Cancer Causes and Control (2005) 16:865–875
DOI 10.1007/s10552-005-2370-3
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Colorectal screening is associated with reduced colorectal cancer risk: a case–control study within the population-based Ontario Familial Colorectal Cancer Registry★

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Received 2 December 2004; accepted in revised form 16 February 2005

Key words: case–control study, colorectal cancer, incidence, prevention, screening.

Abstract

Objective: This is the first study to evaluate the association between colonic screening and colorectal cancer risk among Canadians.
Methods: A case–control study was conducted. Cases were diagnosed with cancer of the colorectum, between 1997 and 2000, aged 20 to 74 years, identified through the population-based Ontario Cancer Registry and recruited by the Ontario Familial Colorectal Cancer Registry. Controls were a sex- and age-matched random sample of the population of Ontario. 971 cases and 1944 controls completed questionnaires (including colorectal screening history and many risk factors). Multivariate logistic regression analysis was used to obtain adjusted odds ratios (OR) estimates.
Results: Having had a fecal occult blood screen was associated with reduced colorectal cancer risk (OR = 0.76; 95% confidence interval (CI): 0.59, 0.97). Having had a screening sigmoidoscopy was associated with a halving of colorectal cancer risk (OR = 0.52; 95% CI: 0.34, 0.80). Having had a screening colonoscopy did not significantly reduce colorectal cancer risk (OR = 0.69; 95% CI: 0.44, 1.07); however, having had either screening endoscopy was associated with a significant reduction in colorectal cancer risk (OR = 0.62; 95% CI: 0.44, 0.87). Findings differed slightly by anatomic sub-site (proximal and distal colorectum).
Conclusions: We report a reduction in colorectal cancer risk among persons who underwent colorectal cancer screening; in particular, sigmoidoscopy. Findings are of great importance for the prevention of colorectal cancer.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death in Canada, with 18,000 new cases and 8200 deaths each year [1]. Despite improvements in surgical treatment and chemotherapeutics, colorectal cancer has a poor prognosis, with a five-year survival rate of 50% [2]. Thus, the prevention of colorectal cancer is of utmost importance.

Colorectal screening is known to result in the removal of polyps that may otherwise have progressed to cancer, thus *preventing* colorectal cancer. As well, screening may identify early stage colorectal cancer, thus conferring a survival benefit. Several colorectal screening modalities are widely available in Canada: sigmoidoscopy, colonoscopy, and FOBT. FOBT detects blood in stool, and endoscopy physically examines the colon for abnormal growths (both pre-cancerous and cancerous). While sigmoidoscopy/colonoscopy results in the detection and removal of both bleeding and non-bleeding pre-cancerous polyps, the FOBT is only able to detect bleeding lesions (with subsequent endoscopy to remove these). The financial cost of these procedures are covered by

★ Financial Support – This work was supported by the National Cancer Institute, National Institutes of Health under RFA # CA-95-011 (grant no. U01-CA74783).
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the publicly funded healthcare system and, in theory, are accessible to all Canadians. To date, no study has evaluated the effectiveness of colorectal screening in reducing the incidence of colorectal cancer among Canadians.

Recently, the Minnesota randomized screening trial reported a reduction in colorectal cancer risk following FOBT [3], while a US population-based case–control study reported no statistically significant association between FOBT and colorectal cancer risk [4]. Studies have more consistently reported that FOBT reduces mortality from colorectal cancer [5–7]. Many observational studies in the United States (US) and Europe found that screening endoscopies were associated with a lower mortality and incidence of colorectal cancer, however, lifestyle factors were not controlled for in many of these studies and only a few studies evaluated colonoscopy – most evaluated only sigmoidoscopy [4, 8–11]. The only randomized control study of screening sigmoidoscopy (with polypectomy and follow-up colonoscopy) reported an 80% reduction in colorectal cancer risk after 13 years of follow-up among 50 to 59-year-olds in Norway [12]. It is not clear whether screening by sigmoidoscopy (which views only the distal colon) is protective for proximal colon cancer risk as most previous studies have not evaluated their data by anatomic sub-site.

We conducted a population-based case–control study to evaluate the association between colorectal screening and subsequent colorectal cancer risk among several thousand participants in the population-based Ontario Familial Colorectal Cancer Registry (OFCCR) [13], one of six international sites participating in the Consortium of Colon Cancer Familial Registries, established in 1997 by the US National Cancer Institute.

