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Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study

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ABSTRACT

Objective Screening colonoscopy's effectiveness in reducing colorectal cancer mortality risk in community populations is unclear, particularly for right-colon cancers, leading to recommendations against its use for screening in some countries. This study aimed to determine whether, among average-risk people, receipt of screening colonoscopy reduces the risk of dying from both right-colon and left-colon/rectal cancers.

Design We conducted a nested case–control study with incidence-density matching in screening-eligible Kaiser Permanente members. Patients who were 55–90 years old on their colorectal cancer death date during 2006–2012 were matched on diagnosis (reference) date to controls on age, sex, health plan enrolment duration and geographical region. We excluded patients at increased colorectal cancer risk, or with prior colorectal cancer diagnosis or colectomy. The association between screening colonoscopy receipt in the 10-year period before the reference date and colorectal cancer death risk was evaluated while accounting for other screening exposures.

Results We analysed 1747 patients who died from colorectal cancer and 3460 colorectal cancer-free controls. Compared with no endoscopic screening, receipt of a screening colonoscopy was associated with a 67% reduction in the risk of death from any colorectal cancer (adjusted OR (aOR)=0.33, 95% CI 0.21 to 0.52). By cancer location, screening colonoscopy was associated with a 65% reduction in risk of death for right-colon cancers (aOR=0.35, CI 0.18 to 0.65) and a 75% reduction for left-colon/rectal cancers (aOR=0.25, CI 0.12 to 0.53).

Conclusions Screening colonoscopy was associated with a substantial and comparably decreased mortality risk for both right-sided and left-sided cancers within a large community-based population.

Significance of this study

What is already known on this subject?

- Screening is effective at reducing the risk of death from colorectal cancer.
- There is only limited evidence in the ability of currently available tests to substantially reduce the risk of death from right colon cancers.
- Some studies have questioned colonoscopy's effectiveness for cancers in the right colon, but many previous studies had methodological limitations such as the inability to know which tests were for screening or for diagnostic purposes.

What are the new findings?

- Screening colonoscopy use was associated with a 65% reduction in risk of death in the right colon and a 75% reduction in risk of death for left-colon/rectal cancers.
- The effectiveness of screening colonoscopy in the right colon was not significantly different from that in the left colon/rectum.

How might it impact on clinical practice in the foreseeable future?

- The current study supports colonoscopy as an effective screening test for reducing mortality from both left-sided and right-sided colon cancers.
- The results should help allay concerns that colonoscopy could be substantially less effective in the right than the left colon/rectum or less effective in real-world community-based populations.

INTRODUCTION

Colorectal cancer is a leading cause of cancer deaths worldwide.[1 2] Evidence from multiple randomised trials has established that screening with either faecal occult blood tests (FOBTs)[3–5] or sigmoidoscopy[6–9] can reduce colorectal cancer incidence and death. However, evidence of the ability of screening to substantially reduce risk for right-colon disease is limited. Although colonoscopy is the most commonly used colorectal cancer screening test in the USA,[10–12] its effectiveness is not yet supported by evidence from randomised trials.[13 14] Some studies have also questioned colonoscopy's effectiveness for cancers in the right (or proximal) colon.[15–17] Randomised trials of screening colonoscopy are under way,[18–21] but results are not expected for several years. Additionally, the practice of screening

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colonoscopy has advanced with improved technologies, training and bowel preparation, making it unclear if prior observational studies accurately assessed its current level of effectiveness.[22]

Few observational studies have examined the effectiveness of colonoscopy, separately, in the right and left colon/rectum, and results have been mixed. Early studies found little or no effectiveness in the right colon,[15–17] raising the possibility that clinically important lesions in the right colon are either biologically different and/or less readily detectable by colonoscopy. However, those studies used administrative data and thus were unable to distinguish screening colonoscopies from those performed for symptoms or account for confounding.[13] More recent studies found some evidence of effectiveness in the right colon, but with wide CIs and design limitations, including the use of self-reported screening exposure[23] and the use of cancer stage instead of mortality as an endpoint.[24] Rational screening policy depends on knowing the presence of and possible magnitude of screening colonoscopy's effectiveness in the right and left colon to justify the added inconvenience, risk and cost of colonoscopy, particularly relative to sigmoidoscopy. The Canadian Task Force on Preventive Health Care recently recommended against using colonoscopy as a screening test for colorectal cancer, citing the low quality of evidence on its use.[25]

We conducted a study in members of two large community-based integrated health systems to examine the extent to which screening colonoscopy use reduced the risk of death from colorectal cancer overall, and in the right colon, an area of continuing uncertainty. We also evaluated the association between screening sigmoidoscopy and colorectal cancer mortality to gauge the validity of our methods by comparing with results of randomised trials.[6–9] The study used methodologies and settings nearly identical to those of a prior analysis, which grounded the original US Preventive Services Task Force recommendations for sigmoidoscopy as an effective screening test.[26–28] Stable memberships in the health systems allowed us to define a historical cohort of average-risk people and identify patients who died from colorectal cancer along with matched controls. The use of community-based practices allowed estimates of effectiveness in settings where most screening and cancers occur, and extensive electronic and text-based medical record clinical data allowed evaluation of a wide range of potential confounding factors.[13]

METHODS

Study design and setting

This was a nested case–control study conducted in a large, racially, ethnically and socioeconomically diverse historical cohort of members of the Kaiser Permanente Northern California (KPNC) and Southern California (KPSC) healthcare systems. We used electronic and medical record-based clinical information linked to data from tumour and vital status registries to identify screening-eligible people in the underlying population and evaluate patients' clinical histories over a period of up to 10 years. Details of the study design have been described previously.[13] The study was approved by the Institutional Review Boards at KPNC, KPSC and the University of Pennsylvania.

