Screening colonoscopy and risk of incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study

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Abstract

Background—The effectiveness of screening colonoscopy in average-risk adults is uncertain, particularly for right colon cancers.

Objective—Examine the association between screening colonoscopy and incident late-stage colorectal cancer (CRC) risk.

Design—Nested case-control study.

Setting—Four U.S. health plans

Patients—Average-risk adults with 5 years of enrollment in one of the health plans (n=1,039). Cases were 55–85 years old on their diagnosis date (reference date) of stage IIB (late-stage) CRC during 2006–2008. We selected 1–2 controls for each case, matched on birth year, gender, health plan, and prior enrollment duration.

Measurements—Receipt of CRC screening between 3 months and up to 10 years before the reference date, ascertained through medical record audits. We compared cases and controls on receipt of screening colonoscopy or sigmoidoscopy using conditional logistic regressions that accounted for health history, socioeconomic status and other screening exposures.

Results—In analyses restricted to 471 eligible cases and their matched controls (n=509), 13 cases (2.8%) and 46 controls (9.0%) had undergone screening colonoscopy, which corresponded to an adjusted odds ratio (AOR) of 0.30 (95% confidence interval [CI]: 0.15–0.59) for any late-stage CRC, 0.37 (CI: 0.16–0.82) for right colon cancers, and 0.26 (CI: 0.06–1.11) for left-sided colon/rectum cancers. Ninety-two cases (19.5%) and 173 controls (34.0%) underwent screening sigmoidoscopy, corresponding to an AOR of 0.51 (CI: 0.36–0.71) overall, 0.80 (CI: 0.52–1.25) for right colon late-stage cancers, and 0.26 (CI: 0.14–0.49) for left colon/rectum cancers.

Limitations—The small number of screening colonoscopies affected the precision of our estimates.

Conclusions—Screening with colonoscopy in average-risk persons was associated with reduced risk of diagnosis with incident late-stage CRC in both the right colon and left colon/rectum. For sigmoidoscopy, this association was observed for left-sided CRC, but the association for right colon late-stage cancer was not statistically significant.

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INTRODUCTION

Evidence from randomized trials and observational studies has established that screening with sigmoidoscopy(1–4) or fecal occult blood tests (FOBT)(5–7) reduces the risk of colorectal cancer (CRC) incidence and death. In contrast, evidence for the effectiveness of screening colonoscopy is limited. There are no reports from randomized trials in average-risk individuals; and the few observational studies have not evaluated the effects of screening colonoscopy, as compared to unscreened controls, on CRC incidence or mortality. (8, 9) Microsimulation studies suggest that screening with colonoscopy every 10 years, sigmoidoscopy every 5 years with mid-interval FOBT, or annual FOBT alone, could all achieve comparable effects, based on assumptions about colonoscopy effectiveness.(10) Thus, the use of colonoscopy for screening in average-risk individuals remains controversial and its effectiveness in the right colon, the location of nearly 50% of new CRC cases in the US, has been questioned.(11–14)

Despite limited evidence of effectiveness, limited capacity, and higher cost and risk of potential complications relative to other screening tests,(15, 16) colonoscopy is rapidly replacing sigmoidoscopy and FOBT in the U.S.,(17) and its use is increasing in other countries.(18)

We conducted a case-control study to evaluate the association between receipt of screening colonoscopy and the risk of incident late-stage CRC diagnosis in average-risk adults, overall and separately for the right colon and left colon/rectum. Prevention of advanced CRC is an important attribute of effective CRC screening because advanced CRCs have a higher burden of cancer-related illness and mortality risk than early-stage disease.(14, 19) We also examined the effects of screening sigmoidoscopy, given the accumulated evidence of its efficacy, to help gauge the validity of our results for colonoscopy.

METHODS

Design and setting

We conducted a nested case-control study in four U.S. managed care organizations that participate in the HMO Cancer Research Network.(20) The study sites were Group Health Cooperative in western Washington State; Kaiser Permanente in Hawaii; Kaiser Permanente Northwest in Oregon and southern Washington states; and Reliant Medical Group/Fallon Community Health Plan in central Massachusetts. All sites have electronic utilization data on their populations dating back to at least 1995 and have used electronic medical records since 2005 or earlier. Subjects' clinical data were linked to data from state or local tumor registries and to socioeconomic status (SES) information from the U.S. Census Bureau using a unique study identifier. This allowed us to define the study's base population, evaluate the demographic and clinical characteristics of eligible subjects retrospectively for 10 years, and accrue cases and controls from an historical cohort. The Institutional Review Boards at the University of Massachusetts Medical School and participating sites approved the project.