Methods

Cases and controls

Incident cases of colorectal cancer and population controls participating in the OFCCR were used to conduct this case–control study. Using the population-based Ontario Cancer Registry (OCR), the OFCCR identified and recruited living, incident colorectal cancer cases (pathology confirmed; International Classification of Diseases (ICD) – 9th revision codes 153.0–153.9, 154.1–154.3, 154.8) [14] aged 20 to 74 and diagnosed between 1 July 1997 and 30 June 2000. The OCR registers all cases of invasive cancer diagnosed among residents of Ontario using computerized probabilistic record linkage to resolve the four main sources of cancer information (i.e., pathology reports with any mention of cancer, hospital discharge summaries which include a diagnosis of cancer, reports from Ontario's regional cancer centers, and death certificates). However, only living cases with pathology confirmation were recruited by the OFCCR.

Controls recruited by the OFCCR were comprised of a random sample of Ontario residents identified using two methods. Population-based controls were randomly selected and frequency-matched, within sex and five-year age groups, to the colorectal cancer cases. In 1999 to 2000, persons were identified using Infodirect (service of Bell Canada) which provided a list of residential telephone numbers in Ontario. Households were randomly selected from this list, and telephoned to obtain a census of household members (age, sex). If an eligible person was identified they were invited to participate in the OFCCR, and if there was more than one eligible person within a household then only one was randomly selected. To increase the sample size and obtain a $\sim$1:2 case:control ratio, additional population-based control recruitment was conducted in 2001 to 2002. An age- and sex-stratified random sample of persons was selected from a listing of all Ontario residents based on population-based assessment rolls (owners and occupants) made available by the provincial government. The Ontario assessment rolls database fields include full name, age, sex, and address for all homeowners and tenants in Ontario. A re-abstraction study was able to link more than 95% of persons in the OCR to this population database, suggesting that its accuracy and completeness is high [15].

Data collection

Physicians identified from pathology reports were asked to permit contact of their patient(s), and to provide the patient address, telephone number and vital status. Once a physician provided consent, his/her patient was mailed a package containing a letter, a brochure describing the various phases of the OFCCR, a family history questionnaire, and a return postage paid envelope. A reminder post-card was sent several weeks after this mailing and non-responders were then followed up with a telephone call approximately eight weeks following the initial mailing.

Following the completion and return of the family history questionnaire, pedigrees were constructed based on the family information provided. The colorectal cancer case was then classified as (1) high familial risk (satisfying hereditary non-polyposis colorectal cancer (HNPCC) Amsterdam criteria) [16], (2) intermediate familial risk, or (3) low (sporadic) risk. Intermediate

familial risk is a very broad definition and consists of cases satisfying at least one of the following: (a) two relatives with HNPCC cancers (this includes 14 cancer sites), and two (of three) are first degree kin, (b) case and relative both with colorectal cancer <50 years of age, and (c) any relative with colorectal cancer <35 years of age. All other cases not classified as high or intermediate familial risk were classified as sporadic (with the exception of a few cases that were categorized as Intermediate due to selected ''pathology criteria''). All high and intermediate risk cases and a 25% random sample of the low risk cases were selected to continue. This involved completing a self-administered mailed epidemiologic risk factor and diet questionnaire, providing a blood sample, and permission to contact their relatives.

The epidemiologic questionnaire included many close-ended questions about colorectal screening, medical conditions, medication use, diet, reproductive factors, physical activity, sociodemographics, and anthropometric measures.

Variable definitions

Using the information obtained from the OFCCR personal history questionnaire, three colorectal screening procedures were considered: FOBT, sigmoidoscopy, and colonoscopy. In addition, endoscopy was derived and defined as those reporting having had either a sigmoidoscopy or colonoscopy. A ''true screener'' was defined as a person who reported (1) having had a colorectal screening procedure (FOBT, sigmoidoscopy, colonoscopy, or combination), *and* (2) the reason for having this procedure was family history of colorectal cancer *or* routine/yearly examination or check-up. A screen had to have occurred at least one year prior to diagnosis date for cases and referent date (mid-point of case diagnosis dates) for controls. Other screening variables evaluated include: age at first test, number of tests, reason for test (screening/diagnostic), and years since last test.

Using ICD codes obtained from the pathology reports, colorectal cancer cases were subdivided by location into proximal colon, and distal colon/rectum (defined in Table 3 footnote). This sub-site information was available for nearly 90% of the cases. A sub-study we performed found that the ICD codes (based on pathology reports) were very accurate when compared to operative notes (gold standard); the weighted kappa was 0.86 (0.82–0.88) [17].

