% to 31%. Also, in one study, the magnitude of the reduction in CRC mortality was significantly larger after four rounds of biennial screening compared with one, two, or three rounds of screening (Scheitel et al., 1999). In addition, Lazovich et al. (1995) observed a significant reduction in CRC mortality only in those aged 74 years and younger at diagnosis of CRC.

In a study in Italy, Zappa et al. (1997) reported an odds ratio for CRC mortality of 0.60 (95% CI, 0.4–0.9) comparing ever screened versus never screened (205 cases and 1030 controls). The reduction in CRC mortality decreased with an increasing number of years since the most recent screening test.

A study conducted in France was published in 1999 (Faivre et al., 1999) and updated in 2014 (Hamza et al., 2014; see Section 3.2.3(a)). This population-based case–control study (178 cases and 712 population-based controls) reported an odds ratio for CRC mortality of 0.64 (95% CI, 0.46–0.91) for individuals screened with biennial gFOBT versus non-screened individuals, as well as decreasing CRC mortality with an increasing number of screening rounds (P_{trend} = 0.03). No significant reduction in CRC mortality was observed more than 24 months after the most recent round of screening.

(ii) FIT

Two case–control studies were conducted in the same region in Japan. One evaluated FIT screening and CRC mortality (Saito et al., 1995), and the other reported on FIT screening and CRC stage distribution (Nakajima et al., 2003).

Saito et al. (1995) reported a significant reduction of 60% in CRC mortality in those screened within 1 or 2 years of the case diagnosis compared with those who were unscreened; the reduction in CRC mortality decreased after 3 years and became non-significant after 4 or more years. The authors also reported trends of

Table 3.2.8 Case–control studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
gFOBT						
Selby et al. (1993) Northern California, USA Kaiser Permanente Medical Care Program (KPMCP)	1979 1981–1987 ≥ 50	Cases: 486 deaths, from KPMCP, identified by the SEER cancer registry. Death ascertained through registry or by automated linkage to California state death certificates Controls: 727, same source as cases. Matched for age, sex, and date of health plan entry. Alive at the time the case died	1 or more 1 or 2	Number of health check-ups, screening sigmoidoscopies and rectal examinations during the 10 yr before the index date, and personal history of colorectal polyps or CRC	Within 5 yr of screening test: 0.69 (0.52–0.91) Within 2 yr of screening test: 0.76 (0.55–1.03)	Probably gFOBT without rehydration was used
Lazovich et al. (1995) Washington State, USA Group Health Cooperative (GHC) of Puget Sound	1983 1986–1991 ≥ 50	Cases: 248 deaths from GHC, aged 40–84 yr at diagnosis. Ascertained from the Seattle-Puget Sound SEER cancer registry. Cause of death from medical records or from death certificate. Screening history from medical records (both cases and controls) Controls: 496 (2 per case, randomly selected), same source as cases. Matched by year of birth, sex, and year of enrolment at GHC	At least 1 2	–	Ever screened: 0.72 (0.51–1.02)	In stratified analyses, a reduction in risk was seen only in those aged ≤ 74 yr, OR, 0.65 (0.44–0.97) [Possible misclassification of diagnostic tests as screening]

Table 3.2.8 (continued)

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
Zappa et al. (1997) Florence District (rural area), Italy	1982 1984–1995 40–70	Cases: 206 deaths from CRC after age 41 yr, identified from the Florence cancer and mortality registry Screening histories of both cases and controls ascertained by automated linkage with the archives of the Centre for the Study and Prevention of Cancer in Florence Controls: 1030 (5 per case, randomly selected), same source as cases, alive at time of diagnosis of case. Matched by sex, age, and place and length of residence	At least 1 Average, 2.5	Place of birth (as indicator of socioeconomic status and lifestyle), marital status, education level, prevalent job, smoking, and family history of CRC	Ever vs never screened: 0.60 (0.4–0.9) Time (years) since most recent gFOBT test Never: 1.00 1 < 3: 0.54 (0.03–0.9) 3–6: 0.77 (0.4–1.7) > 6: 0.78 (0.3–2.2)	gFOBT without rehydration was used until 1992, then gFOBT with rehydration was used, and lastly FIT was used
Faivre et al. (1999) Burgundy, France	1988 Until 1994 45–74 8–9 yr of follow-up available for all case–control sets	Cases: 178 deaths (diagnosed in 1988–1999 and died up to December 1996) identified from the population-based cancer registry or through the data collection system of the screening programme or general practitioners. Screening histories collected from medical records Controls: 712 (4 per case, randomly sampled), same source as cases. Matched by sex, year of birth, and place of residence. Alive at the time the matched case died	1–4 2	–	Ever vs never screened: 0.67 (0.48–0.94) Number of rounds: Never: 1.00 1: 1.04 (0.67–1.58) 2: 0.50 (0.29–0.88) 3: 0.52 (0.28–0.94) 4: 0.30 (0.12–0.76) Time (months) since most recent screen: Never: 1.00 1–3: 2.02 (1.12–3.65) 4–12: 0.58 (0.34–0.99) 13–24: 0.40 (0.23–0.68) 25–36: 0.32 (0.10–1.10) 37–48: 0.84 (0.22–3.22) 49–60: 0.41 (0.05–3.72) > 60: 2.09 (0.61–7.14)	Population-based case–control study. gFOBT screening offered to all residents of the 12 districts No differences in CRC mortality by sex or cancer subsite (proximal colon, distal colon, or rectum) Screening history taken from the time screening started to the date of diagnosis of the case gFOBT without rehydration was used

Table 3.2.8 (continued)

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
Scheitel et al. (1999) Rochester, Minneapolis, USA	Screening 10 yr before diagnosis in cases 1970–1993 ≥ 45	Cases: 218 deaths, Rochester community residents, ascertained by death certificates Controls: 435 from the same area (2 per case). Matched by age, institution of diagnosis of the case, and sex, identified through the Mayo Clinic or Olmsted Medical Center registers. Alive at the time the case died	At least 1 NR	Number of periodic health examinations, number of hospitalizations, family history of CRC, and personal history of colon polyps	Years before date of CRC diagnosis of case: 0–1: 0.38 (0.13–1.08) 0–2: 0.61 (0.30–1.26) 0–3: 0.83 (0.45–1.52)	Population-based case–control study Both gFOBT without rehydration and the haem-derived porphyrin assay test were used
FIT						
Saito et al. (1995) Aomori Prefecture, Japan	1986 or 1987 40–79	Cases: 193 deaths between 1986 and 1992, identified from death certificates or the Aomori cancer registry. Cause of death from hospital medical records Controls: 577 (3 per case, randomly selected), same source as cases, alive at time of diagnosis of case, and had been living in the same area. Matched by sex and year of birth. Without history of previous CRC	At least 1 1	–	Screening within a range of the case diagnosis (years) Unscreened: 1.00 0–1: 0.40 (0.17–0.92) 0–2: 0.41 (0.20–0.82) 0–3: 0.48 (0.25–0.92) 0–4: 0.69 (0.34–1.39) 0–5: 0.77 (0.34–1.74) Time (years) since last screen: 0–1: 0.40 (0.11–0.92) 1–2: 0.39 (0.12–1.33) 2–3: 0.58 (0.16–2.07) 3–4: 0.90 (0.09–8.68) 4–5: 1.20 (0.16–9.20)	Screening histories for both cases and controls were retrieved from the staff at the Aomori Screening Centre

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NR, not reported; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results Program; yr, year or years.

increasing CRC mortality with time since the last screen [no P_{trend} was reported].

In a subsequent analysis in a subset of the same population, Nakajima et al. (2003) reported that subjects who had undergone at least one FIT screen during the previous 4 years had a reduced risk of developing advanced CRC (stage T2 to T4) by 28–46%, compared with those who were unscreened. The odds ratios for developing advanced cancer within 2–5 years after FIT were lower for the rectum (OR, 0.32–0.73) than for colon (OR, 0.84–1.18).

(iii) gFOBT and FIT

An additional case–control study in Japan showed a large reduction in CRC mortality based on only 28 CRC cases (Hiwatashi et al., 1993). [The Working Group excluded this study from the evaluation primarily because of the sample size limitations and the use of a mixture of gFOBT and FIT screening.]

(c) Ecological studies

Two ecological studies conducted in Italy compared CRC mortality and incidence in late screened areas versus early screened areas within the same geographical regions. Both of these studies reported reductions in CRC mortality (Table 3.2.9). [The Working Group considered that these results should be interpreted with caution because of limitations in study design.]

The first ecological study covered individuals aged 40–69 years in two regions in Tuscany, Italy: the Empolese–Mugello district, where screening with biennial gFOBT or FIT started in 1980 (early screened regions), and the provinces of Florence and Prato, where screening was implemented in 1985–2006 (late screened regions) (Costantini et al., 2008). The reduction in CRC mortality was larger in the early screened regions than in the late screened regions: the estimated annual percentage decrease in the age-adjusted CRC mortality rate was 2.7% (95% CI, 1.7–3.7%) in the early screened regions and 1.3% (95% CI, 0.8–1.7%) in the late screened regions. [The Working Group noted that gFOBT was used until 1996, and FIT later.]

The second ecological study evaluated the impact of a biennial FIT-based screening programme implemented in 2002–2009 in Veneto, Italy, for residents aged 50–69 years, by comparing early screened areas, where screening started in 2002–2004, with late screened areas, where screening was implemented in 2008–2009 (Zorzi et al., 2015). Before the implementation of screening, CRC mortality and incidence rates in the two areas were similar. Compared with 1995–2000, the 2006–2011 CRC mortality rates were 22% lower in the early screened areas than in the late screened areas (RR, 0.78; 95% CI, 0.68–0.89), and the mortality reduction was larger in women than in men. A substantial increase in the percentage of stage I CRCs detected by screening was observed in 2006 (> 50%) compared with no screening programme in 2000–2001 (12%), which could explain the observed reduction in mortality rates in the population in the early screened areas. [A possible limitation of this study is the contamination in the late screened areas by the presence of opportunistic screening before the introduction of the organized screening programmes.]

(d) Meta-analyses

A meta-analysis of both RCTs and observational studies evaluated the effects of gFOBT screening on CRC mortality (Elmunzer et al., 2015). Overall, the study reported a reduction of 18% in CRC mortality (n = 17; RR, 0.82; 95% CI, 0.76–0.88) and a significant reduction of 20% when only observational studies were included (n = 12; RR, 0.80; 95% CI, 0.71–0.91).

A recent meta-analysis included 44 studies (both RCTs and observational studies) published in 1992–2016 and evaluated the effects of five different CRC screening methods (gFOBT, FIT, sigmoidoscopy, colonoscopy, and a combination of sigmoidoscopy plus gFOBT) (Zhang

Table 3.2.9 Ecological studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
Costantini et al. (2008) Tuscany, Italy, 2 regions	Study population: Empolese–Mugello district, 1980 (early screened) Reference population: Florence and Prato provinces, 2000 (late screened) 40–69 until 1996 50–69 since 1996 Follow-up: 1985–2006	Study (early screened): 17 500 tested each year Reference (late screened): 38 000 tested each year	Early screened: 13 Late screened: 8 2	Different period Different population	Age at death, sex, calendar year, and geographical area (early screened or late screened)	Mortality rate Annual decrease (%) Early screened: 2.7 (1.7–3.7) Late screened: 1.3 (0.8–1.7)	gFOBT with and without rehydration was used until 1996, and FIT thereafter No differences were observed between early screened and late screened regions in overall cancer mortality rates, and both areas had similar patterns of increasing CRC incidence In the early screened area, a slight reduction in incidence was observed in 2000–2004 (after longer follow-up) A significant interaction of geographical area and calendar year in relation to mortality was found
Zorzi et al. (2015) Veneto Region, Italy, 2 areas	Study population: 2002–2004 (early screened) Reference population: 2008–2009 (late screened) 50–69 Followed-up until 2011 Early screened: 9–11	Study (early screened): 294 319 Reference (late screened): 360 468	Early screened: 3 or 4 Late screened: 1 2	Different period Same counties	Age and sex	Mortality Early screened vs late screened (2006–2011 vs 1995–2000): RR: 0.78 (0.68–0.89) Women RR: 0.64 (0.51–0.80) Men RR: 0.87 (0.73–1.04)	The study used FIT Incidence rates not available for all the local health units. In early screened areas, incidence rates reached a peak at introduction of screening and then returned to the baseline in 2007

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; RR, relative risk.

et al., 2017). When gFOBT was compared with no screening in a total of 19 studies including 2 264 603 participants, the meta-analysis reported a reduction of 14% in CRC mortality (RR, 0.86; 95% CI, 0.82–0.90), and a statistically non-significant reduction in CRC incidence, based on nine studies (RR, 0.99; 95% CI, 0.96–1.03). When FIT was compared with no screening in three observational studies (two cohort studies and one case–control study), the same meta-analysis reported a reduction of 59% in CRC mortality (RR, 0.41; 95% CI, 0.29–0.59), and a reduction of 21% in CRC incidence, based on only two studies (RR, 0.79; 95% CI, 0.69–0.92). [The Working Group noted the mixture of experimental and observational study designs included in this meta-analysis, which limits its interpretation in terms of effectiveness. Also, in the pooled estimate of FIT, one observational study in a non-screened Japanese population was included.]

