

RESEARCH

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

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Abstract

Objectives To review, summarise, and compare the evidence for effectiveness of screening sigmoidoscopy and screening colonoscopy in the prevention of colorectal cancer occurrence and deaths.

Design Systematic review and meta-analysis of randomised controlled trials and observational studies.

Data sources PubMed, Embase, and Web of Science. Two investigators independently extracted characteristics and results of identified studies and performed standardised quality ratings.

Eligibility criteria Randomised controlled trials and observational studies in English on the impact of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality in the general population at average risk.

Results For screening sigmoidoscopy, four randomised controlled trials and 10 observational studies were identified that consistently found a major reduction in distal but not proximal colorectal cancer incidence and mortality. Summary estimates of reduction in distal colorectal cancer incidence and mortality were 31% (95% confidence intervals 26% to 37%) and 46% (33% to 57%) in intention to screen analysis, 42% (29% to 53%) and 61% (27% to 79%) in per protocol analysis of randomised controlled trials, and 64% (50% to 74%) and 66% (38% to 81%) in observational studies. For screening colonoscopy, evidence was restricted to six observational studies, the results of which suggest tentatively an even stronger reduction in distal colorectal cancer incidence and mortality, along with a significant reduction in mortality from cancer of the proximal colon. Indirect comparisons of results of observational studies on screening sigmoidoscopy and colonoscopy suggest a 40% to 60% lower risk of incident colorectal cancer and death from colorectal cancer after screening colonoscopy even though this incremental risk

reduction was statistically significant for deaths from cancer of the proximal colon only.

Conclusions Compelling and consistent evidence from randomised controlled trials and observational studies suggests that screening sigmoidoscopy and screening colonoscopy prevent most deaths from distal colorectal cancer. Observational studies suggest that colonoscopy compared with flexible sigmoidoscopy decreases mortality from cancer of the proximal colon. This added value should be examined in further research and weighed against the higher costs, discomfort, complication rates, capacities needed, and possible differences in compliance.

Introduction

Since 1992, several observational studies have suggested a major protective effect of lower gastrointestinal endoscopy (in particular sigmoidoscopy and colonoscopy) against colorectal cancer through detection and removal of precancerous lesions.¹⁻³ As a result, and supported by further improvements in technology, use of sigmoidoscopy and colonoscopy for diagnostic and screening purposes has substantially increased in many countries.⁴⁻⁵ Both procedures have been recommended as screening options for colorectal cancer by expert committees and offered as primary screening in several European countries (including Germany, Italy, Poland, and Austria) long before the availability of results from randomised controlled trials.⁶⁻⁹ Recent studies of trends in incidence and mortality from colorectal cancer suggest that increased use of lower gastrointestinal endoscopy has already led to major reductions in the incidence of and deaths from colorectal cancer in the United States.¹⁰⁻¹¹

Emerging evidence on the protective effects of endoscopy from detection and removal of adenomas also prompted the initiation

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Supplementary file

of several randomised controlled trials to prove the efficacy of endoscopy based screening for reducing colorectal cancer incidence and mortality. In the 1990s four large scale randomised controlled trials began to investigate the effects of screening by flexible sigmoidoscopy, and the first results were published in 2009,¹² 2010,¹³ 2011,¹⁴ and 2012.¹⁵ Screening colonoscopy has the potential to prevent colorectal cancer of the entire large bowel but is associated with higher costs, discomfort, complication rates, and capacities needed. Given that colonoscopy is recommended and offered for primary screening in an increasing number of countries, it is important to know its relative effectiveness compared with sigmoidoscopy. The only randomised controlled trial to assess the impact of screening colonoscopy (compared with no screening) on colorectal cancer incidence and mortality started recruitment in 2009, and the first results on reduction of colorectal cancer incidence and mortality are not expected before the mid-2020s.¹⁶

We reviewed, summarised, and compared the evidence from published randomised controlled trials and observational studies investigating the effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality in the population at average risk for colorectal cancer available to date.

Methods

We carried out a systematic literature review and meta-analysis according to a predefined protocol. Reporting follows the PRISMA and MOOSE statements.^{17 18}

Data sources and searches

We searched PubMed, Web of Science, and Embase for eligible studies from inception to 7 November 2013 (for Embase until 2 August 2012 only, owing to termination of our institutional licence; until then, no additional relevant article had been retrieved through Embase). The combinations of keywords used were ("sigmoidoscopy" or "colonoscopy" or "endoscopy" or "polypectomy") and ("colorectal" or "colon" or "large bowel") and ("cancer") and ("relative risk" or "relative risks" or "ratio" or "ratios" or "rate" or "rates") and ("cohort" or "case control" or "trial" or "intervention" or "randomized" or "follow up"). We searched the reference lists of identified sources for additional relevant studies.

Study selection

Published randomised controlled trials and observational studies were eligible for inclusion if they assessed the effects of screening sigmoidoscopy or screening colonoscopy versus no endoscopy on colorectal cancer incidence or mortality, or both in the general population at average risk for colorectal cancer. The review was restricted to original articles published in English. We excluded studies published as abstracts only as we considered the information to be insufficient for our assessment. Two reviewers (CS, MH) independently performed study selection according to eligibility criteria. Disagreements were resolved by discussion or a third reviewer (HB).