Study subjects

Subjects included in this study were 55–85 years old between January 1, 2006 and December 31, 2008 and enrolled in their health plan for 5 years before their reference date (defined below). Because we wanted to study adults at average-risk for CRC,(21, 22) we excluded persons with a history of total colectomy, inflammatory bowel disease, or CRC in one or more first-degree relatives before age 50 or in two or more second-degree relatives at any age, or other familial CRC syndromes (strong family history).(23, 24)

Case definition and control selection

Diagnosis date and tumor stage of incident CRCs were ascertained from tumor registry data. Cases were subjects with primary late-stage CRC, defined as stage IIB or higher at the time of diagnosis, based on American Joint Commission on Cancer (AJCC) criteria. We included stage IIB tumors because their mortality risk is higher than that of some stage III CRCs.(25) Cancer location was categorized as: 'right' colon if proximal to the splenic flexure; 'left' if in or distal to the splenic flexure; or 'unspecified'. The diagnosis date was set as the reference date for ascertaining test history and selecting controls. Each case was individually matched to 1–2 controls using incidence-density matching(26) according to calendar year of birth (±1 year), gender, health plan, and length of continuous health plan enrollment before the reference date (±1 year). With incidence-density matching, a person's eligibility to be a control for a case is determined on the case's diagnosis date; also, the same person can be selected as a control for more than 1 patient and/or become a case later on in the study. To increase sample size at the health plan with the fewest cases, two controls were selected for each case there only. Four cases and three controls initially included were later excluded

because a strong family history of CRC was found during the medical records audit; 20 additional cases were excluded because of insufficient information for assigning an AJCC cancer stage (Figure 1).

Exposures

Receipt of screening colonoscopy and sigmoidoscopy in the 10-year period before the reference date was ascertained in a multistep data collection process. First, we collected data on CRC tests using automated searches for procedure codes in electronic administrative and clinical databases, as described previously.(27) With these data as a guide, trained auditors collected the dates of, reasons for, and findings of all relevant CRC tests received from medical records using a structured electronic data collection tool.

We applied an algorithm with blinded adjudication of selected tests by a 5-member committee to classify the indication for each test into seven mutually exclusive categories (excluding 'high-risk'): surveillance, 'definite' diagnostic, 'probable' diagnostic, 'possible' diagnostic, 'probable' screening, 'definite' screening, or unknown. We considered a subject to be screened by a particular modality if exposed to a 'definite' or 'probable' screening test. In sensitivity analyses, we used a more restrictive definition of exposure to only 'definite' screening tests because of potential for misclassification in the 'probable' screening group. (28)

We sought to restrict screening exposures to tests received before the onset of late-stage CRC, since tests performed during the preclinical phase of late-stage CRC would not prevent the study outcome.(29) Hereafter, we refer to the period from the time at which a cancer transitioned from early- to late-stage, to the date of clinical diagnosis (reference date) as the 'preclinical period'. We estimated the length of the preclinical period *a priori* to be 3 months. Thus, for our primary analyses, we defined the relevant screening exposure window as a period extending from up to 10 years to 3 months before the reference date (hereafter referred to as 'observation period').

Covariates

Data collection on CRC tests, as described above, included information on double contrast barium enemas (BE), CT colonographies, and FOBTs. None of six CT colonographies identified in the sample were for screening. Receipt of screening FOBT was defined using tests received within 2 years of the reference date, but before the preclinical period, based on evidence of the duration of effectiveness.(5–7) We also collected information on the following ('other covariates'): number of preventive health care visits in the 5-year period before the reference date using Common Procedural Terminology codes as an indicator of health-seeking behavior; baseline modified Charlson comorbidity index(30) categorized as 0, 1, or 2+ (as an indicator of wellness to undergo screening); and SES (in quartiles) measured by the percentage of households in the census block-group with incomes below the 1999 federal poverty level based on the 2000 decennial census.(27, 31) Family history of CRC (relationship, number and diagnosis age) was collected from specific sections in the charts and from clinical notes in the 2-year period before the reference date. We created a dichotomous variable for any family history of CRC documented during the observation period that did not meet the exclusion criteria.

We also considered the following factors in sensitivity analyses: the specialty of the performing provider (categorized as gastroenterologist vs. others); whether the quality of bowel preparation was adequate;(32) and whether a colonoscopy was complete to the cecum.(32, 33) Examinations that found a pathological obstruction were considered complete. Bowel preparation was classified as *adequate* if described as 'good' to 'excellent',

or obscuring <5 mm polyps or <10% of the mucosa; and *inadequate* if described as 'poor', 'fair', 'suboptimal', 'borderline', or not described in the procedure report.(33) We classified a complete colonoscopy with an adequate bowel preparation as a 'high-quality' test.

Statistical analysis

We estimated the association between receipt of screening and any late-stage CRC and, separately, for cancers in the right colon and left colon/rectum, with colonoscopy being the key predictor of interest: sigmoidoscopy was of secondary interest and was estimated in the same models as colonoscopy.