3.2.4 Adverse effects

This section considers the harms of screening with stool-based tests for blood, from observational studies and RCTs. One might consider three sources of harms: harms attributable to the process of screening per se, harms directly attributable to the test, and harms of managing individuals with a positive screening result. These harms can be psychological harms or physical harms.

(a) Psychological harms

Parker et al. (2002) sent the 30-question General Health Questionnaire (a self-administered instrument for identifying minor psychiatric disorders in the general population) to 2184 people 1 month before gFOBT screening and to 1693 people 3 months after screening. Among the 843 people who completed both questionnaires, there was no significant difference in the proportion showing probable psychiatric morbidity before and after screening. The same study compared suicides among all randomized individuals in the Nottingham trial of gFOBT-based CRC screening (Hardcastle et al., 1996). There were 48 [0.06%] suicides among 74 998 controls compared with 53 [0.07%] among 75 253 people invited to screening. [The Working Group noted that the percentages reported in the article are slightly different, so either the absolute numbers or the percentages in the article must be incorrect, but this would not affect the similarity between the two groups.]

Laing et al. (2014) carried out surveys at 7–14 days and at 4 months after gFOBT screening and assessed short-term situational anxiety (using the State-Trait Anxiety Inventory) (Spielberger et al., 1983), frequency of CRC-specific worry, and mood disturbance. At 7–14 days after screening, 55 respondents with positive screening results had higher situational anxiety (mean score, 38.8) compared with 110 respondents with negative screening results matched on age and sex (mean score, 30.9; $P_{\text{difference}} = 0.007$). Respondents with positive screening results were also nearly 4 times as likely to report CRC-related mood disturbances compared with respondents with negative screening results (RR, 3.82; 95% CI, 1.09–13.43). [The Working Group noted the small sample size of the study.] There was a non-significant increase in the frequency of colon cancer-specific worry (based on answers to the question, "How often do you worry about getting colon cancer?") in those with positive screening results. At 4 months after receipt of the screening result, both situational anxiety and mood disturbance (in both groups) had returned to baseline (pre-screening) levels.

Lindholm et al. (1997) sent a questionnaire to individuals invited to participate in the Gothenburg trial of gFOBT screening (Kewenter et al., 1994). A total of 2932 participants completed the questionnaire, and 16% of them reported that they were very worried or extremely worried when they received the invitation. Subsets of participants were also interviewed by telephone. Of the 156 participants interviewed after

receiving a positive gFOBT result, 60% were very worried or extremely worried after they received that result. Of the 96 participants with a negative result on a second gFOBT, only 4% remained very worried or extremely worried after they received their second result.

In another study, Mant et al. (1990) identified 56 individuals who had received a positive gFOBT result followed by a negative gFOBT result or colonoscopy. Using a structured questionnaire, they interviewed 54 of them about their experience (e.g. "How distressed were you at the initial result?"). Two thirds reported some degree of distress after the initial positive result, but of those, only 14% were very distressed.

In the study by Parker et al. (2002), anxiety scores (using the State-Trait Anxiety Inventory) were highest after notification of a positive gFOBT result (mean scores of 44) but fell immediately after notification of a negative colonoscopy (mean scores of 31). [The Working Group noted that these findings highlight the importance of prompt follow-up of positive findings, to minimize the duration of anxiety.]

Another potential harm from screening per se is an inappropriate reaction to a negative screening result, such as ignoring subsequent cancer symptoms or adopting an unhealthy lifestyle. Miles et al. (2015) asked 296 people with CRC to complete a questionnaire on quality of life, depression, and perceived diagnostic delay. Patients with interval cancer after a negative gFOBT result reported greater perceived diagnostic delay than did patients with screen-detected disease, after adjustment for age, sex, deprivation (using the Scottish Index of Multiple Deprivation), time since diagnosis, receipt of radiotherapy or chemotherapy, and presence of comorbidities (OR, 0.37; 95% CI, 0.17–0.83; P = 0.02). However, there were no differences in perceived diagnostic delay between CRC patients with interval cancers and those not offered screening. [Hence, the Working Group noted that there is no evidence supporting that a negative screening result leads to delayed diagnosis.] Similarly, Bouvier et al. (2001) found that interval cancers (after gFOBT screening) had later stage at diagnosis than screen-detected CRC, but earlier stage at diagnosis than CRC detected in individuals who had not been screened. They also found no increased delay in cancer diagnosis in screening non-responders compared with individuals not invited for screening. [The Working Group concurred that a high rate of false-negatives does not have adverse effects, although it does of course reduce the efficacy of screening.]

(b) Physical harms of FOBT tests

There are no reports of physical harms directly associated with FOBT screening. Theoretically, one might imagine that poor hygiene associated with FOBT procedures could lead to the spread of gastrointestinal infections, but there are no published studies of such harm.

(c) Physical harms of follow-up treatment

This section considers (i) harm done while investigating a positive screening result and (ii) harm done by the treatment of an overdiagnosed CRC.

To assess the harm done while evaluating a positive screening result, one might simply consider the proportion of those screened who have a positive test result and the harms of investigating such a result. Most FOBT-positive subjects are referred for colonoscopy. Good data are available on the harms associated with screening colonoscopy (see Section 3.3.4), but fewer data are available about the harms of triage colonoscopy (i.e. colonoscopy as a result of a positive FOBT screening result). Apart from discomfort (from both the bowel preparation and the endoscopy itself), the main harms are the risks of serious bleeding, perforation of the bowel, and other serious complications leading to hospitalization. The nature of the harms is the same as with screening colonoscopy, but the frequencies of such harms are different, because

FOBT-positive subjects are more likely to require a polypectomy (Rao et al., 2009).

Table 3.2.10 presents serious harms from colonoscopy in studies of FOBT-based screening expressed as major events per 10 000 screens. Table 3.2.10 includes both RCTs and reports from routine screening programmes. [The Working Group calculated the harms per 10 000 screens. The Working Group found it difficult to ascertain how many screens were carried out in some of the studies, and approximated those from the numbers of colonoscopies and the screening positivity in some cases.] The studies had a varying number of screening rounds (range, 1–11). Based on 11 CRC screening studies (four RCTs, five programmes or pilot programmes, and two cohort studies), the colonoscopy rate (test positivity, expressed as colonoscopies per 100 screens) for stool-based testing for blood ranges from 1.0% to 8.5%, and up to 9.8% if considering the rehydrated slides of the Mandel et al. (1993) trial only. The serious harms generally increased in studies with a larger proportion receiving colonoscopy. In the reports of the two largest programmes, each with more than half a million screens (Steele et al., 2009; Logan et al., 2012), the combined rate of serious adverse events was less than 1 per 10 000 screens. Higher rates of bleeding were reported in a regional programme in France (Denis et al., 2013) and in one small study in Spain (Quintero et al., 2012), and higher rates of perforations were reported in an early trial from Sweden (Kewenter & Brevinge, 1996). In the four studies (with a total of nearly 2 million FOBT screens and 30 000 colonoscopies) that reported on deaths from colonoscopy, there were none.

(d) False-positive results

Often the frequency of the harm of a positive screening result is expressed in terms of the harm of a false-positive screening result (on the grounds that there is no real harm associated with a true-positive screening result). There is then a question about what constitutes a false-positive screening result. Given that most authors would say that the aim of FOBT is to diagnose cancer earlier, a false-positive result would be a positive test result in an individual who does not have CRC. However, many authors consider a positive test result in the presence of an advanced adenoma to be a true-positive, and some would consider it to be a true-positive if there was any adenoma.

(e) Overdiagnosis

The four RCTs of gFOBT with individual randomization all reported on CRC incidence, and none of them showed any evidence of net overdiagnosis. For the Funen trial (Kronborg et al., 2004), the relative incidence was 1.02 (95% CI, 0.93–1.12) over 17 years. For the Gothenburg trial (Lindholm et al., 2008), it was 0.96 (95% CI, 0.86–1.06) over up to 19 years. For the Nottingham trial (Scholefield et al., 2012), it was 0.97 (95% CI, 0.91–1.03) after a mean of 17 years. Scholefield et al. (2012) included a graph of cumulative incidence, which was initially larger in the screening arm, but the curves crossed at 5 years. In contrast, the Minnesota trial (Mandel et al., 2000) showed a reduction in CRC incidence ratios of 0.80 (95% CI, 0.70–0.90) for the annual screening arm and 0.83 (95% CI, 0.73–0.94) for the biennial screening arm (see Section 3.2.2). The cumulative CRC incidence curves in the screening and non-screening arms crossed at 7 years. [The Working Group concluded that depending on the sensitivity of the stool-based tests, there would be overdiagnosis of CRC if screening were to be offered to individuals with less than 5–7 years of residual life expectancy.]

(f) Harms related to the detection of adenomas

The potential harms of detection of adenomas (whether or not they are overdiagnosed) include the effects of labelling the individual as a patient, the effects of adenoma removal, and the effects of

Table 3.2.10 Serious harms from colonoscopy after a positive stool-based test for blood

Reference Country	FOBT used Setting	Number of FOBT screening tests	Test positivity (%) Number of colonoscopies	Perforation, *n* (% of colonoscopies) [per 10 000 screens]	Bleeding, *n* (% of colonoscopies) [per 10 000 screens]	Other serious events, *n* (% of colonoscopies) [per 10 000 screens]
Mandel et al. (1993, 2000); Towler et al. (1998) USA	gFOBT, with or without rehydration RCT	[> 124 959] [< 510 250] (6–11 rounds)	2.4 (without rehydration) 9.8 (with rehydration) 8.5 (combined) 12 246	4 (0.03) [0.08–0.32]	11 (0.09) [0.21–0.88]	NR
Kewenter & Brevinge (1996) Sweden	gFOBT RCT	23 916	4.1 FS: 2108 Colonoscopy: 190	FS: 3 (0.1) Colonoscopy: 2 (1.1) Combined: [2.1]	FS: 0 (0) Colonoscopy: 1 (0.5) Combined: [0.4]	NR
Robinson et al. (1999) England, United Kingdom	gFOBT RCT	136 548 (3–6 rounds)	1.1 1474	5 (0.34) [0.36]	1 (0.07) [0.07]	Deaths: 0
Faivre et al. (2004) France	gFOBT Cohort study	133 878 (6 rounds)	1.5 1298	0 (0) [0]	0 (0) [0]	Deaths: 0
Denis et al. (2007) France	gFOBT Pilot programme	90 706	3 2724	2 (0.07) [0.22]	4 (0.15) [0.44]	Hospitalizations (minor bleeding): 9 (0.33) [0.99]
Dancourt et al. (2008) France	gFOBT or FIT Cohort study	17 215	6.99 1205	0 (0) [0]	0 (0) [0]	NR
Steele et al. (2009) Scotland, United Kingdom	gFOBT Programme	507 345	1.7 8631	0 (0) [0]	0 (0) [0]	Hospitalizations: 25 (0.28) [0.49] Deaths: 0
Logan et al. (2012) England, United Kingdom	gFOBT Programme	1 079 293	1.6 17 518	17 (0.1) [0.15]	12 (0.07) [0.11]	Hospitalization: 5 (0.03) [0.04] Hemicolectomy: 1 (0.01) [0.01] Deaths: 0
Quintero et al. (2012) Spain	FIT RCT	9089 (106 had screening colonoscopy)	6.5 587	0 (0) [0]	8 (1.4) [8.8]	Hypotension or bradycardia: 2 (0.3) [2.2]
Denis et al. (2013) France	gFOBT Pilot programme	342 212	3 10 277	10 (0.09) [0.29]	31 (0.3) [0.90]	NR
Parente et al. (2013) Italy	FIT Programme	81 218	6.2 (round 1); 5.8 (round 2) 4373	2 (0.05) [0.25]	5 (0.1) [0.62]	Hospitalization: 5 (0.1) [0.62]

FIT, faecal immunochemical test; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac FOBT; NR, not reported; RCT, randomized controlled trial.

offering more intensive surveillance for individuals with advanced adenomas. The serious harms of polypectomy (such as causing major bleeding or perforation) are described and quantified in Section 3.3.4.