Data extraction and quality assessment

Two reviewers (HB, MH) independently extracted relevant information from both types of studies into a standardised form. Information extracted from randomised controlled trials was first author, year of publication, country, number and age range of participants, type of intervention, years of enrolment, and median follow-up time. In addition we extracted participation

rates in the intervention group and contamination proportions (that is, the proportions undergoing lower gastrointestinal endoscopy in the control group) where reported. Information extracted from observational studies was first author, year of publication, country, years of colorectal cancer diagnosis or death, type of lower gastrointestinal endoscopy (sigmoidoscopy, colonoscopy), time frame of endoscopies, and covariates considered.

For both randomised controlled trials and observational studies we extracted estimates of relative risk along with 95% confidence intervals according to site of colorectal cancer (any, proximal, distal) and outcome (incidence, mortality) as far as reported. For randomised controlled trials we extracted the results from both the intention to screen and the per protocol analyses.

The two reviewers resolved disagreements in data extracted by further review and discussion.

A quality assessment of included studies was conducted for descriptive purposes and to evaluate potential differences in results according to quality criteria (see supplementary table 1 for details of the quality indicators). Two reviewers (HB, MH) independently assessed study quality and resolved disagreements by further review and discussion.

Data synthesis and analysis

We combined the studies in a narrative synthesis, focusing on differences in effect estimates according to study design, type of endoscopy, and cancer site. To simplify terminology, we uniformly refer to the effect estimates of relative incidence or mortality from randomised controlled trials and cohort studies and of odds ratios from case-control studies as estimates of "relative risk." We calculated pooled effect sizes together with 95% confidence intervals using random effects models,¹⁹ stratified by study design (randomised controlled trials or observational) and type of endoscopy (screening sigmoidoscopy or screening colonoscopy). From reported confidence intervals we calculated standard errors using the delta method. Subgroup analyses were conducted according to cancer site and type of analysis (intention to screen, per protocol; randomised controlled trials only). We assessed heterogeneity in effect estimates using I^2 , τ^2 , and Cochran's Q statistic.²⁰ Publication bias was assessed by funnel plots.²¹ The Bucher method was applied to indirectly compare the effectiveness of sigmoidoscopy and colonoscopy for colorectal cancer screening.²²

We used the "meta" package in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) to perform meta-analyses.²³

Results

Study selection

After full text review of 33 articles, we excluded one study assessing the association between colonoscopy use and colorectal cancer in an ecological approach—that is, on an aggregate (regional) level only (figure 1).²⁴ Furthermore, we excluded two studies that reported no effect measures or only separate estimates of risk reduction after positive or negative sigmoidoscopy results.^{25 26} We also excluded one small randomised controlled trial primarily designed to assess the feasibility and safety of sigmoidoscopy screening,²⁷ and reporting on a combination of incident and prevalent colorectal cancers as outcome, detected by the study's follow-up colonoscopy.²⁸ Twelve studies were excluded as they did not specifically deal with the effects of screening sigmoidoscopy

or colonoscopy.²⁹⁻⁴⁰ Four articles on randomised controlled trials¹²⁻¹⁵ and 12 articles on observational studies^{1 2 41-50} were included.

Study characteristics of randomised controlled trials

Table 1¹ provides an overview on design aspects of the four large randomised controlled trials, all of which assessed the impact of screening by flexible sigmoidoscopy on colorectal cancer incidence and mortality. Three studies were from Europe (Norway, United Kingdom, and Italy)¹²⁻¹⁴ and one study was from the United States.¹⁵ The numbers of randomised participants ranged from 55 736 in the Norwegian study to 170 432 in the UK trial, but even considerably larger numbers had undergone prescreening for their interest to participate in the UK and Italian trial, whereas the Norwegian study was the only true population based trial. The age range at recruitment was 55-64 in the European trials and 55-74 in the US trial. Participants were enrolled between 1993 and 2001. Median follow-up was 7 years in the Norwegian trial and between 10 and 12 years in the other trials. The three European trials offered once only flexible sigmoidoscopy, which was supplemented by the offer of an additional faecal occult blood test in the Norwegian trial. In the US trial, a second sigmoidoscopy was offered after 3-5 years.

Participation rates in the intervention group ranged from 58.3% in the Italian trial to 86.6% in the US trial. The high participation rate in the US trial refers to use of at least one screening sigmoidoscopy. Participation rates for individual screening offers at recruitment and after 3-5 years were lower (83.5% and 54.0%, respectively). The US report is the only one that included information on use of lower gastrointestinal endoscopy among controls. Almost half of the controls (46.5%) had any lower gastrointestinal endoscopy during the screening phase (years 0-5), and 48% had a lower gastrointestinal endoscopy after the screening phase. A per protocol analysis, adjusting for non-adherence in the screening group, was reported for the European trials. As per protocol analysis is prone to potential self selection bias, the authors of the UK trial¹³ and Italian trial¹⁴ corrected the per protocol analysis for potential differences in outcomes among non-responders and controls. However, differences were small, and the correction had little impact on point estimates of the per protocol analyses. None of the studies provided effect estimates adjusted for contamination of the control group. Apart from lack of information on and correction for contamination, the quality criteria were mostly fulfilled (see supplementary table 2). Exceptions were the short follow-up of the Norwegian study and non-reporting of per protocol analyses in the US study.

