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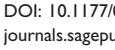

The effect of using fecal testing after a negative sigmoidoscopy on the risk of death from colorectal cancer

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Abstract

Objective: To examine whether receiving a fecal occult blood test after a negative sigmoidoscopy reduced mortality from colorectal cancer.

Methods: We used a nested case–control design with incidence-density matching in historical cohorts of 1,877,740 50–90-year-old persons during 2006–2012, in an integrated health-system setting. We selected 1758 average risk patients who died from colorectal cancer and 3503 matched colorectal cancer-free persons. Colorectal cancer-specific death was ascertained from cancer and mortality registries. Screening histories were determined from electronic and chart–audit clinical data in the 5- to 10-year period prior to the reference date. We evaluated receipt of subsequent fecal occult blood test within five years of the reference date among patients with negative sigmoidoscopy two to six years before the reference date.

Results: Of the 5261 patients, 831 patients (204 colorectal cancer deaths/627 controls) had either negative sigmoidoscopy only ($n = 592$) or negative sigmoidoscopy with subsequent screening fecal occult blood test ($n = 239$). Fifty-six (27.5%) of the 204 patients dying of colorectal cancer and 183 (29.2%) of the 627 colorectal cancer-free patients received fecal occult blood test following a negative sigmoidoscopy. Conditional regressions found no significant association between fecal occult blood test receipt and colorectal cancer death risk, overall (adjusted odds ratio = 0.93, confidence interval: 0.65–1.33), or for right (odds ratio = 1.02, confidence interval: 0.65–1.60) or left-colon/rectum (odds ratio = 0.77, confidence interval: 0.39–1.52) cancers. Similar results were obtained in sensitivity analyses with alternative exposure ascertainment windows or timing of fecal occult blood test.

Conclusions: Our results suggest that receipt of at least one fecal occult blood test during the several years after a negative sigmoidoscopy did not substantially reduce mortality from colorectal cancer.

Keywords

Early detection of cancer, Endoscopy, Gastrointestinal, occult blood, Colorectal Neoplasms, comparative effectiveness, historical cohort, case control study

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death,[1,2] and screening is an effective strategy for reducing the risk of dying from CRC.[3–7] There is a general belief that combining screening tests would augment effectiveness by overcoming structural or functional limitations. Thus, for many years, the US Preventive Services Task Force (USPSTF) and other guidelines have included a recommendation to use sigmoidoscopy in combination with fecal tests.[8] This strategy involves fecal testing following a negative sigmoidoscopy based on the belief that fecal occult blood test (FOBT) screening could help overcome the inability of sigmoidoscopy to visualize the right colon. Randomized controlled trials (RCTs) have shown that guaiac-FOBT and sigmoidoscopy are each effective at reducing the risk of CRC death,[9–13] except in older women.[14] The only existing study comparing people assigned to sigmoidoscopy alone versus sigmoidoscopy plus one-time fecal testing did not find a statistically significant difference in CRC mortality between the two groups.[13]

Because FOBT is less effective in detecting right-colon than left colon/rectal cancers,[15–18] it may not confer the added theoretical benefit assumed by modeling studies and guidelines.[3] However, fecal testing during the years after a negative sigmoidoscopy has the potential to detect missed or interval tumors within the reach of the sigmoidoscope. Whether such a strategy further reduces CRC mortality through improved colorectal neoplasia detection in the right-colon and/or left-colon/rectum has not been evaluated previously.

In this study, we examined whether, in patients at average risk who have had a negative sigmoidoscopy, receiving FOBT was associated with a reduced risk of CRC death relative to no subsequent screening. Although sigmoidoscopy use has declined in the US, interest remains in its use in screening programs in other countries and fecal testing alone is a commonly used strategy. During the years under study, the USPSTF recommended using sigmoidoscopy every five years alone or with a mid-interval FOBT.[8] That, along with the unique integrated health systems data resources of our study setting, allowed us to evaluate the effect of a strategy of FOBT use after a negative sigmoidoscopy.

