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Colonoscopy Reduces Colorectal Cancer Incidence and Mortality in Patients With Non-Malignant Findings: A Meta-Analysis

REVIEW

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OBJECTIVES: **Observational studies have shown that colonoscopy reduces colorectal cancer (CRC) incidence and mortality in the general population. We aimed to conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy.**

METHODS: **PubMed, EMBASE, and conference abstracts were searched through 30 April 2015. The primary outcomes were overall CRC incidence and mortality. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effect models.**

RESULTS: **Eleven observational studies with a total of 1,499,521 individuals were included. Pooled analysis showed that colonoscopy was associated with a 61% RR reduction in CRC incidence (RR: 0.39; 95% CI: 0.26–0.60; I^2=93.6%) and a 61% reduction in CRC mortality (RR: 0.39; 95% CI: 0.35–0.43; I^2=12.0%) in patients with non-malignant findings, although there was high heterogeneity for the outcome of CRC incidence. After excluding one outlier study, there was low heterogeneity for the outcome of incidence (I^2=44.7%). Subgroup analysis showed that the effect of screening colonoscopy was more prominent, corresponding to an 89% reduction in CRC incidence (RR: 0.11; 95% CI: 0.08–0.15), in comparison with settings involving diagnostic colonoscopy (RR: 0.51; 95% CI: 0.43–0.59; P<0.001).**

CONCLUSIONS: **On the basis of this meta-analysis of observational studies, CRC incidence and mortality in patients with non-malignant findings are significantly reduced after colonoscopy. The effect of screening colonoscopy on CRC incidence is more marked than diagnostic colonoscopy.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death throughout the world (1). By means of detection and subsequent resection of precancerous lesions and early-stage CRCs, screening is effective in reducing CRC incidence and mortality, which has already been demonstrated in trials with fecal occult blood test (2–6) and flexible sigmoidoscopy (7–11). Evidence for the effectiveness of colonoscopy screening in average-risk general population, however, is still limited as related large-scale randomized trials are still ongoing (12–15).

Since 2009, mounting evidence from observational studies has shown that colonoscopy screening is associated with reductions in both CRC incidence and mortality (16–19). However, colonoscopy screening programs have not been implemented in many European countries (20,21) and most of the Asia-Pacific region (22); even the colonoscopy screening rates in the United States and Germany, where screening programs were introduced early this

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century, were only 54% by 2013 (23) and ~20–30% by 2012 (24), respectively. A great number of studies from the real-world settings in which indications for colonoscopy included both screening and diagnostic also supported the protective effect of colonoscopy in the general population (25–29).

Two previous meta-analyses found significant reductions in CRC mortality (and incidence) after (screening) colonoscopy (30,31), but the generalizability of the findings in the general population is less than ideal due to the heterogeneity of the baseline population, as subjects with malignant findings were enrolled in some included studies but not in others. Ranging from negative findings, hyperplastic polyps, adenomas to serrated lesions, non-malignant findings at the index colonoscopy, which constitutes over 90% of the yield of colonoscopy in clinical practice (32,33), differ with malignant findings in the following aspects: non-malignant nature, mostly non-surgical treatment, longer surveillance interval, and better prognosis (34,35). We therefore aim to evaluate the magnitude of protection against CRC by colonoscopy, with screening and diagnostic indications, in patients with non-malignant findings and further determine the potentially more marked effect of screening over diagnostic colonoscopy in the magnitude of reductions in CRC incidence and mortality.

METHODS

Search strategy

The meta-analysis was performed according to MOOSE statement (MOOSE Checklist is available in **Supplementary Appendix A** online) (36). A comprehensive, computerized literature search was conducted in PubMed and EMBASE from the beginning of indexing for each database to 30 April 2015 by two reviewers (J.P. and L.X.) independently, with no restrictions in language. The search for relevant studies was performed using the following text words and corresponding Medical Subject Heading/Emtree terms: "colonoscopy or endoscopy" AND "colorectal, colon, rectum, or large bowel" AND "cancer, carcinoma, neoplasm, tumo(u)r, or adenocarcinoma" AND "relative risk(s), odds ratio(s), rate ratio(s), risk ratio(s), or hazard ratio(s)" AND "cohort, or case–control" (detailed search strategy is available in **Supplementary Appendix B**). Abstracts from Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW) were searched manually. In addition, we searched for additional studies in reference lists of identified articles.