Results of randomised controlled trials

Table 2¹ summarises the results of the four trials. With relative risks between 0.69 and 0.78 in intention to screen analysis, effect estimates for total colorectal cancer mortality were close in all the trials (even though the estimate failed to reach statistical significance in the Italian trial), suggesting a 22-31% reduction in overall colorectal cancer mortality. Slightly weaker reductions were estimated for total incidence of colorectal cancer, and no reduction was seen in the Norwegian trial. The latter finding most likely results from the shorter follow-up period: in all of the trials it took several years before the initial peak in incidence resulting from identification of prevalent cases at screening was offset by much lower incidence rates in the subsequent years. The pooled estimates (95% confidence intervals) of risk reduction were 18% (11-25%) for incidence

of colorectal cancer and 28% (20-35%) for deaths from colorectal cancer (table 2). The per protocol analyses, adjusting for non-adherence in the intervention groups, yielded considerably stronger effect estimates, with pooled estimates for reduction of colorectal cancer incidence and mortality of 28% (16-38%) and 44% (31-54%), respectively.

Effect estimates were considerably stronger when the analyses were restricted to distal colorectal cancer (table 2). Pooled estimates for reduction in distal colorectal cancer incidence and mortality were 31% (26-37%) and 46% (33-57%), respectively, in intention to screen analysis, and 42% (29-53%) and 61% (27-79%), respectively, in per protocol analyses. Even though point estimates of relative incidence and mortality were also consistently below 1 for cancer of the proximal colon in all studies, risk reductions were small and, with the exception of proximal colon cancer incidence in the US trial, not statistically significant, neither in individual studies nor in meta-analysis. Heterogeneity was not evident between studies for any of the mortality outcomes. The apparent heterogeneity in the incidence estimates was due to the Norwegian trial with its shorter follow-up period and was no longer seen when this trial was excluded in sensitivity analyses.

Study characteristics of observational studies

Table 3¹ provides an overview on the observational studies, which included eight case-control studies and four cohort studies. In one cohort study, participants undergoing screening colonoscopy were compared with the general population⁴⁶; all other studies compared participants with and without endoscopy. Eight studies were conducted in the United States, and one study each in Canada, Sweden, Switzerland, and Germany.^{1 2 41-50} The studies were published between 1992 and 2013 and referred to colorectal cancer diagnoses or deaths between 1970 and 2012, with time frames of endoscopies mostly including 10 or more years before diagnosis or death (or recruitment among controls). One nested case-control study examined the risk for late stage colorectal cancer only (stages IIB to IV).⁴⁸ All studies were matched or adjusted for age and sex, but other potential confounders were controlled for to a heterogeneous and often limited extent. Apart from lack of or limited control for confounding, lack of assessment of impact of screening on colorectal cancer mortality was the most commonly identified limitation in quality ratings (see supplementary table 3).

Results of observational studies

Overall, results of the observational studies were more heterogeneous than those of the randomised controlled trials (table 4¹). Despite the heterogeneity in study designs, settings, populations, and methods, a history of screening sigmoidoscopy or screening colonoscopy was consistently associated with reduced colorectal cancer incidence and mortality in all studies, even though not all results from single studies were statistically significant.

Meta-analyses of observational studies on screening sigmoidoscopy yielded reductions in colorectal cancer incidence and mortality that were similar to or slightly stronger than those of the per protocol analyses of the randomised controlled trials: a strong reduction in distal colorectal cancer incidence and mortality by 64% (95% confidence interval 50% to 74%) and 66% (38% to 81%), respectively (table 4), weak or no reduction in proximal colon cancer incidence and mortality, and moderate reduction in total colorectal cancer incidence and mortality (table 4). Heterogeneity in the meta-analyses of overall and distal colorectal cancer mortality was mostly due to the study

by Newcomb and colleagues,¹ a case-control study that had reported an exceptionally strong effect of screening sigmoidoscopy. Excluding this study removed heterogeneity and yielded a slightly less pronounced reduction in mortality (35% and 63% rather than 47% and 66% for overall and distal colorectal cancer mortality, respectively).

Meta-analyses of observational studies on colonoscopy screening consistently yielded stronger reductions in incidence and mortality (table 4). Overall, the incidence of colorectal cancer was estimated to be reduced by 69% (95% confidence interval 23% to 88%). Even though all five studies included in this analysis reported a substantial reduction in colorectal cancer incidence (significantly so in four of the studies), there was substantial heterogeneity in the strength of the estimated reduction of incidence. This heterogeneity was mainly due to the studies by Cotterchio and colleagues from Canada⁴⁴ and Brenner and colleagues from Germany,⁴⁹ which showed substantially weaker and stronger risk reductions, respectively, than the remaining studies. Excluding these two studies removed heterogeneity, left the overall estimate of risk reduction essentially unchanged (64%), and strongly increased its precision (95% confidence interval 47% to 75%).

