# 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

## 3.3 Endoscopic methods

### 3.3.1 Techniques

#### (a) Introduction

The endoscopic methods for CRC screening use flexible cameras to directly visualize the rectum and colon. These techniques have five primary roles within the CRC screening process: (i) primary screening; (ii) follow-up of other abnormal screening tests (diagnosis); (iii) removal of precancerous lesions (prevention); (iv) removal of early cancers (treatment); and (v) long-term follow-up of patients who are at high risk because of previous neoplasms or increased individual risk (surveillance) (Tiro et al., 2014). Although these roles differ substantially in concept, they are similar with respect to equipment, expertise of personnel, quality control, screening performance, and the host factors that affect the examination. In this section, these concepts are summarized for the two main endoscopic techniques for CRC screening: sigmoidoscopy and colonoscopy.

#### (b) Endoscopic techniques for CRC screening

Sigmoidoscopy and colonoscopy are the two primary endoscopic techniques for CRC screening.

Sigmoidoscopy is the insertion of an endoscopic camera, typically flexible, for examination of the rectum and sigmoid colon; it can also potentially evaluate the descending colon, splenic flexure, and distal transverse colon. The process includes insertion of the scope into the anus, injection of air through the scope to expand the intestinal lumen and allow better visualization (also called insufflation), and passage of the scope to the desired extent of the examination. This is followed by gradual withdrawal of the scope. The examination of the intestinal lining for polyps and other abnormalities is performed both on insertion and on withdrawal, as is the washing and suctioning of any residual liquid. Because sigmoidoscopy is usually performed without sedation, the extent of the examination depends on patient comfort, bowel preparation, and instrument length (see Sections 3.3.1(d) and 3.3.1(f)). Sigmoidoscopy can remove smaller polyps and biopsy larger polyps; patients who are found to have precancerous polyps can be referred for colonoscopy.

The goal of colonoscopy is examination of the entire colon, from rectum to caecum. In many countries and settings, colonoscopy is commonly performed with sedation, which allows for instrument manipulation with greater patient comfort. Colonoscopy can remove small polyps and most large polyps; advanced techniques enable the removal of polyps up to several centimetres in size.

#### (c) Equipment and expertise of personnel

#### (i) Equipment

Gastrointestinal endoscopic procedures use flexible tubes with four main components: an imaging system, illumination devices, channels for passing instruments and performing suction, and mechanisms for adjusting the direction and performance characteristics of the tube (Konda et al., 2015). Scopes are provided by several different manufacturers; the primary differences are the imaging methods and the controls.

Imaging is provided through either small charge-coupled device-type camera chips or a fibre-optic bundle (Classen & Phillip, 1984). Camera chip-based units either directly detect or impute colours; these require a base unit for converting the electronic signals into images (Cho, 2015). In contrast, fibre-optic-based devices directly transmit images, although these are becoming less commonly used because of their lower optical resolution and fewer advanced imaging options compared with chip-based devices (Classen & Phillip, 1984; Cho, 2015). Numerous visualization methods have

been tested for enhancing polyp detection, such as narrow-band imaging and the use of dyes (chromoendoscopy), although none of them has convincingly increased the number of polyps detected in populations at average risk, independent of inspection time (Nagorni et al., 2012; Pasha et al., 2012; Omata et al., 2014; Bisschops et al., 2017). Several additional mechanical devices, scope designs (e.g. wide-angle viewing and multiple-screen images), and scope attachments for increasing visualization and polyp detection have been developed. Some of these may improve polyp detection; however, given their variety, an in-depth review of this topic is beyond the scope of this *Handbook*.

Illumination is provided by small light portals at the scope tip, using single or multiple sources; light sources can also be manipulated for image enhancement (Longcroft-Wheaton et al., 2012; Nagorni et al., 2012; Wallace et al., 2014). Some guidelines recommend high-definition white light endoscopes as the standard for screening, although the equipment version and imaging methods may vary by location. Continued improvements in imaging resolution are likely to further enhance screening performance. Single or multiple instrument channels within the scope allow the passage of forceps for biopsy, snares for polyp removal, devices for applying thermal current, and other tools.

### (ii) Bowel preparation

A bowel preparation is needed before a sigmoidoscopy or a colonoscopy, to remove the stool and to enable adequate visualization of the colon. For bowel cleansing, it is recommended that patients have a low-residue or full-liquid diet on the day before the colonoscopy (Johnson et al., 2014); a clear liquid diet is not necessary and is associated with lower compliance.

Recommended bowel preparations before sigmoidoscopy include sodium phosphate enemas, often with an additional oral laxative, such as magnesium citrate. The combination of an oral agent and an enema is associated with a better preparation (Levin et al., 2005).

Numerous bowel preparations for colonoscopy exist, although the most effective ones include the patient receiving a dose within 4–6 hours of the colonoscopic examination (Johnson et al., 2014; Martel et al., 2015). The most common method currently used for colonoscopy is the split-dose preparation, such as with 4 litres of polyethylene glycol, in which the patient receives one half of the preparation the evening before the examination and the other half on the day of the examination. Patients who receive split-dose preparations are significantly more likely to have an adequate bowel preparation than those who receive day-before preparations (OR, 2.51; 95% CI, 1.86–3.39) (Martel et al., 2015). Patients also report being more willing to repeat a split-dose preparation than a single-dose day-before preparation. Same-day regimens may have equal effectiveness and can be considered for patients who undergo an examination in the afternoon (Johnson et al., 2014).

### (iii) Expertise of personnel

Endoscopic training requires supervised education and proctoring (Adler et al., 2012; Sedlack et al., 2014). Substantial data exist on performance and training for both physician and non-physician endoscopists (Stephens et al., 2015). Competency standards have evolved from a minimum number of completed procedures to the documentation of a reliable ability to complete specific tasks (Sedlack et al., 2014; Rutter et al., 2016). Different skill levels are required for different procedures, and skill levels vary substantially. Sigmoidoscopies and colonoscopies can be completed within in-hospital settings, dedicated outpatient procedure units, and office-based settings; sigmoidoscopies, in particular, can be performed as high-volume activities. For CRC screening programmes in developed medical systems, it has been suggested that different levels of competency are required

for different procedures; at least level 1 competency is recommended to avoid otherwise unnecessary follow-up procedures to remove small polyps (Table 3.3.1) (Valori et al., 2012). Endoscopic examinations can be safely and effectively performed by both physician and non-physician endoscopists (Day et al., 2014). However, the lower direct costs of non-physician endoscopists may be offset by greater requirements for repeat examinations, specialty follow-up, and additional consultations (Stephens et al., 2015).

Requirements for endoscopy room personnel vary by the procedure performed, governmental regulations, and local practices (Dumonceau et al., 2013, 2015). At a minimum, the endoscopist should be assisted by one additional medical professional, typically a nurse or similarly certified member of personnel, responsible for patient monitoring and assisting with interruptible tasks such as biopsies. In some settings, a second assistant is routinely used, although guidelines suggest that this is required only if sustained additional technical assistance is required (Calderwood et al., 2014). Minimum competencies indicate that unlicensed personnel with sufficient initial and current training can assist with biopsies and similar procedures (Calderwood et al., 2014).

### (iv)    Infection control

Guidelines exist for endoscope processing, infection control, and administration of prophylactic antibiotics during procedures (Petersen et al., 2011; Jover et al., 2012; Hookey et al., 2013; Calderwood et al., 2014; SGNA Practice Committee 2013–14, 2015; Herrin et al., 2016; Son et al., 2017). These include recommendations for routine hand hygiene before patient contact; use of personal protective equipment, such as gloves, facial protection, and impervious gowns; administration of medication; and methods for handling potentially contaminated equipment (Petersen et al., 2011; Jover et al., 2012; Hookey et al., 2013; Calderwood et al., 2014; SGNA

Practice Committee 2013–14, 2015; Herrin et al., 2016; Son et al., 2017).

### (v)    Sedation

Many colonoscopies and some sigmoidoscopies use conscious sedation according to patient preference, tolerance, and local practice (Bretthauer et al., 2016; Rees et al., 2016). Data on sedation are mainly for colonoscopies. Guidelines and training curricula exist for sedation and monitoring, although their evidence base is weak on whether routine compliance improves patient-related outcomes (Vargo et al., 2012; Dietrich et al., 2013; Calderwood et al., 2014); commonly used agents include midazolam, fentanyl, meperidine, and propofol (Dumonceau et al., 2015; Obara et al., 2015). Guidelines recommend pre-procedure evaluations of each patient's physical status, such as with the criteria established by the American Society of Anesthesiologists; the Mallampati airway classification and risk factors for sedation; intraprocedural monitoring by qualified personnel of blood pressure, respiratory rate, heart rate, and pulse oximetry; availability of medication reversal agents; and post-procedure monitoring until the patient is stabilized (Calderwood et al., 2014).

### (d)    Technical quality control

Several performance standards and quality measures are recommended for lower gastrointestinal endoscopy (Minoli et al., 1999; Ball et al., 2004; Rex et al., 2006, 2015; Rembacken et al., 2012; Valori et al., 2012; Rutter et al., 2016; Kaminski et al., 2017a). A recent European guideline noted 44 different performance measures, many of which evaluate processes (e.g. documentation of certain findings) rather than evidence-based factors that influence outcomes (Rees et al., 2016). Additional recommendations exist for particular techniques, such as endoscopic polypectomy and endoscopic mucosal resection (Ferlitsch et al., 2017).

**Table 3.3.1 Levels of operator ability required to perform endoscopy procedures for colorectal cancer screening**

| Competency level | Skills required | Comments |
|---|---|---|
| Level 0 | Operator does not remove any lesions, but refers all patients with detected lesions; lesion biopsies can be performed, with pathological results informing referral decisions. | Basic competency level for diagnostic sigmoidoscopy; not recommended for screening. |
| Level 1 | Operator can remove lesions < 10 mm in diameter at sigmoidoscopy. Larger lesions are removed at colonoscopy. Tissue biopsy is required to decide whether colonoscopy is necessary. | People performing screening sigmoidoscopy should have this competency level. |
| Level 2 | Operator can remove polypoid and sessile lesions < 25 mm provided the lesion is endoscopically accessible. | All colonoscopists should have this competency level. |
| Level 3 | Operator can remove most smaller flat lesions (< 20 mm), larger sessile and polypoid lesions, and small lesions with difficult endoscopic access. | Any colonoscopists completing follow-up for positive screening results require this competency level. |
| Level 4 | Operator can remove large flat lesions or challenging polypoid lesions that otherwise might require surgery. These lesions would not be removed at the first colonoscopy, because of time constraints or because of the need for discussion of surgical options. | This competency level is expected only among a small number of referral, regionally-based colonoscopists. |

Adapted with permission from © Georg Thieme Verlag KG (Valori et al., 2012).

The three main measures of endoscopy quality that are clearly associated with patient outcomes are completion of the examination to the minimum desired extent, thoroughness of the endoscopic inspection, and adequacy of bowel preparation (see also Section 3.3.1(f)) (Minoli et al., 1999; Ball et al., 2004; Rex et al., 2006, 2015; Rembacken et al., 2012; Valori et al., 2012; Rutter et al., 2016; Kaminski et al., 2017a). The minimum desired extent of the examination is the junction of the sigmoid and the descending colon for sigmoidoscopy (Atkin et al., 2002), and the caecum for colonoscopy. The actual proximal extent achieved for most sigmoidoscopies is not precisely defined, given the ambiguity of landmarks, and is often considered the maximum tolerated scope insertion distance, or approximately 60 cm of scope length (Painter et al., 1999; Weissfeld et al., 2000). The caecum is identified using the appendiceal orifice, ileocecal valve, and caecal sling fold (a combination of muscular folds around the appendix) (Rex et al., 2015).

The most validated measurement of the thoroughness of endoscopic inspection is the adenoma detection rate (ADR) of the physician. The physician ADR is the percentage of the physician's examinations in which one or more adenomas are detected (Rex et al., 2006). Reported ADRs varied from less than 10% to more than 60% among reports from both academic and community-based colonoscopy providers (Hixson et al., 1990; Rex et al., 1997, 2006; Bretthauer et al., 2003; Hosokawa et al., 2003; Schoen et al., 2003; Atkin et al., 2004; Bressler et al., 2004; Leaper et al., 2004; Pickhardt et al., 2004; Sanchez et al., 2004; Barclay et al., 2006; Chen & Rex, 2007; Corley et al., 2011, 2014; Jensen et al., 2015) and from 8.6% to 15.9% for sigmoidoscopy in the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST) (Atkin et al., 2004). The prevalence of adenomas is higher with increasing patient age and is higher in men than in women, but no large differences in prevalence exist between racial or ethnic groups (Corley et al., 2013). Adjusting for differences in patient demographics only modestly influenced the overall variability in physician ADRs in a large community-based setting (Jensen et al.,

2015). Therefore, physician ADR appears to vary with physician-related factors during endoscopic inspection, rather than patient-related factors.

Variation in physician ADR is strongly inversely associated with patients' subsequent CRC outcomes for both colonoscopy and sigmoidoscopy. Studies in large populations in Europe and the USA demonstrated substantially lower future risks of post-colonoscopy CRC and death from CRC in patients of physicians with higher ADRs than in patients of those with lower ADRs (Kaminski et al., 2010; Rogal et al., 2013; Corley et al., 2014); a similar analysis for sigmoidoscopy demonstrated higher risks of post-sigmoidoscopy distal CRCs in patients of providers with lower ADRs. A community-based study demonstrated that each absolute increase of 1% in a physician's ADR was associated with 3% and 5% decreases in their patients' risks of future CRC (HR, 0.97; 95% CI, 0.96–0.98) and death from CRC (HR, 0.95; 95% CI, 0.94–0.97), respectively (Corley et al., 2014). A complementary modelling study estimated that lifetime risks of CRC incidence and mortality decreased by 11–13% for every 5% increase in ADR, translating to 53–60% lifetime differences between the lowest and the highest ADR quintiles (Meester et al., 2015). Variation in ADR could be associated with approximately one third of the total estimated mortality benefit from screening, compared with no screening (Meester et al., 2015). Improvements in ADR over time have also been associated with fewer deaths from CRC (Kaminski et al., 2017b). The physician ADR may have a comparably large influence on FIT-based screening programmes, because colonoscopy is required for follow-up after a positive FIT result. In response to these collective findings, minimum target ADRs recommended in quality guidelines for screening colonoscopy were recently increased to 25% (or from 15% to 20% for women and from 25% to 30% for men) (Rex et al., 2015), and ADR was adopted by the United States Centers for Medicare & Medicaid Services as a quality measure (Centers for Medicare &
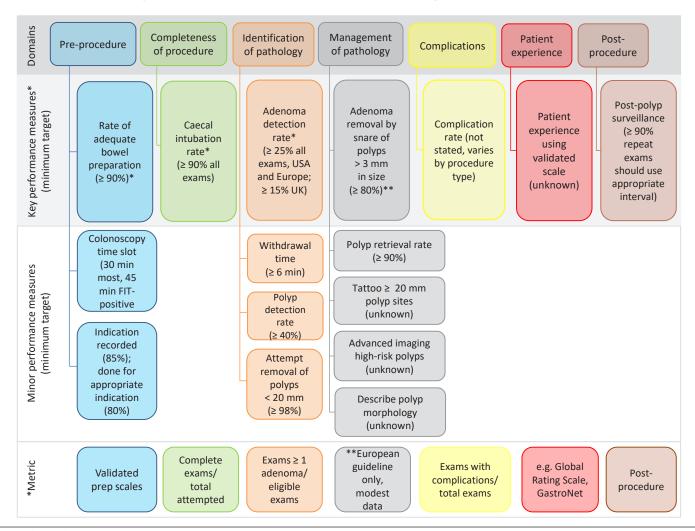
Medicaid Services, 2017). The polyp detection rate can be a surrogate for ADR if pathology data are not readily available (Williams et al., 2012; Patel et al., 2013). Fewer data exist on ADR guidelines for sigmoidoscopy; the United Kingdom Joint Advisory Group recommends a minimum ADR of 10% for sigmoidoscopy (Valori & Barton, 2007). The relative paucity of recommendations for sigmoidoscopy is partly due to the fact that sigmoidoscopy has a less standardized extent of examination, which influences polyp detection rate (Segnan et al., 2007; Fracchia et al., 2010). Cumulatively, these findings and recommendations indicate that measures to increase ADR at either the patient level (e.g. adequate bowel preparation) or the provider level are appropriate targets for ADR interventions for both sigmoidoscopy and colonoscopy providers.

Incomplete resection of precancerous polyps is also likely to influence patients' risk of post-colonoscopy CRC, although it is difficult to calculate the effect magnitude versus such cancers arising from undetected or new polyps (Erichsen et al., 2013; Pohl et al., 2013; Samadder et al., 2014; Pullens et al., 2015). In one recent study, approximately one third of post-colonoscopy cancers were in the same colorectal segment (e.g. ascending colon or transverse colon) as a previously resected adenoma (Belderbos et al., 2017). To decrease the risk of incomplete removal, a guideline recommends snare removal (instead of biopsy forceps) for polyps larger than 3 mm, although the recommendation's evidence base is modest, particularly for relatively small polyps such as those 4–6 mm in size (Lee et al., 2013; Kim et al., 2015).

Although this was not explicitly stated by the guidelines, many of the listed metric methods are readily adaptable to measuring the quality of sigmoidoscopy, but few data are available to support metrics for sigmoidoscopy (Fig. 3.3.1). Performance guidelines for sigmoidoscopy focus primarily on technical skills, such as threshold limit of complications (Rees et al., 2016) and

**Fig. 3.3.1 Recommended quality and performance measures for colonoscopy**

| Domains | Pre-procedure | Completeness of procedure | Identification of pathology | Management of pathology | Complications | Patient experience | Post-procedure |
|---|---|---|---|---|---|---|---|
| **Key performance measures\* (minimum target)** | Rate of adequate bowel preparation (≥ 90%)\* | Caecal intubation rate\* (≥ 90% all exams) | Adenoma detection rate\* (≥ 25% all exams, USA and Europe; ≥ 15% UK) | Adenoma removal by snare of polyps > 3 mm in size (≥ 80%)\*\* | Complication rate (not stated, varies by procedure type) | Patient experience using validated scale (unknown) | Post-polyp surveillance (≥ 90% repeat exams should use appropriate interval) |
| **Minor performance measures (minimum target)** | Colonoscopy time slot (30 min most, 45 min FIT-positive) | | Withdrawal time (≥ 6 min) | Polyp retrieval rate (≥ 90%) | | | |
| | Indication recorded (85%); done for appropriate indication (80%) | | Polyp detection rate (≥ 40%) | Tattoo ≥ 20 mm polyp sites (unknown) | | | |
| | | | Attempt removal of polyps < 20 mm (≥ 98%) | Advanced imaging high-risk polyps (unknown) | | | |
| | | | | Describe polyp morphology (unknown) | | | |
| **\*Metric** | Validated prep scales | Complete exams/ total attempted | Exams ≥ 1 adenoma/ eligible exams | \*\*European guideline only, modest data | Exams with complications/ total exams | e.g. Global Rating Scale, GastroNet | Post-procedure |

FIT, faecal immunochemical test; min, minutes.

Data from the European working group (Valori et al., 2012; Kaminski et al., 2017a), United States (Levin et al., 2005), and United Kingdom guidelines (Rees et al., 2016), and with reference scales/metrics for bowel preparation (Aronchick et al., 1999; Rostom & Jolicoeur, 2004), procedure indication (American Society for Gastrointestinal Endoscopy, 2000; Juillerat et al., 2009), and patient experience (Breivik et al., 2000; Skovlund et al., 2005).

completion of a minimum number of examinations to a depth of at least 50 cm (JAG, 2004; Enns et al., 2008), although even the definition of a complete sigmoidoscopy, based on clinically important outcomes, was not fully specified by an international working group (Levin et al., 2005).

## (e)  Performance of screening endoscopy

The goals of screening are to detect CRC (early detection) and to remove precancerous polyps (cancer prevention). Therefore, the performance of screening endoscopy is the ability of the examination to detect CRC and to remove precancerous polyps.

The performance of sigmoidoscopy, particularly for proximal colon cancer, depends in part on the threshold for referral to colonoscopy, as regards polyp characteristics. Colonoscopy referral criteria used by some recent RCTs included (i) any polyp or mass (Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial in the USA; biopsies not routinely performed); (ii) any CRC, polyp > 5 mm in diameter, ≥ 3 adenomas, or any adenoma with high-grade dysplasia or villous histology (Screening for Colon and Rectum [SCORE] trial in Italy); (iii) any CRC, any adenoma, or any polyp > 10 mm (Norwegian Colorectal Cancer Prevention [NORCCAP] trial); and (iv) any CRC, any polyp > 10 mm, any polyp with tubulovillous or villous histology, or ≥ 3 adenomas (UKFSST) (Castells et al., 2013; Holme et al., 2017). A comparison of the latter three strategies suggested that for the goal of detecting an advanced adenoma or an invasive cancer of the proximal colon with colonoscopy, the NORCCAP trial criteria provided the greatest sensitivity, whereas the UKFSST criteria provided the lowest number of people needed to refer to colonoscopy per advanced proximal neoplasm detected (Castells et al., 2013).

Comprehensive summaries estimated that the sensitivity of endoscopy, within the examined segments, was approximately 95% for the detection of CRC; these estimates are derived mainly from tandem colonoscopy studies, in which a patient underwent two examinations. The estimated sensitivity of endoscopy for the detection of adenomas varied by polyp size: 95% for adenomas ≥ 10 mm, 85% for adenomas of 6–9 mm, and 75% for adenomas of 1–5 mm (van Rijn et al., 2006). The sensitivity of colonoscopy for the detection of proximal colorectal polyps may be somewhat lower, although the absence of a reference standard for identifying difficult-to-see sessile lesions complicates these sensitivity calculations. An RCT of a standard inspection of the proximal colon followed by either an additional inspection in retroflexion or a second forward-view examination demonstrated overall ADRs of 47% and 47%, respectively, and found that at least one additional adenoma was detected on second withdrawal in similar proportions (7.5% with retroflex and 10.5% with repeat forward view) (Kushnir et al., 2015). Sigmoidoscopy has similar assumed performance characteristics for lesions within reach of the examination (e.g. within 50 cm) (Knudsen et al., 2016).

Direct comparisons of the yields of sigmoidoscopy and colonoscopy are difficult, given that the typical sigmoidoscopy can inspect from the rectum up to the mid-sigmoid colon or, less commonly, the distal transverse colon. A multicentre colonoscopy trial estimated that of 3121 people who underwent a colonoscopy, 37.5% had ≥ 1 neoplastic lesion anywhere in the colon, and 329 (10.5%) had an advanced neoplasia/adenoma (≥ 10 mm, villous histology, high-grade dysplasia, or cancer). Of the 329 patients with an advanced neoplasia, in 128 it was proximal to the splenic flexure (the typical maximum extent of a sigmoidoscopy) and in 228 it was distal to the splenic flexure. The likelihood that the advanced proximal neoplasia would have been detected if the patients were initially screened with sigmoidoscopy was estimated, using the assumption that a full colonoscopy would be performed for

any distal colon adenoma. Of the patients with an advanced proximal neoplasia, 48.4% (62 of 128) had ≥ 1 distal colon adenoma (Lieberman et al., 2000). Therefore, a sigmoidoscopy screening strategy would presumably detect a large majority of distal advanced adenomas and, when a distal advanced adenoma is detected, lead to a colonoscopic examination of the proximal colon. However, these results may be due to the fact that most of the study population in the trial were men ($n = 3021$), in whom the prevalence of advanced adenoma and invasive cancer of the colon and the rectum was higher than that in adults at average risk (Heitman et al., 2009). The relative effects of sigmoidoscopy versus colonoscopy on small adenomas and sessile adenomas were less clear.