Eligibility criteria

Three reviewers (J.P., L.X., and Y.-F.M.) independently evaluated all of the studies retrieved according to the eligibility criteria. Disagreements were resolved by consensus. Studies were included if they met all of the following criteria: (i) studies from which effect estimates assessing the effect of colonoscopy on CRC incidence and/or mortality in patients with non-malignant findings vs. no colonoscopy were extractable (patients with non-malignant findings were defined as a consecutive collection of both cases detected with non-malignant polyps and those with negative findings at the index colonoscopy; the index colonoscopy was defined as the initial colonoscopy performed during the study period for either screening or diagnostic purpose); (ii) all of the participants with and without the exposure to colonoscopy are from the same population source; (iii) all of the participants had no history of CRC; (iv) all (or the vast majority) of the participants had no history of inflammatory bowel disease and no family history of hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, or sporadic CRC; (v) effect estimates and the corresponding 95% confidence intervals (CIs) were adjusted for age at least; and (vi) studies with an observational design (prospective cohort, retrospective cohort, or case–control studies). For studies with multiple publications from the same population source, only data from the most recent publication was included.

Data extraction and quality assessment

Two reviewers (J.P. and L.X.) extracted the data independently, and disagreements were resolved by consensus. The following data were extracted from each study: first author, publication year, indications for index colonoscopy, study design, setting, study period, number of participants, age at baseline, sex, duration of follow-up, effect estimates with 95% CIs, and adjustments. For studies with several multivariable-adjusted estimates, we extracted those reflecting the greatest degree of control for potential confounders. The primary outcomes were overall CRC incidence and mortality; the secondary outcomes were CRC incidence and mortality according to indications for colonoscopy, site of cancer, sex, and study design. The study quality was assessed using the Newcastle–Ottawa Scale (37), and the studies awarded seven or more stars were considered of high quality.

Statistical analysis

The measure of effect of interest was the relative risk (RR). Odds ratio, rate ratio, risk ratio, or hazard ratio yielded similar estimates of RR (38). Study-specific RR estimates were combined using a random-effects model, which considers both within- and between-study variation (39). Statistical heterogeneity among studies was evaluated by I^2 and Q statistics (40). Studies with an I^2 of <25%, 25–50%, 50–75%, and >75% were considered to have no, low, moderate, and high heterogeneity, respectively. An I^2 of >50% indicated significant heterogeneity (41). Sensitivity analysis was performed to evaluate the robustness of results, in which pooled estimates were computed omitting one study in each turn (42). Subgroup analysis was performed by indications for colonoscopy, site of cancer, sex, and study design. We compared the pooled RR estimates from different subgroups with a test of interaction (43). Publication bias was evaluated by Begg's test and Egger's test (44,45). All statistical analyses were performed with Stata software, version 12.0 (Stata Corp, College Station, TX). $P<0.05$ was considered statistically significant.

RESULTS

Literature search

PubMed and EMBASE were searched for relevant studies. As shown in **Figure 1**, a total of 1,247 studies met our search strategy.