Study subjects

We included health plan members who were 55–90 years old between 1 January 2006 and 31 December 2012 and had ≥5 years of enrolment prior to their reference date, which was the diagnosis date for each patient who died of colorectal cancer that was used to ascertain patient eligibility and exposure status (figure 1). In KPSC, cases were accrued in the 2011 and 2012 calendar years because this site was added later in the study. Because our interest was in people at average-risk for colorectal cancer, we excluded those with IBD; colorectal cancer in ≥1 first-degree relatives before age 50, or ≥2 first-degree or second-degree relatives at any age; or familial colorectal cancer syndromes.[29 30] We also excluded those who had GI cancer or colectomy before the reference date.[13]

Case patient ascertainment and control selection

Given colonoscopy may decrease the risk of death from colorectal cancer for an extended period after its performance, and several years may elapse between screening events, cancer diagnosis and death, we selected as cases men or women who were 55–90 years old on the date of death from colorectal adenocarcinoma as the underlying cause during 2006–2012. Vital status and the cause of death were obtained from state mortality files. Cancer diagnosis date and tumour characteristics (histology, stage and location) were obtained from the health plans' Surveillance, Epidemiology and End Results Programme-affiliated tumour registries. Tumours located proximal to the splenic flexure were categorised as 'right-colon', others as 'left-colon/rectum' or 'unspecified.'

Each case patient was individually matched to controls using an incidence-density matching approach[24] on the reference date on birth year (±1 year), sex, the duration of health plan enrolment prior to diagnosis (±1 year) and the geographical region in each health plan where the majority of patients' care was received. The use of incidence-density matching in a dynamic population that could be tracked longitudinally along with matching on geographical location helped reduce socioeconomic variation between cases and controls and thus minimised selection bias. Eight controls were initially identified for each case, with a goal of completing chart audits on two randomly selected eligible controls per case.

Screening colonoscopy exposures

We ascertained receipt of colonoscopy, sigmoidoscopy, CT colonography and/or FOBT in the 10-year period before the reference date (observation period), including tests that detected the index cancer. Test indication was determined in a multistep process as described previously (see online supplementary technical appendix).[13 24 31] Briefly, trained auditors collected the dates, findings and reasons for all relevant tests from progress, referral and endoscopy procedure notes in medical records. This approach allowed us to integrate information from the primary care or referring provider and the endoscopist with information on laboratory and imaging studies to assign test indication.[13] We then used a previously developed algorithm to classify each test's indication into mutually exclusive categories: definite-screening, probable-screening, surveillance, possible-diagnostic, probable-diagnostic, definite-diagnostic or unknown (see online supplementary table S1). Tests were classified as probable-screening if both screening and non-specific abdominal symptoms such as diarrhoea were recorded as reasons for performing it.[31] The indication was definite-screening if screening alone and no colorectal cancer-related conditions were recorded (see online supplementary technical appendix).[13]

A colonoscopy was classified as surveillance if performed for follow-up of previously detected polyps; 'definite' diagnostic if used to work-up a positive FOBT, abnormal sigmoidoscopy, a mass or other abnormal finding such as on imaging; 'probable' diagnostic if the medical records noted clinical conditions that were deemed to represent a high pretest probability for