The ability of sigmoidoscopy and colonoscopy to distinguish between cancerous and non-cancerous lesions depends largely on pathology, which has moderate interobserver variability for villous, dysplastic (Costantini et al., 2003; Mahajan et al., 2013; Osmond et al., 2014), and malignant features, and for identifying serrated polyps and adenomas versus non-adenomas (Turner et al., 2013; Schachschal et al., 2016); interobserver variability includes differences between pathologists within the same country and differences in interpretation between countries (Schlemper et al., 1998). Classification methods based solely on the endoscopic appearance of polyps have been proposed to enable more selective pathological confirmation, but these are currently not widely used.

### (f) Host factors that affect screening performance

The primary host factors that influence screening performance are the patient's ability to complete the examination and the quality of the bowel preparation. Patient factors associated with inadequate bowel cleansing include a history of constipation, inability to complete the bowel preparation (primarily because of nausea), and

use of neuroleptic or antidepressant medications (Hautefeuille et al., 2014). Other factors related to incomplete sigmoidoscopy and colonoscopy include older patient age, female sex, and previous abdominal or pelvic surgery (Ramakrishnan & Scheid, 2003; Shah et al., 2007; Laiyemo et al., 2012).

Bowel preparation is central to screening performance for both sigmoidoscopy and colonoscopy. For colonoscopy, adenoma detection is substantially reduced among patients with inadequate bowel preparations, for both non-advanced adenomas (OR, 0.53; 95% CI, 0.46–0.62) and advanced adenomas (OR, 0.74; 95% CI, 0.62–0.87) (Sulz et al., 2016). However, bowel preparation represents a continuum, and how different levels of preparation influence adenoma detection is less certain. A recent data synthesis of different levels of bowel preparation found, when comparing low-, intermediate-, and high-quality bowel preparations, an absolute increase of 5% in colonoscopy ADRs for both intermediate- and high-quality preparations, compared with low-quality preparation (OR, 1.39; 95% CI, 1.08–1.79 for intermediate quality; OR, 1.41; 95% CI, 1.21–1.64 for high quality), but no large differences were found between intermediate- and high-quality preparations (Clark et al., 2014). Therefore, for patients who undergo routine screening or surveillance examinations with "inadequate" preparations, it is recommended that the examination should be repeated within 1 year (Johnson et al., 2014).

Patient education may improve the quality of the bowel preparation. A meta-analysis of RCTs of patient education measures suggested that a brief information or counselling session significantly improved the adequacy of bowel preparation (RR, 1.22; 95% CI, 1.10–1.36), with a marginal trend towards decreasing the likelihood of needing a repeat colonoscopy (RR, 0.52, CI, 0.25–1.04) (Chang et al., 2015). Similar findings were noted for a greater likelihood of an adequate bowel preparation among those receiving "enhanced" instructions, consisting

of both verbal and written information, versus written information alone (OR, 2.35; 95% CI, 1.65–3.35) (Guo et al., 2017).

### 3.3.2 Randomized controlled trials

#### (a) RCTs of sigmoidoscopy

Four RCTs of sigmoidoscopy with CRC mortality and/or CRC incidence as end-points have been published. Note that this excludes one very small trial with 799 total subjects randomized (Thiis-Evensen et al., 1999a). Table 3.3.2, Table 3.3.3, Table 3.3.4, and Table 3.3.5 describe the design and findings of the four RCTs.

#### (b) Descriptions of RCTs

#### (i) PLCO trial

The PLCO trial in the USA examined screening for four different cancers (Schoen et al., 2012). In 1993–2001 at 10 screening centres, subjects aged 55–74 years were individually randomized to either an intervention arm or a usual-care arm. All subjects provided informed consent, with consent generally before randomization. Subjects in the intervention arm were offered screening for CRC, lung cancer, and either prostate cancer (men) or ovarian cancer (women). For the CRC screening component, subjects were offered sigmoidoscopy at baseline and either at 3 years (for those who were randomized before April 1995) or at 5 years. A positive sigmoidoscopy screening result was defined as the detection of a polyp or mass. Subjects with a positive screening result were referred to their health-care providers for follow-up; the PLCO trial did not dictate or perform follow-up. By trial protocol, polyps were not removed at the screening sigmoidoscopy. Subjects with adenomas (or CRC) detected on follow-up endoscopy after a positive screening result were advised not to return for the subsequent screening; they received surveillance colonoscopy in accordance with community standards.

Exclusion criteria for the PLCO trial included a history of prostate cancer, lung cancer, ovarian cancer, or CRC and current treatment for cancer. Starting in April 1995, subjects who had undergone a colonoscopy or sigmoidoscopy in the previous 3 years were also ineligible for the trial.

The primary outcome of the CRC screening component was CRC-specific mortality, with CRC incidence as a secondary outcome. Planned follow-up was for 13 years or until 31 December 2009, whichever came first.

A total of 77 445 individuals were randomized to the intervention arm and 77 455 to the usual-care arm; 50.5% of the subjects in each arm were women. In the intervention arm, 83.5% of subjects received the baseline sigmoidoscopy screen and 54.0% received the second-round screen; 86.6% of subjects received at least one sigmoidoscopy screen. The rates of positive screening results were 23.4% at the baseline screen and 23.5% at the subsequent screen. Of those with a positive screening result, 80.5% received some diagnostic follow-up within 1 year, of whom 95.6% received colonoscopy. Of all subjects in the intervention arm, 21.9% received a colonoscopy follow-up of a positive sigmoidoscopy screening result.

The use of sigmoidoscopy and colonoscopy in the usual-care arm was monitored on a sampling basis. The estimated rates of endoscopic examination during the screening phase of the trial (the first 6 years of the study) were 25.8% for sigmoidoscopy, 34.4% for colonoscopy, and 46.5% for either sigmoidoscopy or colonoscopy. An ancillary study was performed to examine the use of surveillance colonoscopy in subjects in the intervention arm who had a positive baseline screening result and had adenomas removed on the subsequent colonoscopy. After a median follow-up of 8.9 years, 79.3% of subjects with advanced adenomas, 81.9% of subjects with ≥ 3 non-advanced adenomas, and 74.2% of subjects with 1 or 2 non-advanced adenomas had received at least one post-baseline colonoscopy.

**Table 3.3.2 Characteristics of randomized controlled trials on colorectal cancer screening with sigmoidoscopy**

| Trial Country | Randomization | Number of subjects Intervention arm/ control arm | Accrual period | Age at entry (years) | Referral protocol |
|---|---|---|---|---|---|
| PLCO USA | Individual | 154 900 77 445/77 455 | 1993–2001 | 55–74 | Contingent on personal physician and medical care |
| UKFSST United Kingdom | Individual | 170 038 57 099/112 939 | 1994–1999 | 55–64 | ≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy |
| NORCCAP Norway | Individual | 98 792 20 572/78 220 | 1999–2001 | 50–64 | ≥ 10 mm polyp, any adenoma or malignancy |
| SCORE Italy | Individual/ cluster[a] | 34 292 17 136/17 136 | 1995–1999 | 55–64 | ≥ 5 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy |

NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.
[a] Cluster randomization was adopted for 3 out of 6 centres, and the unit of randomization was the physician.

*(ii)    UKFSST*

The UKFSST was an RCT of once-only screening with sigmoidoscopy (Atkin et al., 2010). Men and women aged 55–64 years who were registered with participating general practices in the United Kingdom were eligible for the trial, provided they had no history of CRC, adenomas, or inflammatory bowel disease, had a life expectancy of at least 5 years, and had not received a colonoscopy or sigmoidoscopy in the previous 3 years. Eligible subjects (368 142) were first sent a questionnaire asking whether they would participate in an RCT of CRC screening. Those who agreed to participate were then randomized in a 2:1 ratio to the control arm or the intervention arm of the trial.

Subjects in the intervention arm underwent baseline sigmoidoscopy with polypectomy. Those with polyps meeting any of the following criteria were referred for colonoscopy: ≥ 10 mm in diameter, ≥ 3 adenomas, tubulovillous or villous histology, high-grade dysplasia, malignancy, or ≥ 20 hyperplastic polyps above the distal rectum.

Trial enrolment began in November 1994 and was completed in March 1999. A total of 170 432

individuals were randomized, and after exclusions for deaths and previous CRC, 170 038 were included in the analysis (112 939 in the control arm and 57 099 in the intervention arm); 50.0% were women. The participation rate in the baseline screening was 71%; of those screened, 5% underwent follow-up colonoscopy, of whom 85% subsequently entered a surveillance programme.

*(iii)    NORCCAP trial*

The NORCCAP trial was an RCT of once-only screening with sigmoidoscopy (Holme et al., 2014). Men and women aged 55–64 years living in the city of Oslo or in Telemark County, Norway, were identified through population registers. In 1998, birth cohorts were randomly sampled to be invited to the screening arm or included in the control arm; subjects in the control arm were not contacted. In 2000, the trial was extended to include individuals aged 50–54 years. The ratios of subjects aged 55–64 years to those aged 50–54 years differed between the screening arm and the control arm; subjects in the control arm were younger than those in the screening arm. Subjects in the screening arm were further randomized in a 1:1 ratio to receive either

## Table 3.3.3 Designs of randomized controlled trials on colorectal cancer screening with sigmoidoscopy

| Trial | Intervention | Number of screening rounds | Screening interval | Compliance with first round (%) | Determination of end-point (for mortality) | Median duration of follow-up (years) |
|---|---|---|---|---|---|---|
| PLCO | Sigmoidoscopy at baseline and after 3 or 5 years | 2 | 3 or 5 years[a] | 84 | Independent death review | 11.9 (incidence) 12.1 (mortality) |
| UKFSST | Once-only sigmoidoscopy | 1 | N/A | 71 | Independent death review | 17.1 (mortality) |
| NORCCAP | Once-only sigmoidoscopy, with or without a single FIT | 1 | N/A | 63 | Official statistics | 11.2 screened (incidence) 10.9 controls (incidence) |
| SCORE | Once-only sigmoidoscopy | 1 | N/A | 58 | Independent death review | 10.5 (incidence) 11.4 (mortality) |

FIT, faecal immunochemical test; N/A, not applicable. NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a]  The screening interval was 3 years for participants randomized before April 1995 and 5 years for other participants.

## Table 3.3.4 Results of randomized controlled trials on colorectal cancer screening with sigmoidoscopy (intention-to-treat analyses)

| Trial | Incidence | | | Mortality | | |
|---|---|---|---|---|---|---|
| | Rate per 100 000 person-years | | RR or HR (95% CI) | Rate per 100 000 person-years | | RR or HR (95% CI) |
| | Intervention arm | Control arm | | Intervention arm | Control arm | |
| PLCO | 119 | 152 | 0.79 (0.72–0.85) | 29 | 39 | 0.74 (0.63–0.87) |
| UKFSST[a] | 114 | 149 | 0.77 (0.70–0.84) | 30 | 44 | 0.69 (0.59–0.82) |
| UKFSST[b] | 137 | 184 | 0.74 (0.70–0.80) | 39 | 56 | 0.70 (0.62–0.79) |
| NORCCAP | 112.6 | 141.0 | 0.80 (0.70–0.92) | 31.4 | 43.1 | 0.73 (0.56–0.94) |
| SCORE | 144.1 | 176.4 | 0.82 (0.69–0.96) | 34.7 | 44.5 | 0.78 (0.56–1.08) |

CI, confidence interval; HR, hazard ratio; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a]  Based on initial report; median follow-up, 11.2 years.

[b]  Based on extended follow-up analysis; median follow-up, 17.1 years.

**Table 3.3.5 Results of randomized controlled trials on colorectal cancer screening with sigmoidoscopy (per-protocol analyses)**

| Trial | RR or HR (95% CI) | |
|---|---|---|
| | Incidence | Mortality |
| PLCO | – | – |
| UKFSST[a] | 0.67 (0.60–0.76) | 0.57 (0.45–0.72) |
| UKFSST[b] | 0.65 (0.59–0.71) | 0.59 (0.49–0.70) |
| NORCCAP | 0.68 (0.56–0.86) | 0.63 (0.40–1.40) |
| SCORE | 0.69 (0.56–0.86) | 0.62 (0.40–0.96) |

CI, confidence interval; HR, hazard ratio; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Based on initial report; median follow-up, 11.2 years.

[b] Based on extended follow-up analysis; median follow-up, 17.1 years.

sigmoidoscopy plus FIT at baseline or only a baseline sigmoidoscopy. All visible lesions were removed at sigmoidoscopy and subjected to histopathology; subjects with a polyp ≥ 10 mm, any adenoma or suspected CRC, or a positive FIT result were referred for colonoscopy, at which time all polyps were removed.

A total of 20 780 subjects were randomized to the screening arm and 79 430 to the control arm. After exclusions for deaths and previous CRC, 20 572 subjects were analysed in the screening arm and 78 220 in the control arm; 50.1% were women. The participation rate for screening sigmoidoscopy was 63.0%; of those screened, 19.5% attended follow-up colonoscopy and 9.8% were recommended for surveillance colonoscopy.

### (iv)    SCORE trial

The SCORE trial in Italy was an RCT of once-only screening with sigmoidoscopy (Segnan et al., 2002). Ineligibility criteria included a personal history of CRC, adenoma, or inflammatory bowel disease, having undergone a lower gastrointestinal endoscopy in the previous 2 years, having two or more first-degree relatives with CRC, or having a medical condition that precluded a benefit from screening. Individuals aged 55–64 years who responded to a mailed questionnaire that they certainly or probably would attend screening if offered were randomized to an intervention arm (17 148) or a control arm (17 144); 50.0% were women. In three centres (Biella, Genoa, and Milan), with 16 690 subjects, randomization was at the individual level; in the three other centres (Arezzo, Rimini, and Turin), with 17 602 subjects, cluster randomization was used, and the unit of randomization was the general practitioner. Subjects in the control arm were not contacted further. The data set for the final analysis excluded 12 subjects in the intervention arm and 8 subjects in the control arm, because of death or CRC diagnosis before randomization; therefore, it included 17 136 subjects in each arm.

Diminutive polyps (≤ 5 mm) were removed at sigmoidoscopy. Subjects with larger polyps (> 5 mm), 3 or more adenomas, adenomas with more than 20% villous component, severe dysplasia, or CRC and subjects with inadequate bowel preparation and at least one polyp were referred for colonoscopy.

Of the 17 148 individuals in the screening arm, 9999 (58.3%) attended the screening and 9911 (57.8%) were actually screened (the remaining 88 were referred for later screening because of inadequate bowel preparation but did not return for screening). After screening,

20 (0.2%) were immediately referred to surgery and 775 (8%) attended colonoscopy. Subsequent surveillance colonoscopy was indicated for 395 subjects.

### (c) Effects on CRC incidence and mortality and all-cause mortality

This section summarizes findings from the RCTs on the effects of sigmoidoscopy on CRC mortality, CRC incidence, and all-cause mortality. All relative risks and hazard ratios are from intention-to-treat analyses, unless otherwise stated. For per-protocol analyses, the UKFSST and the SCORE trial reported adjusted relative risks derived using the Cuzick method (Cuzick et al., 1997). The NORCCAP trial reported per-protocol 10-year risk differences using an instrumental variable approach; these were converted to relative risks to obtain a comparable metric to that reported for the other trials. The PLCO trial did not report per-protocol analyses.

[For the SCORE trial, in the statistical methods section of the final outcome publication (Segnan et al., 2011), there is no indication that the statistical analysis took into account the cluster randomization of the three centres; the computed 95% confidence intervals seem to have been calculated from only person-years and the number of reported events.]

### (i) CRC mortality

In the PLCO trial, after a median follow-up of 12.1 years, the relative risk of CRC-specific mortality was 0.74 (95% CI, 0.63–0.87) (Schoen et al., 2012). The relative risk was 0.50 (95% CI, 0.38–0.64) for distal CRC and 0.97 (95% CI, 0.77–1.22) for proximal CRC. Stratified analyses showed that the relative risk of CRC-specific mortality was 0.84 (95% CI, 0.67–1.06) for those aged 55–64 years and 0.65 (95% CI, 0.52–0.82) for those aged 65–74 years ($P_{interaction}$ = 0.11). By sex, the relative risk was 0.66 (95% CI, 0.53–0.81)

for men and 0.87 (95% CI, 0.68–1.12) for women ($P_{interaction}$ = 0.10).

In the UKFSST, an initial analysis of the primary end-points, published in 2010, with a median follow-up of 11.2 years, showed a hazard ratio for CRC mortality of 0.69 (95% CI, 0.59–0.82) (Atkin et al., 2010). By anatomical location, the mortality rate ratio was 0.58 (95% CI, 0.46–0.74) for distal CRC and 0.87 (95% CI, 0.68–1.12) for proximal CRC (Lin et al., 2016b). An extended follow-up analysis was published in 2017, with a median follow-up of 17.1 years (Atkin et al., 2017). The hazard ratio for CRC mortality was 0.70 (95% CI, 0.62–0.79). The hazard ratio for CRC mortality was also reported by anatomical location: 0.54 (95% CI, 0.45–0.65) for distal CRC and 0.91 (95% CI, 0.76–1.08) for proximal CRC. The hazard ratio for CRC mortality (in the extended follow-up analysis) by age was 0.67 (95% CI, 0.55–0.81) for those aged 55–59 years and 0.72 (95% CI, 0.62–0.84) for those aged 60–64 years ($P_{interaction}$ = 0.519). By sex, the hazard ratio was 0.67 (95% CI, 0.57–0.79) for men and 0.74 (95% CI, 0.61–0.90) for women ($P_{interaction}$ = 0.417). In the per-protocol analysis (extended follow-up), the relative risk was 0.59 (95% CI, 0.49–0.70) for overall CRC mortality and 0.34 (95% CI, 0.26–0.46) for distal CRC mortality.

In the NORCCAP trial, the (age-adjusted) hazard ratio for CRC mortality was 0.73 (95% CI, 0.56–0.94) (Holme et al., 2014). The hazard ratio was 0.79 (95% CI, 0.55–1.11) for distal CRC mortality and 0.73 (95% CI, 0.49–1.09) for proximal CRC mortality. The hazard ratio for mortality did not differ significantly by subgroup of the screening arm; the hazard ratio was 0.62 for sigmoidoscopy plus FOBT and 0.84 for sigmoidoscopy alone ($P_{heterogeneity}$ = 0.20). By age group, the hazard ratios were similar for those aged 50–54 years (HR, 0.74; 95% CI, 0.40–1.35) and those aged 55–64 years (HR, 0.73; 95% CI, 0.55–0.97). By sex, the hazard ratio was 0.58 (95% CI, 0.40–0.85) for men and 0.91 (95% CI, 0.64–1.30) for women ($P_{interaction}$ = 0.10). In

the per-protocol analysis, the relative risk was 0.63 (95% CI, 0.40–1.40). [After the Working Group meeting, updated results (with a median follow-up of 14.8 years) were reported (Holme et al., 2018).]

In the SCORE trial, the median follow-up was 11.4 years for CRC mortality (Segnan et al., 2011). The relative risk of CRC mortality was 0.78 (95% CI, 0.56–1.08). The relative risk was 0.73 (95% CI, 0.47–1.12) for distal CRC and 0.85 (95% CI, 0.52–1.39) for proximal CRC. In the per-protocol analysis, the relative risk was 0.62 (95% CI, 0.40–0.96) for overall CRC mortality and 0.48 (95% CI, 0.24–0.94) for distal CRC mortality.

*(ii)    CRC incidence*

In the PLCO trial, the relative risk of CRC incidence was 0.79 (95% CI, 0.72–0.85) (Schoen et al., 2012). The relative risk was 0.71 (95% CI, 0.64–0.80) for distal CRC incidence and 0.86 (95% CI, 0.76–0.97) for proximal CRC incidence. The relative risk of CRC incidence was similar by age: 0.78 (05% CI, 0.69–0.87) for those aged 55–64 years and 0.79 (95% CI, 0.71–0.89) for those aged 65–74 years. By sex, the relative risk was 0.73 (95% CI, 0.66–0.82) for men and 0.86 (95% CI, 0.76–0.98) for women, indicating a borderline significant interaction ($P_{interaction}$ = 0.052).

In the UKFSST, the hazard ratio for CRC incidence was 0.77 (95% CI, 0.70–0.84) in the earlier analysis (Atkin et al., 2010). The hazard ratio was 0.64 (95% CI, 0.57–0.72) for distal CRC incidence and 0.98 (95% CI, 0.85–1.12) for proximal CRC incidence (Lin et al., 2016b). In the extended follow-up analysis, the hazard ratio for CRC incidence was 0.74 (95% CI, 0.70–0.80); the hazard ratio was 0.59 (95% CI, 0.54–0.64) for distal CRC incidence and 0.96 (95% CI, 0.87–1.06) proximal CRC incidence (Atkin et al., 2017); the hazard ratios for CRC incidence were similar for those aged 55–59 years (HR, 0.74; 95% CI, 0.67–0.82) and those aged 60–64 years (HR, 0.75; 95% CI, 0.69–0.82). By sex, the hazard

ratio was 0.70 (95% CI, 0.65–0.77) for men and 0.81 (95% CI, 0.73–0.89) for women ($P_{interaction}$ = 0.047). In the per-protocol analysis (extended follow-up), the relative risk was 0.65 (95% CI, 0.59–0.71) for overall CRC incidence and 0.44 (95% CI, 0.38–0.50) for distal CRC incidence.

In the NORCCAP trial, the median follow-up was 11.2 years in the screening arm and 10.9 years in the control arm (Holme et al., 2014). The (age-adjusted) hazard ratio for CRC incidence was 0.80 (95% CI, 0.70–0.92). The hazard ratio was 0.76 (95% CI, 0.63–0.92) for distal CRC incidence and 0.90 (95% CI, 0.73–1.10) for proximal CRC incidence. The hazard ratio for CRC incidence did not differ significantly by subgroup of the screening arm; the hazard ratio was 0.88 for sigmoidoscopy plus FIT and 0.72 for sigmoidoscopy alone ($P_{heterogeneity}$ = 0.11). By age group, the hazard ratio for CRC incidence was 0.68 (95% CI, 0.49–0.94) for those aged 50–54 years and 0.83 (95% CI, 0.71–0.96) for those aged 55–64 years ($P_{interaction}$ = 0.27). By sex, the hazard ratio was 0.73 (95% CI, 0.60–0.89) for men and 0.87 (95% CI, 0.72–1.06) for women ($P_{interaction}$ = 0.26). In the per-protocol analysis, the relative risk of CRC incidence was 0.68 (95% CI, 0.56–0.86). [After the Working Group meeting, updated results (with a median follow-up of 14.8 years) were reported (Holme et al., 2018).]