3.2.5 Benefit–harm ratio of FOBT screening

(a) Background

This section describes the balance between benefits and harms (i.e. benefit–harm ratio) of CRC screening with stool-based tests for blood, based on data from modelling studies that included both endoscopy and stool-based testing for blood, as well as additional studies that only presented results on gFOBT or FIT. The benefits and harms of CRC screening with stool-based tests for blood have been discussed previously (see Section 3.2.2, Section 3.2.3, and Section 3.2.4). The value of FOBT screening can be measured with life years gained (LYG) or QALYs gained. Both are common measures used in health economics, and they translate to the benefit (years of life) and harms and burdens (quality of life) a person may receive as a result of screening. It is important to note that there is not necessarily a standard for how these quality adjustments are included for different studies. Therefore, it is important for authors to carefully define the terms and for readers to understand them.

(b) Systematic reviews of life years gained

The United States Preventive Services Task Force (USPSTF) updated its review for CRC screening in 2016 (Bibbins-Domingo et al., 2016). A systematic literature review (Lin et al., 2016) and a modelling decision analysis (Knudsen et al., 2016) informed the USPSTF review. The modelling was from the three CRC microsimulation models of the Cancer Intervention and Surveillance Modeling Network (Knudsen et al., 2016) (see Table 3.3.14 in Section 3.3.5).

The USPSTF reviewed the current established tests of colonoscopy, sigmoidoscopy, HSgFOBT, and FIT and the emerging tests of computed tomography (CT) colonography and multitarget stool DNA (mt-sDNA). The evidence supported with high certainty that CRC screening provided benefit that is substantially larger than its harms (i.e. there is high certainty that the net benefit is substantial). Here, LYG for gFOBT, HSgFOBT, and FIT are discussed, compared with no screening (comparison between CRC screening tests is addressed in Section 3.4; see text and tables). In the decision analysis for the USPSTF, the LYG with screening for individuals at average risk aged 50–75 years for annual FIT were 231–260 LYG per 1000 individuals aged 40 years and required 1739–1899 colonoscopies (diagnostic and surveillance) per 1000 individuals screened in a lifetime. These numbers amount to a ratio of 6.7–8.5 colonoscopies per LYG. The efficiency ratio (the ratio of incremental colonoscopies per additional LYG compared with a less intensive strategy) varied from 17 to 24 colonoscopies per LYG. The LYG with screening for individuals at average risk aged 50–75 years for annual HSgFOBT were 232–261 LYG per 1000 individuals aged 40 years and required 2230–2287 colonoscopies (diagnostic and surveillance) per 1000 individuals screened in a lifetime. These numbers amount to a ratio of 8.5–9.8 colonoscopies per LYG. These results suggest that FIT and HSgFOBT with 100% participation can achieve comparable LYG, but that the repeated FIT over 25 years requires considerably fewer colonoscopies.

(c) QALYs and DALYs from modelling studies

This section reviews modelling studies on CRC screening with gFOBT (including HSgFOBT) and FIT. There are 18 studies that have evaluated the impact of FIT and gFOBT screening on QALYs (Table 3.2.11). All of the studies concluded that CRC screening influenced QALYs positively and resulted in a net gain in

QALYs. QALYs gained by screening with gFOBT varied from 2 QALYs per 1000 (Sharp et al., 2012) to 131 QALYs per 1000 (Lam et al., 2015) and up to 486 QALYs per 1000 (Wong et al., 2015) for a population with polyps. When screening with FIT, the net benefit was slightly higher than that for gFOBT, varying from 4 QALYs per 1000 (Dan et al., 2012) to 801 QALYs per 1000 (Wong et al., 2015) for a population with polyps. In those studies where both gFOBT and FIT were included, QALYs gained for FIT were higher than QALYs gained for gFOBT. [The wide variability across studies could be from different assumptions for the model inputs or definition of QALYs, and the Working Group highlighted that internal comparisons are more useful than comparisons across studies. In addition, the variability in estimates can be partly explained by the age of the population to which the estimates were standardized and by different strategies for intervals between screens.]

Only three modelling studies reported their results as DALYs averted for the impact of gFOBT (Table 3.2.12). Ginsberg et al. (2010) considered three regions (East Africa, eastern Europe, and the Americas), and the results ranged from 1.8 DALYs per 1000 individuals in East Africa to 17.8 DALYs per 1000 individuals in the Americas. For an Australian population at average risk aged 55–69 years, Stone et al. (2004) reported 1.5 DALYs per 1000 individuals for biennial gFOBT. For women in Hong Kong Special Administrative Region, China, Woo et al. (2007) reported 7 DALYs per 1000 individuals for annual FOBT and 3 DALYS per 1000 individuals for biennial FOBT.

3.2.6 Cost–effectiveness studies

(a) Background

A screening test can provide high value if its health benefits justify its cost. Determining what the justification boundaries are will vary according to the patient, the payer, the hospital, and even policy measures. From a payer perspective, a typical cost–benefit level in the USA is US$ 100 000 per LYG, whereas lower levels are used elsewhere. Moreover, costs for CRC screening depend on the screening test and strategy used.

Costs for the FOBT strategies can include the test itself, evaluation of each test, subsequent diagnostic colonoscopy for positive FOBT test results with potential pathology costs for evaluation of polyps, surveillance colonoscopy for patients with adenoma, and potential cancer treatment. Administrative costs for FOBT screening, including repeat testing (annually or biennially), processing of the test with reporting back to the primary care provider and to the patient, and scheduling those with positive test results for colonoscopy, are not commonly included in the cost structure, even though there are significant costs associated with the administration of a stool-based test for blood (Heitman et al., 2010; Pignone et al., 2011). Even "no screening" has an associated cost, which is the cost of treating cancers that arise symptomatically in the population. The FOBT tests themselves have limitations; not all positive test results are true positives, and not all negative test results are true negatives. For FIT, the cut-off level for positivity can be varied to accommodate the colonoscopy capacity for screening for a given area.

(b) Cost–effectiveness studies and systematic reviews

In 2000, only a few years after the publication of the results from several RCTs showing CRC mortality reduction with gFOBT screening, Helm et al. (2000) estimated the cost–effectiveness of the Minnesota trial (Mandel et al., 1993), the Nottingham trial (Hardcastle et al., 1996), and the Funen trial (Kronborg et al., 1996). Based on the European trials, gFOBT screening cost US$ 2500 per LYG compared with no screening. In 2004, Whynes et al. (2004) followed up the 1996 Nottingham trial of gFOBT with a

Table 3.2.11 Studies of quality-adjusted life years gained from screening with FOBT compared with no screening[a]

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Heitman et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	68	FIT-high-performance annually	73/76	47	
			FIT-mid-performance annually	71/74	45	
			FIT-low-performance annually	46/48	27	
			gFOBT-high[c] annually	29/30	16	
			gFOBT-low[c] annually	20/23	12	
Telford et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	73	FOBT-low annually	44/55	69	Uncertain if reported incidence/mortality reductions pertain to 100% adherence
			FIT annually	65/74	105	
Barouni et al. (2012) Islamic Republic of Iran	Cohort age 50–75 yr at average risk of CRC	68	gFOBT annually	39/50	68	
			FIT annually	60/69	104	
Dan et al. (2012) Singapore	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	27/26	4	
Sharp et al. (2012) Ireland	Cohort age 30–100 yr at average risk of CRC	53	FIT biennially, age 55–74 yr	15/36	23	
			FIT biennially, age 55–64 yr	NR/NR	17	
			FIT biennially, age 65–74 yr	NR/NR	8	
			gFOBT biennially, age 55–74 yr	1/12	7	
			gFOBT biennially, age 55–64 yr	NR/NR	5	
			gFOBT biennially, age 65–74 yr	NR/NR	2	
Whyte et al. (2012) England, United Kingdom	Cohort age 60–74 yr at average risk of CRC	54	FIT biennially	19/28	31.6	
			gFOBT biennially	9/15	15.4	
Dinh et al. (2013) USA	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	69/68	96	
Sharaf & Ladabaum (2013) USA	Cohort age 50–100 yr at average risk of CRC	100	FIT annually	62/76	77	
			gFOBT annually	47/65	67	
Ladabaum et al. (2014) Germany	Cohort age 50–75 yr at average risk of CRC	100	FIT Annually, age 50–54 yr, Biennially, age 55–75 yr	51/63	102	
			gFOBT Annually, age 50–54 yr, Biennially, age 55–75 yr	34/45	76	

Table 3.2.11 (continued)

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Lam et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas or CRC	NR	FIT annually	NR/NR	225	
			FIT biennially	NR/NR	179	
			gFOBT annually	NR/NR	131	
			gFOBT biennially	NR/NR	81	
Wong et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas	60	FIT annually	NR/NR	801	
			FIT biennially	NR/NR	672	
			gFOBT annually	NR/NR	486	
			gFOBT biennially	NR/NR	321	
Kingsley et al. (2016) USA	Cohort age 50–100 yr at average risk of CRC	67	FIT annually	NR/NR	89	No
Ladabaum & Mannalithara (2016) USA	Cohort age 50–80 yr at average risk of CRC	100	FIT annually	60/77	78	
			FIT biennially	48/70	72	
Lee & Park (2016) Republic of Korea	Cohort age 50–80 yr at average risk of CRC	25	gFOBT annually	NR/NR	246	
Pil et al. (2016) Belgium	Cohort age 56–74 yr at average risk of CRC					
	Men	43–51	FIT biennially	26.6/23	12	
	Women	53–50	FIT biennially	21.5/19	5	
Sekiguchi et al. (2016) Japan	Cohort age 40 yr at average risk of CRC	61.5	FIT annually	58/NR	202	
Aronsson et al. (2017) Sweden	Cohort age 60–80 yr at average risk of CRC	40	FIT twice (baseline and 3 years)	12/NR	26	No
			FIT biennially	NR/NR	51	

Table 3.2.11 (continued)

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Goede et al. (2017) Canada	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	NR/NR	40	
	Cohort age 50–74 yr at average risk of CRC		gFOBT biennially	NR/NR	20	
			FIT200[d] biennially	NR/NR	31	

CRC, colorectal cancer; FIT, faecal immunochemical test; FOBT, faecal occult blood test; gFOBT, guaiac FOBT; NR, not reported; QALYs, quality-adjusted life years; yr, year or years.

[a] Includes studies published after Patel & Kilgore (2015) (for studies within and outside the USA and studies in the USA) or after Lansdorp-Vogelaar et al. (2011) (for studies in the USA).

[b] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period. None of the studies considered the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening test result on an unhealthy lifestyle in their estimates of QALYs.

[c] In Heitman et al. (2010), "FOBT-high" was erroneously labelled "FOBT-low". To correct this issue, the published "FOBT-low" values were assigned to the "FOBT-high" category listed in this table, and the published "FOBT-high" values were assigned to the "FOBT-low" category listed in this table.

[d] FIT with a cut-off level of 200 ng Hb/mL.

Table 3.2.12 Studies measuring disability-adjusted life years averted from screening with gFOBT compared with no screening

Reference	Country	Population simulated[a]	Participation rate (%)	Strategy evaluated	Mortality reduction (%)	DALYs averted per 1000 individuals	Considered disability from screening?
Stone et al. (2004)	Australia	Cohort age 55–69 yr, population in 1996	NR	gFOBT biennially	NR	1.5	
Woo et al. (2007)	Hong Kong Special Administrative Region, China	Cohort age 50–74 yr, female population in 2001	100 100	gFOBT annually gFOBT biennially	17 8	7 3	
Ginsberg et al. (2010)	Canada, Cuba, USA	Cohort age 50–80 yr at average risk of CRC	57 62	gFOBT annually gFOBT biennially	NR	17.8 12.0	No
	East Africa		NR NR	gFOBT annually gFOBT biennially	NR	2.6 1.8	
	Eastern Europe		NR NR	gFOBT annually gFOBT biennially	NR	8.1 5.5	

CRC, colorectal cancer; DALYs, disability-adjusted life years; gFOBT, guaiac faecal occult blood test; yr, year or years.