Data analysis

Descriptive statistics were calculated for all study variables stratified by case–control status, and logistic regression was used to calculate age-adjusted OR estimates and 95% CI. Multivariate unconditional logistic regression analysis was performed to obtain OR estimates for each colorectal screening modality while simultaneously adjusting for identified confounders [18]. Greater than 20 potential confounders were individually evaluated using the 10% change-in-estimate method [19]. Variables evaluated for confounding included: medical conditions (diabetes, inflammatory bowel disease, irritable bowel disorder), medications/supplements (NSAID, calcium, folate), hormone replacement therapy (HRT), oral contraceptive use, alcohol consumption, smoking, weight, body mass index (BMI), physical activity, reproductive history (including age at menarche, age at menopause, parity), family history of colorectal cancer, servings of meat and vegetables, sex, education, and marital status. Only education, non-steroidal anti-inflammatory drug (NSAID) use, family history of colorectal cancer, and body mass index remained as confounders in the final multivariate models. In addition, age and sex were included in the final model because controls were frequency-matched to cases based on age and sex in the design.

Colorectal cancer cases were initially stratified into high/intermediate and sporadic familial risk and simultaneous OR estimates were computed for each case group (each compared to all controls). The case–case p-value was calculated to assess heterogeneity, and no statistically significant difference was observed between the two case groups, therefore, all cases were combined for analyses. To account for over-sampling of high/intermediate cases in the design of the OFCCR, OR estimates were weighted for sampling design; an offset term (the logarithm of the sampling weight) was included in the multivariate logistic regression models.

The possibility of effect modification between sex and screening was assessed by the statistical significance of the likelihood ratio statistic ($p < 0.05$) after the addition of the product term to the model [20]. Sex was not an effect modifier, therefore males and females were combined for all analyses. Colorectal screening reported in the one year period prior to the colorectal cancer diagnosis date (or referent date for controls) was re-coded to ''no screen'' for all analyses.

There were 971 colorectal cancer cases and 1944 controls eligible for this analysis. 1536 incident colorectal cancer cases participating in stage two of the OFCCR were mailed an epidemiology questionnaire, and 1124 (73%) completed this questionnaire. 153 cases over-sampled for pathology studies were excluded, leaving 971 colorectal cancer cases in this analysis. The OFCCR classified cases based on their familial cancer history; of the 971 cases in this analysis 43 were high

(HNPCC) risk, 495 were intermediate familial risk, and 433 were low/sporadic risk. Of the 4876 eligible controls identified and invited to participate, 2131 refused (43%), and of the 2745 mailed the questionnaire package, 1944 (71%) completed the epidemiology questionnaire. Reasons for non-participation included language barrier, illness, too busy, and questionnaire too long, however the majority of cases and controls did not provide a reason.

Results

Table 1 shows the frequency distribution of colorectal cancer cases and controls, and age-adjusted OR estimates for several colorectal cancer risk factors. As expected, family history of colorectal cancer, increased BMI (overweight), and increased red meat intake were significantly more common among the cases than the controls [21]. As well, ever having smoked cigarettes was slightly more common among the cases (vs. controls). Consistent with the literature, calcium supplement use, oral contraceptives, hormone replacement therapy and NSAID use were each associated with a decreased risk of colorectal cancer [21]. An expected colorectal cancer risk factor – physical – activity was not observed to be associated with colorectal cancer in this unadjusted analysis. This is perhaps due to the poor quality and confusing nature of the wording of the physical activity questions in our lengthy questionnaire, or this may simply be due to confounding as Table 1 is only adjusted for age.

Table 2 shows the frequency distribution of cases and controls and multivariate-adjusted OR estimates (MVOR) and 95% CIs for colonic screening procedures and colorectal cancer risk. 26% of controls reported ever having had an FOBT, and over half of these were reported to be for screening (vs. diagnostic). 19% of controls reported having ever had a sigmoidoscopy, with one-quarter of these indicated to be for screening. Only 12% of controls reported ever having had a colonoscopy, with one-third of these indicated to be for screening.

Ever having had either of the colorectal screening procedures was associated with a decreased colorectal cancer risk. Ever having had a screening FOBT was associated with a statistically significant 24% reduction in colorectal cancer risk (OR = 0.76; 95% CI: 0.59, 0.97).

Ever having had a screening sigmoidoscopy was associated with a statistically significant halving of colorectal cancer risk (OR = 0.52; 95% CI: 0.34, 0.80). In addition, having had a diagnostic sigmoidoscopy also conferred a protective benefit (OR = 0.63; 95% CI: 0.47, 0.84). Ever having had a screening colonoscopy was associated with 31% reduction in colorectal cancer risk, although this did not reach statistical significance (OR = 0.69; 95% CI: 0.44, 1.07). Having had a colonoscopy for any reason (screening or diagnostic) conferred a modest protective benefit (OR = 0.70; 95% CI: 0.57, 0.87). Having had screening endoscopy (colonoscopy or sigmoidoscopy) was associated with a statistically significant 38% reduction in colorectal cancer risk (OR = 0.62; 95% CI: 0.44, 0.87). In addition, having had a diagnostic endoscopy also conferred a protective benefit.