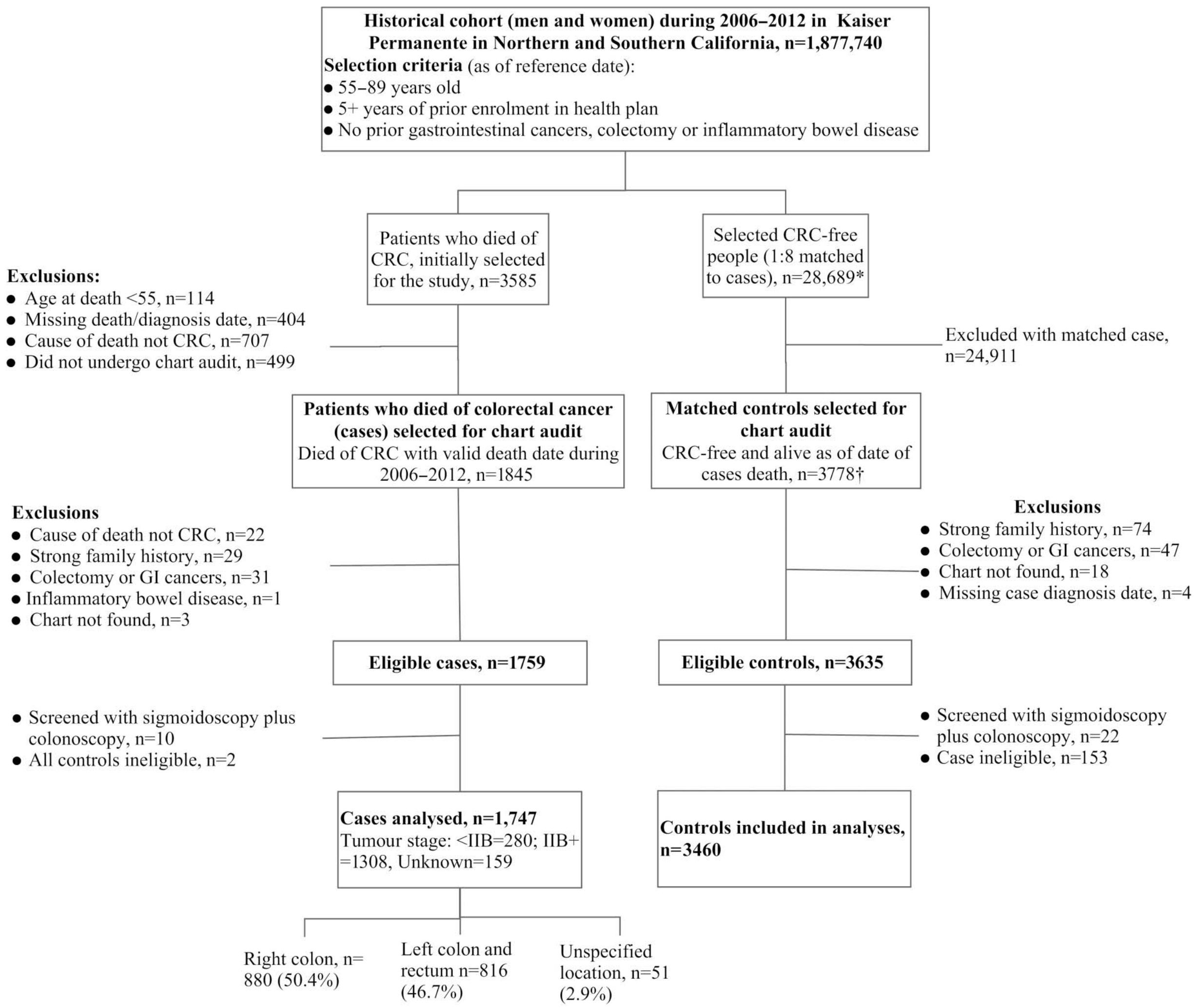

Figure 1 Flow diagram for the study. Note: *controls were matched to cases on sex, birthdate, health plan enrolment duration and medical service area within each health system. The reference date was the date of the case patient's colorectal adenocarcinoma. †Each patient dying from colorectal cancer was matched to eight controls with the intent of performing chart audits on the cases and two of the randomly selected controls. CRC, colorectal adenocarcinoma.

colorectal cancer such as rectal bleeding; 'possible' diagnostic if the only documented reasons were non-specific medical conditions such as diarrhoea or abdominal pain; or 'high-risk' screening, and thus excluded, if the test was performed for screening and the patient had IBD or a strong family history.

Sigmoidoscopies were similarly defined. For FOBTs, tests recorded as performed for screening or performed at home, done in the context of preventive care visit, because of patient preference, or if no specific reason was recorded, were classified as screening.

An adjudication panel (CAD, DAC, MG and RHF) reviewed all available information of patients with colonoscopies that were classified as surveillance, unknown or assigned differing indications across data sources by the computer algorithm. Three panellists independently assigned an indication for tests in each selected patient using a standardised approach. Disagreements were resolved through majority rule or moderated discussions.[13 31]

Covariates

Patients' birthdate, sex, race/ethnicity (categorised as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander or other) and health plan enrolment information were obtained from administrative databases. Our socioeconomic status indicator was the percentage of people ≥25 years with at least a high school diploma in a census tract using 2000 decennial census data.[32 33]

The number of outpatient primary care medical encounters, defined as visits with a family medicine, internal medicine, geriatric or obstetrics/gynaecology specialist, was used as an indicator of health-seeking behaviour; this was enumerated in the 5-year period excluding the 90-day period prior to the reference date and categorised as 0, 1, 2 or ≥3 visits. The Charlson comorbidity index,[34] categorised as 0, 1 or ≥2, was used as an indicator of wellness to undergo screening; the score was ascertained from electronic data in the fourth and fifth calendar years prior to the reference date. Family history of colorectal cancer was collected during chart audit, ignoring information recorded in the 30 days before the reference date to minimise information bias, and created a dichotomous variable for such a history that did not meet the exclusion criteria. Screening colonoscopies were deemed inadequate/low quality if the procedure failed to reach the caecum and/or had poor bowel preparation and a subsequent completed endoscopy was not performed.[35 36]