In our primary analyses, screening by either of these modalities was defined as receipt of a 'definite' or 'probable' screening test, without regard to exam quality or provider specialty. The analyses first adjusted for receipt of other screening tests (Model I) and then further adjusted for the other covariates (Model II). We evaluated our choice of a 3-month preclinical period by varying its length from 1 to 15 months.(29) These analyses were performed using conditional logistic regression on matched cases (n=471) and controls (n=509).

In secondary analyses, we assessed the impact of test quality on the effect of colonoscopy using the primary screening definition, but with restriction, separately, to 'high-quality' tests and tests performed by gastroenterologists. We further assessed the sensitivity of our results to various definitions of screening and to the exclusion of persons screened by multiple tests, colonoscopies or sigmoidoscopies of unknown indication, or tests other than either colonoscopy or sigmoidoscopy (endoscopy) alone. First, we used the more restrictive exposure definition of "definite" screening only, and sequentially excluded 311 subjects who had: 'definite' or 'probable' screening by both colonoscopy and sigmoidoscopy (n=11); any 'probable' screening endoscopy (n=38); screening BE (n=15) or FOBT (n=191); surveillance endoscopy (n=23); diagnostic colonoscopy for positive FOBT (n=21); or endoscopies with unknown indication (n=12).

All secondary analyses were performed using unconditional logistic regression, with adjustment for matching variables (age, sex, health plan, and enrollment duration), to retain patients whose matched case or controls had been excluded;(34) conditional logistic regression produced similar, but less precise, results because of exclusion of discordant cases and controls in the estimations. Therefore, we were able to consider all eligible subjects (n=1,012) including the unmatched controls and cases who were not in the primary analyses because of post-match exclusions (Figure 1).

The analyses were performed using SAS software 9.2 (SAS Institute Inc., Cary, NC; 2008) and Stata Statistical Software: Release 12.1 (StataCorp. 2011. College Station, TX: StataCorp LP). Tests with unknown indication (see Appendix A) were included in the reference group in the primary analyses but excluded in secondary analyses. Missing values for SES were imputed. The exclusion of subjects with missing SES data did not change our results. Sensitivity analyses that retained patients with ambiguous tumor stage data found similar results as our main analyses (see Appendix B). Model fit was evaluated using Hosmer-Lemeshow goodness-of-fit tests and was found to be reasonable (*P*-value>0.93).

Role of the Funding Source

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RESULTS

Subject characteristics

A total of 1,039 subjects were selected for the study, of whom 1,012 eligible subjects (474 cases and 538 controls) with an average age of 71.7 years were analyzed for this report (Figure 1). Figure 1 also shows the distribution of cases by tumor location and stage; most cancers were stage III and few were IIB. Of the 474 cases, 53.0% were right colon cancers, 43.4% left CRCs and 17 (3.6%) had no specified locations. Our primary analyses excluded the three cases and 29 controls who did not have matched subjects.

Table 1 shows the characteristics of the primary analytic sample (n=980) by case-control status. The distribution of age, sex, enrollment duration, family history of CRC, and comorbidity index was similar between cases and controls, but controls were more likely to have had preventive health care visits. The majority had been enrolled in their health plan for 10 years before the reference date. During the observation period, 224 (22.9 %) eligible study subjects had at least one colonoscopy, 59 of which were screening; 340 (34.7%) subjects had at least one sigmoidoscopy, 265 of which were screening (Table 2); 11 subjects received screening by both sigmoidoscopy and colonoscopy. Fifty-four (90%) of the screening colonoscopies reached the cecum, of which 37 also had an adequate bowel preparation. These factors did not differ between cases and controls (data not shown).

Association between screening colonoscopy and late-stage CRC

Table 2 shows the results of our primary analyses. Thirteen cases (2.8%) and 46 controls (9.0%) had undergone screening colonoscopy, which corresponded to an odds ratio of 0.32 (95% confidence interval (CI): 0.17–0.61) after adjustment for other screening exposures; further adjustment for other covariates had a relatively small effect on this association (adjusted odds ratio (AOR)=0.30, CI: 0.15–0.59). These estimates were stable to varying the estimated duration of the preclinical period from 1 to 15 months (Figure 2). In analyses stratified by cancer location, the AOR was 0.37 (CI: 0.16–0.82) for the right colon (cases=250, controls=273) and 0.26 (CI: 0.06–1.11) for the left colon/rectum (cases=204, controls=218).