[a] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period.

Table 3.2.13 Systematic reviews of studies of cost–effectiveness of screening with FOBT compared with no screening

Reference	Country	Studies included	Cost–effectiveness ratios per life year gained
Pignone et al. (2002)	USA	5 studies evaluating annual gFOBT	Annual gFOBT: US$ 5691–17 805
Lansdorp-Vogelaar et al. (2011)	All	16 studies evaluating annual gFOBT 8 studies evaluating biennial gFOBT (2 with annual and biennial gFOBT)	Annual gFOBT: cost savings–US$ 56 300 Biennial gFOBT: US$ 3400–15 500
Patel & Kilgore (2015)	USA	5 studies evaluating FIT and gFOBT (including HSgFOBT) 1 study evaluating FIT only 1 study evaluating gFOBT only	Annual gFOBT: cost savings–US$ 5360 Annual HSgFOBT: cost savings–US$ 10 Annual FIT: cost savings–US$ 800

FIT, faecal immunochemical test; FOBT, faecal occult blood test; gFOBT, guaiac FOBT; HSgFOBT, high-sensitivity gFOBT.

cost–effectiveness analysis. Under conservative assumptions, the cost of screening in the Nottingham trial was £1584 (US$ 2582) per LYG as a result of screening. These studies suggested that gFOBT screening had an acceptable cost for the benefit gained.

Three systematic reviews on the cost–effectiveness of gFOBT or FIT compared with no screening have been published (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015) (Table 3.2.13). Pignone et al. (2002) included seven cost–effectiveness studies, five of which included gFOBT. Given the time period of the review, only the lower-sensitivity gFOBT was included. All studies found gFOBT to be cost-effective, with costs ranging from US$ 5691 to US$ 17 805 per LYG. Lansdorp-Vogelaar et al. (2011) reviewed 22 modelling studies that included gFOBT strategies scheduled either annually or biennially. The cost per LYG ranged from cost savings to US$ 56 300 per LYG. [As noted above, internal comparisons of gFOBT are more informative than comparisons across the different modelling groups.] The studies in Patel & Kilgore (2015) overlapped with those in Lansdorp-Vogelaar et al. (2011) but included five additional studies for gFOBT or FIT (Vijan et al., 2001; Parekh et al., 2008; Knudsen et al., 2012; Dinh et al., 2013; Ladabaum et al., 2014; see Table 3.2.14). All gFOBT CRC screening strategies assessed were more cost-effective than no screening.

Since the review by Patel & Kilgore (2015), two new models have been published that evaluated the cost–effectiveness of CRC screening in the USA (Kingsley et al., 2016; Barzi et al., 2017) and one in the Republic of Korea (Lee & Park, 2016). One model has published updated results (Ladabaum & Mannalithara, 2016) (Table 3.2.14). The findings of these studies are consistent with those of Patel & Kilgore (2015). These newer studies often included evaluations of both gFOBT and FIT. Kingsley et al. (2016) and Barzi et al. (2017) demonstrated cost savings for annual FIT and gFOBT. Since the review by Lansdorp-Vogelaar et al. (2011), 14 new studies have been published that evaluated the cost–effectiveness of gFOBT or FIT screening outside the USA: three in Canada (Heitman et al., 2010; Telford et al., 2010; Goede et al., 2017), four in Europe (Sharp et al., 2012; Whyte et al., 2012; Pil et al., 2016; Aronsson et al., 2017), and seven in Asia (including the Middle East) (Barouni et al., 2012; Dan et al., 2012; Wang et al., 2012; Lam et al., 2015; Wong et al., 2015; Lee & Park, 2016; Sekiguchi et al., 2016), showing that FOBT screening was predominantly cost saving (Table 3.2.13).

Table 3.2.14 summarizes the cost–effectiveness for the studies presented in the previous

Table 3.2.14 Studies of cost–effectiveness of screening with FOBT compared with no screening[a]

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Aronsson et al. (2017) Sweden	Cohort age 60–80 yr at average risk of CRC	40	FIT twice (3-yr interval)	11.7/NR	Euros	26 QALYs	–17 600	–18 507	Cost saving
			FIT biennially	NR/NR	Euros	51 QALYs	136 700	143 747	2839
Barzi et al. (2017) USA	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	6/12	United States dollars	6 LYs	–112	–112	Cost saving
			FIT biennially	5/14		10 LYs	–229	–229	Cost saving
			gFOBT annually	12/17		10 LYs	–251	–251	Cost saving
			gFOBT biennially	5/14		13 LYs	–361	–361	Cost saving
Kingsley et al. (2016) USA	Cohort age 50–100 yr at average risk of CRC	67	FIT annually	NR/NR	United States dollars	89 QALYs	–524	–524	Cost saving
Ladabaum & Mannalithara (2016) USA	Cohort age 50–80 yr at average risk of CRC	100	FIT annually	60/77	United States dollars	78 QALYs	–613	–613	Cost saving
			FIT biennially	48/70	United States dollars	72 QALYs	–809	–809	Cost saving
Sekiguchi et al. (2016) Japan	Cohort age 40 yr at average risk of CRC	61.5	FIT annually (starting at age 40 yr)	58/NR	Yen	202 QALYs	–61 392	–510	Cost saving
Lam et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50 yr with pre-existing adenomas or CRC	NR	FIT annually	NR/NR	Hong Kong dollars	225 QALYs	11 600	1496	6644
			FIT biennially	NR/NR	Hong Kong dollars	179 QALYs	7790	1006	5617
			gFOBT annually	NR/NR	Hong Kong dollars	131 QALYs	19 774	2549	19 461
			gFOBT biennially	NR/NR	Hong Kong dollars	81 QALYs	10 471	1350	16 666

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Wong et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas	60	FIT annually	NR/NR	United States dollars	801 QALYs	2527	2527	3155
			FIT biennially	NR/NR	United States dollars	672 QALYs	2978	2978	4431
			gFOBT annually	NR/NR	United States dollars	486 QALYs	2001	2001	5870
			gFOBT biennially	NR/NR	United States dollars	321 QALYs	1680	1680	5234
Ladabaum et al. (2014) Germany	Cohort age 50–75 yr at average risk of CRC	100	gFOBT annually, age 50–54 yr; biennially, age 55–75 yr	51/63	Euros	102 QALYs	–1014	–1756	Cost saving
			FIT annually, age 50–54 yr; biennially, age 55–75 yr	34/45	Euros	76 QALYs	–1239	–1708	Cost saving
Dinh et al. (2013) USA	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	69/68	United States dollars	96 QALYs	–1426	–1426	Cost saving
Sharaf & Ladabaum (2013) USA	Cohort age 50–100 yr at average risk of CRC	100	FIT annually	62/76	United States dollars	77 QALYs	–498	–498	Cost saving
			gFOBT annually	47/65	United States dollars	67 QALYs	–411	–411	Cost saving

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Sharp et al. (2012) Ireland	Cohort age 30–100 yr at average risk of CRC	53	FIT biennially, age 55–74 yr	15/36	Euros	23 QALYs	40	52	2253
			FIT biennially, age 55–64 yr	NR/NR	Euros	17 QALYs	20	26	1524
			FIT biennially, age 65–74 yr	NR/NR	Euros	8 QALYs	14	18	2267
			gFOBT biennially, age 55–74 yr	1/12	Euros	7 QALYs	33	43	6108
			gFOBT biennially, age 55–64 yr	NR/NR	Euros	5 QALYs	18	23	4664
			gFOBT biennially, age 65–74 yr	NR/NR	Euros	2 QALYs	15	19	9718
Dan et al. (2012) Singapore	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	27/26	United States dollars	4 QALYs	126	126	31 500
Heitman et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	68	FIT-high annually	73/76	Canadian dollars	47 QALYs	103	98	2085
			FIT-mid annually	71/74	Canadian dollars	45 QALYs	−68	−65	Cost saving
			FIT-low annually	46/48	Canadian dollars	27 QALYs	104	99	3664
			HSgFOBT[b] annually	29/30	Canadian dollars	16 QALYs	294	280	17 484
			gFOBT[b] annually	20/23	Canadian dollars	12 QALYs	183	174	14 510
Telford et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	73	gFOBT annually	44/55	Canadian dollars	69 QALYs	632	601	10 022
			FIT annually	65/74	Canadian dollars	105 QALY	654	710	6223

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Goede et al. (2017) Canada	Cohort age 50–74 yr at average risk of CRC	100	FIT annually	NR/NR	Canadian dollars	40 QALYs	−228 300	−169 784	Cost saving
			gFOBT biennially	NR/NR	Canadian dollars	20 QALYs	220 915	164 292	
			FIT200[d] biennially	NR/NR	Canadian dollars	31 QALYs	−130 000	−96 679	Cost saving
Pil et al. (2016) Belgium	Cohort age 56–74 yr at average risk of CRC								
	Men	43–51	FIT biennially	26.6/23	Euros	12 QALYs	19	21	1582 1725
	Women	53–50	FIT biennially	21.5/19	Euros	5 QALYs	18	20	3628
Lee & Park (2016) Republic of Korea	Cohort age 50–80 yr at average risk of CRC	25	gFOBT annually	NR/NR	United States dollars	246 QALYs	−440	−440	Cost saving
Knudsen et al. (2010); Lansdorp-Vogelaar et al. (2010) USA MISCAN	Cohort age 65 yr at average risk of CRC	100	FIT annually	42.1/59.3	United States dollars	80.1 LYs	62	62	800
			gFOBT annually	31.6/51.9	United States dollars	65.7 LYs	−83	−83	Cost saving
			HSgFOBT annually	43.9/63.0	United States dollars	81.1 LYs	1	1	10
USA SimCRC	Cohort age 65 yr at average risk of CRC	100	FIT annually	54.4/70.4	United States dollars	79.8 LYs	−251	−251	Cost saving
			gFOBT annually	40.4/55.6	United States dollars	59.9 LYs	−285	−285	Cost saving
			HSgFOBT annually	56.1/70.4	United States dollars	81.1 LYs	−325	−325	Cost saving

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
USA CRC-SPIN	Cohort age 65 yr at average risk of CRC	100	FIT annually	63/NR	United States dollars	84.7 LYs	−402	−402	Cost saving
			gFOBT annually	46/NR	United States dollars	64.0 LYs	−441	−441	Cost saving
			HSgFOBT annually	67/NR	United States dollars	87.3 LYs	−495	−495	Cost saving
Barouni et al. (2012) Islamic Republic of Iran	Cohort age 50–75 yr at average risk of CRC	68	gFOBT annually	39/50	United States dollars	68 QALYs	−632	−632	Cost saving
			FIT annually	60/69	United States dollars	104 QALYs	−654	−654	Cost saving
Whyte et al. (2012) England	Cohort age 60–74 yr at average risk of CRC	54	FIT biennially	19/28	Pounds sterling	31.6 QALYs	−63	−99	Cost saving
			gFOBT biennially	9/15	Pounds sterling	15.4 QALYs	−35	−55	Cost saving

CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT; LYs, life years; MISCAN, Microsimulation Screening Analysis; NR, not reported; QALYs, quality-adjusted life years; SimCRC, Simulation Model of Colorectal Cancer; yr, year or years.

[a] Includes studies published after Patel & Kilgore (2015) (for studies in the USA) or published after Lansdorp-Vogelaar et al. (2011) (for studies outside the USA).

[b] In Heitman et al. (2010), "HSgFOBT" was erroneously labelled "gFOBT (low sensitivity)". To correct this issue, the published "gFOBT" values were assigned to the "HSgFOBT" category listed in this table, and the published "HSgFOBT" values were assigned to the "gFOBT" category listed in this table.

[c] Currency conversion method: the given currency was converted into United States dollars based on the conversion rate on 1 January of the publication year.

[d] FIT with a cut-off level of 200 ng Hb/mL.

paragraph. All studies found that FOBT screening was either cost saving or below US$ 31 500 per LYG [costs were presented as published and also standardized to United States dollars of the year in which the study was published]. These results with cost estimates also showed wide variability. Screening with FIT annually had higher QALYs gained than screening with FIT biennially but required more screening resources. Strategies with wider age ranges screened also had higher QALYs gained but required more resources. The cost–effectiveness of FOBT screening has been evaluated across the world, with reports from Asia, Europe, and North America showing benefit with acceptable levels of cost. Given the wide variation in costs across countries and studies, the cost per LYG from different studies can only be compared qualitatively.