With nearly 20% of the data missing with respect to age at first procedure and years since last procedure, the odds ratios obtained for these variables must be interpreted with caution. Having an FOBT prior to age 50 appeared to confer a greater protective effect (vs. after age 50); however, due to limited sample size all CIs included 1. Having had an FOBT greater than five years ago provided a similar reduction in colorectal cancer risk compared with having an FOBT within the last two to four years. Having a first endoscopy after age 50 was slightly more protective than having a first endoscopy prior to age 50. Having had an endoscopy greater than five years ago provided a nearly identical reduction in colorectal cancer risk (OR = 0.28; 95% CI: 0.18, 0.44) compared with having had an endoscopy within the last two to four years (OR = 0.31; 95% CI: 0.16, 0.60).

Table 3 shows the MVOR and 95% CIs for colorectal screening procedures stratified by proximal (n = 325 cases) and distal (n = 544) colorectal cancer sites compared to controls. FOBT was significantly protective for distal cancers, and only modestly protective for proximal cancers. Sigmoidoscopy most protective for distal colorectal cancer (OR = 0.41; 95% CI: 0.30, 0.56); however it also showed a non-statistically significant association with proximal colon cancer (OR = 0.72; 95% CI: 0.51, 1.01). Colonoscopy was protective for distal cancer (OR = 0.68; 95% CI: 0.49, 0.94), but not for proximal cancer (OR = 1.02; 95% CI: 0.72, 1.45) – this was an unexpected finding.

Since colorectal cancer cases with a strong family history were over-sampled in the OFCCR design, we were able to evaluate sporadic and high/intermediate familial risk case groups separately (each compared with controls). While no significant differences between these two case groups were observed; in general, colorectal screening appeared to be slightly less protective for the high/intermediate cases compared to the sporadic cases. As the differences were not statistically significant the two case groups were combined for all analyses.

Table 1. Distribution of colorectal cancer cases, controls, and age-adjusted odds ratio (AOR) estimates for subject characteristics and several established colorectal cancer risk factors

Variable	Cases (n = 971) No.[a] (%)	Controls (n = 1944) No.[a] (%)	AOR (95% CI)
Age group[b]			
20–44	55 (6)	130 (7)	N/A
45–49	65 (7)	108 (6)	
50–54	120 (12)	291 (15)	
55–59	158 (16)	373 (19)	
60–64	223 (23)	407 (21)	
65–69	226 (23)	392 (20)	
70–74	124 (13)	237 (12)	
Sex			
Female	466 (48)	907 (47)	1.00
Male	505 (52)	1037 (53)	0.94 (0.81, 1.10)
Education			
High school	579 (60)	988 (51)	1.00
College/bachelor	287 (30)	716 (37)	0.70 (0.59, 0.83)
Graduate	94 (10)	227 (12)	0.72 (0.56, 0.94)
Marital status (current)[c]			
Not married	189 (20)	430 (22)	1.00
Married	775 (80)	1498 (78)	1.19 (0.98, 1.44)
Household income (2 years ago)			
< $40,000	341 (35)	584 (30)	1.00
40,000–59,999	228 (23)	415 (21)	0.97 (0.78, 1.20)
≥$60,000	157 (16)	375 (19)	0.74 (0.59, 0.94)
Don't know/missing	245 (25)	570 (29)	0.77 (0.63, 0.95)
Inflammatory bowel disease[d]			
No	901 (98)	1847 (98)	1.00
Yes	19 (2)	33 (2)	1.13 (0.64, 2.01)
Non-steroidal anti-inflammatory drug use[e]			
No	586 (62)	1095 (57)	1.00
Yes	360 (38)	822 (43)	0.80 (0.68, 0.94)
Calcium supplement use[f]			
No	707 (74)	1356 (70)	1.00
Yes	251 (26)	578 (30)	0.82 (0.69, 0.97)
Ever smoked cigarettes[g]			
No	376 (39)	798 (41)	1.00
Yes	590 (61)	1134 (59)	1.10 (0.94, 1.29)
BMI 2 years ago (kg/m^2)			
< 25	344 (36)	790 (41)	1.00
25–29.9 (overweight)	428 (45)	789 (41)	1.24 (1.04, 1.48)
≥30 (obese)	179 (19)	337 (18)	1.23 (0.98, 1.53)
Alcohol intake (lifetime average, drinks/week)[h]			
Never	237 (26)	444 (24)	1.00
1–2	204 (22)	454 (25)	0.85 (0.68, 1.07)
3–7	246 (27)	503 (27)	0.93 (0.75, 1.16)
> 7	229 (25)	435 (24)	1.01 (0.80, 1.26)
Family history of CRC in 1st degree relative			
No	671 (69)	1709 (89)	1.00
Yes	298 (31)	217 (11)	3.46 (2.84, 4.22)
Vegetable servings/week[i]			
0–7	130 (14)	277 (14)	1.00
7.1–14	290 (31)	645 (34)	0.95 (0.74, 1.22)
14.1–15.5	271 (29)	512 (27)	1.12 (0.87, 1.45)
> 15.5	257 (27)	478 (25)	1.14 (0.88, 1.47)