Risk reduction associated with screening colonoscopy was most pronounced for distal colorectal cancer in two out of three studies assessing this association. These two studies, from the United States and Germany, published in 2013^{49 50} are those with the highest quality scores (see supplementary table 3). By contrast, no or only a weak risk reduction was found in the case-control study by Cotterchio and colleagues from Canada,⁴⁴ which was published in 2005 and pertained to colonoscopies conducted before years 1997-2000, the years that cases were diagnosed. Excluding this study, which also had a lower quality score, from the meta-analysis substantially reduced heterogeneity in relative risk estimates for both proximal and distal colorectal cancer and led to stronger, statistically significant risk reductions (75%, 95% confidence interval 62% to 84%) and 90% (95% confidence interval 52% to 98%), respectively.

Only three studies tackled reduction of mortality associated with screening colonoscopy. They consistently found a strong reduction of overall colorectal cancer mortality, with a summary estimate of 68% (95% confidence interval 57% to 77%). Only the most recently reported cohort study from the United States provided specific estimates for reduction in mortality from proximal and distal colorectal cancer, respectively. Even though mortality reduction was much stronger for distal colorectal cancer (82%, 95% confidence interval 69% to 90%), a substantial and significant mortality reduction was also found for cancer of the proximal colon (53%, 24% to 71%). Indirect comparisons of results of observational studies on screening sigmoidoscopy and colonoscopy suggest a 40% to 60% lower risk of colorectal cancer and death from colorectal cancer after screening colonoscopy even though this incremental risk reduction was statistically significant for deaths from cancer of the proximal colon only (table 4).

Funnel plots did not suggest relevant publication bias (see supplementary figure 1).

Discussion

This systematic review of randomised controlled trials and observational studies on the impact of lower gastrointestinal endoscopy on colorectal cancer incidence and mortality underlines the strong potential of lower gastrointestinal endoscopy screening to reduce the incidence and mortality from

colorectal cancer. Evidence from randomised controlled trials is restricted to screening sigmoidoscopy. The four randomised controlled trials available so far suggest a reduction of total colorectal cancer incidence and mortality by approximately 20-30% in intention to screen analysis and 30-45% in per protocol analyses, with substantially stronger reductions for distal colorectal cancer and no or at best modest reductions for cancer of the proximal colon. Meta-analyses of the identified 10 observational studies on screening sigmoidoscopy suggest similarly strong or even stronger risk reductions than meta-analyses of the randomised controlled trials' per protocol estimates. Still stronger reductions in colorectal cancer incidence and mortality were seen in the six observational studies on screening colonoscopy, even though the difference between studies on screening sigmoidoscopy and screening colonoscopy was statistically significant for mortality from cancer of the proximal colon only in indirect comparisons.

Comparison with other studies

During the work on this manuscript two meta-analyses exclusively focusing on the randomised controlled trials on screening sigmoidoscopies were published. Despite some differences in inclusion criteria and analyses presented, the main results were consistent.^{51 52} To our knowledge, ours is the first systematic review and meta-analyses of observational studies. Given the lack of randomised controlled trial results for screening colonoscopy, systematic, joint presentation of results from both types of studies is required to enable the most comprehensive summary of the evidence available to date.

In general, randomised controlled trials are considered the gold standard for estimating screening effects, as they are less prone to several biases than observational studies, such as bias by self selection of screening participants, confounding, and recall bias. It is therefore reassuring that suggestions for the effectiveness of lower gastrointestinal endoscopy screening, which have been raised by multiple case-control and cohort studies since the beginning of the 1990s and which have led to the inclusion of endoscopic examinations in colorectal cancer screening recommendations and offers in several countries, have been consistently supported by results from the four sigmoidoscopy randomised controlled trials that have become available since 2009.¹²⁻¹⁵

Comparisons of results from randomised controlled trials and observational studies

A fundamental difference in intention to screen analyses of randomised controlled trials and observational studies on screening is that intention to screen analyses of randomised controlled trials estimate the impact of the offer of screening (irrespective of its actual use), whereas observational studies, like the per protocol analyses of randomised controlled trials, aim to estimate the effects of actual use of screening. The impact of the offer of screening is the variable of primary interest for health policy decisions on implementation of screening offers, whereas the effect of actual use of screening (compared with non-use) is the parameter of primary interest for individual patient consulting and patient decisions. In case of non-negligible non-adherence and contamination, both parameters are necessarily different if screening is effective.

Meta-analyses of observational studies on screening sigmoidoscopy yielded, overall, similar results to the per protocol analyses from the randomised controlled trials. Higher agreement with the per protocol analyses than with the intention to screen analyses is to be expected given that the observational

studies, like the per protocol analyses of the randomised controlled trials, deal with the impact of sigmoidoscopies actually performed rather than the impact of the mere offer of screening sigmoidoscopy. Nevertheless, some of the effect estimates from observational studies were even stronger than those of the per protocol analyses from the randomised controlled trials. Several reasons may explain the somewhat stronger effects suggested by the observational studies.

