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Association of Colonoscopy and Death From Colorectal Cancer: A Population-Based, Case–Control Study

Nancy N. Baxter, MD, PhD; Meredith A. Goldwasser, ScD; Lawrence F. Paszat, MD, MS; Refik Saskin, MSc; David R. Urbach, MD, MSc; and Linda Rabeneck, MD, MPH

Background: Colonoscopy is advocated for screening and prevention of colorectal cancer (CRC), but randomized trials supporting the benefit of this practice are not available.

Objective: To evaluate the association between colonoscopy and CRC deaths.

Design: Population-based, case–control study.

Setting: Ontario, Canada.

Patients: Persons age 52 to 90 years who received a CRC diagnosis from January 1996 to December 2001 and died of CRC by December 2003. Five controls matched by age, sex, geographic location, and socioeconomic status were randomly selected for each case patient.

Measurements: Administrative claims data were used to detect exposure to any colonoscopy and complete colonoscopy (to the cecum) from January 1992 to an index date 6 months before diagnosis in each case patient and the same assigned date in matched controls. Exposures in case patients and controls were compared by using conditional logistic regression to control for comorbid conditions. Secondary analyses were done to see whether associations differed by site of primary CRC, age, or sex.

Results: 10 292 case patients and 51 460 controls were identified; 719 case patients (7.0%) and 5031 controls (9.8%) had undergone colonoscopy. Compared with controls, case patients were less likely to have undergone any attempted colonoscopy (adjusted conditional odds ratio [OR], 0.69 [95% CI, 0.63 to 0.74; $P < 0.001$]) or complete colonoscopy (adjusted conditional OR, 0.63 [CI, 0.57 to 0.69; $P < 0.001$]). Complete colonoscopy was strongly associated with fewer deaths from left-sided CRC (adjusted conditional OR, 0.33 [CI, 0.28 to 0.39]) but not from right-sided CRC (adjusted conditional OR, 0.99 [CI, 0.86 to 1.14]).

Limitation: Screening could not be differentiated from diagnostic procedures.

Conclusion: In usual practice, colonoscopy is associated with fewer deaths from CRC. This association is primarily limited to deaths from cancer developing in the left side of the colon.

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For author affiliations, see end of text.

Colorectal cancer (CRC) is the second most common cause of cancer death in North America (1). Although colonoscopy is untested in randomized trials, many lay organizations (2, 3) and specialty societies (4–6) advocate it as the preferred screening method (7, 8). In the United States, screening colonoscopy rates have rapidly increased (9–11). The evidence for effectiveness of screening colonoscopy is indirect, inferred from reductions in CRC deaths in randomized trials of screening with fecal occult blood testing (12), a test that is much less sensitive than colonoscopy (13). In case–control studies, large-bowel endoscopy was associated with a 50% reduction in CRC development and 60% reduction in CRC deaths (14, 15). However, most of these studies included few women and evaluated sigmoidoscopy. Case–control studies of the association of colonoscopy with the incidence of CRC (16, 17) have been conducted but are more prone to bias than those defining case status by cancer death (18).

Colonoscopy has real-world limitations. In a population-based study, 6% of patients with newly discovered right-sided CRC had undergone colonoscopy 6 months to 3 years before diagnosis, indicating a substantial miss rate in the community setting (19). Detection rates vary by endoscopist and by endoscope withdrawal time (20). The accuracy of colonoscopy done in the real world is unknown but may be substantially less than that in published reports (21–23). We studied colonoscopy throughout Ontario, Canada, hypothesizing that it would be associated with fewer CRC deaths, but to a lesser degree than estimated in the literature.

Methods

The research ethics board of St. Michael's Hospital, Toronto, Ontario, Canada, approved the study.

Study Design

We did a case–control study of the association of colonoscopy and CRC deaths. We measured the odds of exposure to colonoscopy in case patients (persons who died of CRC) and controls (persons who did not die of CRC)

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Context

The effect of colonoscopy on colorectal cancer (CRC) mortality is unknown.

Contribution

By using a province-wide data set, the authors identified 10 292 case patients who died of CRC and, for each case patient, 5 matched controls who did not. A total of 7.0% of the case patients and 9.8% of the controls had colonoscopy. Therefore, colonoscopy was associated with fewer CRC deaths (odds ratio, 0.69 [95% CI, 0.63 to 0.74]). The odds ratios for death from CRC that developed in the left and right colon were 0.33 (CI, 0.28 to 0.39) and 0.99 (CI, 0.86 to 1.14), respectively.