Table 1. (Continued)

Variable	Cases (n = 971) No.[a] (%)	Controls (n = 1944) No.[a] (%)	AOR (95% CI)
Red meat servings/week[i]			
0–2	272 (28)	717 (37)	1.00
2.1–3	192 (20)	383 (20)	1.31 (1.05, 1.64)
3.1–5	237 (25)	423 (22)	1.48 (1.19, 1.83)
>5	249 (26)	391 (20)	1.69 (1.36, 2.08)
Physical activity in 20s (hours/week)[j]			
≤2.00	331 (35)	628 (33)	1.00
2.01–8.60	305 (32)	646 (34)	0.91 (0.75, 1.10)
>8.60	315 (33)	632 (33)	0.94 (0.77, 1.13)
Physical activity in 30s/40s (hours/week)[j]			
≤1.30	321 (34)	624 (33)	1.00
1.31–6.20	284 (30)	630 (33)	0.89 (0.74, 1.09)
>6.20	336 (36)	628 (33)	1.03 (0.85, 1.25)
Females only	(n = 466)	(n = 907)	
Parity (≥6 months pregnancy)			
None	50 (11)	95 (11)	1.00
1 or 2	182 (41)	373 (45)	0.93 (0.63, 1.37)
3	105 (24)	216 (26)	0.88 (0.58, 1.34)
≥4	104 (24)	154 (18)	1.22 (0.79, 1.89)
Oral contraceptives use (≥1year)			
No	231 (51)	378 (42)	1.00
Yes	221 (49)	518 (58)	0.71 (0.56, 0.91)
Post-menopausal hormone replacement therapy			
No	188 (41)	329 (37)	1.00
Yes	165 (36)	372 (42)	0.80 (0.61, 1.04)
Pre-menopausal	102 (22)	191 (21)	N/A

[a] Numbers may not add to total due to missing values.
[b] Age at colorectal cancer diagnosis date for cases and referent date (June 30, 1999) for controls.
[c] Not married – single, divorced, separated, widowed; Married – married, common-law.
[d] Diagnosed with Crohn's disease or ulcerative colitis.
[e] Took aspirin or Ibuprofen-based medications at least twice a week for more than a month.
[f] Reported taking at least twice a week for more than a month
[g] Ever smoked at least one cigarette per day for 3 months or longer, and started at least 1 year prior to diagnosis/referent date.
[h] Average number of drinks (glass of wine, can/bottle of beer, 1 ounce serving of liquor/mixed drinks) per week in 20s, 30/40's, 50+. Quartile distribution based on controls.
[i] Average number of servings/week 2 years ago; quartile distribution based on controls.
[j] Hours reported from a list of 9 common physical activities (walking, jogging, running, bicycling, swimming laps, racquet sports, aerobics, sports, heavy household work) plus additional activities; tertile distribution based on controls.
Note: all exposures occurred at least 1 year prior to diagnosis (cases) or referent (controls) date.

Discussion

The protective effect attributed to the use of colorectal screening is of great public health importance. This case–control study found a reduction in colorectal cancer risk among persons who had undergone either of the three main colorectal screening modalities (colonoscopy, sigmoidoscopy and FOBT). Observational studies have shown that sigmoidoscopy reduces colorectal cancer mortality [9] and there is randomized control trial evidence that FOBT reduces mortality from colorectal cancer [6]. The evidence is now mounting to support that FOBT and endoscopy also reduce the risk of developing colorectal cancer in the first place [3, 10–11].

Generally, our findings are consistent with the literature suggesting that colorectal cancer screening reduces the incidence of colorectal cancer. Mandel *et al.* [3] reported a 20% reduction in colorectal cancer risk among those in the FOBT arm of the Minnesota randomized control trial. This magnitude of reduction in cancer risk is very similar to our findings. Similar to our findings, Slattery *et al.* [4] and Brenner *et al.* [10] both observed a

Table 2. Distribution of colorectal cancer cases and controls and multivariate-adjusted odds ratio (MVOR) estimates for colonic screening procedures