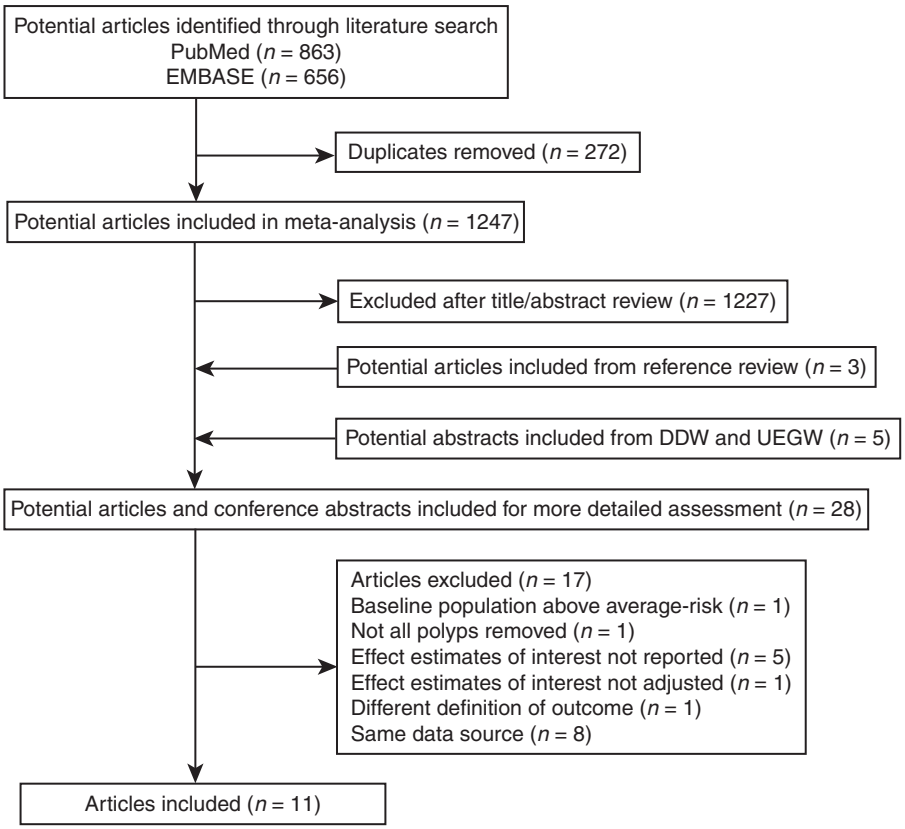

Figure 1. Flow diagram of literature search and study selection.

After title/abstract review, we excluded 1,227 studies; after including 3 studies from reference review and 5 abstracts from DDW and UEGW, 28 studies remained. Another 17 studies were further excluded for reasons listed as follows: baseline population above average risk (*n*=1) (46), not all polyps removed (*n*=1) (47), effect estimates of interest not reported (*n*=5) (17,48–51), effect estimates of interest not adjusted (*n*=1) (52), different definition of outcome (*n*=1) (53), and same data source (*n*=8) (25,27,54–59). Finally, 11 studies were included in the meta-analysis (18,19,28,29,60–66).

Study characteristics and quality assessment

Details of the 11 included studies are listed in **Table 1**. Of the 11 observational studies, 5 were cohort studies (18,60–63) (3 prospective (18,60,61) and 2 retrospective (62,63)) and 6 were case–control studies (19,28,29,64–66). A total of 1,499,521 individuals were included, in which 1 study enrolled over 1,000,000 individuals (62), 7 studies enrolled 10,000–100,000 individuals each (18,28,60,61,63–65), and the other 3 enrolled <10,000 individuals each (19,29,66). Duration of follow-up for cohort studies (or corresponding duration from exposure of colonoscopy to CRC occurrence/death for case–control studies) varied, with three studies of over 10 years (18,60,61), seven studies of 5–10 years (19,28,29,62–65), and one study of <5 years (66). Six studies reported CRC incidence only (19,29,61,63,64,66), four reported CRC mortality only (18,28,60,65), and one reported both CRC incidence and mortality (62). Indication(s) for index colonoscopy varied among studies, with screening in three studies (18,19,60), screening/diagnostic in five (28,29,61–63), and diagnostic in three (64–66). Eight studies were conducted in North America (18,28,29,60,62–65), and three in Europe (19,61,66). In each of the 11 studies, colonoscopy at baseline (combination of polypectomy with removal of all detected lesions and negative colonoscopy) was compared with no colonoscopy.

Effect estimate of the study by Brenner *et al.* (19) was extracted from authors' reply letter in which a widely accepted definition of screening exposure was adopted (67,68). One study by Müller and Sonnenberg (64) separately reported effect estimates for colon and rectal cancer, and we included the combined RR by pooling the two estimates using a random-effect model.

Strategies for excluding CRC cases to form the group of patients with non-malignant findings at the index colonoscopy varied among studies: two studies excluded CRC cases diagnosed at the index colonoscopy (64,65), four studies excluded CRC cases diagnosed at or within 6 months (exclusion window) of the index colonoscopy (28,29,63,66), one study used a longer exclusion window of 12 months (19), three studies used variable exclusion windows ranging from 0 to 24 or 36 months (18,60,61), and one study used a variable exclusion window ranging from 0 to 60 months (62).

Results for study quality assessment are also shown in **Table 1** (for details see **Supplementary Appendices C and D**). Six out of the 11 studies were awarded seven or more stars, indicating high study quality.