Over-representation of health conscious people who may be more likely to have undergone screening endoscopies among participants in control groups of case-control studies may have led to some overestimation of the prevalence of screening endoscopy and of screening endoscopy effects in observational studies. Furthermore, the possibility of confounding by additional factors, including factors that are of specific concern in screening studies, such as different temporal distribution of screening between cases and controls, or the administering of other screening tests that may have interfered with application of screening endoscopies has to be kept in mind.⁵³

However, even per protocol analyses of randomised controlled trials may have underestimated the impact of screening sigmoidoscopies actually conducted, owing to contamination—that is, the conduction of lower gastrointestinal endoscopies in some proportion of the control group.⁵⁴ Detailed quantitative data on contamination were provided in the report of the randomised controlled trial from the United States.¹⁵ In this trial, contamination was substantial: 46.5% of the controls had either sigmoidoscopy or colonoscopy during the screening phase—that is, the initial 3-5 years, and 48.0% had sigmoidoscopy or colonoscopy after the screening phase. The European trials probably had less contamination owing to less common use of lower gastrointestinal endoscopy in European countries in the past,^{55 56} but data on the degree of contamination were not provided, and none of the randomised controlled trials accounted for contamination in the analyses.

Other limitations of the randomised controlled trials include the generalisability of results for the population as a whole and for application of screening in routine practice. Finally, the follow-up of the randomised controlled trials may not have been long enough to disclose the full reduction of colorectal cancer incidence. In all the randomised controlled trials there was an initial apparent (and expected) increase in colorectal cancer in the screening group owing to detection of prevalent colorectal cancer, which was compensated by substantially lower incidence in subsequent years. An overall reduction of cumulative incidence was observed after several years only, and this reduction continued to increase during the follow-up periods for which data are available. The apparent lack of reduction of colorectal cancer incidence in the Norwegian trial¹² may be primarily due to the shorter follow-up of the participants in this trial compared with the other trials. It remains to be seen in future analyses with longer follow-up times to what extent reduction of incidence will further increase.

In both randomised controlled trials and observational studies on screening sigmoidoscopy the reduction of colorectal cancer incidence and mortality was much stronger or even confined to distal colorectal cancer, which is consistent with expectations given the limited reach of the sigmoidoscope. With a lack of randomised controlled trials and only six observational studies, evidence for the effect of screening colonoscopy is still rather limited, even though it has been substantially strengthened by four most recent studies from the United States, Germany, and Switzerland published in 2012 and 2013.⁴⁷⁻⁵⁰ Despite some heterogeneity in results, which was to a large extent due to a less rigorous earlier study, meta-analyses suggest a substantially

stronger reduction of colorectal cancer incidence and mortality by screening colonoscopy than by screening sigmoidoscopy, in particular for cancer of the proximal colon. Nevertheless, protection from cancer of the proximal colon seems to be less pronounced than for distal colorectal cancer even in cases of screening colonoscopy, which might be explained by lower detection rates of proximal compared with distal neoplasms⁵⁷⁻⁵⁹ as well as differences in tumour biology.⁶⁰⁻⁶² Major differences between proximal and distal cancers have also been found in studies not differentiating between screening and other colonoscopies (which were not included in our review), several of which had not found a protective effect of colonoscopy for proximal cancers.^{33-35 38} Given the still limited data on screening colonoscopy, its impact and relative effectiveness compared with screening sigmoidoscopy should be tackled in further studies. Also, further research is needed in which the incremental effectiveness of screening colonoscopy compared with sigmoidoscopy is weighed against the higher costs, complexity, discomfort, complication rates, and capacities needed compared with screening sigmoidoscopy.^{63 64} Furthermore, effectiveness of screening colonoscopy may strongly depend on qualification of endoscopists. Performing high quality screening with colonoscopy is challenging and requires major resources in terms of colonoscopy capacity, training, and quality assurance that may not be available or may be difficult to establish in many healthcare systems.

Strengths and limitations of this study

Our review and meta-analysis has several limitations. Firstly, despite a comprehensive literature search in three well established databases independently conducted by two reviewers, and careful cross referencing, we cannot exclude the possibility of having missed a relevant study. Furthermore, we cannot rule out overestimation of screening effects due to publication bias, even though there was no indication of relevant publication bias in the funnel plots. Secondly, there was large heterogeneity in the design of observational studies and in the reporting of results in both randomised controlled trials and observational studies. As a result, the number of studies that could be included in specific meta-analyses was often small. Even though statistical heterogeneity was observed in several of the meta-analyses of the observational studies, especially the studies on screening colonoscopy, results remained essentially unchanged (and heterogeneity was strongly reduced) when excluding the studies with the highest or lowest estimate of risk reduction. Finally, despite inclusion of the most recent studies, the impact was assessed of endoscopies mostly conducted many years if not decades ago. Endoscopies conducted to date might have potentially larger effects due to enhanced detection of neoplasms resulting from advancements in technology, training, and experience of endoscopists.

Conclusions and policy implications

Compelling and consistent evidence from randomised controlled trials and observational studies shows that screening sigmoidoscopy and screening colonoscopy prevent the majority of deaths from distal colorectal cancer. Data suggest added value of colonoscopy versus sigmoidoscopy, especially for prevention of deaths from cancer of the proximal colon, which should be elaborated in further research and weighed against the higher costs, complexity, discomfort, complication rates, and high quality capacities and quality assurance needed,⁶⁴⁻⁶⁷ as well as possible differences in compliance. To disclose the full benefits of screening sigmoidoscopy, continued follow-up of the large randomised controlled trials will be essential. Future analyses

of these trials as well as future analysis of the recently initiated randomised controlled trial on screening colonoscopy¹⁶ should pay particular attention to possible underestimation of screening efficacy by non-adherence and contamination. Observational studies should tackle additional issues of major relevance for clinical practice, such as potential variation of risk reduction according to quality of endoscopy, age at endoscopy, or profiles of risk factors (including genetic factors), which might be relevant for risk stratification in colorectal cancer screening.