Variable	Cases (n = 971) No. (%)	Controls (n = 1944) No. (%)	MVOR[a] (95% CI)
FOBT[b]			
Never	680 (77)	1332 (74)	1.00
Ever	203 (23)	478 (26)	0.81 (0.66, 1.00)
Screening	121 (14)	292 (16)	0.76 (0.59, 0.97)
Diagnostic	82 (9)	186 (10)	0.91 (0.68, 1.23)
Don't know	88	134	
Age at first FOBT[c]			
Never	680 (84)	1332 (81)	1.00
≤50	67 (8)	174 (11)	0.77 (0.56, 1.06)
>50	61 (8)	134 (8)	0.91 (0.64, 1.28)
Don't know age	75	170	
Years since last FOBT[d]			
Never	680 (91)	1332 (88)	1.00
2–4 years	22 (3)	67 (4)	0.75 (0.45, 1.25)
≥5 years	47 (6)	114 (8)	0.79 (0.54, 1.16)
Missing/post-diagnosis*	134	297	
Sigmoidoscopy[b]			
Never	773 (87)	1495 (81)	1.00
Ever	114 (13)	354 (19)	0.59 (0.46, 0.76)
Screening	34 (4)	101 (5)	0.52 (0.34, 0.80)
Diagnostic	80 (9)	253 (14)	0.63 (0.47, 0.84)
Don't know	84	95	
Age at first sigmoidoscopy[c]			
Never	773 (89)	1495 (84)	1.00
≤50	60 (7)	159 (9)	0.72 (0.52, 1.01)
>50	33 (4)	118 (7)	0.54 (0.35, 0.83)
Don't know age	21	77	
Years since last sigmoidoscopy[d]			
Never	773 (94)	1495 (87)	1.00
2–4 years	12 (1)	49 (3)	0.49 (0.25, 0.97)
≥5 years	41 (5)	173 (10)	0.46 (0.31, 0.66)
Missing/post-diagnosis*	61	132	
Colonoscopy[b]			
Never	831 (89)	1676 (88)	1.00
Ever	105 (11)	221 (12)	0.70 (0.57, 0.87)
Screening	40 (4)	69 (4)	0.69 (0.44, 1.07)
Diagnostic	65 (7)	152 (8)	0.81 (0.59, 1.13)
Don't know	35	47	
Age at first colonoscopy[c]			
Never	831 (90)	1676 (90)	1.00
≤50	40 (4)	71 (4)	0.96 (0.62, 1.49)
>50	48 (5)	114 (6)	0.68 (0.47, 1.00)
Don't know age	17	36	
Years since last colonoscopy[d]			
Never	831 (99)	1676 (94)	1.00
2–4 years	2 (0)	40 (2)	0.10 (0.02, 0.41)
≥5 years	1 (0)	63 (4)	0.04 (0.01, 0.28)
Missing/post-diagnosis*	102	118	
Endoscopy[b] (sigmoidoscopy or colonoscopy)			
Never	701 (79)	1389 (75)	1.00
Ever	181 (21)	453 (25)	0.70 (0.57, 0.87)
Screening	64 (7)	147 (8)	0.62 (0.44, 0.87)
Diagnostic	117 (14)	306 (17)	0.74 (0.58, 0.96)
Don't know	89	102	

Table 2. (Continued)

Variable	Cases (n = 971) No. (%)	Controls (n = 1944) No. (%)	MVOR[a] (95% CI)
Age at first endoscopy[c]			
Never	701 (83)	1389 (79)	1.00
≤ 50	81 (10)	189 (11)	0.80 (0.60, 1.09)
> 50	58 (7)	169 (10)	0.61 (0.43, 0.86)
Don't know age	42	95	
Years since last endoscopy[d]			
Never	701 (95)	1389 (85)	1.00
2–4 years	11 (1)	73 (4)	0.31 (0.16, 0.60)
≥5 years	23 (3)	175 (11)	0.28 (0.18, 0.44)
Missing/Post-diagnosis[e]	147	205	

[a] Adjusted for age, sex, NSAID, education, BMI at age 20, family history of colorectal cancer in first degree relative.
[b] Reported having *first* procedure at least 1 year prior to diagnosis/referent date (for reason of screening, or diagnostic).
[c] Age at first test (regardless of reason) and if done at least one year prior to diagnosis.
[d] Years since last reported test (regardless of reason) if more than once, years since first test if done only once, among those whose first test was at least one year prior to diagnosis.
[e] Post-diagnosis date was used for cases and post-referent date for controls; and as only "first" and "last" procedure date was asked for in questionnaire it was not possible to compute most recent test prior to diagnosis if last procedure reported was post-diagnosis.
Note: numbers may not add to total due to missing values.

halving of colorectal cancer risk associated with sigmoidoscopy screening among their case–control study participants. Similarly, a large American cohort study found a halving of colorectal cancer risk associated with screening endoscopy [8]. A recent population-based case–control study in the US observed a 75% reduction in colorectal cancer risk among those ever having had a sigmoidoscopy – this magnitude of protection was greater than we report [11]. Thiis-Evensen *et al.* [12] also reported a 75% reduction in colorectal cancer risk among persons undergoing sigmoidoscopy (and polypectomy) within a Norwegian randomized controlled trial.