Association between screening sigmoidoscopy and late-stage CRC

We performed analyses on screening sigmoidoscopy similar to those described for, and in the same models as, colonoscopy. In the primary analyses shown in Table 2, 92 (19.5%) cases and 173 (34.0%) controls had screening sigmoidoscopy, which corresponded to an AOR of 0.51 (CI: 0.36–0.71). Receipt of screening sigmoidoscopy was associated with a similar AOR as colonoscopy in the left colon/rectum (AOR=0.26, CI: 0.14–0.49), but only a modest reduction in the right colon (AOR=0.80, CI: 0.52–1.25, p=0.13). Analyses that varied the length of the preclinical period (data not shown) also yielded results similar to our primary analyses.

Sensitivity analysis of the Association between screening colonoscopy and late-stage CRC

In analyses restricted to 'high-quality' colonoscopies (cases=469, controls=520) using the primary definition of 'definite' or 'probable' screening, the AOR was 0.28 (CI: 0.12–0.65) overall, 0.47 (CI: 0.19–1.19) for right colon cancers, and 0.07 (CI: 0.01–0.53) for left CRC. Analyses restricted to tests performed by gastroenterologists (cases=471, controls=532) also yielded similar results as our primary analyses (overall, AOR=0.24, CI: 0.11–0.53; right colon, AOR=0.33, CI: 0.14–0.80; and left colon/rectum, AOR=0.15, CI: 0.04–0.53) (data not shown).

We also examined the association between screening colonoscopy and late-stage CRC risk using the more restrictive definition of screening (Table 3). In analyses of 365 cases and 336 controls, seven (1.9%) cases compared to 16 (4.8%) controls had screening colonoscopy. In unconditional logistic regressions, the effect of screening colonoscopy was unchanged, even after adjustment for all covariates (AOR=0.36, CI: 0.11–0.81). Analyses stratified by tumor location also yielded similar results as our primary analyses (right colon [cases=182]: AOR=0.72, CI: 0.25–2.05; left colon/rectum [cases=169]: AOR=0.09, CI: 0.01–0.72). Analysis of the effect of sigmoidoscopy based on the more restrictive definition of screening yielded similar results as the primary analyses (Table 3).

We also performed conditional logistic regressions to evaluate the effect of non-screening tests on late-stage CRC risk using the following alternative exposure definitions: 1) a single variable for screening and non-screening combined; 2) one variable each for screening and non-screening tests; and 3) separate variables for screening and each of the non-screening test categories. The non-screening tests were surveillance, 'possible' diagnostic and 'probable' diagnostic; screening was based on our primary exposure definition and the comparison group was comprised of 'definite' diagnostic tests, tests with unknown indication, and no colonoscopy or sigmoidoscopy. We found that the effect for screening colonoscopy on overall late-stage CRC risk was similar to the results of our primary analyses, but was stronger than the estimates for the individual non-screening indications (AOR of 0.38 [0.15–1.00] for surveillance, 0.40 [0.18–0.87] for 'possible' diagnostic, and 0.48 [0.18–1.24] for 'probable' diagnostic). The effect of screening was also stronger than the estimate for the non-screening tests considered together as a single variable (AOR: 0.42 [0.24–0.71]) (Appendix B).

DISCUSSION

We found that screening average-risk persons with colonoscopy was associated with a large reduction in risk of diagnosis with new-onset late-stage CRC. Receipt of screening colonoscopy was associated with reduction in risk of diagnosis with incident late-stage CRC diagnosis in both the right colon and left colon/rectum. Our results remained unchanged when we only considered 'high-quality' tests or tests performed by gastroenterologists. Although there are few studies of screening colonoscopy and the prevention of advanced CRC, our results of about a 70% reduction for any late-stage CRC associated with receipt of colonoscopy were similar to those of a German case-control study, published in 2011, which found a 78% and 83% reduction in risk of stage III and IV CRC, respectively, in relation to receipt of 'any' colonoscopy during the 1–10 years prior to the diagnosis date.(9)

Our study also simultaneously examined the association between screening sigmoidoscopy and late-stage CRC risk. Screening sigmoidoscopy receipt was associated with a similar reduction in risk of left-sided late-stage CRC as colonoscopy, but showed only a modest, statistically non-significant effect on risk of right-sided late-stage colon cancers. These results were similar to those of Selby et al.'s case-control study, which observed reduced risk of death from left-sided, but not right-sided, CRC with receipt of screening rigid sigmoidoscopy.(4) Also, each of the two randomized trials that reported on CRC site-specific mortality associated with screening sigmoidoscopy observed about a 50% mortality reduction for distal tumors; for fatal tumors arising in the proximal (right) colon, the relative risks were close to the null – 0.78 (CI 0.45–1.35)(1) and 0.97 (CI 0.77–1.22).(3)

Our study defined cases as persons with advanced CRC at the time of diagnosis. Thus, so long as colonoscopy can detect CRC at an early or precancerous stage, we can expect to observe a case-control difference in receipt of screening, regardless of whether treatment is effective. There is ample evidence that detection and treatment of precancerous colorectal

lesions or early-stage CRCs in the left colon/rectum reduces the risk of death from CRC as reported by both case-control studies(4) and randomized trials of screening sigmoidoscopy. (1–3) In contrast, evidence on the benefits of detection and treatment of CRC precursors or early-stage cancers in the right colon is limited.(13)