In the SCORE trial, the median follow-up was 10.5 years for CRC incidence (Segnan et al., 2011). The relative risk of CRC incidence was 0.82 (95% CI, 0.69–0.96). The relative risk was 0.76 (95% CI, 0.62–0.94) for distal CRC incidence and 0.91 (95% CI, 0.69–1.20) for proximal CRC incidence. By age group, the relative risk was 0.84 (95% CI, 0.67–1.06) for those aged 55–59 years and 0.79 (95% CI, 0.62–1.00) for those aged 60–64 years. By sex, the relative risk was 0.88 (95% CI, 0.71–1.09) for men and 0.72 (95% CI, 0.55–0.96) for women. In the per-protocol analysis, the relative risk was 0.69 (95% CI, 0.56–0.86) for overall CRC incidence and 0.60 (95% CI, 0.46–0.80) for distal CRC incidence.

### (iii) All-cause mortality

In the UKFSST, the hazard ratio for all-cause mortality was 0.97 (95% CI, 0.94–1.00) in the earlier analysis and 0.99 (95% CI, 0.97–1.01) in the extended follow-up analysis (Atkin et al., 2010, 2017).

In the NORCCAP trial, the relative risk of all-cause mortality was 0.97 (95% CI, 0.93–1.02) (Holme et al., 2014).

In the SCORE trial, all-cause mortality rates were reported as 660.26 per 100 000 person-years in the control arm and 640.96 per 100 000 person-years in the intervention arm, based on 1233 deaths in the control arm and 1202 deaths in the intervention arm (Segnan et al., 2011). [From these mortality rates and numbers of deaths, the relative risk is 0.75 (95% CI, 0.55–1.02).]

In the PLCO trial, the numbers of deaths from all causes excluding cancers of the colorectum, prostate, ovary, and lung were reported as 9138 in the intervention arm and 9286 in the control arm (Schoen et al., 2012). [Using the number of deaths from CRC (252 in the intervention arm and 341 in the control arm) and the total person-years for mortality, the relative risk of mortality from all causes excluding cancers of the lung, ovary, and prostate is 0.98 (95% CI, 0.95–1.01).]

### (iv) Meta-analyses and pooled analyses of RCTs of sigmoidoscopy

Several meta-analyses of RCTs of sigmoidoscopy have been performed using the results from the four RCTs described above (PLCO, UKFSST, NORCCAP, and SCORE) (Fitzpatrick-Lewis et al., 2016; Lin et al., 2016a, b; Tinmouth et al., 2016). None of these included the updated findings of the UKFSST. Another meta-analysis, performed as a Cochrane systematic review (Holme et al., 2013), included only preliminary findings from the NORCCAP trial, with 7 years of follow-up, compared with the 11 years of follow-up used in the later NORCCAP publication; therefore, quantitative estimates from that meta-analysis are not included here. However,

the trial ratings from Holme et al. (2013), as well as those from Lin et al. (2016a), are summarized below.

The Cochrane review (Holme et al., 2013) examined six potential factors related to risk of bias in the trials: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. For three of the four RCTs (UKFSST, NORCCAP, and SCORE), the risk of bias was rated as low for all factors; for the PLCO trial, the risk of bias was rated as low for all factors except selective reporting, which was rated as unclear risk. Lin et al. (2016a) evaluated each trial for overall quality using criteria developed by the USPSTF. All four trials were rated as of fair quality.

The meta-analyses differed quantitatively with respect to several minor factors (Table 3.3.6). In addition, two (Fitzpatrick-Lewis et al., 2016; Lin et al., 2016b) of the three analyses did not adjust for age in the NORCCAP trial (i.e. they used the unadjusted instead of the adjusted relative risks). This had a relatively small effect on the final relative risk estimates for CRC incidence and mortality but a larger relative effect on all-cause mortality. [Because subjects in the screening arm were (by design) older than subjects in the control arm in the NORCCAP trial, not adjusting for age in the NORCCAP trial in a meta-analysis severely biased the overall relative risk estimate against finding an overall mortality reduction in the screening arm versus the control arm. Therefore, the results for all-cause mortality in the meta-analyses that did not adjust for age in the NORCCAP trial are not valid.]

For CRC mortality, the results for the three meta-analyses were similar, with combined relative risk estimates ranging from 0.72 (95% CI, 0.65–0.80) to 0.74 (95% CI, 0.67–0.83). Two of the meta-analyses (Lin et al., 2016b; Tinmouth et al., 2016) examined CRC incidence, with combined

**Table 3.3.6 Meta-analyses of randomized controlled trials on colorectal cancer screening with sigmoidoscopy, by outcome**

| Outcome measure | Reference | Number of trials included[a] | Control arm | | Screening arm | | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | Population (PYs) | Number of events | Population (PYs) | Number of events | |
| CRC incidence | Tinmouth et al. (2016) | 4 | 285 758 (3 067 081) | 4579 | 172 264 (1 860 990) | 2218 | 0.78 (0.74–0.83) |
| CRC incidence | Lin et al. (2016b)[b] | 4 | (3 067 081) | 4497 | (1 860 990) | 2222 | 0.79 (0.75–0.85) |
| Distal CRC incidence | Lin et al. (2016b)[b] | 4 | (3 068 922) | 2680 | (1 862 062) | 1154 | 0.71 (0.64–0.82) |
| Proximal CRC incidence | Lin et al. (2016b)[b] | 4 | (3 071 386) | 1755 | (1 862 971) | 1034 | 0.92 (0.84-1.02) |
| CRC mortality | Tinmouth et al. (2016) | 4 | 285 758 (3 114 546) | 1321 | 172 264 (1 902 184) | 576 | 0.72 (0.65–0.80) |
| CRC mortality | Lin et al. (2016a)[b] | 4 | (3 114 546) | 1391 | (1 902 184) | 609 | 0.73 (0.66–0.82) |
| CRC mortality | Fitzpatrick-Lewis et al. (2016)[b,c] | 4 | 285 752 | 1292 | 161 963 | 547 | 0.74 (0.67–0.83) |
| Distal CRC mortality | Lin et al. (2016b)[b] | 4 | (3 114 546) | 702 | (1 902 184) | 253 | 0.63 (0.49–0.84) |
| Proximal CRC mortality | Lin et al. (2016b)[b] | 4 | (3 114 546) | 529 | (1 902 184) | 295 | 0.90 (0.77–1.04) |
| All-cause mortality[d] | Tinmouth et al. (2016) | 4 | 285 758 (3 114 546) | 32 903 | 172 264 (1 902 184) | 19 525 | 0.97 (0.96–0.99) |
| All-cause mortality[d] | Lin et al. (2016a)[b] | 3 | (2 243 271) | 22 774 | (1 030 254) | 10 166 | 1.00 (0.94–1.06) |
| All-cause mortality[d] | Fitzpatrick-Lewis et al. (2016)[b,c] | 4 | 285 752 | 33 865 | 161 963 | 19 971 | 1.00 (0.96–1.04) |

CI, confidence interval; CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PYs, person-years; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Trials included were PLCO, UKFSST, NORCCAP, and SCORE.

[b] Did not adjust for age in the NORCCAP trial.

[c] Excluded the sigmoidoscopy plus FIT subgroup in the NORCCAP trial.

[d] For PLCO, deaths from lung, ovarian, and prostate cancers were not reported; Lin et al. excluded the PLCO trial for this reason.

relative risk estimates of 0.79 (95% CI, 0.75–0.85) and 0.78 (95% CI, 0.74–0.83), respectively. With respect to all-cause mortality, the one meta-analysis that adjusted for age in the NORCCAP trial (Tinmouth et al., 2016) found a significant reduction with sigmoidoscopy in all-cause mortality, with a relative risk of 0.97 (95% CI, 0.96–0.99) (Table 3.3.6).

A pooled analysis of the PLCO, NORCCAP, and SCORE trials estimated the relative risk of CRC incidence and mortality in men and women (Holme et al., 2017). For CRC incidence, the relative risks were 0.76 (95% CI, 0.70–0.83) for men and 0.83 (95% CI, 0.75–0.92) for women. No difference in the effect of screening was seen between men younger than 60 years and those aged 60 years or older. In contrast, screening reduced the incidence of CRC in women younger than 60 years (RR, 0.71; 95% CI, 0.59–0.84) but not significantly in those aged 60 years or older (RR, 0.90; 95% CI, 0.80–1.02). For CRC mortality, the relative risks were 0.67 (95% CI, 0.57–0.80) for men and 0.82 (95% CI, 0.67–1.00) for women. Screening reduced CRC mortality significantly in both younger and older men as well as in women younger than 60 years.

### (d) Colonoscopy

There are currently four trials under way of screening colonoscopy versus FIT and/or no screening: one in Spain; one in Sweden; one in the Netherlands, Norway, and Poland; and one in the USA (Robertson et al., 2015). To date, there are no reported results on CRC incidence or mortality from these trials.

### 3.3.3 Observational studies on preventive effects of endoscopy

The observational studies that fulfilled the two Working Group criteria (see Section 3.1) and were included in the cited systematic review (Brenner et al., 2014a) and/or found separately in

the literature search are described in detail under cohort and case–control studies below.

### (a) Sigmoidoscopy

### (i) Meta-analyses

The most recent systematic review of observational studies of endoscopy (Brenner et al., 2014a) included a total of two cohort studies and seven case–control studies (published in 1992–2013) in a meta-analysis of the effectiveness of sigmoidoscopy screening. [All nine studies met the Working Group criteria except Nishihara et al. (2013), which excluded prevalent cancers at baseline (the study is reported in the tables because it is included in the meta-analysis of mortality, but it is otherwise not highlighted in the text). There was heterogeneity among the included studies, for example in the designs, in the study populations (seven in the USA, one in Canada, and one in Sweden), and in adjustment for confounders (from only sex and age up to 16 variables) in the analyses, potentially biasing the effectiveness and maximum time frames of sigmoidoscopy before CRC diagnosis or mortality from 8–25 years.] The included studies are presented in Table 3.3.7 and Table 3.3.8.

The estimated meta-risk reduction for CRC incidence (five studies) was 49% (RR, 0.51; 95% CI, 0.39–0.65), with an incidence reduction of 64% (RR, 0.36; 95% CI, 0.26–0.50) for distal CRC, compared with 24% (RR, 0.76; 95% CI, 0.65–0.90) for proximal CRC. Mortality reduction was evaluated by pooling the results from four studies including Nishihara et al. (2013). The estimated overall risk reduction for CRC mortality was 47% (RR, 0.53; 95% CI, 0.30–0.97), with a mortality reduction of 66% (RR, 0.34; 95% CI, 0.19–0.62) for distal CRC, but with no mortality reduction for proximal CRC (RR, 0.96; 95% CI, 0.74–1.23). The heterogeneity in the meta-analysis of distal CRC mortality (and overall CRC mortality) was mostly caused by the large risk reduction (79%) demonstrated in the small case–control study

**Table 3.3.7 Cohort studies of colorectal cancer incidence and mortality with screening sigmoidoscopy**

| Reference Country | Study population | Recruitment | Age (years) | Follow-up (years) | Total number of CRCs | Adjustment | RR or HR (95% CI) |
|---|---|---|---|---|---|---|---|
| *Incidence* | | | | | | | |
| Blom et al. (2008)[a] Sweden | 1986 | Randomly from population register | 59–61 | 9 | 21 | Sex | RR, 0.5 (0.2–1.3)[b] |
| Nishihara et al. (2013)[c] USA | 88 902 | Nurses' Health Study and Health Professionals Follow-up Study | W, 30–55 M, 40–75 | 25 | 1512 | Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use | HR, 0.60 (0.53–0.68) after negative sigmoidoscopy D: HR, 0.44 (0.36–0.53) P: HR, 0.92 (0.77–1.11) |
| *Mortality* | | | | | | | |
| Nishihara et al. (2013)[a] USA | 88 902 | Nurses' Health Study and Health Professionals Follow-up Study | W, 30–55 M, 40–75 | 25 | 1512 | Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use | HR, 0.59 (0.45–0.76) D: HR, 0.31 (0.20–0.49) P: HR, 1.04 (0.73–1.48) |

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; M, men; P, proximal; RR, relative risk; W, women.

[a] Included in meta-analyses of CRC incidence and mortality of sigmoidoscopy by Brenner et al. (2014a).

[b] Data retrieved by Brenner et al. (2014a).

[c] Not fulfilling the Working Group criteria, and the data on incidence are not included in the meta-analysis by Brenner et al. (2014a). [Included here for completeness.]

**Table 3.3.8 Case–control studies of colorectal cancer incidence and mortality with screening sigmoidoscopy**

| Reference Country | Study population | Recruitment | Age of cases (number < 50 years) | Retrospective follow-up (years) | Total number of CRCs | Adjustments in analysis in addition to matching | Risk OR (95% CI) |
|---|---|---|---|---|---|---|---|
| *Incidence* | | | | | | | |
| Slattery et al. (2000)[a] USA | 2257 | Kaiser Permanente Medical Care Program and Utah | 30–79 (80) | 10 | 1048 | Age, BMI, total energy intake, physical activity, aspirin use, NSAID use, heredity, dietary fibre, calcium, and cholesterol | M, overall: 0.6 (0.4–0.8) M, D: 0.5 (0.3–0.7) M, P: 0.7 (0.5–1.1) W, overall: 0.5 (0.3–0.8) W, D: 0.5 (0.3–0.9) W, P: 0.5 (0.3–0.9) |
| Newcomb et al. (2003)[a] USA | 2962 | Cases from SEER registry and community-based controls | 20–75 | 16 | 1668 | Age, sex, heredity, HRT use (women), education level, smoking, BMI, number of previous tests | D: 0.24 (0.17–0.33) P: 0.89 (0.68–1.16) |
| Cotterchio et al. (2005)[a] Canada | 2915 | Ontario Familial Colorectal Cancer Registry and population-based controls | 20–74 (120)[b] | ≥ 5 | 971 | Age, sex, NSAID use, education level, BMI, heredity | 0.52 (0.34–0.80) D: 0.41 (0.30–0.56) P: 0.72 (0.51–1.01) |
| Doubeni et al. (2013)[a] USA | 980 | Managed care organizations with electronic patient data | 55–85 | ≥ 5 | 471 | CRC tests, number of preventive health-care visits, Charlson Comorbidity Index score, socioeconomic status, heredity | 0.51 (0.36–0.71) D: 0.26 (0.14–0.49) P: 0.80 (0.52–1.25) |
| Kahi et al. (2014) USA | 2492 | The VA Center for Integrated Healthcare system | Mean, 81 SD, ± 3.9 | 10 | 623 | Race, NSAID use, Charlson Comorbidity Index score | 0.91 (0.68–1.23) (10 yr) 0.75 (0.46–1.24) (5 yr) D and P: non-significant |
| *Mortality* | | | | | | | |
| Newcomb et al. (1992)[a] USA | 262 | Medical records of the Greater Marshfield Community Health Plan | < 50 – ≥ 80 | 10 | 66 | Heredity, other screening tests, duration of health plan enrolment | 0.21 (0.08–0.52) D: 0.05 (0.08–0.52) P: 0.36 (0.11–1.20) |
| Selby et al. (1992)[a] USA | 1129 | Kaiser Permanente Medical Care Program of Northern California | 45–91 | 10 | 261 | History of CRC/polyp, heredity, number of periodic health check-ups | D: 0.41 (0.25–0.69) P: 0.96 (0.61–1.50) |
| Scheitel et al. (1999)[a] USA | 653 | Mayo Clinic and Olmstead Medical Center medical record systems | 45–95 | 10 | 218 | Number of hospitalizations, periodic health examinations, history of polyps, heredity | 1.04 (0.21–5.13) |

**Table 3.3.8 (continued)**

| Reference Country | Study population | Recruitment | Age of cases (number < 50 years) | Retrospective follow-up (years) | Total number of CRCs | Adjustments in analysis in addition to matching | Risk OR (95% CI) |
|---|---|---|---|---|---|---|---|
| Doubeni et al. (2018) USA | 5207 | Kaiser Permanente Northern and Southern California health-care systems | 50–89 | 10 | 1747 | Age, sex, race, family history, education level, health plan enrolment duration, geographical region, Charlson Comorbidity Index score, number of primary care visits, faecal occult blood testing | 0.64 (0.56–0.75) D: 0.52 (0.41–0.66) P: 0.75 (0.62–0.92) |

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; M, men; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; P, proximal; RR, relative risk; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results Program; W, women; yr, year or years.

[a] Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).

[b] Of all screening modalities evaluated, not sigmoidoscopy specifically.

by Newcomb et al. (1992); when that study was excluded, the mortality reduction was 63% for distal CRC (compared with 66% reported earlier) and 35% for overall CRC mortality (compared with 47% reported earlier).

*(ii)    Cohort studies*

There were only two cohort studies performed in a screening setting: the study by Nishihara et al. (2013), which did not fulfil the inclusion criteria because it excluded prevalent cancers at baseline and only reported outcome measures after a negative endoscopy, and a smaller study by Blom et al. (2008) (Table 3.3.7). The study by Blom et al. (2008) was a prospective pilot study of screening sigmoidoscopy in the population at average risk. Approximately 2000 individuals aged 59–61 years were randomly selected and invited for a sigmoidoscopy examination. During follow-up, only 5 CRCs were diagnosed among participants and 16 among non-participants; the reduction in incidence was a non-significant 50%.

*(iii)   Case–control studies*

With respect to the effect of screening sigmoidoscopy on CRC incidence, four case–control studies have been performed, all in North America (Table 3.3.8). In three of the studies (Slattery et al., 2000; Newcomb et al., 2003; Cotterchio et al., 2005), the participants were asked to report – in questionnaires or interviews – background factors and any screening examination (check-up). [The use of questionnaires adds recall bias to the bias of self-selection to screening. Another limitation of the generalizability of the three studies is that the CRC cases and controls had a wide range of ages, including relatively young individuals who did not represent an eligible screening population at average risk.]

Slattery et al. (2000) stratified by sex and demonstrated a reduction in overall CRC incidence of 40% (OR, 0.6; 95% CI, 0.4–0.8) in men

and 50% (OR, 0.5; 95% CI, 0.3–0.8) in women. There was a significant reduction in incidence in men for distal CRC (OR, 0.5; 95% CI, 0.3–0.7) but not for proximal CRC (OR, 0.7; 95% CI, 0.5–1.1). In women, the reduction in CRC incidence was 50% for both distal CRC and proximal CRC (OR, 0.5; 95% CI, 0.3–0.9 for both) (Table 3.3.8).

In the population-based case–control study by Newcomb et al. (2003), screening with sigmoidoscopy was associated with a significant reduction in incidence (OR, 0.24; 95% CI, 0.17–0.33) for distal CRC, but not for proximal CRC (OR, 0.89; 95% CI, 0.68–1.16), up to 16 years of follow-up.

The study by Cotterchio et al. (2005) reported an overall incidence reduction with sigmoidoscopy of close to 50% (OR, 0.52; 95% CI, 0.34–0.80), with a strong reduction for distal CRC (OR, 0.41; 95% CI, 0.30–0.56) and a non-significant reduction for proximal CRC (OR, 0.72; 95% 0.51–1.01).

Doubeni et al. (2013) performed a case–control study of adults at average risk enrolled for at least 5 years in one of different health plans. CRC screening ascertainment was done by auditing electronic patient data files. In a population of just more than 1000 individuals, 92 case patients and 173 controls had undergone a screening sigmoidoscopy, resulting in an incidence reduction of 49% (OR, 0.51; 95% CI, 0.36–0.71) for overall CRC and of 74% (OR, 0.26; 95% CI, 0.14–0.49) for distal CRC, but no incidence reduction was found for proximal CRC (OR, 0.80; 95 CI, 0.52–1.25).

No protective effect was observed in the study by Kahi et al. (2014). The study of Kahi et al. (2014) primarily evaluated the protective effects of colonoscopy but reported non-significant associations between sigmoidoscopy and CRC incidence reduction after 5 years (OR, 0.75; 95% CI, 0.46–1.24) and 10 years (OR, 0.91; 95% CI, 0.68–1.23) of follow-up. [The figures were relatively small: only seven patients with distal CRC had undergone sigmoidoscopy in the 5-year window.]

With respect to the effect of sigmoidoscopy on CRC mortality, two relatively small, older case–control studies (with a total of 327 cases and 1064 controls) by Newcomb et al. (1992) and Selby et al. (1992) reported an association of having had a sigmoidoscopy screening examination with a decreased risk of CRC mortality, by approximately 80% (OR, 0.21; 95% CI, 0.08–0.52) for overall CRC (Newcomb et al., 1992) and by 59% (OR, 0.41; 95% CI, 0.25–0.69) for distal CRC (Selby et al., 1992). [The exposure was screening with rigid sigmoidoscopy in Selby et al. (1992).]

The association of a decreased risk of CRC mortality with sigmoidoscopy was not observed in the smaller study in the USA (Scheitel et al., 1999) (OR, 1.04; 95% CI, 0.21–5.13). Scheitel et al. (1999) found the same frequency of having had a sigmoidoscopy within 10 years of diagnosis in 218 cases (10.6%) and 435 controls (9.9%) and speculated that the low frequency could be the reason for a lack of a protective effect. In the study by Newcomb et al. (1992), the frequency of screening sigmoidoscopy was 10.6% in cases and 29.1% in controls, and in the study by Selby et al. (1992), the frequency was 8.8% in cases and 24.2% in controls.

A recently published case–control study of the effectiveness of endoscopy in a screening-eligible population in the USA (with 1747 cases and 3460 controls) (Doubeni et al., 2018) reported an overall CRC mortality reduction of 36% (OR, 0.64; 95% CI, 0.56–0.75) with sigmoidoscopy after extensive adjustment for potential confounders (e.g. matching and adjustments), with a strong preventive effect for CRC on both the distal and the proximal side of the colon (OR, 0.52; 95% CI, 0.41–0.66 for distal CRC and OR, 0.75; 95% CI, 0.62–0.92 for proximal CRC).

### (b) Colonoscopy

There are few high-quality observational studies that have evaluated the preventive effects of colonoscopy screening in the population at average risk and even fewer that have evaluated incidence and mortality outcomes in current colonoscopy screening programmes. Most of the studies retrospectively evaluated colonoscopy by any indication or the quality indicators of the procedure (e.g. the ADR, which is a prerequisite for a screening programme to be effective but will not be highlighted in this section).

### (i) Meta-analyses

The systematic review of observational studies of endoscopy (Brenner et al., 2014a) included three cohort studies and three case–control studies of colonoscopy (published in 2005–2014) in a meta-analysis of the effectiveness of colonoscopy screening. [All of the studies met the Working Group criteria except Nishihara et al. (2013) and Manser et al. (2012), both of which excluded prevalent cancers at baseline (included in Table 3.3.9). There was heterogeneity among the included studies, for example in the designs, in the study populations (four in the USA, one in Switzerland, and one in Germany), and in adjustment for confounders (from only 3 up to 14 variables) in the analyses, potentially biasing the effectiveness and maximum time frames of sigmoidoscopy before CRC diagnosis or mortality from 6–22 years.] The included studies are presented in Table 3.3.9 and Table 3.3.10.

The meta-estimates demonstrated a reduction of 69% (RR, 0.31; 95% CI, 0.12–0.77) in CRC incidence (five studies) and of 68% (RR, 0.32; 95% CI, 0.23–0.43) in CRC mortality (three studies) at any site. When stratified by anatomical location, the incidence reduction disappeared for either distal CRC or proximal CRC (RR, 0.21; 95% CI, 0.03–1.53 for distal CRC; RR, 0.44; 95% CI, 0.15–1.31 for proximal CRC). However, there was a mortality reduction of 82% (RR, 0.18; 95% CI, 0.10–0.31) for distal CRC and of 53% (RR, 0.47; 95% CI, 0.29–0.76) for proximal CRC.