Methods

Study design and setting

This was a retrospective study conducted among members of Kaiser Permanente Northern (KPNC) and Southern California (KPSC) and using a nested case–control design within a historical cohort. KPNC and KPSC are integrated health systems with stable cohorts from a large and diverse population base that enables longitudinal cancer screening outcomes studies. Prior to 2006, the health systems promoted flexible sigmoidoscopy with or without FOBT before introducing screening outreach programs using fecal immunochemical tests (FITs) and screening colonoscopy by referral during 2006–2007.[19] Institutional review boards at KPNC and KPSC approved the study.

Study population

The underlying study population was adults with $\geqslant 5$ years of enrollment prior to a reference date, defined as the diagnosis date for patients who died of CRC that was also used for controls (Figure 1). Case patients were 55–90 years old on the date of CRC death as the underlying cause between 1 January 2006 and 31 December 2012 (1 January 2011 to 31 December 2012 in KPSC), identified using tumor registry and state mortality files.[20–22] The reference date was then used to individually match each patient dying from CRC during that time period to eight randomly selected CRC-free patients (about two controls per case were selected for chart audit with replacement when ineligible) and to ascertain eligibility and exposure status (Figure 2).[20–22] Matching to CRC-free patients was based on birth year (± 1 year), sex, health plan enrollment duration prior to diagnosis (± 1 year), and medical center/geographic region. The median diagnosis-to-death interval was two years (interquartile [IQR] one to three years) and the enrollment duration was nine years (IQR = 7–11 years). We used an incidence–density matching approach to obtain a representative sample of patients in the source population at risk for CRC death. Because USPSTF recommendations are for people at average-risk for CRC, we excluded those with documented inflammatory bowel disease, colectomy, or gastrointestinal cancer, or who had a strong family history of CRC recorded prior to the reference date during chart audits.[22–24]

Data sources

Electronic databases on medical encounters provided information on healthcare utilization, diagnoses and procedures, treating physician specialty, and the healthcare facilities. Administrative databases provided information on patients' birth date, sex, race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, or other), health plan enrollment information, and place of residence. Socioeconomic status (SES) information at the census tract was obtained from 2000 census data.[25,26] Cancer diagnosis date and tumor location were obtained from Surveillance, Epidemiology and End Results program-affiliated tumor registries.[24] With these data, we evaluated patients' clinical histories, including the receipt of CRC tests, and whether tests were performed for screening or for diagnostic work-up of cancer-related symptoms and/or signs.[22]

Data collection on CRC testing

Data regarding sigmoidoscopy receipt, stool tests, and other CRC screening tests were collected during the

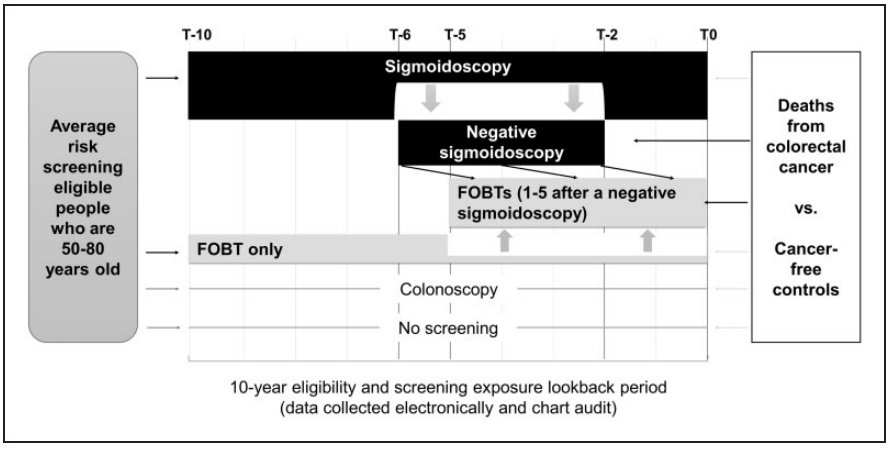

Figure 1. Design of the study. *Note*: T0 is the reference date. The primary exposure definitions were: (1) negative sigmoidoscopies in the two- to six-year period prior to the reference date and (2) FOBT/FIT in the zero- to five-year period prior to the reference date. Alternative definitions used in sensitivity analyses were: (1) negative sigmoidoscopy in the two to five years before the reference date; (2) FOBT/FIT in the zero- to two-year period before the reference date; and (3) exclusion of sigmoidoscopies with non-screening indications or preceded by an FOBT.