(c) Comparison of cost–effectiveness of FIT versus gFOBT

The modelling studies also estimated the cost–effectiveness (or comparative effectiveness) of FIT and gFOBT (see Section 3.4.3).

A next step is to assess whether there are optimal strategies that balance LYG and resources required. Strategies to consider are the screening test, intervals of rescreening, and age groups for screening.

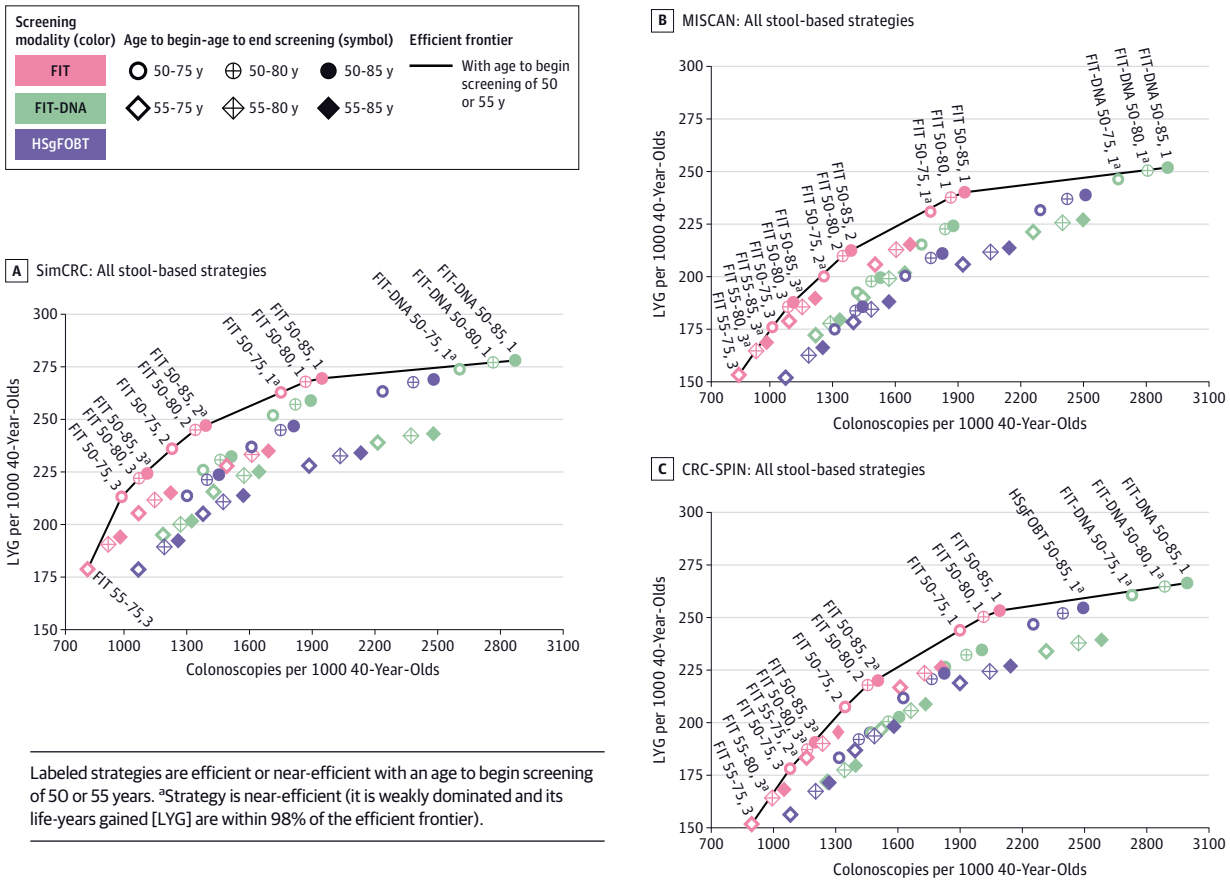
The Cancer Intervention and Surveillance Modeling Network provided a decision analysis for the USPSTF, based on three different microsimulation models (Knudsen et al., 2016), to inform the USPSTF review for different CRC screening tests in the population at average risk, starting at age 50 or 55 years and ending at age 75, 80, or 85 years for those with consistently negative screening results since starting screening. Repeat intervals of 1, 2, or 3 years were considered for FOBT. The USPSTF is not allowed to use costs per se. Instead, the number of colonoscopies for a strategy (per 1000 individuals) was used to represent costs. Fig. 3.2.1 is a comparison of LYG on the vertical axis relative to the number of colonoscopies required (per 1000 individuals aged 40 years) for the process of screening (with surveillance for patients with adenoma) over the ages screened on the horizontal axis. The line connecting the strategies on the outer envelope of data points represents strategies that provide the largest incremental increase in LYG per additional colonoscopy required for that strategy. This line is called the efficient frontier. Efficient screening strategies are on the efficient frontier, and near-efficient strategies have LYG within 98% of the efficient frontier. The strategies on the efficient frontier are all acceptable choices provided the resources required are available. Fig. 3.2.1 shows the efficient frontier for FIT and HSgFOBT screening. When evaluated together, the FIT strategies comprised almost all points on the efficient or near-efficient frontier. In addition, under the assumption of higher sensitivity and specificity of FIT relative to HSgFOBT, the FIT-based screening strategies provide more LYG for each level of colonoscopy resources across all age groups and repeat intervals. The strategy to start screening at age 50 years and end screening at age 75 years with annual FIT testing provided the optimal strategy given about 1700 colonoscopies per 1000 individuals with 25 years of screening. Note that the strategies that start screening at older ages or with longer intervals before retesting are along the curve with fewer LYG but also fewer colonoscopies required. It is a societal choice as to what resources to commit to reach a given level of LYG.

(d) Additional cost–effectiveness considerations

(i) Strategies for limited budgets

Although RCTs are considered to be the reference standard for efficacy, it is not feasible to compare multiple strategies within an RCT setting (especially in a community setting). The microsimulation modelling groups can provide virtual trials that can explore many

Fig. 3.2.1 Lifetime number of colonoscopies and life years gained for a cohort of individuals aged 40 years screened with FIT or HSgFOBT, from different microsimulation models



FIT, faecal immunochemical test.
The life years gained (LYG) and the colonoscopy burden are plotted for each screening strategy for faecal immunochemical test (FIT) and high-sensitivity guaiac faecal occult blood test (HSgFOBT), for screening starting at age 50 or 55 years and ending at age 75, 80, or 85 years, and repeat intervals of 1, 2, or 3 years. Three different microsimulation models are presented: Simulation Model of Colorectal Cancer (SimCRC), Microsimulation Screening Analysis (MISCAN), and Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRC-SPIN). Strategies providing the largest incremental increase in LYG per additional colonoscopy were connected by a continuous line, thereby composing the efficient frontier. All strategies on the efficient frontier were considered efficient CRC screening options.

(Knudsen et al. (2016)).

more possible strategies based on the performance (sensitivity and specificity of advanced neoplasia) of FOBT from RCTs or observational studies. Other scenarios have also been explored with modelling for the best balance between LYG and resources in population screening. For example, in a setting where there is a limited budget that can cover only a fraction of the population, a programme of annual or biennial FIT for those aged 50–64 years would provide more LYG in a population setting compared with a one-time colonoscopy (van der Steen et al., 2015). If there is limited colonoscopy capacity to support screening, FIT could be used with a higher Hb cut-off level, to provide cost-effective strategies for a lower level of endoscopy service. However, FIT with a lower cut-off level of 10 µg Hb/g faeces is the most effective health outcome and cost compared with gFOBT (Wilschut et al., 2011).

(ii) FOBT screening in the context of new treatments

Lansdorp-Vogelaar et al. (2009) showed that as the costs for cancer care rise with increased use of newer and more expensive biological drugs, FOBT testing would be cost saving compared with no screening, because of preventing advanced cancers and deaths from CRC and avoiding costs of expensive biological drugs. Parekh et al. (2008) showed similar results.

(iii) Hybrid strategies

Early on in the development of CRC screening, Eddy (1990) suggested a hybrid strategy using sigmoidoscopy at 5-year intervals with FOBT annually, although this hybrid approach is not used very frequently in practice. More recently, Whyte et al. (2012) suggested starting with sigmoidoscopy at age 55 years and with biennial FIT at age 60 years as an effective and cost-effective strategy for the United Kingdom.

Dinh et al. (2013) suggested a screening strategy of annual or biennial FIT starting at age 50 years and a single colonoscopy at age 66 years as a favourable strategy for population screening. Knudsen et al. (2012) determined that those with a negative colonoscopy at age 50 years could be followed up with annual HSgFOBT or annual FIT with approximately the same benefit as rescreening at 10 years with colonoscopy.

References

Ahlquist DA, McGill DB, Fleming JL, Schwartz S, Wieand HS, Rubin J, et al. (1989). Patterns of occult bleeding in asymptomatic colorectal cancer. *Cancer*, 63(9):1826–30. doi:10.1002/1097-0142(19900501)63:9<1826::AID-CNCR2820630928>3.0.CO;2-P PMID:2702590

Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, et al. (2008). Stool DNA and occult blood testing for screen detection of colorectal neoplasia. *Ann Intern Med*, 149(7):441–50, W81. doi:10.7326/0003-4819-149-7-200810070-00004 PMID:18838724

Ahlquist DA, Wieand HS, Moertel CG, McGill DB, Loprinzi CL, O'Connell MJ, et al. (1993). Accuracy of fecal occult blood screening for colorectal neoplasia. A prospective study using Hemoccult and HemoQuant tests. *JAMA*, 269(10):1262–7. doi:10.1001/jama.1993.03500100060028 PMID:8437303

Allison JE, Fraser CG, Halloran SP, Young GP (2014). Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). *Gut Liver*, 8(2):117–30. doi:10.5009/gnl.2014.8.2.117 PMID:24672652

Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. (2007). Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst*, 99(19):1462–70. doi:10.1093/jnci/djm150 PMID:17895475

Allison JE, Tekawa IS, Ransom LJ, Adrain AL (1996). A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med*, 334(3):155–9. doi:10.1056/NEJM199601183340304 PMID:8531970

Aronsson M, Carlsson P, Levin L-Å, Hager J, Hultcrantz R (2017). Cost-effectiveness of high-sensitivity faecal immunochemical test and colonoscopy screening for colorectal cancer. *Br J Surg*, 104(8):1078–86. doi:10.1002/bjs.10536 PMID:28561259

Auge JM, Pellise M, Escudero JM, Hernandez C, Andreu M, Grau J, et al.; PROCOLON Group (2014). Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. *Gastroenterology*, 147(3):628–636.e1. doi:10.1053/j.gastro.2014.06.008 PMID:24937264

Bang KM, Tillett S, Hoar SK, Blair A, McDougall V (1986). Sensitivity of fecal Hemoccult testing and flexible sigmoidoscopy for colorectal cancer screening. *J Occup Med*, 28(8):709–13. doi:10.1097/00043764-198608000-00033 PMID:3746495

Barouni M, Larizadeh MH, Sabermahani A, Ghaderi H (2012). Markov's modeling for screening strategies for colorectal cancer. *Asian Pac J Cancer Prev*, 13(10):5125–9. doi:10.7314/APJCP.2012.13.10.5125 PMID:23244122

Barrows GH, Burton RM, Jarrett DD, Russell GG, Alford MD, Songster CL (1978). Immunochemical detection of human blood in feces. *Am J Clin Pathol*, 69(3):342–6. doi:10.1093/ajcp/69.1.342 PMID:416710

Barzi A, Lenz H-J, Quinn DI, Sadeghi S (2017). Comparative effectiveness of screening strategies for colorectal cancer. *Cancer*, 123(9):1516–27. doi:10.1002/cncr.30518 PMID:28117881

Bertario L, Russo A, Crosignani P, Sala P, Spinelli P, Pizzetti P, et al. (1999). Reducing colorectal cancer mortality by repeated faecal occult blood test: a nested case-control study. *Eur J Cancer*, 35(6):973–7. doi:10.1016/S0959-8049(99)00062-3 PMID:10533481

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, et al.; US Preventive

Services Task Force (2016). Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*, 315(23):2564–75. doi:10.1001/jama.2016.5989 PMID:27304597

Bjerrum A, Andersen O, Fischer A, Lindebjerg J, Lynge E (2016). Colorectal cancer mortality 10 years after a single round of guaiac faecal occult blood test (gFOBT) screening: experiences from a Danish screening cohort. *BMJ Open Gastroenterol*, 3(1):e000120. doi:10.1136/bmjgast-2016-000120 PMID:28074150

Boas I (1914). Die Lehre von den okkulten Blutungen. Leipzig, Germany: Thieme.