Statistical analysis

We estimated adjusted ORs (aOR) and 95% CIs for the association between receipt of screening colonoscopy during the observation period and the risk of any colorectal cancer death, and separately for right-colon and left-colon/rectum cancer deaths, using conditional logistic regression. We also estimated the effects of screening sigmoidoscopy in the same models as colonoscopy. Incidence-density matching generates a representative sample of the historical cohort, and because colorectal cancer mortality is a rare event, we interpreted the ORs as reasonable approximations of relative risks.[37] The multivariate analyses were adjusted for race/ethnicity, family history of colorectal cancer, socioeconomic status indicator, comorbidity score, number of primary care encounters and screening FOBT exposure. We explored unconditional models adjusting for matching variables in all those eligible including unmatched patients (1759 cases and 3635 controls, see figure 1), as previously described[24] and the results were similar.

Screening was defined by exposure to a definite-screening or probable-screening test. People receiving colonoscopy for an abnormal screening sigmoidoscopy were classified as only having received screening with sigmoidoscopy. Thus, the comparison group in all analyses was patients who had not received any screening endoscopy. We used an indicator in the model for missing data on socioeconomic status (1.8%). Patients with unknown race/ethnicity status (2.7%) were included with the 'other' race category. Our primary analysis excluded 10 case patients and 22 controls screened by both sigmoidoscopy and colonoscopy; we also excluded their matched case/control patients (n=22).

In sensitivity analyses, we restricted the exposure definition to definite-screening only and we recoded probable-screening as diagnostic. We also assessed the sensitivity of our results to restricting the analysis to patients diagnosed with cancer before age 85 years, excluding persons screened by screening FOBT, excluding persons screened by FOBT or sigmoidoscopy, restricting screening exposure to only 'high-quality' colonoscopies, and retaining and alternately coding individuals screened by both colonoscopy and sigmoidoscopy as either screening only by sigmoidoscopy or only by screening colonoscopy. All analyses were performed using Stata Statistical Software: Release V.14.1 (StataCorp. 2015. College Station, Texas, USA: StataCorp LP).

RESULTS

Patient characteristics

We identified a total of 3585 potential cases from a historical cohort of 1 877 740 people during the study period and audited charts of 1845 potentially case patients who met eligibility criteria and 3778 matched controls (figure 1). During chart audits, we excluded 86 case patients and 143 control patients who did not meet study criteria. Of the eligible 1759 cases and 3635 controls, 33.7% (n=1817) had colonoscopy including 180 for screening, 40.1% (n=2165) had sigmoidoscopy including 1474 for screening (see online supplementary table S1) and 43.4% had at least one prior screening FOBT.

Those excluded from the primary analysis are shown in figure 1. Of the 1747 cases and 3460 matched controls considered in our primary analyses, about half were female, and the majority was non-Hispanic white, had ≥10 years of health plan enrolment and had no significant comorbid illnesses. There was a higher proportion of non-Hispanic blacks, persons of low-socioeconomic status and high comorbidity score in case patients than in control patients (all p values <0.01) (table 1).

Table 1 Demographic and clinical characteristics of patients who died from colorectal cancer and matched controls

Characteristics, n (%)	Cases (n=1747)	Controls (n= 3460)
Used for case–control matching		
Age at diagnosis, years*		
50–54	23 (1.3)	65 (1.9)
55–64	570 (32.6)	1107 (32.0)
65–74	504 (28.8)	983 (28.4)
75–84	556 (31.8)	1103 (31.9)
85–89	94 (5.4)	202 (5.8)
Female	883 (50.5)	1756 (50.8)
Study sites		
KPNC	1443 (82.6)	2881 (83.3)
KPSC	304 (17.4)	579 (16.7)
Length of enrolment with health plan before reference date, years		
5.0–7.4	304 (17.4)	600 (17.3)
7.5–9.9	315 (18.0)	636 (18.4)
≥10	1128 (64.6)	2224 (64.3)
Characteristics not used for matching		
Race ethnicity		
Non-Hispanic white	1170 (67.0)	2318 (67.0)
Non-Hispanic black	208 (11.9)	244 (7.1)
Hispanic	164 (9.4)	374 (10.8)
Asian/Pacific Islander	156 (8.9)	397 (11.5)
Other/unknown	49 (2.8)	127 (3.7)
Per cent with at least a high school diploma, quartiles†		
1	374 (21.4)	871 (25.2)
2	419 (24.0)	873 (25.2)
3	435 (24.9)	833 (24.1)
4	482 (27.6)	824 (23.8)
Unknown	37 (2.1)	59 (1.7)
Family history (chart audit)‡	115 (6.6)	202 (5.8)
Primary care outpatient visits§		
0	83 (4.8)	71 (2.1)
1	45 (2.6)	50 (1.4)
2	96 (5.5)	110 (3.2)
3+	1523 (87.2)	3227 (93.3)
Charlson score at beginning of observation window		
0	1184 (67.8)	2626 (75.9)
1	293 (16.8)	461 (13.3)
2+	268 (15.3)	369 (10.7)
Unknown	2 (0.1)	4 (0.1)
Screening sigmoidoscopy	365 (20.9)	1030 (29.8)
Screening faecal occult blood test	702 (40.2)	1542 (44.6)