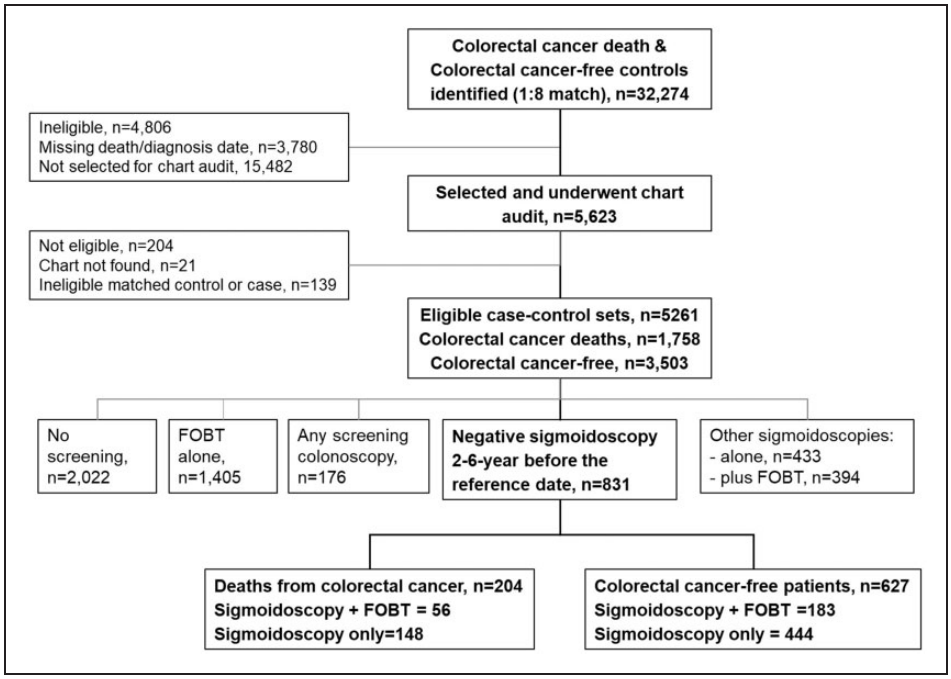

Figure 2. Flow diagram for the study. *Note*: The first box represents 3586 cases and 28,688 controls (total = 32,274 case–control sets with a 1:8 match). Of those, the 3586 cases and 2 controls were initially selected for chart audits and controls found to be ineligible were replaced. Not all cases were eligible. Other sigmoidoscopies refer to sigmoidoscopies that were positive or occurred outside the two- to six-year window (i.e., patients with sigmoidoscopies that were >6 years prior or <2 years to the reference date).
FOBT: fecal occult blood test.

10-year period before the reference date (Figure 1). Trained auditors collected the dates, findings, and reasons for all relevant tests from the medical records, including the quality of the bowel preparation, completeness, results, and follow-up recommendations of sigmoidoscopies and colonoscopies.[27,28] Electronic data were obtained on medical diagnoses, imaging studies, results of sigmoidoscopies and colonoscopies, and laboratory studies, such as FOBT/FIT and iron deficiency tests to assign test indication using a multistep process including adjudication of selected tests.[20–22] The indication for each test was categorized as screening, diagnostic, surveillance, or

unknown.[21,22] The indication for FOBT or FIT was classified as screening if performed as part of the screening program, at home, or for health maintenance; FOBT performed during other office visits, during in-patient encounters, or for documented diagnostic indication were classified as non-screening.