Contributors: HB designed the study. MH and CS carried out the literature search. HB and MH extracted the data from the identified articles. CS conducted the meta-analyses. HB drafted the manuscript. All authors critically reviewed the manuscript, contributed to its revision, and approved the final version submitted. The researchers are independent from funders. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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What is already known on this topic

Observational studies reported since 1992 have suggested a major reduction in incidence of colorectal cancer by screening sigmoidoscopy or screening colonoscopy

Reduction of overall and distal colorectal cancer incidence and mortality by screening sigmoidoscopy was confirmed by four randomised controlled trials published since 2009

In the absence of evidence from randomised controlled trials, which will not be available before the mid 2020s, the added value of screening colonoscopy compared with screening sigmoidoscopy is uncertain

What this study adds

Evidence that screening sigmoidoscopy is able to prevent the majority of deaths from distal colorectal cancer was consistent and compelling

The evidence also suggests substantial added value of screening colonoscopy, especially in the prevention of deaths from cancer of the proximal cancer

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Tables

Table 1 | Overview of randomised controlled trials on impact of flexible sigmoidoscopy: design aspects

Study	Country	No randomised (approached)	Age	Intervention	Years enrolled	Median follow-up (years)	No (%) with lower gastrointestinal endoscopy		Report of per protocol analysis	
							Intervention	Control	Adjusted for non-compliance	Adjusted for contamination
Hoff et al 2009 ¹²	Norway	55 736	55-64	Once only FS, with or without single FOBT	1999-2000	7	8846/13 653 (64.8)	NR	Yes	No
Atkin et al 2010 ¹³	United Kingdom	170 432 (368 142)	55-64	Once only FS	1994-99	11.2	40 674/57 237 (71.1)	NR	Yes*	No
Segnan et al 2011 ¹⁴	Italy	56 532 (236 536)	55-64	Once only FS	1995-99	10.5	9999/17 148 (58.3)	NR	Yes*	No
Schoen et al 2012 ¹⁵	United States	154 900 (NR)	55-74	FS at baseline and after 3-5 years	1993-2001	11.9	67 071/77 445 (86.6)	NR (46.5)	No	No

FOBT=faecal occult blood test; FS=flexible sigmoidoscopy; NR=not reported.

*With correction for potential differences in outcomes among non-responders and controls.

Table 2| Overview and meta-analysis of randomised controlled trials on impact of flexible sigmoidoscopy: results on colorectal cancer incidence and mortality. Values are relative risks (95% confidence intervals) unless stated otherwise

Type of analysis and studies	Incidence			Mortality		
	Any site	Proximal	Distal	Any site	Proximal	Distal
Intention to screen:						
Hoff et al 2009 ¹²	1.02 (0.83 to 1.25)*	NR	NR	0.73 (0.47 to 1.13)	NR	0.63 (0.34 to 1.18)
Atkin et al 2010 ¹³	0.77 (0.70 to 0.84)	0.98 (0.85 to 1.12)	0.64 (0.57 to 0.72)	0.69 (0.59 to 0.82)	NR	NR
Segnan et al 2011 ¹⁴	0.82 (0.69 to 0.96)	0.91 (0.69 to 1.20)	0.76 (0.62 to 0.94)	0.78 (0.56 to 1.08)	0.85 (0.52 to 1.39)	0.73 (0.47 to 1.12)
Schoen et al 2012 ¹⁵	0.79 (0.72 to 0.85)	0.86 (0.76 to 0.97)	0.71 (0.64 to 0.80)	0.74 (0.63 to 0.87)	0.97 (0.77 to 1.22)	0.50 (0.38 to 0.64)
Meta-analysis:						
No of studies	4	3	3	4	2	3
Pooled estimate	0.82 (0.75 to 0.89)	0.91 (0.83 to 0.99)	0.69 (0.63 to 0.74)	0.72 (0.65 to 0.80)	0.95 (0.77 to 1.17)	0.54 (0.43 to 0.67)
Heterogeneity: I^2 (%) / τ^2 / P value	52/0.004/0.10	0/0.0/0.38	24/0.002/0.27	0/0.0/0.90	0/0.0/0.63	0/0.0/0.52
Per protocol†:						
Hoff et al 2009 ¹²	0.89 (0.69 to 1.15)*	NR	0.73 (0.51 to 1.05)*	0.41 (0.21 to 0.82)	NR	0.24 (0.08 to 0.76)
Atkin et al 2010 ¹³	0.67 (0.60 to 0.76)	0.97 (0.80 to 1.17)	0.50 (0.42 to 0.59)	0.57 (0.45 to 0.72)	NR	NR
Segnan et al 2011 ¹⁴	0.69 (0.56 to 0.86)	0.85 (0.61 to 1.19)	0.60 (0.46 to 0.80)	0.62 (0.40 to 0.96)	0.78 (0.45 to 1.35)	0.48 (0.24 to 0.94)
Schoen et al 2012 ¹⁵	NR	NR	NR	NR	NR	NR
Meta-analysis:						
No of studies	3	2	3	3	1	2
Pooled estimate	0.72 (0.62 to 0.84)	0.94 (0.80 to 1.11)	0.58 (0.47 to 0.71)	0.56 (0.46 to 0.69)	0.78 (0.45 to 1.35)	0.39 (0.21 to 0.73)
Heterogeneity: I^2 (%) / τ^2 / P value	49/0.002/0.14	0/0.0/0.50	49/0.02/0.14	0/0.0/0.60	—/—/1.00	6/0.02/0.30

NR=not reported.