Table 1. Characteristics of included studies

Authors (reference)	Indications for the index colonoscopy	Study design	Setting	Study period	Number of participants[a]	Age at enrollment (years)[b]	Men (%)	Duration of follow-up[c]	Adjustments	Study quality[d]
Eldridge *et al.* (60)	Screening	Prospective cohort	NIH-AARP Study, USA	1995–2008	68,531 (22,780/45,751)	50–71[e]	62	11 years[f]	Age, sex, hormone replacement therapy, education, race, diabetes, family history of CRC, and healthy lifestyle score	6
Nishihara *et al.* (18)	Screening	Prospective cohort	Nurses' Health Study and Health Professionals Follow-up Study, USA	1988–2012	88,902 (NA/NA)	Men: 42–77[e] Women: 32–57[e]	35.7	1,841,586 person-years	Age, sex, calendar year of the questionnaire cycle, body mass index, smoking status, family history of CRC, status with respect to regular use of aspirin, physical activity level, red-meat intake, total caloric intake, alcohol intake, folate intake, calcium intake, multivitamin use, nonsteroidal antiinflammatory drug use, and cholesterol-lowering drug use	7
Brenner *et al.* (19)[g]	Screening	Case–control	Rhine-Neckar, Germany	1993–2010	4,800 (2,516/2,284)	70[h]	59	1–10 years[e]	Age, sex, county of residence, education, family history of CRC, smoking, body mass index, ever regular use of NSAIDs, ever use of hormone replacement therapy, and ever participation in a general health screening examination	7
Morois *et al.* (61)	Screening/ diagnostic	Prospective cohort	E3N Study, France	1990–2008	92,048 (37,459/54,589)	Colonoscopy group: 49.9±6.6 Control group: 48.8±6.6	0	15.4 years[h]	Age, physical activity, smoking status, family history of CRC, educational level, and body mass index	7
Jacob *et al.* (62)	Screening/ diagnostic	Retrospective cohort	Ontario, Canada	1996–2007	1,089,998 (86,837/1,003,161)	62[f]	45.1	Incidence: 7 years Mortality: 5 years	Age, sex, comorbidity as measured by the Adjusted Diagnostic Groups case-mix system, neighborhood income quintile, rural residence, and PCP characteristics (age, sex, and country of medical education)	9
Wang *et al.* (63)	Screening/ diagnostic	Retrospective cohort	SEER-Medicare, USA	1998–2005	53,676 (12,266/41,410)	Colonoscopy group: 73.1±3.8 Control group: 73.3±4.0	39.3	Colonoscopy group: 5 years[f] Control group: 5.3 years[f]	Age, sex, race, zip code, income and educational level, metropolitan county residence, endoscopist subspecialty, and SEER registry stratification	7
Baxter *et al.* (28)	Screening/ diagnostic	Case–control	SEER-Medicare, USA	1991–2007	37,099 (9,458/27,641)	Cases: 79.9 (70.0–89.9)[i] Controls: 79.8 (69.1–90.8)[i]	42.6	9.4 years[h]	Age, sex, race, SEER registry, individual comorbid conditions, socioeconomic status, and urban/rural status	6

Table 1 continued on following page

Table 1. Continued

Authors (reference)	Indications for the index colonoscopy	Study design	Setting	Study period	Number of participants[a]	Age at enrollment (years)[b]	Men (%)	Duration of follow-up[c]	Adjustments	Study quality[d]
Kahi *et al.* (29)	Screening/ diagnostic	Case–control	Veterans Affairs, USA	1997–2007	2,492 (623/1,869)	81.22±3.89	98.7	5.19 years[f]	Age, sex, race, NSAID use, and Charlson comorbidity index.	5
Müller and Sonnenberg (64)[j]	Diagnostic	Case–control	Veterans Affairs, USA	1981–1993	32,702 (16,351/16,351)	Cases (CC): 67.2±9.3 Cases (RC): 66.2±9.4 Controls: 57.0[f]	97.8	Cases (CC): 6.8 years[f] Cases (RC): 6.1 years[f] Controls: 7.1 years[f]	Age, sex, and race.	4
Müller and Sonnenberg (65)	Diagnostic	Case–control	Veterans Affairs, USA	1978–1992	20,889 (4,358/16,531)	Cases (CC): 69.1 (68.7–69.5)[k] Cases (RC): 68.3 (67.8–68.8)[k] Controls: 57.0 (57.0–57.1)[k]	97.7	Cases: 6.4 years[f] Controls: 8.3 years[f]	Age, sex, race, number of other colorectal procedures, procedures other than colorectal, length of coverage by the Department of Veterans Affairs, and presence of arthritis-related diseases.	4
Mulder *et al.* (66)	Diagnostic	Case–control	The Netherlands	1996–2005	8,384 (594/7,790)	Cases: 69.5±11.9 Controls: 69.3±11.9	51.7	2.8 years[h]	Age, sex, calendar time, duration of follow-up before the date of diagnosis (index date), and IBD.	7

CC, colon cancer; CRC, colorectal cancer; IBD, inflammatory bowel disease; NA, not available; NIH-AARP, National Institutes of Health American Association of Retired Persons; NSAID, nonsteroidal anti-inflammatory drug; RC, rectal cancer.