Definition of negative sigmoidoscopy and exposure to FOBT/FIT

A negative sigmoidoscopy was defined as one that reached at least 40 cm of insertion, had adequate bowel preparation, found no abnormalities or only found a polyp of $\leqslant$6 mm, and noted a routine follow-up or follow-up of $\geqslant$5 years. Based on USPSTF recommendations during the period under study,[8] and our base assumption of the FOBT detectable preclinical period as described later,[29] the primary subpopulation of interest for this analysis were people with negative sigmoidoscopy in the two to six years prior to the reference date (Figure 2). We then created a variable for receipt of FOBT (our primary exposure) after such negative sigmoidoscopies. The two-year cutoff also avoids bias related to differential clustering of negative sigmoidoscopies occurring close to the reference date in the sigmoidoscopy-only group.

Covariates

We assessed SES from the percentage of people $\geqslant$25 years in the subject's census tract with less than a high school diploma.[25,26] We evaluated measures of health-seeking behavior to address potential confounding that was not addressed by matching. We enumerated outpatient encounters with a primary care provider (PCP) in the five years prior to the reference date, categorized as 0–2 vs. 3+ visits as a proxy for health-seeking behavior. We derived the Charlson comorbidity score[30] (0, 1, or $\geqslant$2), as a proxy of wellness to undergo screening. Tumors located proximal to the splenic flexure were categorized as "right-colon," others as "left-colon/rectum" or "unspecified."

Statistical analysis

We estimated whether screening FOBT further reduced the risk of CRC death in people with a negative sigmoidoscopy by using conditional logistic regressions to generate adjusted odd ratios (OR) and 95% confidence intervals (CI). Incidence–density matching generates a representative sample of the cohort and given that CRC mortality is a rare condition, the odds ratios reasonably approximate the relative risks.[31]

The analyses compared those who died of CRC with control patients on receipt of FOBT after a negative sigmoidoscopy, overall and stratified on tumor location. We also evaluated mortality risk associated with negative sigmoidoscopy with and without a subsequent FOBT relative to no screening as context for assessing the effect of the added FOBT. The models adjusted for SES, race/ethnicity, family history of CRC, and comorbidity score. We did not adjust for PCP visits because of potential for collinearity. To minimize loss of precision or information, we used dummy variables for screening exposures other than negative sigmoidoscopy (i.e., screening colonoscopy and FOBT alone, see Figure 1) in the models, which also allowed for assessment of the magnitude of reduced risk of CRC death associated with a negative sigmoidoscopy compared with no screening.

Case–control studies of the effect of screening in relation to cancer mortality compare controls with fatal cases on receipt of screening in the period prior to diagnosis during which the screening test has the potential to identify preclinical disease or precursors.[20,29] For FOBT we considered that period in our base assumption as two years, but no more than five years. Thus, our primary analysis examined receipt of FOBT during up to five years prior to reference date by patients who had a negative sigmoidoscopy in the two- to six-year period (Figure 1).

We performed several sensitivity analyses, including the influence of differing ascertainment windows in relation to the reference date for negative sigmoidoscopy (two to five years) and FOBT exposures (within two years). Second, due to the possibility that prior testing history may be correlated with risk of fatal CRC, we assess the influence of analysis that did not consider patients with non-screening negative sigmoidoscopies or with FOBT at any time prior to the index sigmoidoscopy. All analyses were performed using the Stata Statistical Software: Release 15.1 (StataCorp. 1985–2015. College Station, TX: StataCorp LP).