P values are based on Cochran's Q statistic.

*Not reported directly by authors but derived from reported data.

†Adjusted for non-adherence but not for contamination.

Table 3| Overview on observational studies: design aspects

Study	Country	Study design	Years (cases)	Lower gastrointestinal endoscopy			Covariates adjusted for or considered
				Reason	Type	Time frame (min, max)	
Newcomb et al 1992 ¹	United States	Case-control	1979-88	Screening	Sigmoidoscopy	bd, ever	Sex, age, family history, duration of enrolment in health plan
Selby et al 1992 ²	United States	Case-control	1971-87	Screening	Sigmoidoscopy	bd, 10 years	Sex, age, personal and family history, other screening examinations
Scheitel et al 1999 ⁴¹	United States	Case-control	1970-93	Screening	Sigmoidoscopy	bd, 10 years	Sex, age, personal and family history, numbers of periodic health examinations and admissions to hospital
Slattery et al 2000 ⁴²	United States	Case-control	NR	Various*	Sigmoidoscopy	2 years, 12 years	Sex, age, family history, body mass index, physical activity, nutritional factors, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, HRT (in sensitivity analyses)
Newcomb et al 2003 ⁴³	United States	Case-control	1998-2002	Various*	Sigmoidoscopy	1 year, ever	Sex, age, education, family history, body mass index, smoking, HRT, number of previous tests
Cotterchio et al 2005 ⁴⁴	Canada	Case-control	1997-2000	Various*	Various†	1 year, ever	Sex, age, marital status, education, family history, medical conditions, body mass index, weight, physical activity, smoking, alcohol consumption, nutritional factors, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, HRT, other drugs
Blom et al 2008 ⁴⁵	Sweden	Cohort	1996-2004	Screening	Sigmoidoscopy	bd, 8 years	Sex, age
Kahi et al 2009 ⁴⁶	United States	Cohort‡	1989-2007	Screening	Colonoscopy	bd, 16 years	Sex, age
Manser et al 2012 ⁴⁷	Switzerland	Cohort	2001-07	Screening	Colonoscopy	bd, 7 years	Sex, age, profession, family history, body mass index, physical activity, smoking, nutritional factors, participation in general health screening examinations
Doubeni et al 2013 ⁴⁸	United States	Case-control	2006-08	Various*	Various†	3 months, 10 years	Sex, age, health plan enrolment, socioeconomic status, comorbidity, family history, other screening exposures
Brenner et al 2013 ⁴⁹	Germany	Case-control	2003-10	Various*	Colonoscopy	1 year, 10 years	Sex, age, education, family history, body mass index, smoking, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, HRT, participation in a general health screening examination
Nishihara et al 2013 ⁵⁰	United States	Cohort	1988-2012	Screening	Various†	bd, 25 years	Sex, age, family history, body mass index, physical activity, smoking, alcohol consumption, nutritional factors, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, HRT, other drugs

bd=before diagnosis (cases) or reference date (controls); NR=not reported; HRT=hormone replacement therapy.

*Various reasons analysed separately.

†Various types analysed separately.

‡Comparison with general population rather than comparison with unexposed group.

Table 4| Results and meta-analyses of observational studies on the effects of screening sigmoidoscopy or colonoscopy on colorectal cancer. Values are relative risks (95% confidence intervals) unless stated otherwise