### (ii) Cohort studies

See Table 3.3.9.

**Table 3.3.9 Cohort studies of colorectal cancer incidence and mortality with screening colonoscopy**

| Reference Country | Study population | Recruitment | Age (years) | Follow-up (years) | Total number of CRCs | Adjustment | Risk RR/absolute risk difference/ HR/SIR/SMR/OR (95% CI) |
|---|---|---|---|---|---|---|---|
| *Incidence* | | | | | | | |
| Kahi et al. (2009)[a] USA | 715 | Health-care personnel and spouses and SEER data | 50–86 | Median, 8 | 12 | Age, sex, calendar year | SIR, 0.33 (0.10–0.62) |
| Manser et al. (2012)[a] Switzerland | 22 686 | Population-based colon cancer screening programme | 50–80 | 6 | 214 (excluding 11 at screen) | "Baseline risk profiles" (e.g. comorbidity, BMI, family tumour history, lifestyle factors, smoking, medication, profession, symptoms) | OR, 0.31 (0.16–0.59) |
| Nishihara et al. (2013)[a] USA | 88 902 | Nurses' Health Study and Health Professionals Follow-up Study | 30–75 | 25 | 1385 | Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use | HR, 0.44 (0.38–0.52) after negative colonoscopy D: HR, 0.24 (0.18–0.32) P: HR, 0.73 (0.57–0.92) |
| García-Albéniz et al. (2017) USA | 1 355 692 | Medicare beneficiaries | 70–79 | 8 | 46 812 | Sex, race, age, original reason for entitlement, comprehensive preventive evaluative in previous 2 yr, use of 3 preventive services in previous 2 yr, United States Census Bureau division, combined comorbidity score, chronic condition, warehouse condition, calendar month | Absolute risk difference: Age 70–74 yr: −0.42% (−0.24% to −0.63%) Age 75–79 yr: −0.14% (−0.41% to 0.16%)[b] RR[c]: [Age 70–74 yr: 0.84 (0.76–0.91)] [Age 75–79 yr: 0.95 (0.87–1.05)] |
| *Mortality* | | | | | | | |
| Kahi et al. (2009)[a] USA | 715 | Health-care personnel and spouses and SEER data | 50–86 | Median, 8 | 12 | Age, sex, calendar year | SMR, 0.35 (0.00–1.06) |
| Manser et al. (2012)[a] Switzerland | 22 686 | Population-based colon cancer screening programme | 50–80 | 6 | 214 (excluding 11 at screen) | "Baseline risk profiles" (e.g. comorbidity, BMI, family tumour history, lifestyle factors, smoking, medication, profession, symptoms) | OR, 0.12 (0.01–0.93) |

**Table 3.3.9 (continued)**

| Reference Country | Study population | Recruitment | Age (years) | Follow-up (years) | Total number of CRCs | Adjustment | Risk RR/absolute risk difference/ HR/SIR/SMR/OR (95% CI) |
|---|---|---|---|---|---|---|---|
| Eldridge et al. (2013) USA | 68 531 | NIH-AARP Diet and Health Study | 50–71 | Mean, 11 | 602 | Age, sex, HRT use, education level, race, diabetes, heredity | RR, 0.40 (0.30–0.55) |
| Nishihara et al. (2013)[a] USA | 88 902 | Nurses' Health Study and Health Professionals Follow-up Study | 30–75 | 25 | 1385 | Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use | HR, 0.32 (0.24–0.45) D: HR, 0.18 (0.10–0.31) P: HR, 0.47 (0.29–0.76) |

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health-American Association of Retired Persons; OR, odds ratio; P, proximal; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

[a] Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).
[b] Absolute 8-year risk difference of screening colonoscopy group versus no-screening group.
[c] Retrieved by personal communication.

**Table 3.3.10 Case–control studies of colorectal cancer incidence and mortality with screening colonoscopy**

| Reference Country | Study population | Recruitment | Age of cases (number < 50 years) | Retrospective follow-up (years) | Total number of CRCs | Adjustments in analysis in addition to matching | Risk OR (95% CI) |
|---|---|---|---|---|---|---|---|
| *Incidence* | | | | | | | |
| Cotterchio et al. (2005)[a] Canada | 2915 | Ontario Familial Colorectal Cancer Registry and population-based controls | 20–74 (120)[b] | ≥ 5 | 971 | Age, sex, NSAID use, education level, BMI, heredity | 0.69 (0.44–1.07) D: 0.68 (0.49–0.94) P: 1.02 (0.72–1.45) |
| Doubeni et al. (2013)[a] USA | 980 | Managed care organizations with electronic patient data | 55–85 | ≥ 5 | 471 | CRC tests, number of preventive health-care visits, Charlson Comorbidity Index score, socioeconomic status, heredity | 0.30 (0.15–0.59) D: 0.26 (0.06–1.11) P: 0.37 (0.16–0.82) 0.69 (0.44–1.07) D: 0.68 (0.49–0.94) P: 1.02 (0.72–1.45) |
| Brenner et al. (2014b)[a] Germany | 318 | Cases from hospitals and controls from population registries | 50– > 80 | 10 | 43 | Age, sex, county of residence, education level, heredity, smoking, BMI, NSAID use, HRT use, health screening examination | 0.09 (0.07–0.13) M: 0.07 (0.05–0.12) W: 0.14 (0.08–0.23) Age ≥ 70 yr: 0.08 (0.05–0.13) Age < 70 yr: 0.11 (0.07–0.18) |
| Kahi et al. (2014) USA | 2492 | The VA Center for Integrated Healthcare system | Mean, 81.2 SD, ± 3.9 | 10 | 623 | Race, NSAID use, Charlson Comorbidity Index score | 0.57 (0.47–0.70) (10 yr) D: 0.45 (0.32–0.62) (10 yr) P: 0.65 (0.46–0.92) (10 yr) 0.49 (0.39–0.61) (5 yr) D: 0.36 (0.25–0.53) (5 yr) P: 0.51 (0.35–0.76) (5 yr) |
| *Mortality* | | | | | | | |
| Doubeni et al. (2018) USA | 5207 | Kaiser Permanente Northern and Southern California health-care systems | 50–89 | 10 | 1747 | Age, sex, race, family history, education level, health plan enrolment duration, geographical region, Charlson Comorbidity Index score, number of primary care visits, faecal occult blood testing | 0.33 (0.21–0.52) D: 0.25 (0.12–0.53) P: 0.35 (0.18–0.65) |

CI, confidence interval; CRC, colorectal cancer; D, distal; HRT, hormone replacement therapy; M, men; OR, odds ratio; P, proximal; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; W, women; y, year or years.

[a]  Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).
[b]  Of all screening modalities evaluated, not colonoscopy specifically.

In a population-based cohort study that estimated the preventive effects of colonoscopy in elderly people [study not included in the systematic review by Brenner et al. (2014a)], approximately 1 355 000 Medicare beneficiaries in the USA were prospectively followed up for 8 years (García-Albéniz et al., 2017). In the age group 70–74 years, the risk of CRC was 2.19% (95% CI, 2.00–2.37%) in those who had a screening colonoscopy, compared with 2.62% (CI, 2.56–2.67%) in the non-colonoscopy group, i.e. an absolute risk reduction of 0.42% (CI, 0.24–0.63%) for those who had a screening colonoscopy. In the age group 75–79 years, the risk of CRC was 2.84% in the colonoscopy group and 2.97% in the non-colonoscopy group (risk difference, −0.14%; CI, −0.41% to 0.16%). [The strength of the study is the large study population and the use of Medicare data to identify screening colonoscopies. Potential confounding factors are not adjusted for, but sensitivity analyses have been performed. Only one quarter of the individuals were followed up for longer than 5.5 years; this may be insufficient to adequately evaluate the protective effects of colonoscopy screening, but it could be valid for the older population studied.]

In another cohort study in the USA, the study population was generated from a diet and health study by the National Institutes of Health that sent questionnaires to people aged 50–71 years (Eldridge et al., 2013). The primary objective was to estimate the magnitude of uncontrolled confounding in observational studies by using medical records. Colonoscopy screening demonstrated a reduction in risk of CRC mortality of 60% (RR, 0.40; 95% CI, 0.30–0.55) after a mean follow-up of 11 years (Table 3.3.9).

In a smaller follow-up study of a previous study that evaluated colonic neoplasia after a negative FOBT result (Rex et al., 1993), Kahi et al. (2009) followed up a population of approximately 700 individuals at average risk (mean age, 61 years); after a median follow-up of 8 years, 12 CRCs were diagnosed. Having had a screening colonoscopy decreased the risk of CRC incidence by 67% (SIR, 0.33; 95% CI, 0.10–0.62) and, statistically non-significantly, the risk of CRC mortality by 65% (SMR, 0.35; 95% CI, 0.00–1.06). [The study cohort did not have a concurrent control group, and observed rates of CRC incidence and mortality were compared with the expected rates from the Surveillance, Epidemiology, and End Results Program.]

(iii)   *Case–control studies*

See Table 3.3.10.

In the study by Kahi et al. (2014) [study not included in the meta-analysis by Brenner et al. (2014a)], the protective effect of colonoscopy in reducing CRC incidence was observed for both the distal colon and the proximal colon. Kahi et al. (2014) demonstrated a 55% reduction in the incidence of distal CRC (OR, 0.45; 95% CI, 0.32–0.62) and a 35% reduction for proximal CRC (OR, 0.65; 95% CI, 0.46–0.92) in older United States veterans who had undergone a colonoscopy in the previous 10 years. The reduction in overall CRC incidence was 43% (OR, 0.57; 95% CI, 0.47–0.70). [The majority of colonoscopies were for diagnostic indications in a population of 99% men with an average age of > 80 years at diagnosis.] When estimated at 5 years, the point estimates were even lower (OR, 0.49; 95% CI, 0.39–0.61 for overall CRC; OR, 0.36; 95% CI, 0.25–0.53 for distal CRC; OR, 0.51; 95% CI, 0.35–0.76 for proximal CRC).

The study by Cotterchio et al. (2005), previously referred to among the case–control studies of sigmoidoscopy, also reported a reduction in CRC incidence in those who had undergone a screening colonoscopy. Cotterchio et al. (2005) did not observe any significant reduction in overall CRC incidence (OR, 0.69; 95% CI, 0.44–1.07) or proximal CRC incidence (OR, 1.02; 95% CI, 0.72–1.45), but observed a significant reduction (OR, 0.68; 95% CI, 0.49–0.94) in distal CRC incidence. [The study population was

relatively young (20–74 years), with few screening colonoscopies (4% in both groups).]

In a case–control study by Brenner et al. (2014b), cases were recruited from 22 hospitals in the study region of Germany and matched with controls from population registries. Standardized personal interviews were used to retrieve information on previous colonoscopy and potential confounding factors. Having had a screening colonoscopy was associated with a reduction in CRC incidence by 91% (OR, 0.09; 95% CI, 0.07–0.13). Brenner et al. (2014b) stratified by sex and age and observed an association in both men (OR, 0.07; 95% CI, 0.05–0.12) and women (OR, 0.14; 95% CI, 0.08–0.23) and in both older individuals (≥ 70 years) (OR, 0.08; 95% CI, 0.05–0.13) and younger individuals (< 70 years) (OR, 0.11; 95% CI, 0.07–0.18). [The self-reported colonoscopies and their indications were validated by medical record audits, which varied in quality, and some misclassification of indication could be present.]

In the case–control study of screening-eligible members of the Kaiser Permanente Medical Care Program in the USA, a preventive effect of colonoscopy on CRC mortality was observed for both distal CRC and proximal CRC (Doubeni et al., 2018). For the association of having had a colonoscopy within 10 years and reduced CRC mortality, the odds ratio was 0.25 (95% CI, 0.12–0.53) for distal CRC and 0.35 (95% CI, 0.18–0.65) for proximal CRC. For the association of having had a colonoscopy within 10 years and reduced overall CRC mortality, the odds ratio was 0.33 (95% CI, 0.21–0.52) (Table 3.3.10).

### (c)  Other measures of performance

A decreased incidence of late-stage CRC is an intermediate measure of screening effectiveness. One case–control study of the population at average risk (471 cases, 509 controls) by Doubeni et al. (2013), previously referred to, evaluated the association between colonoscopy screening and the risk of late-stage CRC. For having undergone a screening colonoscopy up to 10 years before the reference date, the odds ratio was 0.30 (95% CI, 0.15–0.59) for late-stage CRC (stage IIB–IV). Sigmoidoscopy screening was performed in 19.5% of the cases and in 34.0% of the controls, with an associated reduction in the risk of late-stage distal CRC (OR, 0.26; 95% CI, 0.14–0.49) but not of late-stage proximal CRC (OR, 0.80; 95% CI, 0.52–1.25). [The generalizability of the result of the study is limited because of its case–control design. Screening colonoscopies were relatively uncommon at the beginning of the study, and there is potential for unmeasured and unadjusted residual confounders.]

### 3.3.4 Adverse effects

### (a)  False-positive results

Screening techniques are intended for the screening of large numbers of asymptomatic individuals at average risk, and the ultimate goal is further stratification, not final diagnosis. As a result, identifying a small number of cases of cancers and/or precancerous lesions in a large population may, by necessity, result in large numbers of false-positive results.

### (i)  Sigmoidoscopy

The criteria for referral to colonoscopy vary widely among sigmoidoscopy-based screening strategies, because of a lack of consensus about which features of distal lesions predict the risk of advanced proximal neoplasms (Castells et al., 2013). A proportion of individuals who undergo a screening sigmoidoscopy that results in a follow-up colonoscopy will ultimately not be diagnosed with any cancerous or precancerous lesions. [Such false-positive results are not well reported in studies. Therefore, the total number and/or percentage of referrals in these studies are reported here.] The proportion of patients referred for colonoscopy ranged from 5.2% to 23.4% in the RCTs of sigmoidoscopy (Table 3.3.11).

**Table 3.3.11 False-positive results[a] in randomized controlled trials on colorectal cancer screening with sigmoidoscopy**

| Characteristic | Trial | | | |
|---|---|---|---|---|
| | UKFSST | SCORE | NORCCAP | PLCO |
| Number of subjects screened | 40 674 | 9911 | 12 960 | 64 658 |
| Definition of positive screens | Biopsy at screen or referral for colonoscopy or surgery | Biopsy at screen or referral for colonoscopy or surgery | Referral for colonoscopy | Polyp or mass at screen |
| Positive screen, n (%) | 11 268 (27.7) | 1745 (17.6) | 2639 (20.4) | 15 150 (23.4) |
| Criteria for colonoscopy | ≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy | ≥ 5 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy | ≥ 10 mm polyp, any adenoma or malignancy | Contingent on personal physician and medical care |
| Colonoscopy referral, n (%) | 2131 (5.2) | 832 (8.3) | 2639 (20.4) | 15 150 (23.4) |
| Colonoscopy follow-up | 2051 (5.0) | 775 (7.8) | 2524 (19.5) | 11 241 (17.4) |
| Any distal adenoma, n (%)[b] | 4931 (12.1) | 1070 (10.8) | [2208] (17.0)[e] | 4656 (7.2) |
| Advanced distal lesions, n (%)[b,c,d] | 1905 (4.7) | 341 (3.4) | [545] (4.2)[e] | 1746 (2.7) |
| Distal cancer, n (%) | 131 (0.3) | 47 (0.5) | [41] (0.3)[e] | 139 (0.2) |
| True-positives (any distal adenoma or cancer), n[f] | 5062 | 1117 | 2249 | 4795 |
| True-positives (advanced neoplasia), n[f] | 1905 | 388 | 586 | 1885 |

NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PPV, positive predictive value; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] False-positive rate can be calculated as (1 − PPV)*100.

[b] For PLCO in subjects without distal cancer.

[c] For UKFSST, advanced distal lesions defined as a ≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous adenoma, severe dysplasia, malignancy, or ≥ 20 hyperplastic polyps above the distal rectum, as determined by screening sigmoidoscopy and associated biopsies; for SCORE, advanced distal lesions defined as a ≥ 10 mm adenoma, tubulovillous or villous adenoma, or severe dysplasia, as determined by screening sigmoidoscopy and associated biopsies; for PLCO, advanced distal lesions defined as a ≥ 10 mm adenoma, tubulovillous or villous adenoma, or severe dysplasia in rectum, sigmoid colon, or descending colon or within 50 cm of anal verge (if segment not specified), as determined by diagnostic follow-up procedures completed within 1 year of screening.

[d] For UKFSST, proximal to sigmoid colon; for SCORE, proximal to the descending colon or in the descending colon, if not detected at screening sigmoidoscopy; for PLCO, segment proximal to descending colon or more than 50 cm from anal verge (if segment not specified).

[e] For NORCCAP, proximal lesions were included.

[f] The denominator to calculate the percentage of true-positives were individuals with a positive screen regardless of whether they underwent a colonoscopy.

Adapted from Weissfel et al., Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial, *JCNI: Journal of the National Cancer Institute*, 2005, volume 97, issue 13, pages 989–997, adapted by permission of Oxford University Press (Weissfeld et al., 2005).

Results are available online from population-based programmes in Italy (Osservatorio Nazionale Screening, 2017) and the United Kingdom (Bowel Cancer Screening Southern Programme Hub; National Health Service, 2015). In Italy, approximately 50 000 individuals aged 55 years were offered sigmoidoscopy for CRC screening for 2014, and the percentage of patients who met the criteria for referral for colonoscopy was 10.9%. The roll-out of the sigmoidoscopy programme in the United Kingdom started in 2013. In 2014, 12 of 18 screening centres of the Bowel Cancer Screening Southern Programme Hub invited individuals older than 55 years for a single sigmoidoscopy ($n$ = 8433). On average, 5.2% of those screened were referred for colonoscopy, although some variability was observed between centres, with referral rates ranging from 2.8% to 11.5%.

### (ii) Colonoscopy

False-positive results are not an issue for primary colonoscopy screening, in which, if it is appropriate, polyps can be removed during the screening procedure and no further assessment is required.

### (b) Overdiagnosis

Overdiagnosis refers to the detection of cancerous or precancerous lesions that would not, in the absence of screening, have caused symptoms or death in the individual's lifetime (Esserman et al., 2014).

### (i) Sigmoidoscopy

There are no publications that address overdiagnosis of CRC via sigmoidoscopy screening.

### (ii) Colonoscopy

Brenner et al. (2015) estimated the probabilities of prevention of CRC, early detection of CRC, or overdiagnosis of CRC according to sex and age at screening colonoscopy. This was the first and only attempt to date to estimate overdiagnosis from a national CRC screening programme. In the analysis of Brenner et al. (2015), the proportion of overdiagnosis among CRCs detected with screening colonoscopy was 11% in men and 8% in women overall, and 7% in men and 4% in women for screening colonoscopies in individuals younger than 70 years. [The Working Group noted that the validity of their calculations depends on the validity of the assumed transition rates from adenomas to CRCs. Even a small change in these rates would result in a large change in the estimated proportion of overdiagnosis. Therefore, the Working Group considered that the level of overdiagnosis is uncertain.]

Yang et al. (2014) calculated the difference between the observed CRC incidence and an expected baseline incidence for each year from 1979 to 2009. Then, for each year, they multiplied the difference in incidence by the number of individuals aged 50 years and older in the same year. Finally, they summed the results for each year from 1979 to 2009. This was similar to the approach used by Bleyer & Welch (2012) to estimate the number of breast cancers overdiagnosed because of mammography screening. Yang et al. (2014) concluded that there is probably little overdiagnosis of CRC. [The Working Group noted that this study has little validity, because (i) it only demonstrates that the preventive effect of CRC screening is higher than the rate of overdiagnosis and (ii) it is of ecological design.]

### (c) Endoscopy-related complications

Endoscopy-related complications can occur immediately or several days after the procedure. Although endoscopy services must have processes in place to identify and record adverse outcomes that occur after the patient leaves the endoscopy unit, the accurate identification of those events that occur after the patient is dismissed from the endoscopy unit is still a challenge. Late complications may still be underestimated because of underreporting.

The following complications in CRC screening with sigmoidoscopy or colonoscopy are

defined as serious: death within 30 days or hospitalization within 30 days (because of serious haemorrhage involving transfusion, or because of perforation, vagal syndrome, or peritonitis-like syndrome as a consequence of primary screening with endoscopic techniques) (Segnan et al., 2010). [Because serious harms from endoscopy other than perforation and bleeding are not routinely reported or defined, the reported rates of serious harms are of limited value.] On the basis of a few large-scale studies, the mortality rate within 30 days associated with endoscopic procedures was estimated to be 1 in 15 000 (Bacchus et al., 2016).

### (i) Sigmoidoscopy

Compared with colonoscopy, sigmoidoscopy has fewer adverse effects, requires less bowel preparation, and poses a lower risk of bowel perforation (Lin et al., 2016a). Physical adverse effects of the screening procedure and of colonoscopy follow-up were reported in all the RCTs of CRC screening with sigmoidoscopy (Table 3.3.12 and Table 3.3.13, respectively) but only partly in the PLCO trial in the USA (Schoen et al., 2012). There was incomplete reporting of deaths related to the follow-up colonoscopy and surgery (Holme et al., 2013).

Lin et al. (2016a) reported harms from different CRC screening methods in pooled analysis using observational studies and RCTs. In a population at average risk, perforations from sigmoidoscopy were relatively uncommon (0.1 per 1000 procedures; $I^2 = 18.4\%$), as were episodes of major bleeding (0.2 per 1000 procedures; $I^2 = 52.2\%$). The risk of complications increased markedly in examinations where a polypectomy was performed. In a large prospective, multicentre study that focused on colonoscopy polypectomy, major bleeding complications occurred in 1.6% of the examinations, and the perforation rate was 1.1%. Large polyp size and distal polyp location were found to be significant risk factors for major complications (OR, 31.01; 95% CI, 7.53–128.1 for large polyp size; OR, 2.40; 95% CI, 1.34–4.28 for distal polyp location) (Heldwein et al., 2005).

Recent studies in sigmoidoscopy screening settings showed that the procedure was well tolerated by most participants (Blom et al., 2004; Viiala & Olynyk, 2007; Robb et al., 2012; Bevan et al., 2015). Robb et al. (2012) reported that the most common side-effect that reached moderate or severe levels was wind (16%); abdominal pains and cramps were the next most commonly reported side-effect (7%). Compared with men, women found the procedure more uncomfortable and had a smaller average depth of insertion, which is determined mainly by patient tolerance (Eloubeidi et al., 2003; Viiala & Olynyk, 2008).

### (ii) Colonoscopy

Major complications were reported in two of the four trials of colonoscopy screening currently under way. In the Nordic-European Initiative on Colorectal Cancer (NordICC) trial (Bretthauer et al., 2016), 1 screened individual had a colonoscopy perforation at the baseline screen (0.08 per 1000 procedures), and 18 individuals developed bleeding due to polypectomy (1.5 per 1000 procedures). No deaths or other major complications related to the screening intervention occurred within 30 days after screening. A total of 51 screened individuals experienced minor vasovagal reactions during colonoscopy (4.1 per 1000 procedures). However, all complications were short-term, and none required extra measures for the patient after the procedure.