Results

Patient characteristics

From an underlying population of 1,877,740, we identified 1759 eligible patients who died of CRC during 2006–2012 and 3635 cancer-free eligible people, of whom 5261 (1758 deaths with 3503 matched controls) were considered for the analyses. About 37.3% of the documented FOBT types were FIT. Figure 2 shows the flow of the ascertainment of patients for the analyses and exposure status. A total of 831 persons who had negative sigmoidoscopy in the two- to six-year period prior to reference date were evaluated for the primary analysis. Table 1 shows the characteristics of the patients who had sigmoidoscopy only ($n = 592$) or with FOBT ($n = 239$) in the observation window. A higher proportion of patients receiving sigmoidoscopy-only were aged 50–64, women, non-Hispanic White, enrolled <10 years, or lived in census tracts with higher percentage of people with less than a high school diploma.

Screening FOBT after a negative screening sigmoidoscopy

Of the 831 patients with negative sigmoidoscopy, 204 were case patients who died from CRC, of whom 56 (27.5%)

Table 1. Demographic and clinical characteristics of patients who died from colorectal cancer and matched controls according to receipt of fecal occult blood test (FOBT) after a negative sigmoidoscopy.

Characteristics, *n* (%)	Sigmoidoscopy alone, *n* = 592	Sigmoidoscopy with at least one FOBT, *n* = 239	Total, *n* = 831	Overall sample, *n* = 5261
Age at diagnosis, y[a]				
50–64	218 (36.8)	72 (30.1)	290 (34.9)	1783 (33.9)
65–74	180 (30.4)	93 (38.9)	273 (32.9)	1513 (28.8)
75–90	194 (32.8)	74 (31.0)	268 (32.3)	1965 (37.4)
Women	279 (47.1)	104 (43.5)	383 (46.1)	2599 (49.4)
Race ethnicity				
Non-Hispanic White	413 (69.8)	150 (62.8)	563 (67.7)	3523 (67.0)
Non-Hispanic Black	49 (8.3)	18 (7.5)	67 (8.1)	458 (8.7)
Hispanic	64 (10.8)	28 (11.7)	92 (11.1)	545 (10.4)
Asian/Pacific Islander	50 (8.4)	38 (15.9)	88 (10.6)	558 (10.6)
Other/Unknown	16 (2.7)	5 (2.1)	21 (2.5)	177 (3.4)
Health plan enrollment, y				
5.0–7.4	139 (23.5)	38 (15.9)	177 (21.3)	909 (17.3)
7.5–9.9	116 (19.6)	32 (13.4)	148 (17.8)	956 (18.2)
⩾10	337 (56.9)	169 (70.7)	506 (60.9)	3396 (64.6)
Percent with <high school diploma, quartiles[b]				
1	128 (21.6)	70 (29.3)	198 (23.8)	1262 (24.0)
2	160 (27.0)	53 (22.2)	213 (25.6)	1311 (24.9)
3	149 (25.2)	61 (25.5)	210 (25.3)	1278 (24.3)
4	146 (24.7)	50 (20.9)	196 (23.6)	1314 (25.0)
Missing	9 (1.5)	5 (2.1)	14 (1.7)	96 (1.8)
Primary care visits[c]				
0–2	12 (2.0)	3 (1.3)	15 (1.8)	458 (8.7)
3+	580 (98.0)	236 (98.7)	816 (98.2)	4803 (91.3)
Charlson score, baseline				
0	444 (75.0)	176 (73.6)	620 (74.6)	3859 (73.4)
1	91 (15.4)	38 (15.9)	129 (15.5)	761 (14.5)
2+	57 (9.6)	25 (10.5)	82 (9.9)	641 (12.2)

[a]Shown is the age at time of diagnosis, the date used to assess exposure and covariate information.
[b]Data were obtained from the 2000 US Census data at the tract level.
[c]Defined based on outpatient clinical visits to family medicine, gerontology/geriatrics, general internal medicine, or obstetrics/gynecology.

had received follow-on FOBT. Of the 627 matched CRC-free control patients, 183 (29.2%) received sigmoidoscopy plus FOBT (see Figure 2). In multivariable adjusted conditional logistic models, a negative sigmoidoscopy without subsequent FOBT was associated with close to 50% lower risk of death from CRC (relative to non-screening). The effect was primarily due to left-colon/rectum mortality reduction (nearly 80%) with null effects in the right colon (see Supplementary Table 1). The effects were similar in the analysis on receipt of subsequent FOBT in the years following the negative sigmoidoscopy. The results were relatively stable in analyses using ascertainment windows of zero to two years for FOBT and/or two to five years for sigmoidoscopy and in analyses restricted to screening examinations.