*The age at time of diagnosis, the date used to assess exposure and covariate information is shown.
†Data were obtained from the 2000 US Census data at the tract level.
‡Patients for whom the family history of colorectal cancer documented during the observation period did not meet the exclusion criteria. The exclusion was based on a history of colorectal cancer in one or more first-degree relatives before age 50 or in two or more second-degree relatives at any age, or other familial colorectal cancer syndromes.
§Defined based on outpatient clinical visits to family practice, gerontology/geriatrics, internal medicine, obstetrics/gynaecology and "primary care" clinics.

Association between screening colonoscopy and colorectal cancer mortality

In our sample, 24 (1.4%) cases and 120 (3.5%) controls had screening colonoscopy during the observation period. Compared with patients who did not receive endoscopic screening, those who received screening colonoscopy had a 67% lower risk of dying from any colorectal cancer (aOR=0.33; CI 0.21 to 0.52) (table 2). For right-colon cancers, 13 (2%) patients who died from colorectal cancer had received screening colonoscopy

Table 2 Association between receipt of screening endoscopy and colorectal adenocarcinoma death risk

Screening colonoscopy status according to colon location	Case patients, n=1747	Matched control patients, n=3460	Estimated relative risks (95% CI)	
			Bivariate model	Multivariate model*
All locations in the colon/rectum				
No screening endoscopy	1358	2310	1.00	1.00
Screening colonoscopy	24	120	0.33 (0.21 to 0.52)	0.33 (0.21 to 0.52)
Screening sigmoidoscopy	365	1030	0.60 (0.52 to 0.69)	0.64 (0.56 to 0.75)
Right colon				
No screening endoscopy	649	1151	1.00	1.00
Screening colonoscopy	13	61	0.37 (0.20 to 0.68)	0.35 (0.18 to 0.65)
Screening sigmoidoscopy	218	535	0.72 (0.59 to 0.87)	0.75 (0.62 to 0.92)
Left colon/rectum				
No screening endoscopy	669	1092	1.00	1.00
Screening colonoscopy	9	56	0.25 (0.12 to 0.50)	0.25 (0.12 to 0.53)
Screening sigmoidoscopy	138	468	0.48 (0.38 to 0.59)	0.52 (0.41 to 0.66)

*The multivariate model adjusted for race/ethnicity, family history, percentage of people 25+ years in the census tract with at least a high-school diploma, Charlson comorbidity score and number of primary care visits, as well as an indicator faecal occult blood testing. The estimates were obtained from conditional regression models.

compared with 61 (5.0%) control patients, corresponding to a 65% reduction in the risk of dying from right-colon cancer in those who had received screening colonoscopy as compared with those with no endoscopic screening (aOR=0.35; CI 0.18 to 0.65). We also examined the effect of screening and the risk of death from left-colon/rectum cancers. For this analysis, nine case patients (1.3%) had received screening colonoscopy compared with 56 (4.9%) controls, corresponding to a 75% lower risk for left-colon/rectal cancer deaths (aOR=0.25; CI 0.12 to 0.53). The difference in the size of the associations between the left and right colons was not statistically significant (p value=0.51). These results were not substantively different from those from the bivariate models (table 2). Analyses restricted to patients diagnosed before age 85 years found almost identical results (figure 2). Results were also similar to the primary analysis after excluding patients ever screened with either FOBT or sigmoidoscopy (overall: aOR=0.37, CI 0.16 to 0.84, right colon: aOR=0.36, CI 0.11 to 1.12, and left colon: aOR=0.26, CI 0.06 to 1.02, see table 3), but less precise because of small sample sizes.

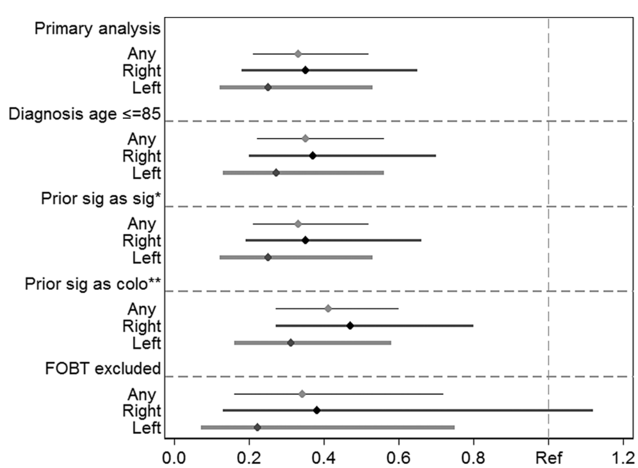

Figure 2 Graphical illustration of associations of screening colonoscopy with colorectal cancer death risk in primary and sensitivity analyses. Note: Models included an indication for screening sigmoidoscopy (not shown). *Patients excluded from the primary analysis because of receiving screening by both colonoscopy and sigmoidoscopy were coded as screening sigmoidoscopy. **Patients excluded from the primary analysis because of receiving screening by both colonoscopy and sigmoidoscopy were coded as screening colonoscopy. FOBT, faecal occult blood tests.