Table 3. Multivariate-adjusted odds ratio (MVOR) estimates for colonic screening procedures stratified by proximal and distal sub-site and compared with controls

Variable	Proximal[a] Cases vs. Controls MVOR[c] (95% CI)	Distal[b] Cases vs. Controls MVOR[c] (95% CI)
FOBT[d]		
No	1.00	1.00
Yes	0.87 (0.65, 1.16)	0.67 (0.53, 0.86)
Sigmoidoscopy[d]		
No	1.00	1.00
Yes	0.72 (0.51, 1.01)	0.41 (0.30, 0.56)
Colonoscopy[d]		
No	1.00	1.00
Yes	1.02 (0.72, 1.45)	0.68 (0.49, 0.94)

[a] ICD includes: hepatic flexure (1530), transverse colon (1531), cecum (1534), appendix (1535), ascending colon (1536), splenic flexure (1537); $N = 325$.
[b] ICD includes: descending colon (1532), sigmoid colon (1533), rectosigmoid junction (1540), rectum (1541), anal canal (1542), anus unspecified (1543), rectum other (1548); $N = 544$.
[c] Adjusted for age, sex, NSAID, education, BMI at age 20, family history of colorectal cancer in first degree relative.
[d] Had procedure/test for any reason (screen or diagnostic) at least 1 year prior to diagnosis/referent date.
Note: 102 cases had no information available on sub-site, and were excluded.

Recent studies have shown that risk reduction appears to last for at least ten years following sigmoidoscopy [10–11]. We found that the risk reduction was maintained for at least five years following endoscopy; however, we did not have the power to evaluate the rare ten year lag period. We observed no significant difference between high/intermediate familial risk and sporadic cases as regards the association between colonic screening and colorectal cancer risk. To our knowledge no other study has evaluated this.

Sigmoidoscopy views the distal colon/rectum only, while colonoscopy views both the distal colon/rectum and the proximal colon. We found that FOBT was protective for distal cancers, but only modestly protective for proximal cancers. Sigmoidoscopy was significantly associated with a reduction in distal colorectal cancer risk, and appeared to also be protective for proximal colon cancer but this finding did not reach statistical significance. This sustained protective effect may be due to the follow-up of abnormal sigmoidoscopy with a colonoscopy. Consistent with our observations,

Slattery *et al.* [4] and Newcomb *et al.* [11] both reported that sigmoidoscopy was associated with a significant reduction in distal colon cancer and was modestly associated with a reduction in proximal colon cancer; however, this finding did not reach statistical significance. We observed that colonoscopy was protective for distal cancer, but was not associated with proximal (right-sided) cancer – this was an unexpected finding. This lack of association may perhaps be due to the large number of colorectal cancers with unknown anatomic sub-site in our dataset and the reduced sample size. It is unlikely that respondents confused sigmoidoscopy with colonoscopy as our questionnaire briefly described (differentiated between) colonoscopy and sigmoidoscopy. Furthermore, several studies have shown that self-reported colorectal cancer screening measures are valid (discussed in detail below). To our knowledge no other study has evaluated colonoscopy and sub-site specific colorectal cancer risk. It is possible that proximal cancers may be biologically different than distal cancers [22, 23]; however, there is no evidence to suggest that proximal cancer may grow faster (making colonoscopy screening less effective). It is possible that distal cancer is more often missed because inexperienced endoscopists' colonoscopes may not reach the cecum (far end of the colon) [24].

The likely biologic mechanism responsible for the overall findings is that pre-cancerous polyps are identified at endoscopy and immediately removed, thus preventing colorectal cancer. Colorectal adenomas are known to progress to cancer, and endoscopic polypectomy (removal of polyps) has been shown to prevent colorectal cancer [25]. An analogy with another cancer site is that it is now widely accepted that the Papanicolaou (Pap) test, and the treatment of precursor lesions, has been responsible for the reduction in cervical cancer incidence rates over the past few decades in North America. Although not the focus of our study, it appears that endoscopy performed for diagnostic reasons (e.g., rectal bleeding due to hemorroids) also confers a protective effect – this is likely because any pre-cancerous lesions would be removed and thus prevent the development of colorectal cancer.