A Canadian case-control study by Baxter et al. did not observe reduced mortality for right colon cancers associated with receipt of 'any' colonoscopy.(8) That study did not distinguish screening from diagnostic tests and its analyses focused on tests done well before diagnosis, most of which would be expected to be negative for cancer. Thus, it could be used to gauge the association between a negative exam and the risk of fatal CRC, but not the potential effectiveness of screening colonoscopy in the right colon. Future randomized trials and well-designed observational studies of the effect of screening colonoscopy on CRC mortality in average-risk individuals are needed to understand if the reduced risk of late-stage CRC in the right colon associated with receipt of screening colonoscopy that we observed in this study translates to lowered CRC mortality risk.

Mortality risk reduction is the most direct outcome for gauging efficacy of screening in non-randomized studies. A valid comparison in case-control studies of fatal disease considers all screening tests performed from the estimated time of onset of precursor lesions or cancer until disease is diagnosed.(29) Because the outcome in the present study was late-stage CRC, we considered only those tests that occurred before the estimated onset of late-stage disease. Our results did not change when we used estimates of this preclinical period that varied from 1–15 months.

There are some limitations of our study. Screening colonoscopy was relatively uncommon during our study's observation period, which limited the precision of our risk estimates, particularly for subgroup analyses. Also, because this is an observational study, unmeasured confounders may have affected our results. Familial risk of cancer is not consistently or comprehensively documented in medical records.(35) It is therefore possible that a few subjects with familial syndromes were included in the analyses. However, this is unlikely to affect our results: the proportion with a family history of CRC was similar between cases and control and any misclassification is likely to have biased our results towards the null. Although our analyses adjusted for use of preventive health care, residual confounding by healthy behaviors or other confounders can affect the associations we observed. However, the similarity of our results for sigmoidoscopy to results of prior observational studies and recent clinical trials provides some assurance that our findings are fundamentally sound.(2, 4)

Another limitation of case-control studies of CRC screening effectiveness arises because the screening tests are also used to evaluate symptomatic disease, and the medical records on which this study is based may not reliably distinguish screening from non-screening tests. There may be greater degree of misclassification of diagnostic tests as screening in cases than in controls, thus, biasing the effect of screening towards the null. Our sensitivity analyses assessing the potential impact of such misclassification, including restriction to tests that were classified unambiguously as screening, produced similar effect sizes as in the primary analyses. We also found that non-screening colonoscopies, particularly tests done for non-specific gastrointestinal conditions, had a strong effect on late-stage CRC risk but was slightly weaker than the effect of average-risk screening. Additionally, our analyses on screening sigmoidoscopy produced results that were similar to those from randomized and observational studies.(1–4, 9)

In conclusion, screening for CRC in average-risk persons using colonoscopy was associated with a substantially reduced risk of diagnosis with new-onset primary late-stage CRC,