Of the major complications reported at baseline in the COLONPREV trial (Quintero et al., 2012), 12 individuals developed bleeding (2.4 per 1000 procedures) and 1 individual had a colonoscopy perforation (0.2 per 1000 procedures). Other serious adverse events were reported: 10 individuals experienced hypotension or bradycardia (2.0 per 1000 procedures), and 1 individual had desaturation (0.2 per 1000 procedures).

Three meta-analyses of population-based studies aimed at estimating complications and

risk factors for colonoscopy have been published recently (Lin et al., 2016a; Reumkens et al., 2016; Vermeer et al., 2017). In two of them, major bleeding occurred in 0.8 per 1000 procedures (Lin et al., 2016a; Vermeer et al., 2017). In contrast, Reumkens et al. (2016) reported overall post-colonoscopy bleeding in 2.4 per 1000 procedures. The perforation rate for screening or surveillance colonoscopies ranged from 0.07 per 1000 procedures to 0.4 per 1000 procedures (Lin et al., 2016a; Reumkens et al., 2016; Vermeer et al., 2017). Reumkens et al. (2016) found that perforation rates for screening or surveillance colonoscopies were about one quarter those for diagnostic examinations in symptomatic patients (0.3 per 1000 procedures vs 1.3 per 1000 procedures; $P < 0.001$), because of a population at average risk with fewer findings that required diagnostic or therapeutic interventions.

Other severe complications that require hospitalization are not consistently reported. Two studies that evaluated harms in people who received colonoscopy versus those who did not found no increased risk of myocardial infarction, cerebrovascular accident, or other cardiovascular events as a result of colonoscopy (Warren et al., 2009; Stock et al., 2013).

The risks of less serious complications, such as self-limited bleeding or abdominal pain, are less well documented than major complications after colonoscopy. One third of individuals who undergo a colonoscopy may report some gastrointestinal symptoms after the procedure (Zubarik et al., 1999; Bini et al., 2003; Ko et al., 2007). Reported symptoms include abdominal pain (10.5%), bloating (25%), self-limited gastrointestinal bleeding (3.8%), diarrhoea (6.3%), and nausea (4.0%). These symptoms generally are mild and resolve within 2 days after colonoscopy (Ko & Dominitz, 2010). Screening colonoscopy performed with conscious sedation is associated with less patient-reported abdominal discomfort compared with screening sigmoidoscopy without conscious sedation (Zubarik et al., 2002).

Findings from systematic reviews suggested similar tolerability, based on the number of minor adverse events, no difference in efficacy of bowel preparation, and no differences in the number and type of clinically significant adverse events between colon cleansing regimens (such as polyethylene glycol solution, oral sodium phosphate solution, sodium picosulfate or magnesium citrate, and enemas) (Tan & Tjandra, 2006; Belsey et al., 2007).

Complications from conscious sedation for colonoscopy are also uncommon but include respiratory depression, hypoxia, chest pain, cardiac arrhythmias, hypotension or hypertension, and vasovagal reactions (Ko & Dominitz, 2010). Sharma et al. (2007) found an overall risk of cardiopulmonary complications after colonoscopy of 1.1%.

### (d) Psychosocial harms

Short-term or long-term adverse psychosocial consequences of factors related to cancer screening can occur in any phase of the screening programme. Most of the evidence about the psychological effects of being screened was derived from RCTs and was reported according to the individuals' screening results.

### (i) Sigmoidoscopy

False-positive results have the potential to cause symptoms of anxiety, distress, and depression as well as changes in the overall perception of one's health status (Kirkøen et al., 2016), and therefore individuals who have had a false-positive result may be more reluctant to undergo successive screening. In results from RCTs, the psychological consequences in individuals who were found not to have advanced neoplasia have been reported to be transient (Wardle et al., 2003; Taylor et al., 2004; Miles et al., 2009; Kapidzic et al., 2012). Furthermore, the pilot study of a national screening programme for CRC in Norway showed that a positive screening result did not increase participants' levels of anxiety

**Table 3.3.12 Serious adverse events from sigmoidoscopy in randomized controlled trials on colorectal cancer screening with sigmoidoscopy**

| Reference | Trial | Follow-up | Sigmoidoscopies n | Perforation n (%) | Bleeding n (%) | Mortality n (%) | Other serious events n (%) |
|---|---|---|---|---|---|---|---|
| Atkin et al. (2002) | UKFSST | 30 days | 40 332 | 1 (0.002) | 12 (0.03) | 6 (0.01) | Hospitalization: 12<br>Myocardial infarction: 2<br>Syncope: 95<br>Other 1 (pulmonary embolism) |
| Segnan et al. (2002) | SCORE | 30 days | 9911 | 1 (0.01) | 0 (0) | NR | Other: 4 (colitis, seizure) |
| Gondal et al. (2003) | NORCCAP | NR | 12 960 | 0 (0) | 0 (0) | NR | Syncope: 26<br>Other: 1 (pulmonary embolism) |
| Segnan et al. (2005) | SCORE | NR | 4466 | NR | 0 (0) | NR | Syncope: 1 |
| Senore et al. (2011) | SCORE | 30 days | 1502 | 0 (0) | 12 (0.8) | NR | Hospitalization:16<br>Emergency department: 2<br>Other: 18 (cardiovascular disease, hernia, severe pain, hypotension) |
| Schoen et al. (2012) | PLCO | NR | 67 071 | 3 (0.004) | NR | NR | NR |

NORCCAP, Norwegian Colorectal Cancer Prevention trial; NR, not reported; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.
Adapted from Lin et al. (2016b).

**Table 3.3.13 Serious adverse events from follow-up colonoscopy in randomized controlled trials on colorectal cancer screening with sigmoidoscopy**

| Reference | Trial | Recruited population | Follow-up | Colonoscopies n | Perforation n (%) | Bleeding n (%) | Mortality n (%) | Other serious events n (%) |
|---|---|---|---|---|---|---|---|---|
| Atkin et al. (2002) | UKFSST | Patients with polyps meeting high-risk criteria | 30 days | 2051 | 4 (0.2) | 9 (0.4) | 1 (0.05) | Hospitalization[a]: 9 |
| Segnan et al. (2002) | SCORE | Sigmoidoscopy-positives | 30 days | 775 | 1 (0.1) | 1 (0.1) | NR | 0 (0) |
| Segnan et al. (2005) | SCORE | Sigmoidoscopy-positives | NR | 332 | NR | 1 (0.3) | NR | Hospitalization[a]: 1 |
| Gondal et al. (2003); Hoff et al. (2009) | NORCCAP | Sigmoidoscopy- or sigmoidoscopy/ FIT-positives | NR | 2 524 | 6 (0.2) | 4 (0.2) | NR | Hospitalization[a]: 4 (0.2) Syncope: 24 (1.0) |
| Schoen et al. (2012) | PLCO | Sigmoidoscopy-positives | NR | 17 672 | 19 (0.1) | NR | NR | NR |
| Rasmussen et al. (1999) | – | Sigmoidoscopy- or gFOBT-positives | NR | 502 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NORCCAP, Norwegian Colorectal Cancer Prevention trial; NR, not reported; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Hospitalizations are not mutually exclusive from the patients with perforation and serious bleeding.

Adapted from Lin et al. (2016b).

or depression, or decrease participants' levels of health-related quality of life (Kirkøen et al., 2016).

Psychological distress derived from a true-positive screening result (i.e. being labelled as sick or at risk) should not be dismissed. Nevertheless, among participants with a positive sigmoidoscopy result, Kapidzic et al. (2012) found similar quality of life scores in those with negative or positive colonoscopy results. Possible explanations for these mainly positive effects of CRC screening in participants with a true-positive result could be that although the participants were worried about the possibility of having CRC, when polyps were detected they were also relieved that the polyps were detected early and that they would be screened regularly to prevent CRC, or when CRC was detected they were reassured because they soon underwent treatment. In the case of a false-positive screening result, the authors hypothesized that the participants were relieved because no abnormalities were found during further investigations.

Robb et al. (2012) examined changes in anxiety levels and self-rated health from before screening to follow-up among participants in a population-based sigmoidoscopy screening programme. No significant changes were found for either anxiety levels or self-reported health. Results did not differ by sex, deprivation index, ethnicity, or screening outcome, and satisfaction with the screening process was high.

In contrast, another study reported that the level of anxiety was directly correlated with levels of pain and discomfort after the procedure and was inversely related to the level of satisfaction. Better management of anxiety may lead to higher procedural comfort in procedures performed without sedation (Carter et al., 2013).

### (ii) Colonoscopy

There is little evidence about adverse psychological effects of colonoscopy among the screened population as a whole (Thiis-Evensen et al., 1999b; Taupin et al., 2006).

### (e) False reassurance

It has been suggested that receiving a negative screening result may cause false reassurance or have a "certificate of health" effect. False reassurance in participants who receive a negative screening result may cause them to wrongly believe that they are at lower risk of the disease, and they may therefore be less likely to engage in health-related behaviours that would lower their risk and/or be less alert to symptoms that may appear or to the need for further evaluation.

### (i) Sigmoidoscopy

Short-term effects on lifestyle and health attitudes were addressed in two reports from the trial in the United Kingdom (Miles et al., 2003; Wardle et al., 2003), and no negative effects were detected. Adverse effects on lifestyle were evaluated prospectively in a randomized controlled study within the NORCCAP trial (Larsen et al., 2007). After 3 years, those who had been screened reduced their intake of fruit, berries, and vegetables, did not follow the trend of increased frequency of physical exercise seen for controls, gained more weight than controls, and did not improve their smoking habits as successfully as did the controls not invited for screening. Also, normal findings at screening (i.e. no neoplasia) were associated with a subsequent statistically significant gain in body weight compared with subjects with positive screening results. These findings persisted after adjustment for confounding factors.

### (ii) Colonoscopy

No studies are available on false reassurance in colonoscopy screening.

The extent to which false reassurance plays a role in CRC screening with endoscopy remains unclear. There are no known studies that have examined the phenomenon of delayed presentation of symptoms after endoscopy screening for CRC.

*(f)    Time/effort and opportunity costs*

For all aspects of participation in the screening process, depending on the health-care system, there are time/effort and opportunity costs (non-financial harms) for the participant, as well as potential financial harms to the participant or family or psychological harm from anticipation of future financial costs related to screening (PDQ Screening and Prevention Editorial Board, 2017).

*(i)    Sigmoidoscopy*

There are no studies available that have aimed to address time/effort and opportunity costs derived from participating in a sigmoidoscopy screening programme.

*(ii)    Colonoscopy*

Two small studies have examined time off from work among asymptomatic individuals undergoing colonoscopy. Ko et al. (2007) reported that 69.3% of individuals who underwent colonoscopy for CRC screening, surveillance, or follow-up of another abnormal screening result lost at least 1 day from their normal activities for the colonoscopy preparation, procedure, or recovery. About 25% of individuals reported that their family or friends lost at least 1 day from their normal activities because of the procedure. Dong et al. (2011) observed that one third of the participants who worked and who underwent midweek screening colonoscopy missed work on days in addition to the day of the procedure. Unanticipated time missed from work could increase the indirect costs of screening colonoscopy.

## 3.3.5 Benefit–harm ratio

In this section, the benefit–harm ratio of endoscopy screening is described. Endoscopy screening, like all other forms of screening, is associated with both benefits and harms (see Section 3.3.2, Section 3.3.3, and Section 3.3.4). It is the balance between these benefits and harms that determines whether a particular form of screening is worthwhile (see Section 3.1).

*(a)    Systematic review and decision modelling for USPSTF*

In 2016, a systematic review (Lin et al., 2016a, b) and decision analysis (Knudsen et al., 2016) of benefits and harms of screening were published alongside the USPSTF recommendations for CRC screening. These studies provide a way to initially assess the benefit–harm ratio of endoscopy screening. The systematic review demonstrated that harms of colonoscopy were greater than those of sigmoidoscopy and may also include harms from bowel preparation and sedation (Lin et al., 2016a, b). Reported harms were mostly proportional to the number of colonoscopies performed with screening. Therefore, in the USPSTF decision analysis, the benefit–harm ratio of screening was expressed as the number of colonoscopies that needed to be performed for every life year gained. This decision analysis showed that repeated colonoscopy at ages 50 years, 60 years, and 70 years could result in 250–275 life years gained per 1000 individuals aged 40 years requiring an average of just more than four colonoscopies in a lifetime (including surveillance colonoscopies). These numbers correspond to 14.5–16.5 colonoscopies per life year gained. The efficiency ratio (i.e. the ratio of incremental colonoscopies per additional life year gained compared with a less intensive colonoscopy strategy) varied between 39 and 65 colonoscopies per life year gained.

*(b)    QALYs and DALYs from modelling studies*

[The Working Group noted that the estimates described in this section are based on Markov models, which mostly assume that the additional adenomas detected by colonoscopy have similar progressive potential to those detected by sigmoidoscopy, and that colonoscopy screening will therefore be more effective than sigmoidoscopy screening. Therefore, all results in the following section should be interpreted with caution.]

Seventeen studies evaluated the impact of endoscopy screening on QALYs or life expectancy (Table 3.3.14). [Most of these studies were conducted in settings characterized by high background cancer incidence rate. As described in Section 3.1.5, benefit–harm ratios depend heavily on this background cancer incidence rate. Therefore, the results of these studies may not easily be transferable to settings characterized by low cancer incidence rate.] All of the studies concluded that screening influenced QALYs positively and resulted in a net gain in QALYs (Table 3.3.14). The QALYs gained for colonoscopy varied substantially, from 17 QALYs per 1000 individuals in a study in Singapore (Dan et al., 2012) to 611 QALYs per 1000 individuals in a study in Hong Kong Special Administrative Region, China (Wong et al., 2015). [The Working Group raised some doubts about the validity of this value.] For sigmoidoscopy, the net benefit of screening was slightly lower than that for colonoscopy, varying from 5 QALYs gained per 1000 individuals (Dan et al., 2012) to 124 QALYs gained per 1000 individuals (Lam et al., 2015). The wide variability in estimates can be explained partly by the age of the population to which the estimates were standardized and partly by variation in disease risk. When studies with questionable validity or young and mixed-age populations were excluded, the reported range in QALYs gained narrowed considerably, to 50–125 QALYs per 1000 individuals for colonoscopy and 65–125 QALYs per 1000 individuals for sigmoidoscopy.

All of the studies consistently showed a net gain in QALYs, indicating a favourable balance between benefits and harms of CRC screening. [The Working Group placed an important caveat on these estimates: 11 studies only took the impact of CRC diagnosis on quality of life into account. The impacts of other harms of screening, such as adverse events, false-positive results, and anxiety, were not considered. Three studies did consider some other harms of screening, such as the disutility of knowledge of being an adenoma patient (Lam et al., 2015; Wong et al., 2015) or the disutility of undergoing colonoscopy and experiencing adverse effects (van Hees et al., 2014b). None of the studies considered in their estimates of QALYs the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening result on an increased risk of adopting an unhealthy lifestyle.]

Of the studies that evaluated 10-yearly colonoscopy and 5-yearly sigmoidoscopy, four found higher QALYs with colonoscopy than with sigmoidoscopy (Heitman et al., 2010; Dan et al., 2012; Sharaf & Ladabaum, 2013; Kingsley et al., 2016). [As noted before, these results should be interpreted with caution because all of these models would have assumed a higher effectiveness of colonoscopy screening compared with sigmoidoscopy screening.]

Only two studies evaluated the impact of endoscopy screening on DALYs (Woo et al., 2007; Ginsberg et al., 2012) (Table 3.3.15). Both studies found endoscopy screening to result in a net decrease in DALYs, ranging from 0.3 to 10 DALYs averted for sigmoidoscopy and from 0.6 to 9 DALYs averted for colonoscopy. [However, again, only one study considered the negative impact of screening on DALYs, taking into account years of life lost because of complications of screening. Disability from adverse effects, anxiety, false-positive results, and adenoma diagnosis could not be taken into account, because disability coefficients for such events have not been established.]

**Table 3.3.14 Studies measuring quality-adjusted life years gained from endoscopy screening compared with no screening**

| Reference | Country | Population simulated[a] | Participation rate (%) | Strategy evaluated | Reduction in incidence/ mortality (%) | QALYs gained per 1000 individuals[b] | Considered disutility from screening?[c] | Comments |
|---|---|---|---|---|---|---|---|---|
| Ness et al. (2000) | USA | Cohort age 40 yr | 100 | Single colonoscopy | 61–64/65–68 | 65–66 | No | – |
| Tappenden et al. (2007) | United Kingdom | Cohort age 30 yr | 60 | Single sigmoidoscopy | 20/23 | 27 | No | Low effectiveness estimates, because young cohort at start of simulation |
| Heitman et al. (2010) | Canada | Cohort age 50–75 yr | 68 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 62/65 58/61 | 41 36 | No | Low effectiveness estimates, because mixed-age cohort |
| Telford et al. (2010) | Canada | Cohort age 50 yr | 73 | 10-yearly colonoscopy | 81/83 | 120 | No | Uncertain whether reported incidence/ mortality reductions pertain to 100% participation |
| Dan et al. (2012) | Singapore | Cohort age 50–75 yr | NR | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 35/38 28/30 | 17 5 | No | Low effectiveness estimates, because mixed-age cohort |
| Sharp et al. (2012) | Ireland | Cohort age 30 yr | 39 | Single sigmoidoscopy at age 60 years | 4.9/7.5 | 6 | No | Low effectiveness estimates, because young cohort at start of simulation |
| Barouni et al. (2012) | Islamic Republic of Iran | Cohort age 50 yr | 68 | 10-yearly colonoscopy | 76/78 | 119 | NR | – |
| Dinh et al. (2013) | USA | Cohort age 50–75 yr | 100 | 10-yearly colonoscopy | 76/77 | 115 | No | – |
| Sharaf & Ladabaum (2013) | USA | Cohort age 50 yr | 100 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 73/80 68/75 | 76 69 | No | – |
| Ladabaum et al. (2014) | Germany | Cohort age 50 yr | 100 | Colonoscopy at ages 55 and 65 years | 62/67 | 90 | NR | – |
| van Hees et al. (2014b) | USA | Cohort age 65 yr | 100 | 10-yearly colonoscopy | NR/NR | 65 | Yes | – |

**Table 3.3.14 (continued)**

| Reference | Country | Population simulated[a] | Participation rate (%) | Strategy evaluated | Reduction in incidence/ mortality (%) | QALYs gained per 1000 individuals[b] | Considered disutility from screening?[c] | Comments |
|---|---|---|---|---|---|---|---|---|
| Lam et al. (2015) | Hong Kong SAR, China | Cohort age 50 yr | NR | 10-yearly colonoscopy 5-yearly sigmoidoscopy | NR/NR | 109 124 | Only for being diagnosed with polyps | – |
| Wong et al. (2015) | Hong Kong SAR, China | Cohort age 50 yr | 60 | 10-yearly colonoscopy | NR/NR | 611 | Only for being diagnosed with polyps | High QALYs, because assumed positive impact of adenoma diagnosis on quality of life |
| Kingsley et al. (2016) | USA | Cohort age 50 yr | 38 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | NR/60[d] | 100 62 | No | – |
| Ladabaum & Mannalithara (2016) | USA | Cohort age 50 yr | 100 | 10-yearly colonoscopy | 73/81 | 77 | No | – |
| Sekiguchi et al. (2016) | Japan | Cohort age 40 yr | 60 | 10-yearly colonoscopy | 69/NR | 219 | NR | Questionable model validity, because incidence reduction higher than participation |
| Aronsson et al. (2017) | Sweden | Cohort age 60 yr | 38 | Single colonoscopy 10-yearly colonoscopy | NR/NR | 49 56 | No | – |

NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; 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.

[b] Estimates for QALYs gained depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

[c] "No" indicates that the studies that only incorporated the disutility of having a CRC diagnosis on quality of life; disutility of harms of screening, such as adverse events, false-positive results, and anxiety, was not considered. "Only for being diagnosed with polyps" indicates that apart from the disutility of CRC diagnosis, studies also incorporated the disutility of knowledge of being an adenoma patient. "Yes" indicates that the study also included the disutility of undergoing colonoscopy and experiencing adverse effects. None of the studies considered in their estimates of QALYs the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening result on an increased risk of adopting an unhealthy lifestyle.

[d] Reported mortality reduction for 100% participation.

**Table 3.3.15 Studies measuring disability-adjusted life-years averted from endoscopy screening compared with no screening**

| Reference | Country[a] | Population simulated[b] | Participation rate (%) | Strategy evaluated | Mortality reduction (%) | DALYs averted per 1000 individuals | Considered disability from screening? |
|---|---|---|---|---|---|---|---|
| Ginsberg et al. (2012) | South-East Asia<br>Sub-Saharan Africa<br>South-East Asia<br>Sub-Saharan Africa | Population in 2005 | 95 | 10-yearly colonoscopy<br>10-yearly colonoscopy<br>Sigmoidoscopy + FOBT<br>Sigmoidoscopy + FOBT | NR | 8<br>9<br>10<br>9 | No |
| Woo et al. (2007) | Hong Kong Special Administrative Region, China | Female population in 2001 | 100 | 10-yearly colonoscopy<br>5-yearly sigmoidoscopy | 41<br>23 | 0.6<br>0.3 | Only for deaths from screening |

DALYs, disability-adjusted life years; FOBT, faecal occult blood test; NR, not reported.

[a] In the WHO classification, sub-Saharan Africa and South-East Asia, including those countries with very high adult mortality and high child mortality, are referred to as AfrE and SearD, respectively.

[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.

[The lack of consideration of disability and disutility of the harms of screening itself in the above-mentioned studies probably reflects the lack of studies assessing the impact of the screening process on quality of life. The one study that included burden of screening and diagnostic follow-up in QALYs estimates used disutility values obtained by making assumptions because estimated values are lacking.] Only one study has directly assessed the burden of colonoscopy in a time-trade-off analysis. That study suggested that the number of days of life that individuals are willing to give up to avoid having to undergo screening depends on screening status (Dominitz & Provenzale, 1997). Those who had not been screened were willing to give up a median of 91 days to avoid screening sigmoidoscopy and 183 days to avoid screening colonoscopy. However, those who had already been screened were not willing to give up any time to avoid screening, indicating that the impact of the screening examination on quality of life was negligible for those individuals. A study in Hong Kong Special Administrative Region, China, evaluated health-related quality of life after diagnosis with colorectal neoplasia (Lam et al., 2015). Interestingly, quality of life was higher in patients with adenomas than in the Hong Kong reference population. [The better quality of life in this patient group probably reflects a "healthy screenee effect": those who participate in screening are on average healthier than the average population and therefore experience better health-related quality of life.]

[The outcomes of these studies indicate the difficulty of obtaining reliable estimates of the impact of screening on quality of life, and therefore of weighing the benefits of screening against its harms.]

### 3.3.6 Cost–effectiveness studies

#### (a) Background

[Like estimates of QALYs and DALYs, cost–effectiveness estimates are based mostly on Markov models, assuming that the benefits of colonoscopy screening are larger than those of sigmoidoscopy screening. Therefore, comparative results should be interpreted with caution. Several studies have been published that assessed the cost–effectiveness of CRC screening. The majority of these studies have been conducted in high-income countries, which are often characterized by high background cancer incidence rate. As described in Section 3.1.5, cost–effectiveness estimates depend heavily on this background cancer incidence rate and local costs. Therefore, the results of these studies may not easily be transferable to other settings, such as low- and middle-income countries.]