In analyses of colonoscopies classified by indication as definite screening, the aOR was 0.25 (CI 0.15 to 0.44) for any colorectal cancer death, 0.37 (CI 0.19 to 0.72) for right-colon cancer death and 0.07 (CI 0.02 to 0.28) for left-colon/rectal cancer death. About 3.5% of screening colonoscopies were considered 'low-quality' with no differences in quality between cases and controls. Analyses restricted to 'high-quality' screening colonoscopies yielded adjusted risk estimates similar to the primary analysis: the aORs were 0.31 (CI 0.19 to 0.50) for any colorectal cancer death, 0.31 (CI 0.16 to 0.60) for right-colon cancer death and 0.25 (CI 0.12 to 0.54) for left-colon/rectum cancer death. Results were also stable to exclusion of patients classified as exposed to tests with surveillance or unknown indication (data are not shown). Our results were also stable to the exclusion of patients with missing socioeconomic status or race/ethnicity data (data are not shown).

In the sigmoidoscopy analysis, 365 cases (20.9%) and 1030 (29.8%) controls were exposed during the observation period (table 2). The adjusted aORs for the association between receipt of screening sigmoidoscopy and colorectal cancer mortality risk were 0.64 (CI 0.55 to 0.74) overall, 0.75 (CI 0.61 to 0.92) for right-colon cancer deaths and 0.51 (CI 0.41 to 0.65) for the left colon.

We also performed analyses retaining patients excluded from the primary analysis because of receiving screening by both colonoscopy and sigmoidoscopy, and classifying them alternately as screening sigmoidoscopy or screening colonoscopy. This did not change our findings (figure 2).

DISCUSSION

In this study, we found that receipt of screening colonoscopy, compared with no endoscopic screening, was associated with a 67% lower risk of death from colorectal cancer overall, a 65% lower risk of death from right-colon cancer and a 75% lower risk from left-colon/rectum cancer. The results were similar for analyses restricted to those meeting very strict criteria for screening, high-quality colonoscopies or after excluding patients ever screened with FOBT. The estimate for association of screening colonoscopy with risk of death from cancer in the right colon was smaller than the reduction in the left colon/rectum, which is consistent with findings from other published studies.[15–17 23 24] However, the magnitude of the difference observed in our study was relatively small and was not

Table 3 Association between receipt of screening endoscopy and colorectal adenocarcinoma death risk; excluding persons who had undergone faecal occult blood or sigmoidoscopy screening

Screening colonoscopy status according to colon location	Case patients, n=836	Matched control patients, n=1453	Estimated relative risks (95% CI)	
			Bivariate model	Multivariate model*
All locations in the colon/rectum				
No screening endoscopy	822	1453	1.00	1.00
Screening colonoscopy	14	66	0.39 (0.18 to 0.84)	0.37 (0.16 to 0.84)
Right colon				
No screening endoscopy	370	647	1.00	1.00
Screening colonoscopy	6	34	0.42 (0.15 to 1.17)	0.36 (0.11 to 1.17)
Left colon/rectum				
No screening endoscopy	423	655	1.00	1.00
Screening colonoscopy	7	28	0.29 (0.08 to 1.04)	0.26 (0.06 to 1.02)

*Multivariate conditional logistic regression models were adjusted for race/ethnicity, family history, percentage of people 25+ years in the census tract with at least a high-school diploma, Charlson score and number of primary care visits. Analysis excluded all people exposure to screening with faecal occult blood test or sigmoidoscopy.

statistically significant. However, it remains possible that right-colon cancers are biologically different or less readily detected endoscopically.

The association between colonoscopy and colorectal cancer death has been reported separately for right-colon and left-colon cancers in four studies, but each had potential methodological weaknesses.[15–17 23] The first study reported an OR of 0.99 for the association between colonoscopy use and the risk of death from right-colon cancer.[15] However, the study relied exclusively on administrative data, which lack the details needed to control for confounding and to distinguish tests done for routine screening from those performed for diagnostic purposes such as abdominal masses, or as follow-up to a positive sigmoidoscopy or FOBT. It was thus unable to distinguish screening from diagnostic tests, and instead restricted the analyses to tests received more than 6 months before the diagnosis date, which are expected to be generally negative for cancer. Thus, that study described the degree to which any negative colonoscopy predicts risk of fatal colorectal cancer rather than the effectiveness of screening colonoscopy in reducing the risk of death from colorectal cancer.[38 39] The other studies had similar limitations.[16 17]

An analysis of the Nurses' Health Study and the Health Professionals Follow-up Study cohorts found a lower risk of colorectal cancer deaths in participants who reported a prior screening colonoscopy: 53% lower for the right colon/rectum and 82% lower for the left colon.[23] The screening indication in that study was self-reported and not confirmed by medical records. A previous case–control study by our group in a different population also found protective associations for colonoscopy in both the right and left colon for late-stage cancer.[24] Thus, the magnitude of screening effect on mortality cannot be directly inferred from that study because treatments may be effective regardless of stage, particularly with recent improvements in therapy for clinically advanced disease.