including a reduced risk for right-sided colon cancers. Receipt of screening sigmoidoscopy was also associated with a substantially reduced risk of incident late-stage disease overall and in the left colon/rectum, but not the right colon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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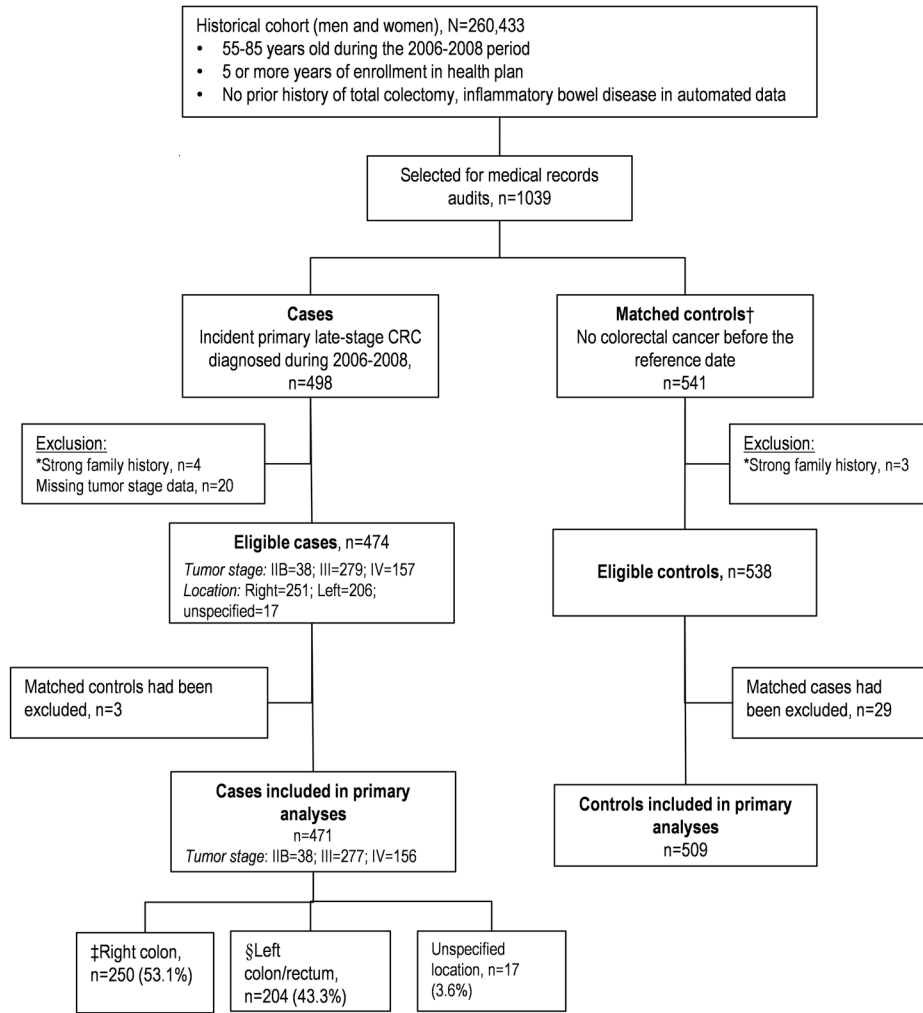
Historical cohort (men and women), N=260,433
- 55-85 years old during the 2006-2008 period
- 5 or more years of enrollment in health plan
- No prior history of total colectomy, inflammatory bowel disease in automated data

Selected for medical records audits, n=1039

Cases
Incident primary late-stage CRC diagnosed during 2006-2008, n=498

Matched controls†
No colorectal cancer before the reference date n=541

Exclusion:
*Strong family history, n=4
Missing tumor stage data, n=20

Exclusion:
*Strong family history, n=3

Eligible cases, n=474
Tumor stage: IIB=38; III=279; IV=157
Location: Right=251; Left=206; unspecified=17

Eligible controls, n=538

Matched controls had been excluded, n=3

Matched cases had been excluded, n=29

Cases included in primary analyses
n=471
Tumor stage: IIB=38; III=277; IV=156

Controls included in primary analyses
n=509

‡Right colon, n=250 (53.1%)

§Left colon/rectum, n=204 (43.3%)

Unspecified location, n=17 (3.6%)

Figure 1.
Selection of Cases and Control for the Study, 2006–2008
*Strong family history refers to colorectal cancer diagnosed in one or more first-degree relatives before age 50 or 2 or more relatives of any age, or other familial syndromes.
†Controls were matched on the reference date to cases according to study site on the calendar year of birth, gender, and length of continuous health plan enrollment (5–10 years) prior to the reference date.
‡Cancer in segments proximal to the splenic flexure were classified as right colon cancer.
§Left colon/rectum refer to the splenic flexure, descending colon, sigmoid and rectum.
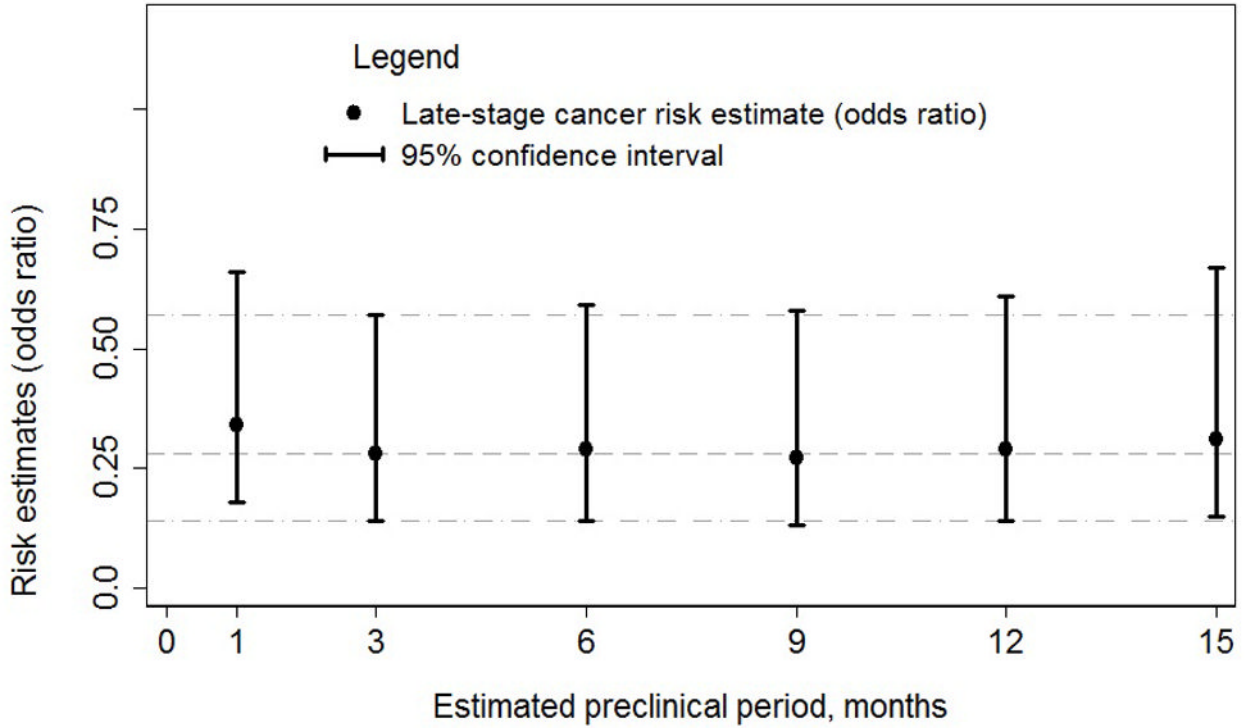
Figure 2.
Sensitivity of the odds ratio estimates for screening colonoscopy on any late-stage colorectal cancer to varying the assumed preclinical period* for excluding tests
Note: Odds ratios and 95% confidence intervals (CI) were obtained with conditional logistic regression with screening defined as exposure to a 'definite or probable' screening test. Analyses were performed on matched case-controls sets using conditional logistic regression which adjusted for receipt of other screening tests (sigmoidoscopy, barium enema and fecal occult blood test), census block-group poverty levels (as a continuous variable), number of preventive health care visits, family history of colorectal cancer, and comorbidity index at baseline. Missing values of poverty level were imputed using predictive mean matching.
*The preclinical period refers to the time from the assumed onset of preclinical late-stage disease to the date of its clinical diagnosis, which we varied from 1 to 15 months.