It is important to discuss the possible limitations and biases of the case–control study design. Since we excluded fatal cases from our study, survival bias may be a concern; if colorectal cancer cases who had colorectal screening also had improved survival they could be over-represented in our study, biasing our findings towards the null. However, a recent study reported that most colon cancer risk factors did not differ by stage of disease, thus if cases with earlier stage disease were more likely to participate, this should not influence associations between exposures and colon cancer risk [26]. As both our cases and controls were selected from population-based sampling frames, selection bias is unlikely. Furthermore, known risk factors [21] were found to be associated with colorectal cancer risk in our dataset suggesting the cases and controls are representative. However, response bias is always a concern if high response rates are not achieved. Although unlikely, bias could have been introduced if participation was differential regarding both case status and exposure status (for example, if cases who underwent colonic screening were less likely to participate in our study than controls who underwent colonic screening). Given the moderate control response rate, it is plausible that participating controls were more health conscious (and more likely to have had screening) and this may have produced an overestimate of the screening benefit. Possible confounding by known colorectal cancer risk factors was evaluated, and adjusted for, in our analyses. Recall bias is always a concern in case–control studies because cases may report exposures differently than controls; however, since information on a wealth of factors was collected in the epidemiologic questionnaire, it would be unlikely that participants would focus on our particular study hypothesis. Furthermore, the usual concern is that cases would over-report the exposure of interest whereas in this study the cases reported a lower prevalence of screening. It is unlikely that over-reporting of colorectal screening (misclassification) by the control subjects is responsible for the large protective effect seen in our study. Misclassification of "ever/never" exposure is likely to be minimal given that self-reports of colorectal cancer screening behaviors have been shown to be quite accurate, with sensitivities and specificities greater than 85% for FOBT, sigmoidoscopy and colonoscopy [27]. In addition, a recent study among Ontarians found that the percent agreement between self-reports and medical records was 72, 80 and 94% for FOBT, sigmoidoscopy and colonoscopy, respectively [28]. However, the accuracy of details regarding colorectal screening modalities (e.g., reason, date) may be problematic. As well, a proportion of participants replied "don't know" to the screening questions. Assuming "missingness" was random, the odds ratio estimates would be biased towards the null.

In North America, it is recommended that average-risk persons greater than 50 years of age be screened for colorectal cancer, with screening beginning earlier in persons at high risk [29, 30]. The American Cancer Society recommends that average risk persons have either: (i) annual FOBT; (ii) sigmoidoscopy every five years; (iii) annual FOBT plus sigmoidoscopy every five years; (iv) double contrast barium enema every five years; or, (v)

colonoscopy every 10 years [30]. The Canadian Task Force on Preventative Health Care has similar recommendations regarding FOBT and sigmoidoscopy, however they caution that there is insufficient evidence to advocate colonoscopy as an initial screening test [29].

Despite the endorsement of colorectal screening by professional organizations, the prevalence of colorectal cancer screening among the target population in Canada is very low [31, 32]. A population-based record-linkage study in Ontario comprised of persons between the ages of 50 to 59 found that only 20% had a colorectal screening procedure between 1995 and 2000 [29], which is in line with the prevalence estimates we report among the controls. The American Behavioral Risk Factor Surveillance System (BRFSS) reported higher colorectal screening rates with approximately 40% of persons aged 50 and greater reporting having had a colorectal screening test in the late 1990s [33]. In 2001, 44% of persons aged 50 and over reported having had a FOBT and 47% a colonoscopy or sigmoidoscopy [34]. Between 1987 and 1998 the prevalence of FOBT screening increased slightly, while screening rates for endoscopies doubled in the US [35]. These colorectal screening rates are likely overestimates as the American studies relied on self-reported data and the Ontario study used health insurance billings so it was not possible to distinguish between diagnostic tests and true colonic screening [32–35].

Death from colorectal cancer is preventable, and indeed, colorectal cancer itself is preventable with appropriate screening. Even though it is well established that colorectal screening can reduce colorectal cancer incidence and mortality, only a small proportion of the Ontario target population receive screening. This study confirmed in a population-based setting that colonic screening is associated with reduced colorectal cancer risk. In particular, for the prevention of cancer in the distal colon/rectum. Further research is needed to enhance the effectiveness of screening in the population, especially so as to prevent cancers in the proximal colon. These results also demonstrate that the benefits of screening are detectable in the population even with a relatively low prevalence of screening. Thus, a further implication is that efforts must continue to enhance the use of colorectal cancer screening, which will result in further benefits in terms of lives saved and colorectal cancer cases prevented.

Acknowledgements

This work was supported by the National Cancer Institute, National Institutes of Health under RFA # CA-95-011 (grant no. U01-CA74783). John McLaughlin is supported as an investigator of the Canadian Institutes for Health Research. The efforts of all the Ontario Familial Colon Cancer Registry (OFCCR) study staff and genetic counselors are gratefully acknowledged. In particular, we would like to thank the study co-ordinator, Darshana Daftary, for her dedication to this study, and Peter Campbell for his assistance with variable derivation. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the Consortium of Familial Registries.

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