[a]Numbers in parentheses represented number of participants in colonoscopy/control group (cohort studies), or number of cases/controls (case–control studies).

[b]Values for age were presented as median (interquartile range) or mean±s.d. unless indicated otherwise.

[c]Duration of follow-up for cohort studies, and duration from the exposure of colonoscopy to CRC occurrence/death for case–control studies.

[d]Study quality was assessed based on the Newcastle–Ottawa Scale (range, 0–9 stars), details see **Supplementary Appendices C and D** online.

[e]Range.

[f]Mean.

[g]Effect estimate was extracted from authors' reply letter by Brenner *et al.* (68).

[h]Median.

[i]Median (range).

[j]Effect estimate was calculated by pooling the two separate estimates for colon and rectal cancer.

[k]Mean (95% CI).

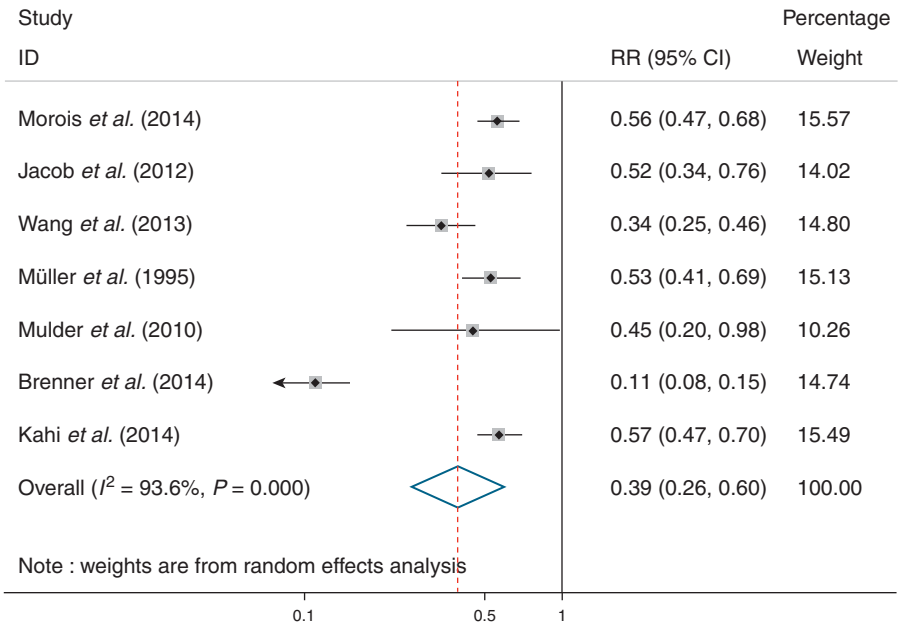

Figure 2. Forest plot of reduction in colorectal cancer incidence after colonoscopy in patients with non-malignant findings.

Primary outcomes

Seven studies were included for outcome of overall CRC incidence. Pooling by a random-effect model (**Figure 2**) yielded a pooled RR of 0.39 (95% CI: 0.26–0.60), corresponding to a 61% RR reduction in CRC incidence after colonoscopy in patients with non-malignant findings. There was evidence of high heterogeneity among studies (I^2=93.6%, P<0.001). Sensitivity analysis revealed that the study by Brenner *et al.* (19) substantially influenced pooled RR. After excluding this study, there was evidence of low heterogeneity (I^2=44.7%, P=0.11), and pooled RR was 0.51 (95% CI: 0.43–0.59). Funnel plot asymmetry test for publication bias was negative using both Begg's test (P=0.07) and Egger's test (P=0.43).

Five studies were included for outcome of overall CRC mortality. Pooling by a random-effect model (**Figure 3**) yielded a pooled RR of 0.39 (95% CI: 0.35–0.43), corresponding to a 61% RR reduction in CRC mortality after colonoscopy in patients with non-malignant findings. There was no evidence of heterogeneity among studies (I^2=12.0%, P=0.34). Sensitivity analysis further confirmed the robustness of our findings. Funnel plot asymmetry test for publication bias was negative using both Begg's test (P=0.22) and Egger's test (P=0.35).