#### (b) Cost–effectiveness studies and systematic reviews

The literature on this topic has been summarized in three systematic reviews that used similar methodology, in 2002, 2011, and 2015 (Table 3.3.16) (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015). The reviews followed a similar methodology except that the review by Lansdorp-Vogelaar et al. (2011) also included studies outside the USA. This description of the cost–effectiveness of CRC screening is based on these reviews and supplemented with individual studies published since then.

Pignone et al. (2002) included seven studies in the USA that evaluated cost–effectiveness of CRC screening with endoscopy. Six studies considered life years gained as the outcome without adjustment for quality of life. Only the study by Ness et al. (2000) considered quality of life, but it did not include disutility for the burden of screening, adverse events, and false-positive results. All of the studies found endoscopy screening to cost

**Table 3.3.16 Reviews of cost–effectiveness of endoscopy screening compared with no screening**

| Reference | Country | Studies included | Range in cost–effectiveness ratios[a] (US$) | Cost–effectiveness analysis of COL vs SIG |
|---|---|---|---|---|
| Pignone et al. (2002) | USA | 5 studies evaluating COL and SIG<br>1 study evaluating COL only<br>1 study evaluating SIG only | COL: 9038–22 012<br>SIG: cost savings, 39 359 | COL dominated in 3 studies<br>COL and SIG both cost-effective in 1 study<br>FOBT + SIG dominated COL in 1 study |
| Lansdorp-Vogelaar et al. (2011) | All | 12 studies evaluating COL and SIG<br>3 studies evaluating COL only | COL: cost savings, 31 700<br>SIG: cost savings, 56 600 | COL dominated in 6 studies<br>COL < US$ 100 000 per LYG compared with SIG in all studies |
| Patel & Kilgore (2015) | USA | 6 studies evaluating COL and SIG<br>5 studies evaluating COL only | COL: cost savings, 27 328<br>SIG: cost savings, 30 671 | COL dominated in 4 simulations<br>COL < US$ 50 000 per LYG compared with SIG in 9 simulations<br>COL > US$ 50 000 per LYG compared with SIG in 2 simulations |

COL, colonoscopy; FOBT, faecal occult blood test; LYG, life year grained; SIG, sigmoidoscopy.

[a] Estimates for cost–effectiveness depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

less than US$ 50 000 per life year gained. One study showed that sigmoidoscopy screening could potentially even be cost saving in a dedicated screening setting (Loeve et al., 2000). For the remainder of studies, costs per life year gained varied between less than US$ 5000 and US$ 40 000 per life year gained. Three of five studies that evaluated both strategies found that colonoscopy dominated sigmoidoscopy (i.e. it was both more effective and had lower costs per life year gained). One study found both strategies to be cost-effective, and one study found that colonoscopy was dominated by the combination of sigmoidoscopy plus FOBT.

The systematic review by Lansdorp-Vogelaar et al. (2011) included 16 studies that evaluated the cost–effectiveness of sigmoidoscopy and/or colonoscopy screening. The review found wide variability in the estimated cost–effectiveness of endoscopy screening across studies. Twelve studies estimated cost–effectiveness of sigmoidoscopy compared with no screening. In two studies, sigmoidoscopy screening was found to be cost saving, whereas in one study, costs per QALY gained were as high as US$ 56 600. Sixteen studies assessed the cost–effectiveness of colonoscopy screening compared with no screening; five of the studies found colonoscopy screening to be cost saving. At a willingness-to-pay threshold of US$ 100 000 per QALY gained, all of the studies found sigmoidoscopy screening and/or colonoscopy screening to be cost-effective compared with no screening. At a threshold of US$ 50 000 per QALY gained, only one study found sigmoidoscopy screening not to be cost-effective. As expected, all of the studies that evaluated both strategies found that colonoscopy screening was more effective than sigmoidoscopy screening. Approximately half of the studies also found that colonoscopy screening cost less per QALY gained and therefore dominated sigmoidoscopy screening. For the other half of the studies, the incremental costs per life year gained for colonoscopy screening compared with sigmoidoscopy screening varied between US$ 1000 and US$ 85 000, and at a willingness-to-pay threshold of US$ 100 000 per life year gained, colonoscopy screening would be considered cost-effective.

The review by Patel & Kilgore (2015) identified 13 studies in the USA in addition to the studies included in the review of Lansdorp-Vogelaar et al. (2011). [It must be noted that there was overlap in the models used between different studies.] Six independent models evaluated 5-yearly sigmoidoscopy screening. Four concluded that this strategy was less costly and more effective than no screening. In the other two models, costs were less than US$ 31 000 per life year gained. Eleven independent models evaluated 10-yearly colonoscopy screening. Three models found this strategy to be cost saving, whereas the cost–effectiveness ratio was less than US$ 30 000 per life year gained for the remainder of the strategies. In the comparison across these sigmoidoscopy and colonoscopy strategies, only two of seven models concluded that the incremental costs per life year gained for colonoscopy screening compared with sigmoidoscopy screening exceeded US$ 50 000.

Since the review by Patel & Kilgore (2015), two new models have been published on the cost–effectiveness of CRC screening in the USA (Kingsley et al., 2016; Barzi et al., 2017), and two models have published updated results (Hassan & Gralnek, 2015; Ladabaum & Mannalithara, 2016) (Table 3.3.17). The findings of these studies were consistent with those of Patel & Kilgore (2015) and demonstrated cost–effectiveness ratios of both sigmoidoscopy screening and colonoscopy screening not exceeding US$ 15 000 per QALY gained. Kingsley et al. (2016) and Barzi et al. (2017) provided estimates for both sigmoidoscopy screening and colonoscopy screening and showed that colonoscopy screening was more effective than sigmoidoscopy screening. Kingsley et al. (2016) found colonoscopy also to be more costly, with an incremental cost–effectiveness ratio of less than US$ 50 000 per QALY gained,

**Table 3.3.17 Studies of cost–effectiveness of endoscopy screening compared with no screening[a]**

| Reference Country | Population simulated[b] | Participation rate (%) | Strategy evaluated | Reduction in incidence/ mortality (%) | QALYs or LYs gained per 1000 individuals[c] | Costs (×1000) (US$) | Cost per QALY or LY gained[c] | Comments |
|---|---|---|---|---|---|---|---|---|
| Heitman et al. (2010) Canada | Cohort age 50–75 yr | 68 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 62/65 58/61 | 41 36 | 154 280 | 3800 7800 | Low effectiveness estimates, because of mixed-age cohort |
| Telford et al. (2010) Canada | Cohort age 50 yr | 73 | 10-yearly colonoscopy | 81/83 | 120 | 578 | 4800 | Uncertain whether reported incidence/ mortality reductions pertain to 100% participation |
| Barouni et al. (2012) Islamic Republic of Iran | Cohort age 50 yr | 68 | 10-yearly colonoscopy | 76/78 | 119 | 746 | 5000 | |
| Dan et al. (2012) Singapore | Cohort age 50–75 yr | NR | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 35/38 28/30 | 17 5 | 573 163 | 33 700 38 300 | Low effectiveness estimates, because of mixed-age cohort |
| Sharp et al. (2012) Ireland | Cohort age 30 yr | 39 | Single sigmoidoscopy at age 60 yr | 4.9/7.5 | 7 | 21 726 | 3000 | Low effectiveness estimates, because of young cohort at start of simulation |
| Wang et al. (2012) China | Cohort age 50–80 yr | 90 | Single colonoscopy 10-yearly colonoscopy | 67/73 66/71 | 1336 1394 | 10 000 93 245 | 7 70 | Questionable model validity, because single endoscopy more effective than repeat endoscopy |
| Whyte et al. (2012) United Kingdom | Cohort age 50 yr | 85 | Sigmoidoscopy at ages 55 yr and 65 yr | 18/22 | 33 | 51 | 1500 | |
| Ladabaum et al. (2014) Germany | Cohort age 50 yr | 100 | Colonoscopy at ages 55 yr and 65 yr | 62/67 | 90 | −1300 | Cost savings | |
| Hassan & Gralnek (2015) USA | Cohort age 50 yr | 100 | 10-yearly colonoscopy | 75/73 | 150 | 663 | 4400 | |

**Table 3.3.17 (continued)**

| Reference Country | Population simulated[b] | Participation rate (%) | Strategy evaluated | Reduction in incidence/ mortality (%) | QALYs or LYs gained per 1000 individuals[c] | Costs (×1000) (US$) | Cost per QALY or LY gained[c] | Comments |
|---|---|---|---|---|---|---|---|---|
| Lam et al. (2015) Hong Kong SAR, China | Cohort age 50 yr | NR | 10-yearly colonoscopy 5-yearly sigmoidoscopy | NR/NR | 124 109 | 1610 2286 | 14 800 18 500 | |
| Wong et al. (2015) Hong Kong SAR, China | Cohort age 50 yr | 60 | 10-yearly colonoscopy | NR/NR | QALY, 611 LY, 97 | 2212 | 3600 | Adjustment for quality of life seems invalid |
| Kingsley et al. (2016) USA | Cohort age 50 yr | 38 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | NR/60[d] NR/NR | 100 62 | 327 −189 | 3300 Cost savings | |
| Ladabaum & Mannalithara (2016) USA | Cohort age 50 yr | 100 | 10-yearly colonoscopy | 73/81 | 77 | 1153 | 15 000 | |
| Sekiguchi et al. (2016) Japan | Cohort age 40 yr | 60 | 10-yearly colonoscopy | 69/NR | 219 | −495 | Cost savings | Questionable model validity, because incidence reduction higher than participation |
| Aronsson et al. (2017) Sweden | Cohort age 60 yr | 38 | Single colonoscopy 10-yearly colonoscopy | NR/NR | 49 56 | −74 142 | Cost savings 2500 | |
| Barzi et al. (2017) USA | Cohort age 50–75 yr | 63 | 10-yearly colonoscopy 5-yearly sigmoidoscopy | 23/34 11/21 | 22 16 | −554 −270 | Cost savings Cost savings | |

LYG, life year gained; LYs, life years; NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; 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] 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.

[c] Estimates for QALYs gained and cost–effectiveness depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

[d] Reported mortality reduction for 100% participation.

whereas Barzi et al. (2017) found colonoscopy to be more cost saving than sigmoidoscopy.

Since the review by Lansdorp-Vogelaar et al. (2011), 12 new studies have been published that evaluated the cost–effectiveness of endoscopy screening outside the USA: two in Canada (Heitman et al., 2010; Telford et al., 2010), four in Europe (Sharp et al., 2012; Whyte et al., 2012; Ladabaum et al., 2014; Aronsson et al., 2017), and six 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; Sekiguchi et al., 2016). Sigmoidoscopy screening was evaluated in seven studies, and colonoscopy screening was evaluated in 10 studies. All of the studies found cost–effectiveness ratios of less than US$ 35 000 per QALY gained. Five studies evaluated both sigmoidoscopy screening and colonoscopy screening, and all of them found that 10-yearly colonoscopy was more effective than 5-yearly sigmoidoscopy (Heitman et al., 2010; Dan et al., 2012; Lam et al., 2015; Kingsley et al., 2016; Barzi et al., 2017). In the other studies, the incremental costs per life year gained moving from sigmoidoscopy screening to colonoscopy screening were less than US$ 35 000.

[Overall, there is high variability in the estimates for cost–effectiveness across these studies. The reviews tried to standardize as much as they could across the studies, either by including only studies in the USA (Pignone et al., 2002; Patel & Kilgore, 2015) or by converting all currencies into United States dollars (Lansdorp-Vogelaar et al., 2011). However, the variability is high even between studies in the USA. All of the authors of the cost–effectiveness reviews mentioned differences in assumptions about natural history, screening characteristics, and screening participation as potential reasons for differences in model outcomes (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015). Limited empirical evidence hinders the assessment of which set of assumptions is the most plausible. In addition, despite recommendations from the Panel on Cost-Effectiveness in Health and Medicine (Weinstein et al. 1996), the studies still differ widely with respect to perspective, population, time horizon, and discount rate, introducing another reason for differences between the studies (Lansdorp-Vogelaar et al. 2011).]

[Although the majority of the studies indicate that colonoscopy screening is more effective and less costly than sigmoidoscopy screening, these results may be biased in favour of colonoscopy. As explained previously, the models estimated a higher effectiveness of colonoscopy by assumptions, and the lower costs may result from higher savings due to treatment avoided because of higher effectiveness as well as from the shorter interval for screening sigmoidoscopy than for screening colonoscopy in the modelling studies. As shown in RCTs, the interval for sigmoidoscopy can be safely extended to at least 10 years without attenuation of its protective effect (Atkin et al., 2010; Segnan et al., 2011; Schoen et al., 2012; Holme et al., 2014).]

*(c) Additional cost–effectiveness considerations*

*(i) Lower age limit of screening*

Very few studies have assessed the optimal age at which to start CRC screening. Two studies have assessed the optimal timing for a single endoscopy to gain the most QALYs. The first study (Ness et al., 2000) found that a single colonoscopy between age 50 years and age 54 years was cost-effective both compared with no screening and compared with colonoscopy at older ages. For men, colonoscopy between age 45 years and age 49 years may also be cost-effective for a willingness-to-pay threshold exceeding US$ 69 000 per QALY gained. The second study (Whyte et al., 2012) assessed the optimal age for a single sigmoidoscopy and found that sigmoidoscopy at age 55 years was associated with the greatest gain in QALYs compared with sigmoidoscopy at older

ages. However, results for a single sigmoidoscopy at any age between 52 years and 58 years resulted in very similar QALYs gained. The results for a single sigmoidoscopy at ages younger than 52 years and older than 58 years showed that the QALYs gained decreased, and these alternatives were not found to be cost-effective.

The Cancer Intervention and Surveillance Modeling Network (CISNET) performed a decision analysis for the USPSTF to determine the optimal age at which to start, the optimal age at which to stop, and the optimal interval for CRC screening (Knudsen et al., 2016). The models suggested that starting CRC screening at age 45 years, rather than at age 50 years, yielded a modest increase in life years gained and had a more favourable balance between life years gained and the clinical burden of colonoscopies. For colonoscopy screening, two of the three models found that performing colonoscopy every 15 years from age 45 years resulted in slightly more life years gained compared with colonoscopy every 10 years from age 50 years without increasing the lifetime number of colonoscopies. However, one model estimated a slight loss in life years gained with a longer screening interval and an earlier age to start screening. On the basis of these discordant findings, the USPSTF concluded that there was insufficient evidence to support a starting age of 45 years for the general population, especially given the lack of empirical evidence of screening in the younger population.

Finally, one study assessed whether the optimal age at which to start colonoscopy screening varied by race and sex (Lansdorp-Vogelaar et al., 2009). This study showed that although the risks of CRC incidence and mortality in women reach levels comparable to those in men 4–8 years later in life, the optimal age at which to start screening does not differ by sex. This finding can be explained by the longer life expectancy in women: the number needed to screen to detect one advanced adenoma may be higher in women than in men, but the

number of detected advanced adenomas needed to prevent one case of CRC is lower in women than in men. This makes the number needed to screen to prevent one CRC case similar for men and women. However, the study did show that the optimal age at which to start screening was approximately 5 years earlier for African Americans (age 47 years) than for Whites (age 53 years) for both men and women.

### (ii) Upper age limit of screening

Few studies have assessed the optimal age at which to stop screening. Maheshwari et al. (2008) performed a life-table analysis to estimate the impact of prematurely stopping screening compared with the maximal potential benefit from lifelong screening. They concluded that stopping screening at approximately age 82 years would retain 80% of the maximal clinical benefit of screening. However, this analysis was based on the risk of dying from CRC among older people and did not take into account the impact of previous screening on this risk.

In the decision analysis for the USPSTF, the CISNET models also evaluated the optimal age at which to stop screening. Screening strategies were compared, with stopping ages varying between 75 years, 80 years, and 85 years (Knudsen et al., 2016). The models showed that in individuals who were consistently screened from age 50 years onwards, the life years gained associated with extending the age at which to stop screening beyond age 75 years were generally small relative to the number of additional colonoscopies required. Therefore, it was concluded that age 75 years would be a reasonable age to stop screening.

Two studies evaluated the age to stop colonoscopy screening in the light of previous screening history, background risk, and comorbidity (van Hees et al., 2014a, 2015). The study by van Hees et al. compared the balance between benefits and harms of screening in elderly individuals for unscreened cohorts of people with and

without comorbidities (van Hees et al., 2014a). For these individuals, the benefits of screening at a later age are much greater than those for previously screened individuals, whereas the harms are relatively similar. Consequently, the modelling suggested that individuals without previous screening can be screened until a much later age and may still have a favourable balance between benefits and harms: up to age 83 years, 80 years, and 77 years for no, moderate, and severe comorbidities, respectively. Ideally, the age at which to stop screening should be based on personal risk, previous screening history, and comorbidity (van Hees et al., 2015). The current recommendation of continuing screening up to age 75 years could result in a loss, rather than a gain, of QALYs in some populations at low risk (e.g. for White women aged 74 years with moderate comorbidities, half the average background risk of CRC, and negative findings from a screening colonoscopy 10 years previously). For other groups, continuing screening was found to be highly cost-effective (e.g. for Black men aged 81 years with no comorbidities, an average background risk of CRC, and no previous screening). According to this study, the optimal age at which to stop screening varies between 66 years and 88 years, depending on individual risk, comorbidity, and previous screening history.

*(iii)    Screening interval*

In the decision analysis for the USPSTF, the CISNET models also addressed the optimal interval for CRC screening (Knudsen et al., 2016). Two of the three models suggested that colonoscopy screening with a 15-year interval starting at age 45 years yielded a modest increase in life years gained and had a more favourable balance between life years gained and the clinical burden of colonoscopies, compared with colonoscopy every 10 years from age 50 years, without increasing the lifetime number of colonoscopies. However, one model estimated a slight loss in life years gained with this longer screening interval. Sigmoidoscopy screening was not found to be a sufficiently effective strategy compared with colonoscopy screening, and therefore no optimal interval was identified for this modality.

Six cost–effectiveness analyses also addressed endoscopy screening at different intervals, often comparing a single endoscopy, endoscopy every 10 years, and/or endoscopy every 5 years. One study even assessed a 3-yearly interval for colonoscopy (Table 3.3.18). The outcomes of the analyses varied widely, and no conclusions could be drawn about the optimal interval for endoscopy screening on the basis of these studies.

**Table 3.3.18 Cost–effectiveness studies assessing different intervals for endoscopy screening**

| Reference Country | Population simulated[a] | Strategy evaluated | Reduction in incidence/ mortality (%) | QALYs gained per 1000 individuals[b] | Costs (×1000) (US$) | Optimal interval | Comments |
|---|---|---|---|---|---|---|---|
| Aronsson et al. (2017) Sweden | Cohort age 60 yr | Single colonoscopy 10-yearly colonoscopy | NR/NR | 49 56 | −74 142 | WTP < US$ 30 000 WTP > US$ 30 000 | |
| Lam et al. (2015) Hong Kong SAR, China | Cohort age 50 yr | 10-yearly colonoscopy 5-yearly colonoscopy 10-yearly sigmoidoscopy 5-yearly sigmoidoscopy | NR/NR | 124 172 70 109 | 1610 2897 1244 2286 | WTP < US$ 26 000 WTP > US$ 26 000 WTP < US$ 26 000 WTP > US$ 26 000 | |
| van Hees et al. (2014b) USA | Cohort age 65 yr | 10-yearly colonoscopy 5-yearly colonoscopy 3-yearly colonoscopy | NR/NR | 65 68 66 | 922 1495 2151 | WTP < US$ 179 000 WTP > US$ 179 000 | |
| Whyte et al. (2012) United Kingdom | Cohort age 50 yr | Single sigmoidoscopy at age 55 yr Sigmoidoscopy at ages 55 yr and 65 yr | 9/11 18/22 | 21 33 | 33 51 | WTP < US$ 2250 WTP > US$ 2250 | |
| Wang et al. (2012) China | Cohort age 50–80 yr | Single colonoscopy 10-yearly colonoscopy | 67/73 66/71 | 1336 1394 | 10 000 93 245 | Repeat 10-yearly colonoscopy not cost-effective compared with single colonoscopy within reasonable WTP values | Questionable model validity, because single endoscopy more effective than repeat endoscopy |
| Dan et al. (2012) Singapore | Cohort age 50–75 yr | Single sigmoidoscopy 5-yearly sigmoidoscopy | 19/16 28/30 | 3 5 | 56 163 | WTP < US$ 53 500 WTP > US$ 53 500 | Low effectiveness estimates, because mixed-age cohort |

NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; WTP, willingness to pay; 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 aged 50–75 years signifies a population of people aged 50–75 years that are followed until death or for a certain period.

[b] Estimates for QALYs gained depend on background risk of cancer. Therefore, estimates may not easily be transferable to low-incidence settings.

# References

Adler DG, Bakis G, Coyle WJ, DeGregorio B, Dua KS, Lee LS, et al.; ASGE Training Committee (2012). Principles of training in GI endoscopy. *Gastrointest Endosc*, 75(2):231–5. doi:10.1016/j.gie.2011.09.008 PMID:22154419

American Society for Gastrointestinal Endoscopy (2000). Appropriate use of gastrointestinal endoscopy. *Gastrointest Endosc*, 52(6):831–7. doi:10.1016/S0016-5107(00)70219-7 PMID:11203479

Aronchick CALW, Wright SH, DuFrayne F, Bergman G (1999). Validation of an instrument to assess colon cleansing. [Abstract] *Am J Gastroenterol*, 94:2667.