Bouvier V, Herbert C, Lefevre H, Launoy G (2001). Stage of extension and treatment for colorectal cancer after a negative test and among non-responders in mass screening with guaiac faecal occult blood test: a French experience. *Eur J Cancer Prev*, 10(4):323–6. doi:10.1097/00008469-200108000-00005 PMID:11535874

Brenner H, Haug U, Hundt S (2010a). Sex differences in performance of fecal occult blood testing. *Am J Gastroenterol*, 105(11):2457–64. doi:10.1038/ajg.2010.301 PMID:20700114

Brenner H, Niedermaier T, Chen H (2017). Strong subsite-specific variation in detecting advanced adenomas by fecal immunochemical testing for hemoglobin. *Int J Cancer*, 140(9):2015–22. doi:10.1002/ijc.30629 PMID:28152558

Buron A, Auge JM, Sala M, Román M, Castells A, Macià F, et al.; PROCOLON Research Group (2017). Association between socioeconomic deprivation and colorectal cancer screening outcomes: low uptake rates among the most and least deprived people. *PLoS One*, 12(6):e0179864. doi:10.1371/journal.pone.0179864 PMID:28622365

Carroll MR, Seaman HE, Halloran SP (2014). Tests and investigations for colorectal cancer screening. *Clin Biochem*, 47(10–11):921–39. doi:10.1016/j.clinbiochem.2014.04.019 PMID:24769265

Castiglione G, Sala P, Ciatto S, Grazzini G, Mazzotta A, Rossetti C, et al. (1994). Comparative analysis of results of guaiac and immunochemical tests for faecal occult blood in colorectal cancer screening in two oncological institutions. *Eur J Cancer Prev*, 3(5):399–405. doi:10.1097/00008469-199409000-00003 PMID:8000308

Chen CH, Wen CP, Tsai MK (2016). Fecal immunochemical test for colorectal cancer from a prospective cohort with 513,283 individuals: providing detailed number needed to scope (NNS) before colonoscopy. *Medicine (Baltimore)*, 95(36):e4414. doi:10.1097/MD.0000000000004414 PMID:27603337

Chiu HM, Chen SL-S, Yen AM-F, Chiu SY-H, Fann JC-Y, Lee Y-C, et al. (2015). Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer*, 121(18):3221–9. doi:10.1002/cncr.29462 PMID:25995082

Chiu SY, Chuang SL, Chen SL, Yen AM, Fann JC, Chang DC, et al. (2017). Faecal haemoglobin concentration influences risk prediction of interval cancers resulting from inadequate colonoscopy quality: analysis of the Taiwanese Nationwide Colorectal Cancer Screening Program. *Gut*, 66(2):293–300. doi:10.1136/gutjnl-2015-310256 PMID:26515543

Clarke P, Jack F, Carey FA, Steele RJ (2006). Medications with anticoagulant properties increase the likelihood of a negative colonoscopy in faecal occult blood test population screening. *Colorectal Dis*, 8(5):389–92. doi:10.1111/j.1463-1318.2005.00919.x PMID:16684082

Costantini AS, Martini A, Puliti D, Ciatto S, Castiglione G, Grazzini G, et al. (2008). Colorectal cancer mortality in two areas of Tuscany with different screening exposures. *J Natl Cancer Inst*, 100(24):1818–21. doi:10.1093/jnci/djn404 PMID:19066268

Dan YY, Chuah BYS, Koh DCS, Yeoh KG (2012). Screening based on risk for colorectal cancer is the most cost-effective approach. *Clin Gastroenterol Hepatol*, 10:3: 266–71. e1, 6. doi:10.1016/j.cgh.2011.11.011 PMID:22100624

Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J (2008). Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *Eur J Cancer*, 44(15):2254–8. doi:10.1016/j.ejca.2008.06.041 PMID:18760592

Denis B, Gendre I, Sauleau EA, Lacroute J, Perrin P (2013). Harms of colonoscopy in a colorectal cancer screening programme with faecal occult blood test: a population-based cohort study. *Dig Liver Dis*, 45(6):474–80. doi:10.1016/j.dld.2013.01.006 PMID:23414583

Denis B, Ruetsch M, Strentz P, Vogel JY, Guth F, Boyaval JM, et al. (2007). Short term outcomes of the first round of a pilot colorectal cancer screening programme with guaiac based faecal occult blood test. *Gut*, 56(11):1579–84. doi:10.1136/gut.2007.126037 PMID:17616542

Digby J, Fraser CG, Carey FA, McDonald PJ, Strachan JA, Diament RH, et al. (2013). Faecal haemoglobin concentration is related to severity of colorectal neoplasia. *J Clin Pathol*, 66(5):415–9. doi:10.1136/jclinpath-2013-201445 PMID:23418340

Dinh T, Ladabaum U, Alperin P, Caldwell C, Smith R, Levin TR (2013). Health benefits and cost-effectiveness of a hybrid screening strategy for colorectal cancer. *Clin Gastroenterol Hepatol*, 11(9):1158–66. doi:10.1016/j.cgh.2013.03.013 PMID:23542330

Doubeni CA, Jensen CD, Fedewa SA, Quinn VP, Zauber AG, Schottinger JE, et al. (2016). Fecal immunochemical test (FIT) for colon cancer screening: variable performance with ambient temperature. *J Am Board Fam Med*, 29(6):672–81. doi:10.3122/jabfm.2016.06.160060 PMID:28076249

Eddy DM (1990). Screening for colorectal cancer. *Ann Intern Med*, 113(5):373–84. doi:10.7326/0003-4819-113-5-373 PMID:2200321

Elmunzer BJ, Singal AG, Sussman JB, Deshpande AR, Sussman DA, Conte ML, et al. (2015). Comparing the effectiveness of competing tests for reducing colorectal cancer mortality: a network meta-analysis. *Gastrointest Endosc*, 81(3):700–709.e3. doi:10.1016/j.gie.2014.10.033 PMID:25708757

Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, et al. (2004). Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology*, 126(7):1674–80. doi:10.1053/j.gastro.2004.02.018 PMID:15188160

Faivre J, Tazi MA, El Mrini T, Lejeune C, Benhamiche AM, Dassonville F (1999). Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. *Br J Cancer*, 79(3–4):680–3. doi:10.1038/sj.bjc.6690107 PMID:10027349

Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P (2016). Screening for colorectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer*, 15(4):298–313. doi:10.1016/j.clcc.2016.03.003 PMID:27133893

Fleisher M, Winawer SJ, Zauber AG, Smith C, Schwartz MK; National Polyp Study Work Group (1991). Accuracy of fecal occult blood test interpretation. *Ann Intern Med*, 114(10):875–6. doi:10.7326/0003-4819-114-10-875 PMID:2014949

Fraser CG, Allison JE, Halloran SP, Young GP; Expert Working Group on Fecal Immunochemical Tests for Hemoglobin, Colorectal Cancer Screening Committee, World Endoscopy Organization (2012). A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. *J Natl Cancer Inst*, 104(11):810–4. doi:10.1093/jnci/djs190 PMID:22472305

Fraser CG, Auge JM; PROCOLON Group (2015). Faecal haemoglobin concentrations do vary across geography as well as with age and sex: ramifications for colorectal cancer screening. *Clin Chem Lab Med*, 53(9):e235–7. doi:10.1515/cclm-2014-1172 PMID:25544746

Fraser CG, Rubeca T, Rapi S, Chen LS, Chen HH (2014). Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. *Clin Chem Lab Med*, 52(8):1211–6. doi:10.1515/cclm-2014-0115 PMID:24637000

Gandhi S, Narula N, Gandhi S, Marshall JK, Farkouh ME (2013). Does acetylsalicylic acid or warfarin affect the accuracy of fecal occult blood tests? *J Gastroenterol Hepatol*, 28(6):931–6. doi:10.1111/jgh.12201 PMID:23517228

Gies A, Cuk K, Schrotz-King P, Brenner H (2018). Direct comparison of diagnostic performance of 9 quantitative fecal immunochemical tests for colorectal cancer screening. *Gastroenterology*, 154(1):93–104. doi:10.1053/j.gastro.2017.09.018 PMID:28958859

Ginsberg GM, Lim SS, Lauer JA, Johns BP, Sepulveda CR (2010). Prevention, screening and treatment of colorectal cancer: a global and regional generalized cost effectiveness analysis. *Cost Eff Resour Alloc*, 8(1):2. doi:10.1186/1478-7547-8-2 PMID:20236531

Giorgi Rossi P, Vicentini M, Sacchettini C, Di Felice E, Caroli S, Ferrari F, et al. (2015). Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. *Am J Gastroenterol*, 110(9):1359–66. doi:10.1038/ajg.2015.240 PMID:26303133

Goede SL, Rabeneck L, van Ballegooijen M, Zauber AG, Paszat LF, Hoch JS, et al. (2017). Harms, benefits and costs of fecal immunochemical testing versus guaiac fecal occult blood testing for colorectal cancer screening. *PLoS One*, 12(3):e0172864. doi:10.1371/journal.pone.0172864 PMID:28296927

Greenberg PD, Cello JP, Rockey DC (1996). Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. *Am J Med*, 100(6):598–604. doi:10.1016/S0002-9343(96)00009-5 PMID:8678078

Greenberg PD, Cello JP, Rockey DC (1999). Relationship of low-dose aspirin to GI injury and occult bleeding: a pilot study. *Gastrointest Endosc*, 50(5):618–22. doi:10.1016/S0016-5107(99)80008-X PMID:10536315

Grobbee EJ, Schreuders EH, Hansen BE, Bruno MJ, Lansdorp-Vogelaar I, Spaander MCW, et al. (2017a). Association between concentrations of hemoglobin determined by fecal immunochemical tests and long-term development of advanced colorectal neoplasia. *Gastroenterology*, 153(5):1251–1259.e2. doi:10.1053/j.gastro.2017.07.034 PMID:28760383

Grobbee EJ, Wieten E, Hansen BE, Stoop EM, de Wijkerslooth TR, Lansdorp-Vogelaar I, et al. (2017b). Fecal immunochemical test-based colorectal cancer screening: the gender dilemma. *United European Gastroenterol J*, 5(3):448–54. doi:10.1177/2050640616659998 PMID:28507758

Halloran SP, Launoy G, Zappa M; International Agency for Research on Cancer (2012). European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Faecal occult blood testing. *Endoscopy*, 44(Suppl 3):SE65–87. doi:10.1055/s-0032-1309791 PMID:23012123

Hamza S, Cottet V, Touillon N, Dancourt V, Bonithon-Kopp C, Lepage C, et al. (2014). Long-term effect of faecal occult blood screening on incidence and mortality from colorectal cancer. *Dig Liver Dis*, 46(12):1121–5. doi:10.1016/j.dld.2014.08.041 PMID:25241134

Hardcastle JD, Chamberlain JO, Robinson MHE, Moss SM, Amar SS, Balfour TW, et al. (1996). Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*, 348(9040):1472–7. doi:10.1016/S0140-6736(96)03386-7 PMID:8942775

Heigh RI, Yab TC, Taylor WR, Hussain FT, Smyrk TC, Mahoney DW, et al. (2014). Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). *PLoS One*, 9(1):e85659. doi:10.1371/journal.pone.0085659 PMID:24465639

Heitman SJ, Hilsden RJ, Au F, Dowden S, Manns BJ (2010). Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Med*, 7(11):e1000370. doi:10.1371/journal.pmed.1000370 PMID:21124887

Helm JF, Russo MW, Biddle AK, Simpson KN, Ransohoff DF, Sandler RS (2000). Effectiveness and economic impact of screening for colorectal cancer by mass fecal occult blood testing. *Am J Gastroenterol*, 95(11):3250–8. doi:10.1111/j.1572-0241.2000.03261.x PMID:11095350

Hewitson P, Glasziou P, Watson E, Towler B, Irwig L (2008). Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): an update. *Am J Gastroenterol*, 103(6):1541–9. doi:10.1111/j.1572-0241.2008.01875.x PMID:18479499