Table 1

Demographic and clinical characteristics of cases and controls, 2006–2008

Characteristics, %	Cases (n= 471)	Controls (n=509)
Age, yr		
55–64	115 (24.4)	126 (24.8)
65–74	158 (33.5)	169 (33.2)
75–85	198 (42.0)	214 (42.0)
Female	229 (48.6)	254 (49.9)
Poverty levels, quartiles *		
1	97 (21.3)	142 (28.5)
2	129 (28.4)	108 (21.7)
3	122 (26.8)	116 (23.3)
4	107 (23.5)	132 (26.5)
Poverty level, % (median [interquartile range])	6.52 (3.77–10.06)	6.37 (3.13–10.87)
Length of enrollment with health plan before reference date, yr		
5.0–7.4	69 (14.6)	88 (17.3)
7.5–9.9	47 (10.0)	64 (12.6)
>10	355 (75.4)	357 (70.1)
Study site		
A	95 (20.2)	95 (18.7)
B	189 (40.1)	189 (37.1)
C	38 (8.1)	76 (14.9)
D	149 (31.6)	149 (29.3)
Number of preventive outpatient health care visits within 5 years of reference date		
0	215 (45.6)	177 (34.8)
1	127 (27.0)	113 (22.2)
2–3	89 (18.9)	137 (26.9)
4+	40 (8.5)	82 (16.1)
Family history of colorectal cancer (CRC) [†]	39 (8.3)	45 (8.8)
Charlson comorbidity index at baseline[‡]		
0	393 (83.4)	407 (80.0)
1	56 (11.9)	79 (15.5)
2+	22 (4.7)	23 (4.5)
Had a healthcare visit during the 2-year period at baseline[‡]	381 (80.9)	440 (86.4)

*
Households below 1999 federal poverty levels within the block-group from 2000 decennial census measures. Analysis was based on 455 case patients and 498 control patients with non-missing data. Higher quartiles correspond to higher levels of household poverty in the census block-group

[†]
This variable refers to family history that did not meet the exclusion – those with a history of colorectal cancer diagnosed in any first degree relative before age 50 or 2 or more relatives of any age, or other familial syndromes.

[‡]
Baseline refers to the 2-year period at the beginning of each subject's observation period.