Aronsson M, Carlsson P, Levin LA, 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

Atkin W, Rogers P, Cardwell C, Cook C, Cuzick J, Wardle J, et al. (2004). Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. *Gastroenterology*, 126(5):1247–56. doi:10.1053/j.gastro.2004.01.023 PMID:15131784

Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, et al. (2017). Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet*, 389(10076):1299–311. doi:10.1016/S0140-6736(17)30396-3 PMID:28236467

Atkin WS, Cook CF, Cuzick J, Edwards R, Northover JM, Wardle J; UK Flexible Sigmoidoscopy Screening Trial Investigators (2002). Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet*, 359(9314):1291–300. doi:10.1016/S0140-6736(02)08268-5 PMID:11965274

Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM et al.; UK Flexible Sigmoidoscopy Trial Investigators (2010). Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*, 375(9726):1624–33. doi:10.1016/S0140-6736(10)60551-X PMID:20430429

Bacchus CM, Dunfield L, Gorber SC, Holmes NM, Birtwhistle R, Dickinson JA, et al.; Canadian Task Force on Preventive Health Care (2016). Recommendations on screening for colorectal cancer in primary care. *CMAJ*, 188(5):340–8. doi:10.1503/cmaj.151125 PMID:26903355

Ball JE, Osbourne J, Jowett S, Pellen M, Welfare MR (2004). Quality improvement programme to achieve acceptable colonoscopy completion rates: prospective before and after study. *BMJ*, 329(7467):665–7. doi:10.1136/bmj.329.7467.665 PMID:15374917

Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL (2006). Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med*, 355(24):2533–41. doi:10.1056/NEJMoa055498 PMID:17167136

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

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

Belderbos TD, Pullens HJ, Leenders M, Schipper ME, Siersema PD, van Oijen MG (2017). Risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: a nationwide, population-based cohort study. *United European Gastroenterol J*, 5(3):440–7. doi:10.1177/2050640616662428 PMID:28507757

Belsey J, Epstein O, Heresbach D (2007). Systematic review: oral bowel preparation for colonoscopy. *Aliment Pharmacol Ther*, 25(4):373–84. doi:10.1111/j.1365-2036.2006.03212.x PMID:17269992

Bevan R, Rubin G, Sofianopoulou E, Patnick J, Rees CJ (2015). Implementing a national flexible sigmoidoscopy screening program: results of the English early pilot. *Endoscopy*, 47(3):225–31. doi:10.1055/s-0034-1378119 PMID:25268309

Bini EJ, Firoozi B, Choung RJ, Ali EM, Osman M, Weinshel EH (2003). Systematic evaluation of complications related to endoscopy in a training setting: a prospective 30-day outcomes study. *Gastrointest Endosc*, 57(1):8–16. doi:10.1067/mge.2003.15 PMID:12518123

Bisschops R, Tejpar S, Willekens H, De Hertogh G, Van Cutsem E (2017). Virtual chromoendoscopy (I-SCAN) detects more polyps in patients with Lynch syndrome: a randomized controlled crossover trial. *Endoscopy*, 49(4):342–50. doi:10.1055/s-0042-121005 PMID:28107763

Bleyer A, Welch HG (2012). Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*, 367(21):1998–2005. doi:10.1056/NEJMoa1206809 PMID:23171096

Blom J, Lidén A, Nilsson J, Påhlman L, Nyrén O, Holmberg L (2004). Colorectal cancer screening with flexible sigmoidoscopy – participants' experiences and technical feasibility. *Eur J Surg Oncol*, 30(4):362–9. doi:10.1016/j.ejso.2004.01.005 PMID:15063888

Blom J, Yin L, Lidén A, Dolk A, Jeppsson B, Påhlman L, et al. (2008). A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. *Cancer Epidemiol*

*Biomarkers Prev*, 17(5):1163–8. doi:10.1158/1055-9965.EPI-07-2764 PMID:18483338

Breivik EK, Björnsson GA, Skovlund E (2000). A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain*, 16(1):22–8. doi:10.1097/00002508-200003000-00005 PMID:10741815

Brenner H, Altenhofen L, Stock C, Hoffmeister M (2015). Prevention, early detection, and overdiagnosis of colorectal cancer within 10 years of screening colonoscopy in Germany. *Clin Gastroenterol Hepatol*, 13(4):717–23. doi:10.1016/j.cgh.2014.08.036 PMID:25218160

Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M (2014b). Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology*, 146(3):709–17. doi:10.1053/j.gastro.2013.09.001 PMID:24012982

Brenner H, Stock C, Hoffmeister M (2014a). Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ*, 348:g2467. doi:10.1136/bmj.g2467 PMID:24922745

Bressler B, Paszat LF, Vinden C, Li C, He J, Rabeneck L (2004). Colonoscopic miss rates for right-sided colon cancer: a population-based analysis. *Gastroenterology*, 127(2):452–6. doi:10.1053/j.gastro.2004.05.032 PMID:15300577

Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, et al.; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group (2016). Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med*, 176(7):894–902. doi:10.1001/jamainternmed.2016.0960 PMID:27214731

Bretthauer M, Skovlund E, Grotmol T, Thiis-Evensen E, Gondal G, Huppertz-Hauss G, et al. (2003). Inter-endoscopist variation in polyp and neoplasia pick-up rates in flexible sigmoidoscopy screening for colorectal cancer. *Scand J Gastroenterol*, 38(12):1268–74. doi:10.1080/00365520310006513 PMID:14750648

Calderwood AH, Chapman FJ, Cohen J, Cohen LB, Collins J, Day LW, et al.; ASGE Ensuring Safety in the Gastrointestinal Endoscopy Unit Task Force (2014). Guidelines for safety in the gastrointestinal endoscopy unit. *Gastrointest Endosc*, 79(3):363–72. doi:10.1016/j.gie.2013.12.015 PMID:24485393

Carter XW, Topolski R, Hatzigeorgiou C, Fincher RK (2013). Role of anxiety in the comfort of nonsedated average-risk screening sigmoidoscopy. *South Med J*, 106(4):280–4. doi:10.1097/SMJ.0b013e31828de613 PMID:23558418

Castells A, Bessa X, Quintero E, Bujanda L, Cubiella J, Salas D, et al.; COLONPREV study investigators (2013). Risk of advanced proximal neoplasms according to distal colorectal findings: comparison

of sigmoidoscopy-based strategies. *J Natl Cancer Inst*, 105(12):878–86. doi:10.1093/jnci/djt117 PMID:23708054

Centers for Medicare & Medicaid Services (2017). Core measures. Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html.

Chang CW, Shih SC, Wang HY, Chu CH, Wang TE, Hung CY, et al. (2015). Meta-analysis: the effect of patient education on bowel preparation for colonoscopy. *Endosc Int Open*, 3(6):E646–52. doi:10.1055/s-0034-1392365 PMID:26716129

Chen SC, Rex DK (2007). Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. *Am J Gastroenterol*, 102(4):856–61. doi:10.1111/j.1572-0241.2006.01054.x PMID:17222317

Cho JH (2015). Advanced imaging technology other than narrow band imaging. *Clin Endosc*, 48(6):503–10. doi:10.5946/ce.2015.48.6.503 PMID:26668796

Clark BT, Rustagi T, Laine L (2014). What level of bowel prep quality requires early repeat colonoscopy: systematic review and meta-analysis of the impact of preparation quality on adenoma detection rate. *Am J Gastroenterol*, 109(11):1714–23, quiz 1724. doi:10.1038/ajg.2014.232 PMID:25135006

Classen M, Phillip J (1984). Electronic endoscopy of the gastrointestinal tract. Initial experience with a new type of endoscope that has no fiberoptic bundle for imaging. *Endoscopy*, 16(1):16–9. doi:10.1055/s-2007-1018518 PMID:6697976

Corley DA, Jensen CD, Marks AR (2011). Can we improve adenoma detection rates? A systematic review of intervention studies. *Gastrointest Endosc*, 74(3):656–65. doi:10.1016/j.gie.2011.04.017 PMID:21741643

Corley DA, Jensen CD, Marks AR, Zhao WK, de Boer J, Levin TR, et al. (2013). Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs. *Clin Gastroenterol Hepatol*, 11(2):172–80. doi:10.1016/j.cgh.2012.09.010 PMID:22985608

Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. (2014). Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med*, 370(14):1298–306. doi:10.1056/NEJMoa1309086 PMID:24693890

Costantini M, Sciallero S, Giannini A, Gatteschi B, Rinaldi P, Lanzanova G, et al.; SMAC Workgroup (2003). Interobserver agreement in the histologic diagnosis of colorectal polyps. the experience of the Multicenter Adenoma Colorectal Study (SMAC). *J Clin Epidemiol*, 56(3):209–14. doi:10.1016/S0895-4356(02)00587-5 PMID:12725874

Cotterchio M, Manno M, Klar N, McLaughlin J, Gallinger S (2005). Colorectal screening is associated with reduced colorectal cancer risk: a case-control

study within the population-based Ontario Familial Colorectal Cancer Registry. *Cancer Causes Control*, 16(7):865–75. doi:10.1007/s10552-005-2370-3 PMID:16132797

Cuzick J, Edwards R, Segnan N (1997). Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med*, 16(9):1017–29. doi:10.1002/(SICI)1097-0258(19970515)16:9<1017::AID-SIM508>3.0.CO;2-V PMID:9160496

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

Day LW, Siao D, Inadomi JM, Somsouk M (2014). Non-physician performance of lower and upper endoscopy: a systematic review and meta-analysis. *Endoscopy*, 46(5):401–10. doi:10.1055/s-0034-1365310 PMID:24627086

Dietrich CG, Kottmann T, Diedrich A, Drouven FM (2013). Sedation-associated complications in endoscopy are not reduced significantly by implementation of the German S-3-guideline and occur in a severe manner only in patients with ASA class III and higher. *Scand J Gastroenterol*, 48(9):1082–7. doi:10.3109/00365521.2013.812237 PMID:23834761

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

Dominitz JA, Provenzale D (1997). Patient preferences and quality of life associated with colorectal cancer screening. *Am J Gastroenterol*, 92(12):2171–8. PMID:9399747

Dong MH, Kalmaz D, Savides TJ (2011). Missed work related to mid-week screening colonoscopy. *Dig Dis Sci*, 56(7):2114–9. doi:10.1007/s10620-010-1545-2 PMID:21221788

Doubeni CA, Corley DA, Quinn VP, Jensen CD, Zauber AG, Goodman M, et al. (2018). Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. 67(2):291–8. https://doi.org/10.1136/gutjnl-2016-312712 PMID:27733426

Doubeni CA, Weinmann S, Adams K, Kamineni A, Buist DS, Ash AS, et al. (2013). Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. *Ann Intern Med*, 158(5 Pt 1):312–20. doi:10.7326/0003-4819-158-5-201303050-00003 PMID:23460054

Dumonceau JM, Riphaus A, Beilenhoff U, Vilmann P, Hornslet P, Aparicio JR, et al. (2013). European curriculum for sedation training in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). *Endoscopy*, 45(6):496–504. doi:10.1055/s-0033-1344142 PMID:23702777

Dumonceau JM, Riphaus A, Schreiber F, Vilmann P, Beilenhoff U, Aparicio JR, et al. (2015). Non-anesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline – updated June 2015. *Endoscopy*, 47(12):1175–89. doi:10.1055/s-0034-1393414 PMID:26561915

Eldridge RC, Doubeni CA, Fletcher RH, Zauber AG, Corley DA, Doria-Rose VP, et al. (2013). Uncontrolled confounding in studies of screening effectiveness: an example of colonoscopy. *J Med Screen*, 20(4):198–207. doi:10.1177/0969141313508282 PMID:24144847

Eloubeidi MA, Wallace MB, Desmond R, Farraye FA (2003). Female gender and other factors predictive of a limited screening flexible sigmoidoscopy examination for colorectal cancer. *Am J Gastroenterol*, 98(7):1634–9. doi:10.1111/j.1572-0241.2003.07480.x PMID:12873591

Enns R, Romagnuolo J, Ponich T, Springer J, Armstrong D, Barkun AN (2008). Canadian credentialing guidelines for flexible sigmoidoscopy. *Can J Gastroenterol*, 22(2):115–9. doi:10.1155/2008/874796 PMID:18299727

Erichsen R, Baron JA, Stoffel EM, Laurberg S, Sandler RS, Sørensen HT (2013). Characteristics and survival of interval and sporadic colorectal cancer patients: a nationwide population-based cohort study. *Am J Gastroenterol*, 108(8):1332–40. doi:10.1038/ajg.2013.175 PMID:23774154

Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, et al. (2014). Addressing overdiagnosis and overtreatment in cancer: a prescription for change. *Lancet Oncol*, 15(6):e234–42. doi:10.1016/S1470-2045(13)70598-9 PMID:24807866

Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, et al. (2017). Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*, 49(3):270–97. doi:10.1055/s-0043-102569 PMID:28212588

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

Fracchia M, Senore C, Armaroli P, Ferraris R, Placido RD, Musso A, et al. (2010). Assessment of the multiple components of the variability in the adenoma detection rate in sigmoidoscopy screening, and lessons for training. *Endoscopy*, 42(6):448–55. doi:10.1055/s-0029-1244131 PMID:20414864

García-Albéniz X, Hsu J, Bretthauer M, Hernán MA (2017). Effectiveness of screening colonoscopy to prevent colorectal cancer among Medicare beneficiaries

aged 70 to 79 years: a prospective observational study. *Ann Intern Med*, 166(1):18–26. doi:10.7326/M16-0758 PMID:27669524

Ginsberg GM, Lauer JA, Zelle S, Baeten S, Baltussen R (2012). Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study. *BMJ*, 344:e614. doi:10.1136/bmj.e614 PMID:22389347

Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G (2003). The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. *Scand J Gastroenterol*, 38(6):635–42. doi:10.1080/00365520310003002 PMID:12825872

Guo X, Yang Z, Zhao L, Leung F, Luo H, Kang X, et al. (2017). Enhanced instructions improve the quality of bowel preparation for colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc*, 85(1):90–97.e6. doi:10.1016/j.gie.2016.05.012 PMID:27189659

Hassan C, Gralnek IM (2015). Cost-effectiveness of "full spectrum endoscopy" colonoscopy for colorectal cancer screening. *Dig Liver Dis*, 47(5):390–4. doi:10.1016/j.dld.2015.01.154 PMID:25704067

Hautefeuille G, Lapuelle J, Chaussade S, Ponchon T, Molard BR, Coulom P, et al. (2014). Factors related to bowel cleansing failure before colonoscopy: results of the PACOME study. *United European Gastroenterol J*, 2(1):22–9. doi:10.1177/2050640613518200 PMID:24918005

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

Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR (2009). Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*, 7(12):1272–8.

Heldwein W, Dollhopf M, Rösch T, Meining A, Schmidtsdorff G, Hasford J, et al.; Munich Gastroenterology Group (2005). The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. *Endoscopy*, 37(11):1116–22. doi:10.1055/s-2005-870512 PMID:16281142

Herrin A, Loyola M, Bocian S, Diskey A, Friis CM, Herron-Rice L, et al.; SGNA Practice Committee 2015–16 (2016). Standards of infection prevention in the gastroenterology setting. *Gastroenterol Nurs*, 39(6):487–96. doi:10.1097/SGA.0000000000000265 PMID:27922521

Hixson LJ, Fennerty MB, Sampliner RE, McGee D, Garewal H (1990). Prospective study of the frequency and size distribution of polyps missed by colonoscopy.

*J Natl Cancer Inst*, 82(22):1769–72. doi:10.1093/jnci/82.22.1769 PMID:2231773

Hoff G, Grotmol T, Skovlund E, Bretthauer M; Norwegian Colorectal Cancer Prevention Study Group (2009). Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. *BMJ*, 338:b1846. doi:10.1136/bmj.b1846 PMID:19483252

Holme Ø, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G (2013). Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev*, 9(9):CD009259. doi:10.1002/14651858.CD009259.pub2 PMID:24085634

Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, et al. (2014). Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA*, 312(6):606–15. doi:10.1001/jama.2014.8266 PMID:25117129

Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, et al.; NORCCAP Study Group (2018). Long-term effectiveness of sigmoidoscopy screening on colorectal cancer incidence and mortality in women and men: a randomized trial. *Ann Intern Med*, 168(11):775–82. doi:10.7326/M17-1441 PMID:29710125

Holme Ø, Schoen RE, Senore C, Segnan N, Hoff G, Løberg M, et al. (2017). Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. *BMJ*, 356:i6673. doi:10.1136/bmj.i6673 PMID:28087510

Hookey L, Armstrong D, Enns R, Matlow A, Singh H, Love J (2013). Summary of guidelines for infection prevention and control for flexible gastrointestinal endoscopy. *Can J Gastroenterol*, 27(6):347–50. doi:10.1155/2013/639518 PMID:23781518

Hosokawa O, Shirasaki S, Kaizaki Y, Hayashi H, Douden K, Hattori M (2003). Invasive colorectal cancer detected up to 3 years after a colonoscopy negative for cancer. *Endoscopy*, 35(6):506–10. doi:10.1055/s-2003-39665 PMID:12783349

JAG (2004). Guidelines for the training, appraisal and assessment of trainees in gastrointestinal endoscopy and for the assessment of units for registration and re-registration. London, UK: Joint Advisory Group on Gastrointestinal Endoscopy.

Jensen CD, Doubeni CA, Quinn VP, Levin TR, Zauber AG, Schottinger JE, et al. (2015). Adjusting for patient demographics has minimal effects on rates of adenoma detection in a large, community-based setting. *Clin Gastroenterol Hepatol*, 13(4):739–46. doi:10.1016/j.cgh.2014.10.020 PMID:25445767

Johnson DA, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, et al.; US Multi-Society Task Force on Colorectal Cancer (2014). Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on

Colorectal Cancer. *Gastroenterology*, 147(4):903–24. doi:10.1053/j.gastro.2014.07.002 PMID:25239068

Jover R, Herráiz M, Alarcón O, Brullet E, Bujanda L, Bustamante M, et al.; Spanish Society of Gastroenterology; Spanish Society of Gastrointestinal Endoscopy Working Group (2012). Clinical practice guidelines: quality of colonoscopy in colorectal cancer screening. *Endoscopy*, 44(4):444–51. doi:10.1055/s-0032-1306690 PMID:22438159

Juillerat P, Peytremann-Bridevaux I, Vader JP, Arditi C, Schusselé Filliettaz S, Dubois RW, et al. (2009). Appropriateness of colonoscopy in Europe (EPAGE II). Presentation of methodology, general results, and analysis of complications. *Endoscopy*, 41(3):240–6. doi:10.1055/s-0028-1119643 PMID:19280536

Kahi CJ, Imperiale TF, Juliar BE, Rex DK (2009). Effect of screening colonoscopy on colorectal cancer incidence and mortality. *Clin Gastroenterol Hepatol*, 7(7):770–5, quiz 711. doi:10.1016/j.cgh.2008.12.030 PMID:19268269

Kahi CJ, Myers LJ, Slaven JE, Haggstrom D, Pohl H, Robertson DJ, et al. (2014). Lower endoscopy reduces colorectal cancer incidence in older individuals. *Gastroenterology*, 146(3):718–725.e3. doi:10.1053/j.gastro.2013.11.050 PMID:24316263

Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, et al. (2010). Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med*, 362(19):1795–803. doi:10.1056/NEJMoa0907667 PMID:20463339

Kaminski MF, Thomas-Gibson S, Bugajski M, Bretthauer M, Rees CJ, Dekker E, et al. (2017a). Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. *United European Gastroenterol J*, 5(3):309–34. doi:10.1177/2050640617700014 PMID:28507745

Kaminski MF, Wieszczy P, Rupinski M, Wojciechowska U, Didkowska J, Kraszewska E, et al. (2017b). Increased rate of adenoma detection associates with reduced risk of colorectal cancer and death. *Gastroenterology*, 153(1):98–105. doi:10.1053/j.gastro.2017.04.006 PMID:28428142

Kapidzic A, Korfage IJ, van Dam L, van Roon AH, Reijerink JC, Zauber AG, et al. (2012). Quality of life in participants of a CRC screening program. *Br J Cancer*, 107(8):1295–301. doi:10.1038/bjc.2012.386 PMID:22955850

Kim JS, Lee BI, Choi H, Jun SY, Park ES, Park JM, et al. (2015). Cold snare polypectomy versus cold forceps polypectomy for diminutive and small colorectal polyps: a randomized controlled trial. *Gastrointest Endosc*, 81(3):741–7. doi:10.1016/j.gie.2014.11.048 PMID:25708763

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

Kirkøen B, Berstad P, Botteri E, Åvitsland TL, Ossum AM, de Lange T, et al. (2016). Do no harm: no psychological harm from colorectal cancer screening. *Br J Cancer*, 114(5):497–504. doi:10.1038/bjc.2016.14 PMID:26867161

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

Ko CW, Dominitz JA (2010). Complications of colonoscopy: magnitude and management. *Gastrointest Endosc Clin N Am*, 20(4):659–71. doi:10.1016/j.giec.2010.07.005 PMID:20889070

Ko CW, Riffle S, Shapiro JA, Saunders MD, Lee SD, Tung BY, et al. (2007). Incidence of minor complications and time lost from normal activities after screening or surveillance colonoscopy. *Gastrointest Endosc*, 65(4):648–56. doi:10.1016/j.gie.2006.06.020 PMID:17173914

Konda V, Chauhan SS, Abu Dayyeh BK, Hwang JH, Komanduri S, Manfredi MA, et al.; ASGE Technology Committee (2015). Endoscopes and devices to improve colon polyp detection. *Gastrointest Endosc*, 81(5):1122–9. doi:10.1016/j.gie.2014.10.006 PMID:25746978

Kushnir VM, Oh YS, Hollander T, Chen CH, Sayuk GS, Davidson N, et al. (2015). Impact of retroflexion vs. second forward view examination of the right colon on adenoma detection: a comparison study. *Am J Gastroenterol*, 110(3):415–22. doi:10.1038/ajg.2015.21 PMID:25732415

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

Laiyemo AO, Doubeni C, Pinsky PF, Doria-Rose VP, Sanderson AK 2nd, Bresalier R, et al. (2012). Factors associated with inadequate colorectal cancer screening with flexible sigmoidoscopy. *Cancer Epidemiol*, 36(4):395–9. doi:10.1016/j.canep.2011.10.013 PMID:22112544

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, van Ballegooijen M, Zauber AG, Boer R, Wilschut J, Winawer SJ, et al. (2009). Individualizing colonoscopy screening by sex and race. *Gastrointest Endosc*, 70(1):96–108. doi:10.1016/j.gie.2008.08.040 PMID:19467539

Larsen IK, Grotmol T, Almendingen K, Hoff G (2007). Impact of colorectal cancer screening on future lifestyle choices: a three-year randomized controlled trial. *Clin Gastroenterol Hepatol*, 5(4):477–83. doi:10.1016/j.cgh.2006.12.011 PMID:17363335

Leaper M, Johnston MJ, Barclay M, Dobbs BR, Frizelle FA (2004). Reasons for failure to diagnose colorectal carcinoma at colonoscopy. *Endoscopy*, 36(6):499–503. doi:10.1055/s-2004-814399 PMID:15202045

Lee CK, Shim JJ, Jang JY (2013). Cold snare polypectomy vs. cold forceps polypectomy using double-biopsy technique for removal of diminutive colorectal polyps: a prospective randomized study. *Am J Gastroenterol*, 108(10):1593–600. doi:10.1038/ajg.2013.302 PMID:24042189

Levin TR, Farraye FA, Schoen RE, Hoff G, Atkin W, Bond JH, et al. (2005). Quality in the technical performance of screening flexible sigmoidoscopy: recommendations of an international multi-society task group. *Gut*, 54(6):807–13. doi:10.1136/gut.2004.052282 PMID:15888789

Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Harford WV, et al.; Veterans Affairs Cooperative Study Group 380 (2000). Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *N Engl J Med*, 343(3):162–8. doi:10.1056/NEJM200007203430301 PMID:10900274

Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, et al. (2016b). 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/.

Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E, et al. (2016a). Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*, 315(23):2576–94. doi:10.1001/jama.2016.3332 PMID:27305422

Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JD (2000). Endoscopic colorectal cancer screening: a cost-saving analysis. *J Natl Cancer Inst*, 92(7):557–63. doi:10.1093/jnci/92.7.557 PMID:10749911

Longcroft-Wheaton G, Brown J, Cowlishaw D, Higgins B, Bhandari P (2012). High-definition vs. standard-definition colonoscopy in the characterization of small colonic polyps: results from a randomized trial. *Endoscopy*, 44(10):905–10. doi:10.1055/s-0032-1310004 PMID:22893132

Mahajan D, Downs-Kelly E, Liu X, Pai RK, Patil DT, Rybicki L, et al. (2013). Reproducibility of the villous component and high-grade dysplasia in colorectal adenomas <1 cm: implications for endoscopic surveillance. *Am J Surg Pathol*, 37(3):427–33. doi:10.1097/PAS.0b013e31826cf50f PMID:23348206

Maheshwari S, Patel T, Patel P (2008). Screening for colorectal cancer in elderly persons: who should we screen and when can we stop? *J Aging Health*, 20(1):126–39. doi:10.1177/0898264307309939 PMID:18089764

Manser CN, Bachmann LM, Brunner J, Hunold F, Bauerfeind P, Marbet UA (2012). Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. *Gastrointest Endosc*, 76(1):110–7. doi:10.1016/j.gie.2012.02.040 PMID:22498179

Martel M, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A (2015). Split-dose preparations are superior to day-before bowel cleansing regimens: a meta-analysis. *Gastroenterology*, 149(1):79–88. doi:10.1053/j.gastro.2015.04.004 PMID:25863216

Meester RG, Doubeni CA, Lansdorp-Vogelaar I, Jensen CD, van der Meulen MP, Levin TR, et al. (2015). Variation in adenoma detection rate and the lifetime benefits and cost of colorectal cancer screening: a microsimulation model. *JAMA*, 313(23):2349–58. doi:10.1001/jama.2015.6251 PMID:26080339

Miles A, Atkin WS, Kralj-Hans I, Wardle J (2009). The psychological impact of being offered surveillance colonoscopy following attendance at colorectal screening using flexible sigmoidoscopy. *J Med Screen*, 16(3):124–30. doi:10.1258/jms.2009.009041 PMID:19805753

Miles A, Wardle J, Atkin W (2003). Receiving a screen-detected diagnosis of cancer: the experience of participants in the UK Flexible Sigmoidoscopy Trial. *Psychooncology*, 12(8):784–802. doi:10.1002/pon.705 PMID:14681952

Minoli G, Meucci G, Prada A, Terruzzi V, Bortoli A, Gullotta R, et al. (1999). Quality assurance and colonoscopy. *Endoscopy*, 31(7):522–7. doi:10.1055/s-1999-54 PMID:10533735

Nagorni A, Bjelakovic G, Petrovic B (2012). Narrow band imaging versus conventional white light colonoscopy for the detection of colorectal polyps. *Cochrane Database Syst Rev*, 1:CD008361. doi:10.1002/14651858.CD008361.pub2 PMID:22258983

National Health Service (2015). Bowel Cancer Screening Southern Programme Hub. Annual Report 2014/2015. Available from: https://www.royalsurrey.nhs.uk/service-list/bowel-cancer-screening/bowel-cancer-screening-southern-programme-hub/.

Ness RM, Holmes AM, Klein R, Dittus R (2000). Cost-utility of one-time colonoscopic screening for colorectal cancer at various ages. *Am J Gastroenterol*, 95(7):1800–11. doi:10.1111/j.1572-0241.2000.02172.x PMID:10925988

Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM (1992). Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst*, 84(20):1572–5. doi:10.1093/jnci/84.20.1572 PMID:1404450

Newcomb PA, Storer BE, Morimoto LM, Templeton A, Potter JD (2003). Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. *J Natl Cancer Inst*, 95(8):622–5. doi:10.1093/jnci/95.8.622 PMID:12697855

Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. (2013). Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med*, 369(12):1095–105. doi:10.1056/NEJMoa1301969 PMID:24047059

Obara K, Haruma K, Irisawa A, Kaise M, Gotoda T, Sugiyama M, et al. (2015). Guidelines for sedation in gastroenterological endoscopy. *Dig Endosc*, 27(4):435–49. doi:10.1111/den.12464 PMID:25677012

Omata F, Ohde S, Deshpande GA, Kobayashi D, Masuda K, Fukui T (2014). Image-enhanced, chromo, and cap-assisted colonoscopy for improving adenoma/neoplasia detection rate: a systematic review and meta-analysis. *Scand J Gastroenterol*, 49(2):222–37. doi:10.3109/00365521.2013.863964 PMID:24328858

Osmond A, Li-Chang H, Kirsch R, Divaris D, Falck V, Liu DF, et al. (2014). Interobserver variability in assessing dysplasia and architecture in colorectal adenomas: a multicentre Canadian study. *J Clin Pathol*, 67(9):781–6. doi:10.1136/jclinpath-2014-202177 PMID:25004943

Osservatorio Nazionale Screening (2017). Lo screening colorettale. [Italian]. Available from: https://www.osservatorionazionalescreening.it/content/lo-screening-colorettale.

Painter J, Saunders DB, Bell GD, Williams CB, Pitt R, Bladen J (1999). Depth of insertion at flexible sigmoidoscopy: implications for colorectal cancer screening and instrument design. *Endoscopy*, 31(3):227–31. doi:10.1055/s-1999-13673 PMID:10344426

Pasha SF, Leighton JA, Das A, Harrison ME, Gurudu SR, Ramirez FC, et al. (2012). Comparison of the yield and miss rate of narrow band imaging and white light endoscopy in patients undergoing screening or surveillance colonoscopy: a meta-analysis. *Am J Gastroenterol*, 107(3):363–70, quiz 371. doi:10.1038/ajg.2011.436 PMID:22186978

Patel NC, Islam RS, Wu Q, Gurudu SR, Ramirez FC, Crowell MD, et al. (2013). Measurement of polypectomy rate by using administrative claims data with validation against the adenoma detection rate. *Gastrointest Endosc*, 77(3):390–4. doi:10.1016/j.gie.2012.09.032 PMID:23199647

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

PDQ Screening and Prevention Editorial Board (2017). Colorectal cancer screening (PDQ®): health professional version (updated July 28, 2017). Bethesda (MD), USA: National Cancer Institute. Available from: https://www.cancer.gov/types/colorectal/hp/colorectal-screening-pdq.

Petersen BT, Chennat J, Cohen J, Cotton PB, Greenwald DA, Kowalski TE, et al.; ASGE Quality Assurance In Endoscopy Committee; Society for Healthcare Epidemiology of America (2011). Multisociety guideline on reprocessing flexible gastrointestinal endoscopes: 2011. *Gastrointest Endosc*, 73(6):1075–84. doi:10.1016/j.gie.2011.03.1183 PMID:21628008

Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR (2004). Location of adenomas missed by optical colonoscopy. *Ann Intern Med*, 141(5):352–9. doi:10.7326/0003-4819-141-5-200409070-00009 PMID:15353426

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

Pohl H, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR, et al. (2013). Incomplete polyp resection during colonoscopy – results of the Complete Adenoma Resection (CARE) study. *Gastroenterology*, 144(1):74–80.e1. doi:10.1053/j.gastro.2012.09.043 PMID:23022496

Pullens HJ, Leenders M, Schipper ME, van Oijen MG, Siersema PD (2015). No decrease in the rate of early or missed colorectal cancers after colonoscopy with polypectomy over a 10-year period: a population-based analysis. *Clin Gastroenterol Hepatol*, 13(1):140–7. doi:10.1016/j.cgh.2014.04.032 PMID:24815328

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

Ramakrishnan K, Scheid DC (2003). Predictors of incomplete flexible sigmoidoscopy. *J Am Board Fam Pract*, 16(6):478–84. doi:10.3122/jabfm.16.6.478 PMID:14963074

Rasmussen M, Kronborg O, Fenger C, Jørgensen OD (1999). Possible advantages and drawbacks of adding flexible sigmoidoscopy to Hemoccult-II in screening for colorectal cancer. A randomized study. *Scand J Gastroenterol*, 34(1):73–8. doi:10.1080/00365529950172862 PMID:10048736

Rees CJ, Thomas Gibson S, Rutter MD, Baragwanath P, Pullan R, Feeney M, et al.; the British Society of Gastroenterology, the Joint Advisory Group on GI Endoscopy, the Association of Coloproctology of Great Britain and Ireland (2016). UK key performance indicators and quality assurance standards for colonoscopy. *Gut*, 65(12):1923–9. doi:10.1136/gutjnl-2016-312044 PMID:27531829

Rembacken B, Hassan C, Riemann JF, Chilton A, Rutter M, Dumonceau JM, et al. (2012). Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy*, 44(10):957–68. doi:10.1055/s-0032-1325686 PMID:22987217

Reumkens A, Rondagh EJ, Bakker CM, Winkens B, Masclee AA, Sanduleanu S (2016). Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. *Am J Gastroenterol*, 111(8):1092–101. doi:10.1038/ajg.2016.234 PMID:27296945

Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, et al. (1997). Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology*, 112(1):24–8. doi:10.1016/S0016-5085(97)70214-2 PMID:8978338

Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, et al. (1993). Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. *Am J Gastroenterol*, 88(6):825–31. PMID:8503374

Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, et al.; ASGE/ACG Taskforce on Quality in Endoscopy (2006). Quality indicators for colonoscopy. *Am J Gastroenterol*, 101(4):873–85. doi:10.1111/j.1572-0241.2006.00673.x PMID:16635231

Rex DK, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, et al. (2015). Quality indicators for colonoscopy. *Gastrointest Endosc*, 81(1):31–53. doi:10.1016/j.gie.2014.07.058 PMID:25480100

Robb KA, Lo SH, Power E, Kralj-Hans I, Edwards R, Vance M, et al. (2012). Patient-reported outcomes following flexible sigmoidoscopy screening for colorectal cancer in a demonstration screening programme in the UK. *J Med Screen*, 19(4):171–6. doi:10.1177/0969141313476629 PMID:23486697

Robertson DJ, Kaminski MF, Bretthauer M (2015). Effectiveness, training and quality assurance of colonoscopy screening for colorectal cancer. *Gut*, 64(6):982–90. doi:10.1136/gutjnl-2014-308076 PMID:25804631

Rogal SS, Pinsky PF, Schoen RE (2013). Relationship between detection of adenomas by flexible sigmoidoscopy and interval distal colorectal cancer. *Clin Gastroenterol Hepatol*, 11(1):73–8. doi:10.1016/j.cgh.2012.08.002 PMID:22902761

Rostom A, Jolicoeur E (2004). Validation of a new scale for the assessment of bowel preparation quality. *Gastrointest Endosc*, 59(4):482–6. doi:10.1016/S0016-5107(03)02875-X PMID:15044882

Rutter MD, Senore C, Bisschops R, Domagk D, Valori R, Kaminski MF, et al. (2016). The European Society of Gastrointestinal Endoscopy Quality Improvement Initiative: developing performance measures. *Endoscopy*, 48(1):81–9. doi:10.1055/s-0035-1569580 PMID:26662057

Samadder NJ, Curtin K, Tuohy TM, Pappas L, Boucher K, Provenzale D, et al. (2014). Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. *Gastroenterology*, 146(4):950–60. doi:10.1053/j.gastro.2014.01.013 PMID:24417818

Sanchez W, Harewood GC, Petersen BT (2004). Evaluation of polyp detection in relation to procedure time of screening or surveillance colonoscopy. *Am J Gastroenterol*, 99(10):1941–5. doi:10.1111/j.1572-0241.2004.40569.x PMID:15447753

Schachschal G, Sehner S, Choschzick M, Aust D, Brandl L, Vieth M, et al. (2016). Impact of reassessment of colonic hyperplastic polyps by expert GI pathologists. *Int J Colorectal Dis*, 31(3):675–83. doi:10.1007/s00384-016-2523-8 PMID:26847619

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

Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. (1998). Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. *Cancer*, 82(1):60–9. doi:10.1002/(SICI)1097-0142(19980101)82:1<60::AID-CNCR7>3.0.CO;2-O PMID:9428480

Schoen RE, Pinsky PF, Weissfeld JL, Bresalier RS, Church T, Prorok P, et al.; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Group (2003). Results of repeat sigmoidoscopy 3 years after a negative examination. *JAMA*, 290(1):41–8. PMID:12837710

Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al.; PLCO Project Team (2012). Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med*, 366(25):2345–57. doi:10.1056/NEJMoa1114635 PMID:22612596

Sedlack RE, Coyle WJ, Obstein KL, Al-Haddad MA, Bakis G, Christie JA, et al.; ASGE Training Committee (2014). ASGE's assessment of competency in endoscopy

evaluation tools for colonoscopy and EGD. *Gastrointest Endosc*, 79(1):1–7. doi:10.1016/j.gie.2013.10.003 PMID:24239255

Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al.; SCORE Working Group (2011). Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial – SCORE. *J Natl Cancer Inst*, 103(17):1310–22. doi:10.1093/jnci/djr284 PMID:21852264

Segnan N, Patnick J, von Karska L, editors (2010). European guidelines for quality assurance in colorectal cancer screening and diagnosis. 1st ed. Luxembourg: European Commission, Publication Office of the European Union.

Segnan N, Senore C, Andreoni B, Arrigoni A, Bisanti L, Cardelli A, et al.; SCORE2 Working Group–Italy (2005). Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst*, 97(5):347–57. doi:10.1093/jnci/dji050 PMID:15741571

Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, et al.; SCORE Working Group–Italy (2002). Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy" – SCORE. *J Natl Cancer Inst*, 94(23):1763–72. doi:10.1093/jnci/94.23.1763 PMID:12464648

Segnan N, Senore C, Andreoni B, Azzoni A, Bisanti L, Cardelli A, et al.; SCORE3 Working Group–Italy (2007). Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology*, 132(7):2304–12. doi:10.1053/j.gastro.2007.03.030 PMID:17570205

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. PMID:26685321

Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS (1992). A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med*, 326(10):653–7. doi:10.1056/NEJM199203053261001 PMID:1736103

Senore C, Ederle A, Fantin A, Andreoni B, Bisanti L, Grazzini G, et al. (2011). Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. *J Med Screen*, 18(3):128–34. doi:10.1258/jms.2011.010135 PMID:22045821

SGNA Practice Committee 2013–14 (2015). Guideline for use of high-level disinfectants and sterilants for reprocessing flexible gastrointestinal endoscopes. *Gastroenterol Nurs*, 38(1):70–80. PMID:25636016

Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L (2007). Factors associated with incomplete colonoscopy: a population-based study. *Gastroenterology*, 132(7):2297–303. doi:10.1053/j.gastro.2007.03.032 PMID:17570204

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

Sharma VK, Nguyen CC, Crowell MD, Lieberman DA, de Garmo P, Fleischer DE (2007). A national study of cardiopulmonary unplanned events after GI endoscopy. *Gastrointest Endosc*, 66(1):27–34. doi:10.1016/j.gie.2006.12.040 PMID:17591470

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

Skovlund E, Bretthauer M, Grotmol T, Larsen IK, Hoff G (2005). Sensitivity of pain rating scales in an endoscopy trial. *Clin J Pain*, 21(4):292–6. doi:10.1097/01.ajp.0000110636.14355.3e PMID:15951645

Slattery ML, Edwards SL, Ma KN, Friedman GD (2000). Colon cancer screening, lifestyle, and risk of colon cancer. *Cancer Causes Control*, 11(6):555–63. doi:10.1023/A:1008924115604 PMID:10880038

Son BK, Kim BW, Kim WH, Myung DS, Cho YS, Jang BI; Disinfection Management and Conscious Sedation Committee of Korean Society of Gastrointestinal Endoscopy (2017). Korean Society of Gastrointestinal Endoscopy guidelines for endoscope reprocessing. *Clin Endosc*, 50(2):143–7. doi:10.5946/ce.2017.029 PMID:28301923

Stephens M, Hourigan LF, Appleyard M, Ostapowicz G, Schoeman M, Desmond PV, et al. (2015). Non-physician endoscopists: a systematic review. *World J Gastroenterol*, 21(16):5056–71. doi:10.3748/wjg.v21.i16.5056 PMID:25945022

Stock C, Ihle P, Sieg A, Schubert I, Hoffmeister M, Brenner H (2013). Adverse events requiring hospitalization within 30 days after outpatient screening and nonscreening colonoscopies. *Gastrointest Endosc*, 77(3):419–29. doi:10.1016/j.gie.2012.10.028 PMID:23410698

Sulz MC, Kröger A, Prakash M, Manser CN, Heinrich H, Misselwitz B (2016). Meta-analysis of the effect of bowel preparation on adenoma detection: early adenomas affected stronger than advanced adenomas. *PLoS One*, 11(6):e0154149. doi:10.1371/journal.pone.0154149 PMID:27257916

Tan JJ, Tjandra JJ (2006). Which is the optimal bowel preparation for colonoscopy – a meta-analysis. *Colorectal Dis*, 8(4):247–58. doi:10.1111/j.1463-1318.2006.00970.x PMID:16630226

Tappenden P, Chilcott J, Eggington S, Patnick J, Sakai H, Karnon J (2007). Option appraisal of population-based colorectal cancer screening programmes in England. *Gut*, 56(5):677–84. doi:10.1136/gut.2006.095109 PMID:17142648

Taupin D, Chambers SL, Corbett M, Shadbolt B (2006). Colonoscopic screening for colorectal cancer improves quality of life measures: a population-based screening study. *Health Qual Life Outcomes*, 4(1):82. doi:10.1186/1477-7525-4-82 PMID:17044941

Taylor KL, Shelby R, Gelmann E, McGuire C (2004). Quality of life and trial adherence among participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *J Natl Cancer Inst*, 96(14):1083–94. doi:10.1093/jnci/djh194 PMID:15265970

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

Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH (1999a). Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol*, 34(4):414–20. doi:10.1080/003655299750026443 PMID:10365903

Thiis-Evensen E, Wilhelmsen I, Hoff GS, Blomhoff S, Sauar J (1999b). The psychologic effect of attending a screening program for colorectal polyps. *Scand J Gastroenterol*, 34(1):103–9. doi:10.1080/00365529950172916 PMID:10048741

Tinmouth J, Vella ET, Baxter NN, Dubé C, Gould M, Hey A, et al. (2016). Colorectal cancer screening in average risk populations: evidence summary. *Can J Gastroenterol Hepatol*, 2016:2878149. doi:10.1155/2016/2878149 PMID:27597935

Tiro JA, Kamineni A, Levin TR, Zheng Y, Schottinger JS, Rutter CM, et al. (2014). The colorectal cancer screening process in community settings: a conceptual model for the Population-Based Research Optimizing Screening through Personalized Regimens consortium. *Cancer Epidemiol Biomarkers Prev*, 23(7):1147–58. doi:10.1158/1055-9965.EPI-13-1217 PMID:24917182

Turner JK, Williams GT, Morgan M, Wright M, Dolwani S (2013). Interobserver agreement in the reporting of colorectal polyp pathology among bowel cancer screening pathologists in Wales. *Histopathology*, 62(6):916–24. doi:10.1111/his.12110 PMID:23611360

Valori R, Barton R (2007). BSG quality and safety indicators for endoscopy. London, UK: Joint Advisory Group on Gastrointestinal Endoscopy.

Valori R, Rey JF, Atkin WS, Bretthauer M, Senore C, Hoff G, et al. (2012). European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition – Quality assurance in endoscopy in colorectal cancer screening and diagnosis. *Endoscopy*, 44(Suppl 3):SE88–105. doi:10.1055/s-0032-1309795 PMID:23012124

van Hees F, Habbema JDF, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG (2014a). Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. *Ann Intern Med*, 160(11):750–9. doi:10.7326/M13-2263 PMID:24887616

van Hees F, Saini SD, Lansdorp-Vogelaar I, Vijan S, Meester RG, de Koning HJ, et al. (2015). Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness. *Gastroenterology*, 149(6):1425–37. doi:10.1053/j.gastro.2015.07.042 PMID:26253304

van Hees F, Zauber AG, Klabunde CN, Goede SL, Lansdorp-Vogelaar I, van Ballegooijen M (2014b). The appropriateness of more intensive colonoscopy screening than recommended in Medicare beneficiaries: a modeling study. *JAMA Intern Med*, 174(10):1568–76. doi:10.1001/jamainternmed.2014.3889 PMID:25133641

van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E (2006). Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol*, 101(2):343–50. doi:10.1111/j.1572-0241.2006.00390.x PMID:16454841

Vargo JJ, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, et al.; American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates (2012). Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterology*, 143(1):e18–41. doi:10.1053/j.gastro.2012.05.001 PMID:22624720

Vermeer NC, Snijders HS, Holman FA, Liefers GJ, Bastiaannet E, van de Velde CJ, et al. (2017). Colorectal cancer screening: systematic review of screen-related morbidity and mortality. *Cancer Treat Rev*, 54:87–98. doi:10.1016/j.ctrv.2017.02.002 PMID:28236723

Viiala CH, Olynyk JK (2007). Outcomes after 10 years of a community-based flexible sigmoidoscopy screening program for colorectal carcinoma. *Med J Aust*, 187(5):274–7. PMID:17767431

Viiala CH, Olynyk JK (2008). Outcomes for women in a flexible sigmoidoscopy-based colorectal cancer screening programme. *Intern Med J*, 38(2):90–4. doi:10.1111/j.1445-5994.2007.01468.x PMID:17916176

Wallace MB, Crook JE, Coe S, Ussui V, Staggs E, Almansa C, et al. (2014). Accuracy of in vivo colorectal polyp discrimination by using dual-focus high-definition narrow-band imaging colonoscopy. *Gastrointest Endosc*, 80(6):1072–87. doi:10.1016/j.gie.2014.05.305 PMID:24973171

Wang ZH, Gao QY, Fang JY (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

Wardle J, Williamson S, Sutton S, Biran A, McCaffery K, Cuzick J, et al. (2003). Psychological impact of colorectal cancer screening. *Health Psychol*, 22(1):54–9. doi:10.1037/0278-6133.22.1.54 PMID:12558202

Warren JL, Klabunde CN, Mariotto AB, Meekins A, Topor M, Brown ML, et al. (2009). Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med*, 150(12):849–57, W152. doi:10.7326/0003-4819-150-12-200906160-00008 PMID:19528563

Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB (1996). Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA*, 276(15):1253–8. doi:10.1001/jama.1996.03540150055031 PMID:8849754

Weissfeld JL, Fagerstrom RM, O'Brien B; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team (2000). Quality control of cancer screening examination procedures in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*, 21(6 Suppl):390S–9S. doi:10.1016/S0197-2456(00)00094-5 PMID:11189690

Weissfeld JL, Schoen RE, Pinsky PF, Bresalier RS, Church T, Yurgalevitch S, et al.; PLCO Project Team (2005). Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J Natl Cancer Inst*, 97(13):989–97. doi:10.1093/jnci/dji175 PMID:15998952

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

Williams JE, Holub JL, Faigel DO (2012). Polypectomy rate is a valid quality measure for colonoscopy: results from a national endoscopy database. *Gastrointest Endosc*, 75(3):576–82. doi:10.1016/j.gie.2011.12.012 PMID:22341104

Wong CK, Lam CL, Wan YF, Fong DY (2015). Cost-effectiveness simulation and analysis of colorectal cancer screening in Hong Kong Chinese population: comparison amongst colonoscopy, guaiac and immunologic fecal occult blood testing. *BMC Cancer*, 15(1):705. doi:10.1186/s12885-015-1730-y PMID:26471036

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

Yang DX, Gross CP, Soulos PR, Yu JB (2014). Estimating the magnitude of colorectal cancers prevented during the era of screening: 1976 to 2009. *Cancer*, 120(18):2893–901. doi:10.1002/cncr.28794 PMID:24894740

Zubarik R, Fleischer DE, Mastropietro C, Lopez J, Carroll J, Benjamin S, et al. (1999). Prospective analysis of complications 30 days after outpatient colonoscopy. *Gastrointest Endosc*, 50(3):322–8. doi:10.1053/ge.1999.v50.97111 PMID:10462650

Zubarik R, Ganguly E, Benway D, Ferrentino N, Moses P, Vecchio J (2002). Procedure-related abdominal discomfort in patients undergoing colorectal cancer screening: a comparison of colonoscopy and flexible sigmoidoscopy. *Am J Gastroenterol*, 97(12):3056–61. doi:10.1111/j.1572-0241.2002.07101.x PMID:12492190