Secondary outcomes

Subgroup analyses were conducted for the following secondary outcomes of CRC incidence (**Table 2**). As for indications, screening colonoscopy was associated with greater protection (RR: 0.11; 95% CI: 0.08–0.15) than screening/diagnostic and diagnostic colonoscopies (RR: 0.51; 95% CI: 0.43–0.59; $P_{interaction}$<0.001). As for site of cancer, colonoscopy was associated with a 28% non-statistically significant reduction in proximal CRC incidence (RR: 0.72; 95% CI: 0.50–1.03), whereas protection against distal CRC (RR: 0.32; 95% CI: 0.20–0.50) was much stronger ($P_{interaction}$=0.01). As for sex, results were similar for studies in men (RR: 0.55; 95% CI: 0.47–0.64) and women (RR: 0.56; 95% CI: 0.47–0.66; $P_{interaction}$=0.88). As for study design, results were also similar for cohort (RR: 0.47; 95% CI: 0.34–0.65) and case–control studies (RR: 0.35; 95% CI: 0.16–0.77; $P_{interaction}$=0.50).

Subgroup analyses were conducted for the following outcomes of CRC mortality (**Table 3**). As for indications, screening colonoscopy was associated with somewhat greater protection (RR: 0.36; 95% CI: 0.29–0.46) than screening/diagnostic and diagnostic colonoscopies (RR: 0.40; 95% CI: 0.32–0.49), but the difference between subgroups was not statistically significant ($P_{interaction}$=0.51). As for the site of cancer, colonoscopy was associated with less protection against proximal CRC mortality (RR: 0.57; 95% CI: 0.52–0.63) than distal CRC (RR: 0.18; 95% CI: 0.11–0.31; $P_{interaction}$<0.001). As for sex, colonoscopy provided a similar magnitude of protection for men (RR: 0.36; 95% CI: 0.32–0.40) and women (RR: 0.23; 95% CI: 0.10–0.54; $P_{interaction}$=0.30). As for study design, results were similar in the cohort (RR: 0.34; 95% CI: 0.26–0.45) and case–control studies (RR: 0.40; 95% CI: 0.37–0.43; $P_{interaction}$=0.26).

DISCUSSION

Overview

This meta-analysis shows that CRC incidence and mortality in patients with non-malignant findings were both 61% lower after colonoscopy. The protective effect was more prominent after screening colonoscopy, corresponding to an 89% reduction in CRC incidence.

Interpretations of study findings

Our study is the first meta-analysis to quantify the magnitude of protection against CRC that patients with non-malignant findings benefit from colonoscopy. When interpreting the study results, both the overall effect of colonoscopy and the individual

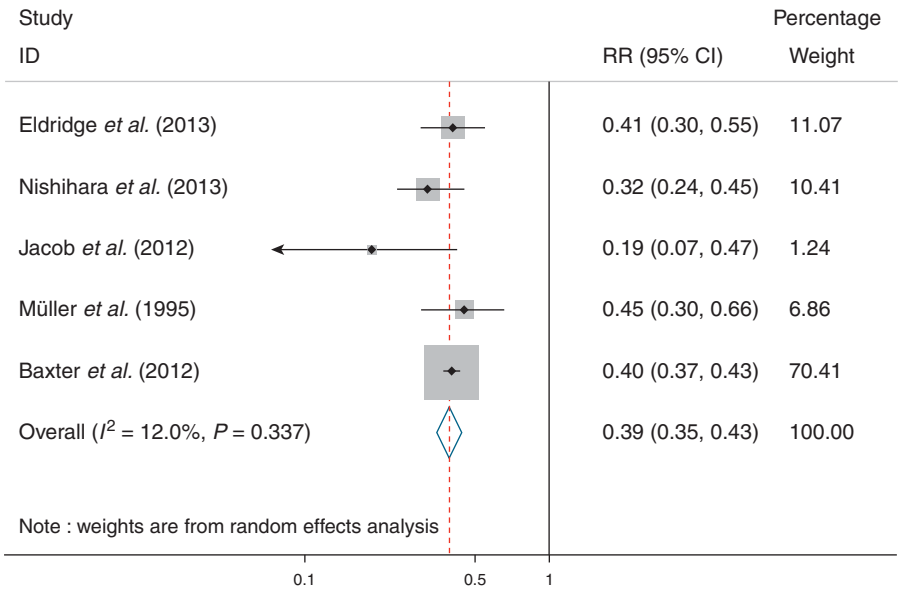

Figure 3. Forest plot of reduction in colorectal cancer mortality after colonoscopy in patients with non-malignant findings.