In multivariable conditional regression analyses compared with negative sigmoidoscopy alone, there was no association between receipt of screening FOBT after the negative sigmoidoscopy and the risk of death from CRC. The estimated OR for the association between receipt of FOBT after negative sigmoidoscopy and risk of CRC death was 0.93 (CI: 0.65–1.33) compared with negative sigmoidoscopy with no subsequent FOBT (see Table 2). In analysis stratified on location of the cancer, there was no significant association between FOBT receipt after negative sigmoidoscopy and the risk of death from right colon cancer relative to negative sigmoidoscopy without further FOBT testing (OR = 1.02, CI: 0.65–1.60). There was also no statistically significant association between FOBT receipt and risk of death from left-colon/rectal cancer (OR = 0.77, CI: 0.39–1.52).

Sensitivity analyses restricted to negative sigmoidoscopy examinations done for a screening indication (148 cases and 467 controls) found similar results (overall: OR = 1.00, CI: 0.66–1.52; right-colon OR = 1.23, CI: 0.73, 2.07; left colon/rectum OR = 0.67, CI: 0.30, 1.51) as shown in Table 2. Patients with a history of a negative FOBT prior to the index sigmoidoscopy may have a

Table 2. Risk of colorectal cancer death in association with use of at least one screening fecal occult blood test after a negative sigmoidoscopy, overall and by tumor location, including sensitivity analysis.

	Analysis with *any* negative sigmoidoscopy			Analysis with negative *screening* sigmoidoscopy		
Tumor location and FOBT exposure status	Patients dying of CRC	CRC-free patients	Adjusted odds ratio (CI)	Patients dying of CRC	CRC-free patients	Adjusted odds ratio (CI)
Primary analysis						
Overall						
Sigmoidoscopy only	148	444	1.00	107	335	1.00
Sigmoidoscopy + FOBT	56	183	0.93 (0.65,1.33)	42	132	1.00 (0.66,1.52)
Right						
Sigmoidoscopy only	102	218	1.00	70	173	1.00
Sigmoidoscopy + FOBT	42	93	1.02 (0.65,1.60)	32	69	1.23 (0.73,2.07)
Left						
Sigmoidoscopy only	41	217	1.00	32	155	1.00
Sigmoidoscopy + FOBT	13	87	0.77 (0.39,1.52)	9	60	0.67 (0.30,1.51)
Sensitivity analysis excluding patients with any FOBT prior to sigmoidoscopy						
Overall						
Sigmoidoscopy only	118	338	1.00	77	229	1.00
Sigmoidoscopy + FOBT	35	110	0.93 (0.60,1.44)	26	74	1.08 (0.64,1.82)
Right						
Sigmoidoscopy only	82	161	1.00	50	116	1.00
Sigmoidoscopy + FOBT	27	55	1.05 (0.61,1.80)	21	40	1.34 (0.71,2.54)
Left						
Sigmoidoscopy only	31	171	1.00	22	109	1.00
Sigmoidoscopy + FOBT	7	52	0.78 (0.31,1.91)	4	31	0.66 (0.20,2.12)

FOBT: fecal occult blood test, including guaiac-based and immunochemical tests.
Models adjusted for enrollment duration, race/ethnicity, percentage of people 25+ years in the census tract with at least a high school diploma, comorbidity score, number of primary care visits, and colorectal cancer CRC family history. Screening history was ascertained in the 5- to 10-year period prior to the reference date: patients were required to have at least 5 years of enrollment in the health plan to be selected for the study.

lower risk of CRC than those without such history. Sensitivity analyses that excluded sigmoidoscopies preceded by FOBT at any time during the 10-year period (21 cases and 72 controls in "any sigmoidoscopy" or 16 cases and 58 controls in "screening sigmoidoscopy" analyses) found similar results as our primary analyses (Table 2). To assess the sensitivity of our results to time periods of exposure to the CRC tests used in our primary analyses, we examined patients with negative sigmoidoscopy ascertained during the two to five years or FOBT during the two years, both prior to the reference date (Table 3), which did not change our findings.