Hiwatashi N, Morimoto T, Fukao A, Sato H, Sugahara N, Hisamichi S, et al. (1993). An evaluation of mass screening using fecal occult blood test for colorectal cancer in Japan: a case-control study. *Jpn J Cancer Res*, 84(11):1110–2. doi:10.1111/j.1349-7006.1993.tb02809.x PMID:8276715

Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME; Colorectal Cancer Study Group (2004). Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med*, 351(26):2704–14. doi:10.1056/NEJMoa033403 PMID:15616205

Jaffe RM, Kasten B, Young DS, MacLowry JD (1975). False-negative stool occult blood tests caused by ingestion of ascorbic acid (vitamin C). *Ann Intern Med*, 83(6):824–6. doi:10.7326/0003-4819-83-6-824 PMID:1200528

Jin P, Wu Z-T, Li S-R, Li S-J, Wang J-H, Wang Z-H, et al. (2013). Colorectal cancer screening with fecal occult blood test: a 22-year cohort study. *Oncol Lett*, 6(2):576–82. doi:10.3892/ol.2013.1402 PMID:24137374

Kahi CJ, Imperiale TF (2004). Do aspirin and nonsteroidal anti-inflammatory drugs cause false-positive fecal occult blood test results? A prospective study in a cohort of veterans. *Am J Med*, 117(11):837–41. doi:10.1016/j.amjmed.2004.05.028 PMID:15589487

Kewenter J, Björk S, Haglind E, Smith L, Svanvik J, Ahrén C (1988). Screening and rescreening for colorectal cancer. A controlled trial of fecal occult blood testing in 27,700 subjects. *Cancer*, 62(3):645–51. doi:10.1002/1097-0142(19880801)62:3<645::AID-CNCR2820620333>3.0.CO;2-# PMID:3292038

Kewenter J, Brevinge H (1996). Endoscopic and surgical complications of work-up in screening for colorectal cancer. *Dis Colon Rectum*, 39(6):676–80. doi:10.1007/BF02056949 PMID:8646956

Kewenter J, Brevinge H, Engaråas B, Haglind E, Ahrén C (1994). Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. *Scand J Gastroenterol*, 29(5):468–73. doi:10.3109/00365529409096840 PMID:8036464

Kingsley J, Karanth S, Revere FL, Agrawal D (2016). Cost effectiveness of screening colonoscopy depends on adequate bowel preparation rates – a modeling study. *PLoS One*, 11(12):e0167452. doi:10.1371/journal.pone.0167452 PMID:27936028

Knudsen AB, Hur C, Gazelle GS, Schrag D, McFarland EG, Kuntz KM (2012). Rescreening of persons with a negative colonoscopy result: results from a microsimulation model. *Ann Intern Med*, 157(9):611–20. doi:10.7326/0003-4819-157-9-201211060-00005 PMID:23128861

Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, et al. (2010). Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population. *J Natl Cancer Inst*, 102(16):1238–52. doi:10.1093/jnci/djq242 PMID:20664028

Knudsen AB, Zauber AG, Rutter CM, Naber SK, Doria-Rose VP, Pabiniak C, et al. (2016). Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. *JAMA*, 315(23):2595–609. doi:10.1001/jama.2016.6828 PMID:27305518

Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O (1996). Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*, 348(9040):1467–71. doi:10.1016/S0140-6736(96)03430-7 PMID:8942774

Kronborg O, Jørgensen OD, Fenger C, Rasmussen M (2004). Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol*, 39(9):846–51. doi:10.1080/00365520410003182 PMID:15513382

Ladabaum U, Alvarez-Osorio L, Rösch T, Brueggenjuergen B (2014). Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. *Endosc Int Open*, 2(2):E96–104. doi:10.1055/s-0034-1377182 PMID:26135268

Ladabaum U, Mannalithara A (2016). Comparative effectiveness and cost effectiveness of a multitarget stool DNA test to screen for colorectal neoplasia. *Gastroenterology*, 151(3):427–439.e6. doi:10.1053/j.gastro.2016.06.003 PMID:27311556

Laine LA, Bentley E, Chandrasoma P (1988). Effect of oral iron therapy on the upper gastrointestinal tract. A prospective evaluation. *Dig Dis Sci*, 33(2):172–7. doi:10.1007/BF01535729 PMID:3257437

Laing SS, Bogart A, Chubak J, Fuller S, Green BB (2014). Psychological distress after a positive fecal occult blood test result among members of an integrated health-care delivery system. *Cancer Epidemiol Biomarkers Prev*, 23(1):154–9. doi:10.1158/1055-9965.EPI-13-0722 PMID:24220914

Lam CL, Law WL, Poon JT, Chan P, Wong CK, McGhee SM, et al. (2015). Health-related quality of life in patients with colorectal neoplasm and cost-effectiveness of colorectal cancer screening in Hong Kong. *Hong Kong Med J*, 21(Suppl 6):4–8. PMID:26645874

Lansdorp-Vogelaar I, Knudsen AB, Brenner H (2011). Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev*, 33(1):88–100. doi:10.1093/epirev/mxr004 PMID:21633092

Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M (2010). Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *Ann Intern Med*, 153(6):368–77. doi:10.7326/0003-4819-153-6-201009210-00004 PMID:20855801

Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut J, Habbema JDF (2009). At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. *Int J Cancer*, 124(5):1161–8. doi:10.1002/ijc.24025 PMID:19048626

Lazovich D, Weiss NS, Stevens NG, White E, McKnight B, Wagner EH (1995). A case-control study to evaluate efficacy of screening for faecal occult blood. *J Med Screen*, 2(2):84–9. doi:10.1177/096914139500200206 PMID:7497161

Lee JK, Liles EG, Bent S, Levin TR, Corley DA (2014). Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med*, 160(3):171–81. doi:10.7326/M13-1484 PMID:24658694

Lee KS, Park EC (2016). Cost effectiveness of colorectal cancer screening interventions with their effects on health disparity being considered. *Cancer Res Treat*, 48(3):1010–9. doi:10.4143/crt.2015.279 PMID:26727714

Lee TJ, Hull MA, Rajasekhar PT, Clifford GM, Ritchie M, James P, et al. (2012). Aspirin users attending for NHS bowel cancer screening have less colorectal neoplasia: chemoprevention or false-positive faecal occult blood testing? *Digestion*, 85(4):278–81. doi:10.1159/000334372 PMID:22538301

Liao CS, Lin YM, Chang HC, Chen YH, Chong LW, Chen CH, et al. (2013). Application of quantitative estimates of fecal hemoglobin concentration for risk prediction of colorectal neoplasia. *World J Gastroenterol*, 19(45):8366–72. doi:10.3748/wjg.v19.i45.8366 PMID:24363529

Libby G, Brewster DH, McClements PL, Carey FA, Black RJ, Birrell J, et al. (2012). The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study. *Br J Cancer*, 107(2):255–9. doi:10.1038/bjc.2012.277 PMID:22735907

Lieberman DA, Weiss DG, Ahnen DJ, et al.; Veterans Affairs Cooperative Study Group 380 (2001). One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med*, 345(8):555–60. doi:10.1056/NEJMoa010328 PMID:11529208

Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, et al. (2016). Screening for colorectal cancer: a systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 135. AHRQ Publication No. 14-05203-EF-1. Rockville (MD), USA: Agency for Healthcare Research and Quality. Available from: https://www.ncbi.nlm.nih.gov/books/NBK373584/.

Lindebjerg J, Osler M, Bisgaard C (2014). Colorectal cancers detected through screening are associated with lower stages and improved survival. *Dan Med J*, 61(1):A4758. PMID:24393588

Lindholm E, Berglund B, Kewenter J, Haglind E (1997). Worry associated with screening for colorectal carcinomas. *Scand J Gastroenterol*, 32(3):238–45. doi:10.3109/00365529709000201 PMID:9085461

Lindholm E, Brevinge H, Haglind E (2008). Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg*, 95(8):1029–36. doi:10.1002/bjs.6136 PMID:18563785

Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C; English Bowel Cancer Screening Evaluation Committee (2012). Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut*, 61(10):1439–46. doi:10.1136/gutjnl-2011-300843 PMID:22156981

Malila N, Hakama M, Pukkala E (2007). A 25-year follow-up of a population screened with faecal occult blood test in Finland. *Acta Oncol*, 46(8):1103–6. doi:10.1080/02841860701442531 PMID:17851857

Malila N, Oivanen T, Hakama M (2008). Implementation of colorectal cancer screening in Finland: experiences from the first three years of a public health programme. *Z Gastroenterol*, 46(Suppl 1):S25–8. doi:10.1055/s-2007-963490 PMID:18368636

Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. (1993). Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*, 328(19):1365–71. doi:10.1056/NEJM199305133281901 PMID:8474513

Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. (2000). The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med*, 343(22):1603–7. doi:10.1056/NEJM200011303432203 PMID:11096167

Mant D, Fitzpatrick R, Hogg A, Fuller A, Farmer A, Verne J, et al. (1990). Experiences of patients with false positive results from colorectal cancer screening. *Br J Gen Pract*, 40(339):423–5. PMID:2271264

McDonald PJ, Strachan JA, Digby J, Steele RJ, Fraser CG (2011). Faecal haemoglobin concentrations by gender and age: implications for population-based screening for colorectal cancer. *Clin Chem Lab Med*, 50(5):935–40. PMID:22149740

Miles A, McClements PL, Steele RJC, Redeker C, Sevdalis N, Wardle J (2015). The psychological impact of a colorectal cancer diagnosis following a negative fecal occult blood test result. *Cancer Epidemiol Biomarkers Prev*, 24(7):1032–8. doi:10.1158/1055-9965.EPI-15-0004 PMID:25924826

Moayyedi P, Achkar E (2006). Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. *Am J Gastroenterol*, 101(2):380–4. doi:10.1111/j.1572-0241.2006.00537.x PMID:16454847

Müftügil N (1985). The peroxidase enzyme activity of some vegetables and its resistance to heat. *J Sci Food Agric*, 36(9):877–80. doi:10.1002/jsfa.2740360918

Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A (2003). Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *Br J Cancer*, 89(1):23–8. doi:10.1038/sj.bjc.6601002 PMID:12838295

Niv Y (1990). Fecal occult blood test – the importance of proper evaluation. *J Clin Gastroenterol*, 12(4):393–5. doi:10.1097/00004836-199008000-00007 PMID:2398247

Norfleet RG (1983). 1,300 mg of aspirin daily does not cause positive fecal Hemoccult tests. *J Clin Gastroenterol*, 5(2):123–5. doi:10.1097/00004836-198304000-00006 PMID:6304182

Parekh M, Fendrick AM, Ladabaum U (2008). As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. *Aliment Pharmacol Ther*, 27(8):697–712. doi:10.1111/j.1365-2036.2008.03632.x PMID:18248653

Parente F, Boemo C, Ardizzoia A, Costa M, Carzaniga P, Ilardo A, et al. (2013). Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. *Endoscopy*, 45(1):27–34. PMID:23254404

Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, et al. (2010). Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol*, 105(9):2017–25. doi:10.1038/ajg.2010.179 PMID:20502450

Parker MA, Robinson MHE, Scholefield JH, Hardcastle JD (2002). Psychiatric morbidity and screening for colorectal cancer. *J Med Screen*, 9(1):7–10. doi:10.1136/jms.9.1.7 PMID:11943790

Parra-Blanco A, Gimeno-García AZ, Quintero E, Nicolás D, Moreno SG, Jiménez A, et al. (2010). Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol*, 45(7):703–12. doi:10.1007/s00535-010-0214-8 PMID:20157748

Patel SS, Kilgore ML (2015). Cost effectiveness of colorectal cancer screening strategies. *Cancer Contr*, 22(2):248–58. doi:10.1177/107327481502200219 PMID:26068773

Phalguni A, Seaman H, Routh K, Halloran S, Simpson S (2015). Tests detecting biomarkers for screening of colorectal cancer: what is on the horizon? *GMS Health Technol Assess*, 11:Doc01. PMID:26131022

Pignone M, Campbell MK, Carr C, Phillips C (2001). Meta-analysis of dietary restriction during fecal occult blood testing. *Eff Clin Pract*, 4(4):150–6. PMID:11525101

Pignone M, Saha S, Hoerger T, Mandelblatt J (2002). Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*, 137(2):96–104. doi:10.7326/0003-4819-137-2-200207160-00007 PMID:12118964

Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John DJ (2011). Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. *Med J Aust*, 194(4):180–5. PMID:21401458