Table 2

Association between receipt of screening colonoscopy or sigmoidoscopy and late-stage colorectal cancers, 2006–2008: Matched Analysis

Receipt of screening colonoscopy or sigmoidoscopy according to colon location	Sample size (n) and % by cases and controls		Odds ratios and 95% confidence intervals	
	Cases	Controls	Model I*	Model II*†
Colonoscopy				
All late-stage colorectal cancers				
Screening colonoscopy	13 (2.8)	46 (9.0)	0.32 (0.17–0.61)	0.30 (0.15–0.59)
No screening colonoscopy	458 (97.2)	463 (91.0)	—	—
Right colon late-stage cancers				
Screening colonoscopy	10 (4.0)	29 (10.6)	0.40 (0.19–0.86)	0.37 (0.16–0.82)
No screening colonoscopy	240 (96.0)	244 (89.4)	—	—
Left colon/rectum late-stage cancers				
Screening colonoscopy	3 (1.5)	14 (6.4)	0.33 (0.09–1.22)	0.26 (0.06–1.11)
No screening colonoscopy	201 (98.5)	204 (93.6)	—	—
Sigmoidoscopy				
All late-stage colorectal cancers				
Screening sigmoidoscopy	92 (19.5)	173 (34.0)	0.46 (0.33–0.63)	0.51 (0.36–0.71)
No screening sigmoidoscopy	379 (81.5)	336 (66.0)	—	—
Right colon late-stage cancers				
Screening sigmoidoscopy	68 (27.2)	89 (32.6)	0.72 (0.48–1.08)	0.80 (0.52–1.25)
No screening sigmoidoscopy	182 (72.8)	184 (67.4)	—	—
Left colon/rectum late-stage cancers				
Screening sigmoidoscopy	23 (11.3)	78 (35.8)	0.24 (0.13–0.42)	0.26 (0.14–0.49)
No screening sigmoidoscopy	181 (88.7)	140 (64.2)	—	—

Note: Screening was defined as exposure to a 'definite or probable' screening test. Analyses were performed on matched case-controls sets using conditional logistic regression. Twelve subjects had screening by both colonoscopy and sigmoidoscopy; 16 had 'definite' screening by barium enema and 191 by fecal occult blood test (FOBT); 18 subjects had both FOBT and colonoscopy, and 73 had both FOBT and sigmoidoscopy. Seventeen cases and 18 controls had an unknown location of cancer.

*
Model I was estimated with indicator variables for colonoscopy and sigmoidoscopy and receipt of 'definite' screening barium enema and FOBT.

†Model II was further adjusted for census block-group poverty levels (as a continuous variable), number of preventive health care visits, family history of colorectal cancer, and comorbidity index at baseline. Missing values of poverty level were imputed using predictive mean matching.

Table 3

Association between use of 'definite' screening colonoscopy or sigmoidoscopy and late-stage colorectal cancers, 2006–2008: Unmatched Analysis

Receipt of screening colonoscopy or sigmoidoscopy according to colon location	Sample size (n) and % by cases and controls		Odds ratios and 95% confidence intervals	
	Cases	Controls[*]	Model I[†]	Model II[‡]
All late-stage colorectal cancers				
Screening colonoscopy	7 (1.9)	16(4.8)	0.36 (0.14–0.91)	0.36 (0.14–0.95)
Screening sigmoidoscopy	62 (17.0)	96 (28.6)	0.47 (0.33–0.68)	0.51 (0.35–0.75)
No screening	296 (81.1)	224 (66.7)	—	—
Right colon late-stage cancers				
Screening colonoscopy	6 (3.3)	16 (4.8)	0.75 (0.28–2.04)	0.72 (0.25–2.05)
Screening sigmoidoscopy	48 (26.4)	96 (28.6)	0.89 (0.58–1.35)	0.94 (0.60–1.45)
No screening	128 (70.3)	224 (66.7)	—	—
Left colon/rectum late-stage cancers				
Screening colonoscopy	1 (0.6)	16 (4.8)	0.08 (0.01–0.65)	0.09 (0.01–0.72)
Screening sigmoidoscopy	13 (7.7)	96 (28.6)	0.18 (0.10–0.33)	0.20 (0.11–0.38)
No screening	155 (91.7)	224 (66.7)	—	—

Note: Screening was defined as exposure to a 'definitely' screening test only, and excluded cases and controls who had: screening by both colonoscopy and sigmoidoscopy; or screening by barium enema and fecal occult blood test (FOBT); surveillance colonoscopy or sigmoidoscopy; diagnostic colonoscopy for positive FOBT; or unknown colonoscopy or sigmoidoscopy indications. Fourteen cases with unknown cancer location were not included in the right or left-sided analyses.

[*] The analyses in this table used the same sample of controls; we used unconditional logistic regressions in order to retain all eligible subjects, including those whose matched controls or case had been excluded.

[†] In Model I, odds ratios and confidence intervals were obtained using unconditional logistic regression that adjusted for matching variables (study site, age, sex, and health plan enrollment duration).

[‡] Model II was further adjusted for census block-group poverty levels (as a continuous variable), number of preventive health care visits, family history of colorectal cancer, and comorbidity index at baseline. Missing values of poverty level were imputed using predictive mean matching.