Discussion

In this population-based study, we found that receiving FOBT in the years following a negative screening sigmoidoscopy was not associated with any additional lowering of the risk of dying from CRC, whether in the right colon or left colon/rectum. These findings are in line with emerging evidence that FOBT, like sigmoidoscopy, is more effective in detecting lesions in the left colon/rectum than in the right colon.[17] The results suggest that using FOBT after a negative screening sigmoidoscopy, and thus a strategy combining two tests with similarly limited effectiveness in the right colon, may not substantially augment overall effectiveness or overcome the structural limitation of sigmoidoscopy in only visualizing the distal colon/rectum.

Fecal testing (annually or biennially) and sigmoidoscopy screening, given as individual tests, have each been shown to reduce CRC mortality risk.[9–13] In RCTs, sigmoidoscopy-only reduced CRC mortality risk by 22–35% depending on the age of participants and the effectiveness was mostly confined to the left colon.[10–14] Meta-analysis of four RCTs of guaiac FOBT in the US and Europe reported a 16% CRC mortality risk reduction in intention-to-treat analysis and 25% in participants who completed at least one screening round out of the 2–11 rounds that were prescribed in the FOBT trials.[9] The FOBT trials did not provide results on effectiveness for right colon cancers. However, in a study of cancers in a FIT screening program by Selby and colleagues, the mean stool hemoglobin concentration was 60.0 μg/g for left colon cancers and 12.4 μg/g in right colon cancers, the latter being below the FIT positivity threshold of 20.0 μg/g in the United States.[18] A trial that randomized people on invitation to no screening, screening sigmoidoscopy alone, or sigmoidoscopy and one-time FIT screening observed a reduction in mortality from CRC in the combined screening arms.[13] Although the effect size was somewhat larger in the group that received both FIT and sigmoidoscopy (hazard ratio 0.62, CI 0.42–0.90) than in the sigmoidoscopy-only group (hazard ratio 0.84, CI 0.61–

Table 3. Sensitivity analysis on risk of colorectal cancer death in relation to use of at least one screening fecal occult blood test after a negative sigmoidoscopy for various ranges of exposure, overall and by tumor location.

	Sigmoidoscopy 2–5 y and FOBT 0–2 y			Sigmoidoscopy 2–5 y and FOBT 0–5 y			Sigmoidoscopy 2–6 y and FOBT 0–2 y		
Exposure type/location	CRC deaths	CRC-free	Odds ratio (CI)	CRC deaths	CRC-free	Odds ratio (CI)	CRC deaths	CRC-free	Odds ratio (CI)
Overall									
Sigmoidoscopy only	112	360	1.00	105	332	1.00	159	495	1.00
Sigmoidoscopy + FOBT	24	76	1.00 (0.59,1.67)	31	104	0.94(0.59,1.49)	45	132	1.10 (0.74,1.62)
Right									
Sigmoidoscopy only	79	183	1.00	75	169	1.00	109	244	1.00
Sigmoidoscopy + FOBT	18	40	1.01 (0.54,1.91)	22	54	0.94 (0.53,1.67)	35	67	1.26 (0.78,2.04)
Left									
Sigmoidoscopy only	29	171	1.00	26	157	1.00	45	242	1.00
Sigmoidoscopy + FOBT	6	34	0.98 (0.36,2.64)	9	48	1.01 (0.44,2.36)	9	62	0.78 (0.35,1.71)

FOBT: fecal occult blood test, including guaiac-based and immunochemical tests.
Models adjusted for enrollment duration, race/ethnicity, percentage of people 25+ years in the census tract with at least a high school diploma, comorbidity score, number of primary care visits, and colorectal cancer family history.