Table 2. Subgroup analyses for reduction in colorectal cancer incidence after colonoscopy in patients with non-malignant findings

Subgroups	Number of studies	Pooled RR (95% CI)	I^2 (%)	$P_{heterogeneity}$	$P_{interaction}$
Indications for colonoscopy					
Screening (19)	1	0.11 (0.08–0.15)	NA	NA	
Screening/diagnostic and diagnostic (29,61–64,66)	6	0.51 (0.43–0.59)	44.7	0.11	<0.001
Site of cancer					
Proximal CRC (29,61–63)	4	0.72 (0.50–1.03)	69.9	0.02	
Distal CRC (29,61–63)	4	0.32 (0.20–0.50)	75.7	0.01	0.01
Sex					
Men (29,62,64)	3	0.55 (0.47–0.64)	0.0	0.89	
Women (61,62)	2	0.56 (0.47–0.66)	0.0	0.82	0.88
Study design					
Cohort (61–63)	3	0.47 (0.34–0.65)	73.7	0.02	
Case–control (19,29,64,66)	4	0.35 (0.16–0.77)	96.3	<0.001	0.50

CI, confidence interval; CRC, colorectal cancer; NA, not available; RR, relative risk.

effect of screening colonoscopy derived from subgroup analysis are informative. As regular colonoscopy screening has not been implemented even in many developed countries (20,21), the primary outcome, which estimated the benefit derived from both screening and diagnostic colonoscopies, reflected the effect of regular colonoscopy in routine clinical practice. Subgroup analysis of screening colonoscopy provides data on the maximum cases of CRCs and CRC-related deaths that may be prevented in patients with non-malignant findings by population-based screening programs in standardized conditions, which is more important from a public health perspective.

There are several explanations for our findings. First, removal of all detected polyps (i.e., clearing colonoscopy) is the main modality responsible for the decreased CRC risk (69,70), while individuals with negative findings are inherently associated with lower risks of developing CRC even compared with postpolypectomy individuals (71). Second, interval CRCs could hardly be avoided because of factors such as missed lesions at the index colonoscopy, rapid growth of specific type of neoplasms, and incomplete resection of polyps (72). Therefore, both the aspects should be considered when interpreting the study findings.

In subgroup analysis, our study showed more prominent protection against CRC incidence by screening colonoscopy than

Table 3. Subgroup analyses for reduction in colorectal cancer mortality after colonoscopy in patients with non-malignant findings

Subgroups	Number of studies	Pooled RR (95% CI)	I^2 (%)	$P_{heterogeneity}$	$P_{interaction}$
Indications for colonoscopy					
Screening (18,60)	2	0.36 (0.29–0.46)	10.4	0.29	
Screening/diagnostic and diagnostic (28,62,65)	3	0.40 (0.32–0.49)	25.7	0.26	0.51
Site of cancer					
Proximal CRC (18,28,62)	3	0.57 (0.52–0.63)	0.0	0.66	
Distal CRC (18,28,62)	3	0.18 (0.11–0.31)	63.9	0.06	<0.001
Sex					
Men (18,28,62,65)	4	0.36 (0.32–0.40)	0.0	0.69	
Women (18,28,62)	3	0.23 (0.10–0.54)	93.5	<0.001	0.30
Study design					
Cohort (18,60,62)	3	0.34 (0.26–0.45)	28.1	0.25	
Case–control (28,65)	2	0.40 (0.37–0.43)	0.0	0.57	0.26

CI, confidence interval; CRC, colorectal cancer; RR, relative risk.

colonoscopy with indications of screening/diagnostic and diagnostic ($P_{interaction}$<0.001), and, similar tendency was observed for CRC mortality (RR: 0.36 (0.29–0.46) vs. 0.40 (0.32–0.49); $P_{interaction}$=0.51), as screening detects a different spectrum of findings (e.g., fewer polyps) compared with that diagnosed in the symptomatic population (35,73,74). Our results showed that colonoscopy was less effective in preventing proximal CRC incidence and mortality (both $P_{interaction}$<0.05) than distal CRC in patients with non-malignant findings, which might be explained by several factors concerning endoscopists, patients, and tumor biology: proximal serrated polyps could be easily missed by endoscopists because of flat or sessile appearance; patients' poor bowel preparation usually results in incomplete colonoscopy examination; differences in tumor biology exist between proximal and distal lesions of the colorectum (75,76).