Pil L, Fobelets M, Putman K, Trybou J, Annemans L (2016). Cost-effectiveness and budget impact analysis of a population-based screening program for colorectal cancer. *Eur J Intern Med*, 32:72–8. doi:10.1016/j.ejim.2016.03.031 PMID:27157827

Pitkäniemi J, Seppä K, Hakama M, Malminiemi O, Palva T, Vuoristo M-S, et al. (2015). Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. *BMJ Open Gastroenterol*, 2(1):e000034. doi:10.1136/bmjgast-2015-000034 PMID:26462283

Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas Á, et al.; COLONPREV Study Investigators (2012). Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med*, 366(8):697–706. doi:10.1056/NEJMoa1108895 PMID:22356323

Rabeneck L, Zwaal C, Goodman JH, Mai V, Zamkanei M (2008). Cancer Care Ontario guaiac fecal occult blood test (FOBT) laboratory standards: evidentiary base and recommendations. *Clin Biochem*, 41(16–17):1289–305. doi:10.1016/j.clinbiochem.2008.08.069 PMID:18796300

Rao SK, Schilling TF, Sequist TD (2009). Challenges in the management of positive fecal occult blood tests. *J Gen Intern Med*, 24(3):356–60. doi:10.1007/s11606-008-0893-5 PMID:19130147

Robinson MH, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NC, et al. (1999). The risks of screening: data from the Nottingham randomised

controlled trial of faecal occult blood screening for colorectal cancer. *Gut*, 45(4):588–92. doi:10.1136/gut.45.4.588 PMID:10486370

Rockey DC (1999). Occult gastrointestinal bleeding. *N Engl J Med*, 341(1):38–46. doi:10.1056/NEJM199907013410107 PMID:10387941

Rockey DC, Auslander A, Greenberg PD (1999). Detection of upper gastrointestinal blood with fecal occult blood tests. *Am J Gastroenterol*, 94(2):344–50. doi:10.1111/j.1572-0241.1999.855_r.x PMID:10022627

Rose IS, Young GP, St John DJB, Deacon MC, Blake D, Henderson RW (1989). Effect of ingestion of hemoproteins on fecal excretion of hemes and porphyrins. *Clin Chem*, 35(12):2290–6. PMID:2556222

Rozen P, Knaani J, Samuel Z (1999). Eliminating the need for dietary restrictions when using a sensitive guaiac fecal occult blood test. *Dig Dis Sci*, 44(4):756–60. doi:10.1023/A:1026618010312 PMID:10219834

Rozen P, Waked A, Vilkin A, Levi Z, Niv Y (2006). Evaluation of a desk top instrument for the automated development and immunochemical quantification of fecal occult blood. *Med Sci Monit*, 12(6):MT27–32. PMID:16733493

Saito H, Soma Y, Koeda J, Wada T, Kawaguchi H, Sobue T, et al. (1995). Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. *Int J Cancer*, 61(4):465–9. doi:10.1002/ijc.2910610406 PMID:7759151

Sawhney MS, McDougall H, Nelson DB, Bond JH (2010). Fecal occult blood test in patients on low-dose aspirin, warfarin, clopidogrel, or non-steroidal anti-inflammatory drugs. *Dig Dis Sci*, 55(6):1637–42. doi:10.1007/s10620-010-1150-4 PMID:20195757

Scheitel SM, Ahlquist DA, Wollan PC, Hagen PT, Silverstein MD (1999). Colorectal cancer screening: a community case-control study of proctosigmoidoscopy, barium enema radiography, and fecal occult blood test efficacy. *Mayo Clin Proc*, 74(12):1207–13. doi:10.4065/74.12.1207 PMID:10593348

Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD (2012). Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut*, 61(7):1036–40. doi:10.1136/gutjnl-2011-300774 PMID:22052062

Schreuders EH, Grobbee EJ, Spaander MCW, Kuipers EJ (2016). Advances in fecal tests for colorectal cancer screening. *Curr Treat Options Gastroenterol*, 14(1):152–62. doi:10.1007/s11938-016-0076-0 PMID:26825703

Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. (2015). Colorectal cancer screening: a global overview of existing programmes. *Gut*, 64(10):1637–49. doi:10.1136/gutjnl-2014-309086 PMID:26041752

Sekiguchi M, Igarashi A, Matsuda T, Matsumoto M, Sakamoto T, Nakajima T, et al. (2016). Optimal use of colonoscopy and fecal immunochemical test for population-based colorectal cancer screening: a cost-effectiveness analysis using Japanese data. *Jpn J Clin Oncol*, 46(2):116–25. doi:10.1093/jjco/hyv186 PMID:26685321

Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS (1993). Effect of fecal occult blood testing on mortality from colorectal cancer. A case-control study. *Ann Intern Med*, 118(1):1–6. doi:10.7326/0003-4819-118-1-199301010-00001 PMID:8416152

Selinger RR, Norman S, Dominitz JA (2003). Failure of health care professionals to interpret fecal occult blood tests accurately. *Am J Med*, 114(1):64–7. doi:10.1016/S0002-9343(02)01350-5 PMID:12543293

Sharaf RN, Ladabaum U (2013). Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol*, 108(1):120–32. doi:10.1038/ajg.2012.380 PMID:23247579

Sharp L, Tilson L, Whyte S, O'Ceilleachair A, Walsh C, Usher C, et al. (2012). Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. *Br J Cancer*, 106(5):805–16. doi:10.1038/bjc.2011.580 PMID:22343624

Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, et al. (2013). Long-term mortality after screening for colorectal cancer. *N Engl J Med*, 369(12):1106–14. doi:10.1056/NEJMoa1300720 PMID:24047060

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto (CA), USA: Consulting Psychologists Press.

Steele RJ, McClements PL, Libby G, Black R, Morton C, Birrell J, et al. (2009). Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut*, 58(4):530–5. doi:10.1136/gut.2008.162883 PMID:19036949

Stone CA, Carter RC, Vos T, John JS (2004). Colorectal cancer screening in Australia: an economic evaluation of a potential biennial screening program using faecal occult blood tests. *Aust N Z J Public Health*, 28(3):273–82. doi:10.1111/j.1467-842X.2004.tb00707.x PMID:15707175

Sung JJY, Chan FKL, Leung WK, Wu JC, Lau JY, Ching J, et al. (2003). Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. *Gastroenterology*, 124(3):608–14. doi:10.1053/gast.2003.50090 PMID:12612899

Telford JJ, Levy AR, Sambrook JC, Zou D, Enns RA (2010). The cost-effectiveness of screening for colorectal cancer. *CMAJ*, 182(12):1307–13. doi:10.1503/cmaj.090845 PMID:20624866

Tinmouth J, Lansdorp-Vogelaar I, Allison JE (2015). Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. *Gut*, 64(8):1327–37. doi:10.1136/gutjnl-2014-308074 PMID:26041750

Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C (1998). A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. *BMJ*, 317(7158):559–65. doi:10.1136/bmj.317.7158.559 PMID:9721111

van der Steen A, Knudsen AB, van Hees F, Walter GP, Berger FG, Daguise VG, et al. (2015). Optimal colorectal cancer screening in states' low-income, uninsured populations – the case of South Carolina. *Health Serv Res*, 50(3):768–89. doi:10.1111/1475-6773.12246 PMID:25324198

van Doorn SC, Stegeman I, Stroobants AK, Mundt MW, de Wijkerslooth TR, Fockens P, et al. (2015). Fecal immunochemical testing results and characteristics of colonic lesions. *Endoscopy*, 47(11):1011–7. doi:10.1055/s-0034-1392412 PMID:26126163

van Roon AH, Hol L, van Vuuren AJ, Francke J, Ouwendijk M, Heijens A, et al. (2012). Are fecal immunochemical test characteristics influenced by sample return time? A population-based colorectal cancer screening trial. *Am J Gastroenterol*, 107(1):99–107. doi:10.1038/ajg.2011.396 PMID:22108450

Ventura L, Mantellini P, Grazzini G, Castiglione G, Buzzoni C, Rubeca T, et al. (2014). The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. *Dig Liver Dis*, 46(1):82–6. doi:10.1016/j.dld.2013.07.017 PMID:24011791

Vijan S, Hwang EW, Hofer TP, Hayward RA (2001). Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. *Am J Med*, 111(8):593–601. doi:10.1016/S0002-9343(01)00977-9 PMID:11755501

Vilkin A, Rozen P, Levi Z, Waked A, Maoz E, Birkenfeld S, et al. (2005). Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol*, 100(11):2519–25. doi:10.1111/j.1572-0241.2005.00231.x PMID:16279909

Wang ZH, Gao Q-Y, Fang J-Y (2012). Repeat colonoscopy every 10 years or single colonoscopy for colorectal neoplasm screening in average-risk Chinese: a cost-effectiveness analysis. *Asian Pac J Cancer Prev*, 13(5):1761–6. doi:10.7314/APJCP.2012.13.5.1761 PMID:22901118

Weiss NS (2013). Commentary: case-control studies of screening for colorectal cancer: tailoring the design and analysis to the specific research question. *Epidemiology*, 24(6):894–7. doi:10.1097/EDE.0b013e3182a777b2 PMID:24076994

Whynes DK; Nottingham FOB Screening Trial (2004). Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial. *JMedScreen*,11(1):11–5.doi:10.1177/096914130301100104 PMID:15006108

Whyte S, Chilcott J, Halloran S (2012). Reappraisal of the options for colorectal cancer screening in England. *Colorectal Dis*, 14(9):e547–61. doi:10.1111/j.1463-1318.2012.03014.x PMID:22390210

Wilschut JA, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp-Vogelaar I, et al. (2011). Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. *Gastroenterology*, 141(5):1648–55.e1. doi:10.1053/j.gastro.2011.07.020 PMID:21784045

Wong MC, Ching JYL, Chan VCW, Sung JJY (2015). The comparative cost-effectiveness of colorectal cancer screening using faecal immunochemical test vs. colonoscopy. *Sci Rep*, 5(1):13568. doi:10.1038/srep13568 PMID:26338314

Woo PP, Kim JJ, Leung GM (2007). What is the most cost-effective population-based cancer screening program for Chinese women? *J Clin Oncol*, 25(6):617–24. doi:10.1200/JCO.2006.06.0210 PMID:17308266

Young GP, St John DJ, Rose IS, Blake D (1990). Haem in the gut. Part II. Faecal excretion of haem and haem-derived porphyrins and their detection. *J Gastroenterol Hepatol*, 5(2):194–203. doi:10.1111/j.1440-1746.1990.tb01824.x PMID:2103398

Young GP, Symonds EL, Allison JE, Cole SR, Fraser CG, Halloran SP, et al. (2015). Advances in fecal occult blood tests: the FIT revolution. *Dig Dis Sci*, 60(3):609–22. doi:10.1007/s10620-014-3445-3 PMID:25492500

Zappa M, Castiglione G, Grazzini G, Falini P, Giorgi D, Paci E, et al. (1997). Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. *Int J Cancer*, 73(2):208–10. doi:10.1002/(SICI)1097-0215(19971009)73:2<208::AID-IJC8>3.0.CO;2-# PMID:9335444

Zhang J, Cheng Z, Ma Y, He C, Lu Y, Zhao Y, et al. (2017). Effectiveness of screening modalities in colorectal cancer: a network meta-analysis. *Clin Colorectal Cancer*, 16(4):252–63. doi:10.1016/j.clcc.2017.03.018 PMID:28687458

Zheng S, Chen K, Liu X, Ma X, Yu H, Chen K, et al. (2003). Cluster randomization trial of sequence mass screening for colorectal cancer. *Dis Colon Rectum*, 46(1):51–8. doi:10.1007/s10350-004-6496-2 PMID:12544522

Zorzi M, Fedeli U, Schievano E, Bovo E, Guzzinati S, Baracco S, et al. (2015). Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. *Gut*, 64(5):784–90. doi:10.1136/gutjnl-2014-307508 PMID:25179811

Zorzi M, Hassan C, Capodaglio G, Fedato C, Montaguti A, Turrin A, et al. (2018). Long-term performance of colorectal cancer screening programmes based on the faecal immunochemical test. *Gut*, 67(12):2124–30. doi:10.1136/gutjnl-2017-314753 PMID:29101260

Zorzi M, Senore C, Da Re F, Barca A, Bonelli LA, Cannizzaro R, et al. ; EQuIPE Working Group (2017). Detection rate and predictive factors of sessile serrated polyps in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). *Gut*, 66(7):1233–40. doi:10.1136/gutjnl-2015-310587 PMID:26896459