1.17), the difference was not statistically significant.[13] Those results suggest that combining fecal testing with sigmoidoscopy may not substantially improve health outcomes. For practical purposes, FOBT would only be offered to patients with negative sigmoidoscopy, but the effectiveness of that strategy on the risk of death from CRC had not been assessed previously.

Our study has several strengths, including a large, diverse, and stable underlying community-based population, detailed clinical data, and the use of incidence–density matching to select control patients from the same population as patients who died from CRC within geographic areas to minimize selection bias. We linked patients to relevant clinical data and databases to enhance the accuracy of outcome and exposure ascertainment.[21] We were able to measure test indications using clinical data from several sources and a pretested algorithm and adjudication by clinicians to assign test indications. We also had information on the findings and completeness of each test. Finally, we accounted for SES and other potential confounders, by exclusion, matching, stratification and adjustment.

The study also has potential limitations, including an inability to evaluate whether a sustained screening program with multiple annual or biennial fecal testing after sigmoidoscopy (as recommended in recent screening guidelines) reduces cancer mortality by detecting interval tumors. The study may not have been large enough to reliably identify modest reductions in mortality from using $\geqslant 1$ FOBT after a negative sigmoidoscopy, which was reflected in somewhat wide CIs; thus future larger studies may be needed. It is possible that our results could partly be due to residual confounding or selection bias such as a spurious enhancement of the effect of FOBT if persons receiving it are at lower disease risk. Also, FOBT's effect could diminish if those receiving it are at higher risk of CRC death. However, the near-absence of a difference between the two strategies and the consistency of the results across the various scenarios evaluated argues against bias in either direction. Our previous analyses of the effectiveness of screening endoscopy showed that the magnitude of potential confounding by unmeasured factors such as lifestyle factors is unlikely to substantially affect our results.[22] Each patient's reason for completing FOBT could not be definitively verified through manual review of the records; tests done in response to signs and symptoms and incorrectly categorized as being screening would result in falsely low estimates of the impact of FOBT screening on CRC mortality.[22,29] However, the exclusion of tests done for a stated diagnostic purposes reduced the effect of any potential misclassification and effect sizes were similar across a number of sensitivity analyses.

In conclusion, our finding that the addition of at least one FOBT within several years after sigmoidoscopy does not substantially enhance its effectiveness does not provide support for combining screening tests with similar limitations. This study's results suggest that FOBT may not overcome the structural limitation of endoscopic examination that is limited to the left colon and thus combining sigmoidoscopy with FOBT could increase complexity of screening delivery without meaningfully improving effectiveness. These may become increasingly important as the location of new CRC cases shifts to a higher proportion in the right colon, particularly in populations such as older women.[32] Further studies are needed on whether, after a negative sigmoidoscopy, screening primarily with more sensitive FIT[33] or a strategy of repeated fecal testing enhances screening outcomes by improving detection of potentially fatal lesions that were missed, or developed de novo.

Author contributions

Study concept and design: CAD, DAC, JKL, CDJ, JES, NRG, TRL, WKZ, CAS, JVW, SJM, KS, VPDR, AGZ, RHF, NSW
Acquisition of data: CAD, DAC, CDJ, JES, NRG, TRL, WKZ
Analysis and interpretation of data: CAD, DAC, CDJ, CAS
Drafting the manuscript: CAD

Critical revision of the manuscript: CAD, DAC, JKL, CDJ, JES, NRG, TRL, WKZ, CAS, JVW, SJM, KS, VPDR, AGZ, RHF, NSW
Statistical analysis: CAD, CAS, AGZ
Obtained funding: CAD, DAC, CDJ, TRL, AGZ
Study supervision: CAD, DAC, CDJ
Dr. Doubeni and Ms. Saia had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' note

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Supplemental material

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