Novelty of the study

Two previous meta-analyses are important studies on the effect of colonoscopy (30,31). Brenner *et al.* (30) found that screening colonoscopy is associated with 69 and 68% reductions in CRC incidence and mortality, respectively, and Elmunzer *et al.* (31) concluded that colonoscopy reduces CRC mortality by 57%. Novelty of our meta-analysis are threefold. First, in the two meta-analyses, patients with malignant findings were enrolled in some included studies but not in others. The significant heterogeneity of baseline population may strongly affect generalizability of their results in the general population. Therefore, we enrolled in our meta-analysis patients with non-malignant findings, a more homogeneous group constituting over 90% of the yield of colonoscopy in clinical practice (32,33) and featured with non-malignant nature, mostly non-surgical treatment, longer surveillance interval, and better prognosis compared with malignant findings (34,35). Second, the effect of screening colonoscopy and the effect of colonoscopy regardless of indication were separately reported in the two meta-analyses, without comparison, whereas our subgroup analysis found a more prominent effect of screening colonoscopy over screening/diagnostic and diagnostic colonoscopies on reducing CRC incidence. Third, with expanded colonoscopy indications (including both screening and diagnostic), study outcomes (including both incidence and mortality), and an updated inclusion of recent studies (18,29), our study (n=1,499,521) is responsible for a more robust conclusion with a larger sample size.

Study limitations

Our study has several limitations. First, in addition to excluding detected CRCs (CRCs diagnosed at or within 6 months of the index colonoscopy) to arrive at non-malignant findings at the index colonoscopy, five of the eleven included studies also excluded interval CRCs (CRCs diagnosed within 6 to 36 (or even 60) months of the index colonoscopy) (18,19,60–62). As interval CRCs certainly argue against the protective effect of colonoscopy (77,78), results of our study might be biased, causing overestimation of the magnitude of protection by colonoscopy. Therefore, study results should be interpreted with caution. Second, it should be noted that indications for colonoscopy according to original publications of some studies may not reflect real circumstances, e.g., studies by Nishihara *et al.* (18) and Eldridge *et al.* (60) initiated earlier than the nationwide introduction of screening colonoscopy. This may offer one of the explanations for the non-significant difference between the effect of screening vs. screening/diagnostic and diagnostic colonoscopy on CRC mortality. Third, statistical heterogeneity was significant for outcome of incidence. This might be explained by the differences in population enrolled, intervention strategy, and study designs. After excluding the study by Brenner *et al.* (19) (screening was the only indication for colonoscopy), statistical heterogeneity became non-significant.

Fourth, results of our study might be biased due to several other factors. Overestimation of the protective effect of colonoscopy might be caused by selection bias introduced by observational studies, e.g., participants in the colonoscopy (exposed) group tended to be more health-conscious (79), whereas underestimation of the

results might be caused by contamination of the control (unexposed) group, e.g., individuals with adenomas in this group may present with symptoms and therefore receive colonoscopy examination with polypectomy (80). Moreover, the initial age for screening in one study (18) is earlier than the guideline-recommended 50 years of age. In this sense, our results should be interpreted with caution, and randomized trials may better resolve this problem. Fifth, our study did not quantify individual CRC risk after either polypectomy or negative colonoscopy, as only one study by Nishihara *et al.* (18) reported effect estimates in subgroups of patients with polyps and those with negative findings.

CONCLUSIONS

In conclusion, findings from this meta-analysis of observational studies indicate that CRC incidence and mortality in patients with non-malignant findings are significantly reduced after colonoscopy, especially after screening colonoscopy. This provides additional evidence for the effectiveness of colonoscopy in the general population.

CONFLICT OF INTEREST

Guarantors of the article: Zhao-Shen Li, MD and Liang-Hao Hu, MD.

Specific author contributions: Jun Pan contributed to the study concept and design, data acquisition and interpretation, and drafting and final approval of the manuscript; Lei Xin and Yi-Fei Ma contributed to the data acquisition, data analysis and interpretation, and revision and final approval of the manuscript; and Zhao-Shen Li and Liang-Hao Hu contributed to the study concept and design, data analysis and interpretation, drafting and revision of the manuscript, and final approval of the manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Both screening and diagnostic colonoscopy have an important role in colorectal cancer (CRC) prevention.
- ✓ Negative findings, hyperplastic polyps, adenomas, and serrated lesions constitute over 90% of the yield of colonoscopy in clinical practice, which are non-malignant in nature and associated with better prognosis compared with malignant findings.
- ✓ There is no meta-analysis quantifying the effect of colonoscopy in patients with non-malignant findings and further demonstrating the potentially more marked effect of screening over diagnostic colonoscopy.

WHAT IS NEW HERE

- ✓ Colonoscopy, regardless of indication of screening or diagnostic, significantly reduced CRC incidence and mortality in patients with non-malignant findings.
- ✓ The protective effect was more prominent for screening colonoscopy compared with diagnostic one.
- ✓ Greater protection was seen against distal CRC than proximal CRC in patients with non-malignant findings.

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