Study	Type of examination	Incidence			Mortality		
		Any site	Proximal	Distal	Any site	Proximal	Distal
Newcomb et al 1992 ¹	Sigmoidoscopy	NR	NR	NR	0.21 (0.08-0.52)	0.36 (0.11 to 1.20)	0.05 (0.01 to 0.43)
Selby et al 1992 ²	Sigmoidoscopy	NR	NR	NR	NR	0.96 (0.61 to 1.50)	0.41 (0.25 to 0.69)
Scheitel et al 1999 ⁴¹	Sigmoidoscopy	NR	NR	NR	0.89 (0.47-1.66)	0.95 (0.46 to 1.96)	1.04 (0.21 to 5.13)
Slattery et al 2000 ⁴²	Sigmoidoscopy	NR	Men 0.7 (0.5 to 1.1), women 0.5 (0.3 to 0.9)	Men 0.5 (0.3 to 0.7)*, women 0.5 (0.3 to 0.9)*	NR	NR	NR
Newcomb et al 2003 ⁴³	Sigmoidoscopy	NR	0.89 (0.68 to 1.16)	0.24 (0.17 to 0.33)	NR	NR	NR
Cotterchio et al 2005 ⁴⁴	Sigmoidoscopy	0.52 (0.34 to 0.80)	0.72 (0.51 to 1.01)	0.41 (0.30 to 0.56)	NR	NR	NR
Blom et al 2008 ⁴⁵	Sigmoidoscopy	0.5 (0.2 to 1.3)†	NR	NR	NR	NR	NR
Doubeni et al 2013 ⁴⁶	Sigmoidoscopy	0.50 (0.36 to 0.70)	0.79 (0.51 to 1.23)	0.26 (0.14 to 0.48)	NR	NR	NR
Nishara et al 2013 ⁵⁰	Sigmoidoscopy	NR	NR	NR	0.59 (0.45 to 0.76)	1.04 (0.73 to 1.48)	0.31 (0.20 to 0.49)
Cotterchio et al 2005 ⁴⁴	Colonoscopy	0.69 (0.44 to 1.07)	1.02 (0.72 to 1.45)	0.68 (0.49 to 0.94)	NR	NR	NR
Kahi et al 2009 ⁴⁶	Colonoscopy	0.52 (0.22 to 0.82)	NR	NR	0.35 (0.00 to 1.06)	NR	NR
Manser et al 2012 ⁴⁷	Colonoscopy	0.31 (0.16 to 0.59)	NR	NR	0.12 (0.01 to 0.93)	NR	NR
Doubeni et al 2013 ⁴⁶	Colonoscopy	0.29 (0.15 to 0.58)	0.36 (0.16 to 0.80)	0.26 (0.06 to 1.11)	NR	NR	NR
Brenner et al 2013 ^{49,‡}	Colonoscopy	0.09 (0.07 to 0.13)	0.22 (0.14 to 0.33)	0.05 (0.03 to 0.08)	NR	NR	NR
Nishihara et al 2013 ⁵⁰	Colonoscopy	NR	NR	NR	0.32 (0.24 to 0.45)	0.47 (0.29 to 0.76)	0.18 (0.10 to 0.31)
Meta-analysis		Sigmoidoscopy					
No of estimates		3	5	5	3	4	4
Pooled estimate		0.51 (0.39 to 0.65)	0.76 (0.65 to 0.90)	0.36 (0.26 to 0.50)	0.53 (0.30 to 0.97)	0.96 (0.74 to 1.23)	0.34 (0.19 to 0.62)
Heterogeneity:							
I ² (%)/τ ² /P value		0/0.0/0.98	0/0.0/0.42	64/0.1/0.02	68/0.18/0.04	0/0.0/0.42	54/0.17/0.09
Meta-analysis:		Colonoscopy					
No of estimates		5	3	3	3	1	1
Pooled estimate		0.31 (0.12 to 0.77)	0.44 (0.15 to 1.31)	0.21 (0.03 to 1.53)	0.32 (0.23 to 0.43)	0.47 (0.29 to 0.76)	0.18 (0.10 to 0.31)
Heterogeneity:							
I ² (%)/τ ² /P value		94/1.0/<0.001	93/0.86/<0.001	97/3.0/<0.001	0/0.0/0.69	—/—/—	—/—/—
Indirect comparison colonoscopy versus sigmoidoscopy							
No of estimates		2	2	2	2	2	2
Pooled estimate		0.61 (0.23 to 1.58)	0.58 (0.19 to 1.74)	0.57 (0.07 to 4.32)	0.59 (0.30 to 1.15)	0.49 (0.29 to 0.85)	0.53 (0.23 to 1.21)
P value		0.31	0.33	0.58	0.12	0.01	0.13

P values are based on Cochran's Q statistic and, in case of indirect comparison, on significance of log(odds ratio).

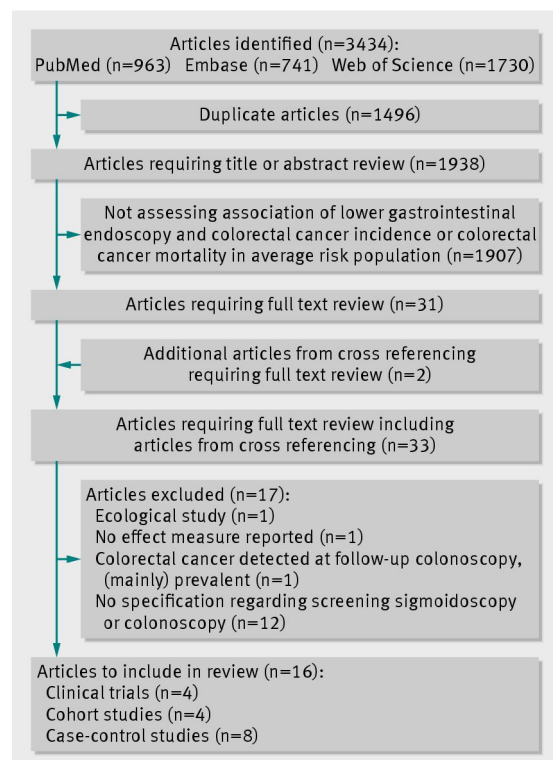
NR=not reported.

*Distal colon only.

†Not reported directly by authors, but derived from reported data.

‡Summary results for diagnostic and any colonoscopy, and for distal colorectal cancer not reported in article but obtained by additional analyses.

Figure



Flow chart of literature search process