Our study also has limitations, mainly the possibility that the results could have partly been due to residual confounding. However, we were able to account for the main potential confounders[40] by exclusion, matching, stratification and adjustment in statistical analysis. Further, our previous analysis found that the magnitude of bias from potentially confounding variables that we were unable to measure, such as lifestyle factors, is small and unlikely to substantially affect our results.[40] Having <10 years of enrolment history (35% of patients in our study) may result in incomplete capture of colonoscopy use. To minimise potential differential ascertainment of exposure, we matched cases and controls on enrolment history. However, screening exposures in cases tend to occur close to the diagnosis date but are more evenly distributed in controls and thus may bias the results towards the null, further supporting our findings.[13]

A particular strength of our study was its setting within large community-based integrated healthcare systems with stable membership and extensive coded and free-text clinical data. Thus, we were able to define a historic cohort of members and, from it, sample average-risk patients to provide estimates that are generalisable to the source population. Also, we could reliably assign indications for colonoscopies and specifically define the subsets that were for screening using clinical information from several sources, a pretested algorithm and adjudication by clinicians. Although this approach resulted in a lower exposure rate than has been reported in this population,[41] a greater threat to validity would arise from classifying diagnostic tests as screening than the converse. Also, clinical databases were linked with detailed information in cancer and death registries.[31]

As in all clinical settings, screening colonoscopy took place in the context of other colorectal cancer screening tests that might confound or modify its effects. During the period of our study, the health systems in this study relied primarily on guaiac-FOBT and sigmoidoscopy before implementing system-wide screening outreach programmes with faecal immunochemical tests.[42] We were able to assess for confounding effects of other screening tests including when both sigmoidoscopy and colonoscopy were used. We found no strong evidence that screening FOBT confounded our estimates. Using the same models as were used for estimating colonoscopy's effectiveness, we also found that receipt of screening sigmoidoscopy was associated with a reduced risk of any colorectal cancer death by 36%. This estimate was similar to results from randomised trials (risk ratios: 0.57[7] and 0.62[6]) and thus supports the validity of our research design and analyses.

Clinical practice guidelines have included colonoscopy among colorectal cancer screening options in average-risk people since 1997, based largely on indirect evidence of effectiveness such as biological plausibility related to the adenoma–carcinoma sequence and generalisations from the established effectiveness of sigmoidoscopy and its use as a follow-up test within FOBT trials.[14 43] The use of colonoscopy has also been supported by results of a cohort study of patients who had undergone polypectomy,[44] and modelling studies.[45] However, conflicting findings of previous studies have left uncertainties about screening colonoscopy's effectiveness, particularly in the right colon.[15–17 23] If right-sided effects are small, as some studies have suggested, then the added inconvenience, risk and cost associated with screening colonoscopy use for average-risk people, compared with sigmoidoscopy, would be difficult to justify.

The current study found a strong association between receipt of screening colonoscopy and a reduced risk of death from colorectal adenocarcinomas arising in either the right colon or left colon/rectum. In contrast to recent recommendations against colonoscopy, which cited a lack of high-quality evidence,[25] the current study from a well-defined cohort supports colonoscopy as an effective screening test for reducing mortality risk from both left and right-sided colon cancers, and should help allay concerns that it could be substantially less effective in the right than the left colon/rectum or less effective in real-world community-based populations. The study's methodological rigour and setting are nearly identical to those from a prior analysis, which supported the inclusion of sigmoidoscopy as a screening test by the US Preventive Services Task Force, prior to randomised trials.[26–28] Randomised trials of screening colonoscopy, currently under way, will add to this body of knowledge but may be underpowered to separately evaluate effects in the right and left colon.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
2 Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.
3 Mandel JS, Bond JH, Church TR, *et al*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993;328:1365–71.
4 Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–7.
5 Kronborg O, Fenger C, Olsen J, *et al*. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
6 Segnan N, Armaroli P, Bonelli L, *et al*. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial—SCORE. *J Natl Cancer Inst* 2011;103:1310–22.
7 Atkin WS, Edwards R, Kralj-Hans I, *et al*. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010;375:1624–33.
8 Schoen RE, Pinsky PF, Weissfeld JL, *et al*. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012;366:2345–57.
9 Holme Ø, Løberg M, Kalager M, *et al*. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA* 2014;312:606–15.
10 Doubeni CA, Laiyemo AO, Reed G, *et al*. Socioeconomic and racial patterns of colorectal cancer screening among Medicare enrollees in 2000 to 2005. *Cancer Epidemiol Biomarkers Prev* 2009;18:2170–5.
11 Fedewa SA, Goodman M, Flanders WD, *et al*. Elimination of cost-sharing and receipt of screening for colorectal and breast cancer. *Cancer* 2015;121:3272–80.
12 Schenck AP, Peacock SC, Klabunde CN, *et al*. Trends in colorectal cancer test use in the medicare population, 1998-2005. *Am J Prev Med* 2009;37:1–7.
13 Goodman M, Fletcher RH, Doria-Rose VP, *et al*. Observational methods to assess the effectiveness of screening colonoscopy in reducing right colon cancer mortality risk: SCOLAR. *J Comp Eff Res* 2015:;4:541–51.
14 Bibbins-Domingo K, Grossman DC, Curry SJ, *et al*., US Preventive Services Task Force. Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA* 2016;315:2564–75.
15 Baxter NN, Goldwasser MA, Paszat LF, *et al*. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1–8.
16 Baxter NN, Warren JL, Barrett MJ, *et al*. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol* 2012;30:2664–9.
17 Singh H, Nugent Z, Demers AA, *et al*. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139:1128–37.
18 Kaminski MF, Bretthauer M, Zauber AG, *et al*. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. *Endoscopy* 2012;44:695–702.
19 Quintero E, Castells A, Bujanda L, *et al*. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012;366:697–706.
20 Dominitz JA, Robertson DJ. Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM). 2012;NCT01239082.
21 Uppsala University Hospital. Colonoscopy and FIT as colorectal cancer screening test in the average risk population. *ClinicalTrialsgov* 2014;NCT02078804.
22 Wallace MB, Kiesslich R. Advances in endoscopic imaging of colorectal neoplasia. *Gastroenterology* 2010;138:2140–50.
23 Nishihara R, Wu K, Lochhead P, *et al*. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095–105.
24 Doubeni CA, Weinmann S, Adams K, *et al*. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. *Ann Intern Med* 2013;158(Pt 1):312–20.
25 Bacchus CM, Dunfield L, Gorber SC, *et al*. Canadian Task Force on Preventive Health Care. Recommendations on screening for colorectal cancer in primary care. *CMAJ* 2016;188:340–8.
26 Selby JV, Friedman GD, Quesenberry CP Jr, *et al*. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653–7.
27 U.S. Preventive Services Task Force. Screening for colorectal cancer: recommendation and rationale. *Ann Intern Med* 2002;137:129–31.
28 U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627–37.
29 Lipton LR, Johnson V, Cummings C, *et al*. Refining the Amsterdam Criteria and Bethesda Guidelines: testing algorithms for the prediction of mismatch repair mutation status in the familial cancer clinic. *J Clin Oncol* 2004;22:4934–43.
30 Umar A, Boland CR, Terdiman JP, *et al*. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;96:261–8.
31 Fassil H, Adams KF, Weinmann S, *et al*. Approaches for classifying the indications for colonoscopy using detailed clinical data. *BMC Cancer* 2014;14:95.
32 Doubeni CA, Schootman M, Major JM, *et al*. Health status, neighborhood socioeconomic context, and premature mortality in the United States: The National Institutes of Health-AARP Diet and Health Study. *Am J Public Health* 2012;102:680–8.
33 Doubeni CA, Jambaulikar GD, Fouayzi H, *et al*. Neighborhood socioeconomic status and use of colonoscopy in an insured population–a retrospective cohort study. *PLoS ONE* 2012;7:e36392.
34 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–19.

35 Lieberman D, Nadel M, Smith RA, *et al*. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of The National Colorectal Cancer Roundtable. *Gastrointest Endosc* 2007;65:757–66.
36 Rex DK, Bond JH, Winawer S, *et al*. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2002;97:1296–308.
37 Hogue CJ, Gaylor DW, Schulz KF. Estimators of relative risk for case-control studies. *Am J Epidemiol* 1983;118:396–407.
38 Weiss NS. Commentary: Cohort studies of the efficacy of screening for cancer. *Epidemiology* 2015;26:362–4.
39 Weiss NS. Commentary: case-control studies of screening for colorectal cancer: tailoring the design and analysis to the specific research question. *Epidemiology* 2013;24:894–7.
40 Eldridge RC, Doubeni CA, Fletcher RH, *et al*. Uncontrolled confounding in studies of screening effectiveness: an example of colonoscopy. *J Med Screen* 2013;20:198–207.
41 Corley DA, Jensen CD, Marks AR, *et al*. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014;370:1298–306.
42 Mehta SJ, Jensen CD, Quinn VP, *et al*. Race/Ethnicity and Adoption of a Population Health Management Approach to Colorectal Cancer Screening in a Community-Based Healthcare System. *J Gen Intern Med* 2016; In press.
43 Winawer SJ, Fletcher RH, Miller L, *et al*. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997;112:594–642.
44 Zauber AG, Winawer SJ, O'Brien MJ, *et al*. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687–96.
45 Knudsen AB, Zauber AG, Rutter CM, *et al*. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US preventive services task force. *JAMA* 2016;315:2595–609.