Caution

This was an observational case–control study. The data set did not identify a reason for colonoscopy.

Implication

Colonoscopy may be much less effective in preventing death from CRC of the right colon compared with the left colon.

—The Editors

and calculated an odds ratio (OR) for exposure. Because this OR is mathematically equal to the ratio of the odds of being a case patient given colonoscopy exposure to the odds of being a control given colonoscopy exposure, it estimates the association between colonoscopy and CRC death.

Data Sources

We used 4 data sources. The Ontario Cancer Registry tracks all incident cancer cases diagnosed in Ontario since 1964; it is more than 95% complete (24). It is linked to the Mortality File, an electronic database maintained by the Registrar General of Ontario to tally deaths of Ontario residents. Data on vital status and cause of death were available through 31 December 2003. The Ontario Health Insurance Plan database contains information on claims billed by physicians for services and has been linkable since 1991, permitting identification of almost all medical procedures occurring in Ontario. The Registered Persons Database, a roster of all Ontario Health Insurance Plan beneficiaries, contains almost all Ontario residents. The Canadian Institute for Health Information hospital discharge abstract database, linkable since 1988, contains information on every patient discharged from a hospital or same-day surgery unit in Ontario and includes patient demographic information, major diagnoses, procedures, and discharge status.

Identification of Case Patients

We identified case patients from the Ontario Cancer Registry. They received a diagnosis of CRC (International Classification of Diseases, Ninth Revision, codes 153.0 to 153.4 or 153.6 to 154.1) from 1 January 1996 to 31 December 2001 and died of CRC or related causes between 1 January 1996 and 31 December 2003 (International Classification of Diseases, Ninth Revision, codes 159 [malignant neoplasm of other or ill-defined sites within the digestive organs and peritoneum], 197 [secondary malignant neoplasm of respiratory and digestive systems], or 199 [malignant neoplasm without specification of site]). Complete identification of CRC deaths by using the cause of death on Ontario death certificates requires including deaths from these closely related causes. We included only persons age 52 to 90 years so that all controls would be in the screening-eligible age range during the exposure period. We excluded persons who had received a previous diagnosis of CRC, lived where physicians do not bill directly (<5% of the sample), or were not continuously eligible for an Ontario Health Insurance Plan from 1 January 1992. For secondary analyses, we stratified case patients by age; sex; and site of primary CRC, as assessed by registrars of the Ontario Cancer Registry from pathology reports and hospital discharge summaries (right-sided cancer [proximal to the splenic flexure], left-sided cancer [splenic flexure to rectum], or unknown site of cancer).

Identification of Controls

From the Registered Persons Database, we selected persons continuously eligible for Ontario Health Insurance Plan coverage from 1 January 1992 to 31 December 2003 or death. Case patients were matched to controls for factors known to influence colonoscopy rates and risk for CRC death: sex (1, 25), socioeconomic status (25, 26), and age (25). To minimize bias from differing access to colonoscopy, we matched for geographic location. Consequently, each case patient had 5 controls matched for sex, income quintile (based on the mean household income of the enumeration area of residence), residence location by health care region during year of diagnosis, and calendar year of birth. For each potential match, we defined the "referent date," the date on which case patients received a diagnosis of cancer, determined from the Ontario Cancer Registry, a source that uses a standardized hierarchy for date of diagnosis. The date of pathologic confirmation of cancer, if available, was considered the date of diagnosis. We then linked the cohort of potential matches to the Ontario Cancer Registry to detect and exclude potential matches with a diagnosis of CRC on or before the referent date or death from CRC before 31 December 2003. Controls were alive at the date of the case patients' death. We included controls who developed CRC after the referent date. By matching for calendar year of birth, case patients and controls had an equal period to be exposed to colonoscopy before the date of CRC diagnosis (referent date). By using random numbers, we randomly selected 5 controls from all matches and assigned them to a case patient to form the control group.

Determining Exposure

By using the Ontario Health Insurance Plan billing codes (**Appendix Table**, available at www.annals.org), we detected exposure to colonoscopy from 1 January 1992 to an index date 6 months before case patients received a diagnosis of CRC. Every case patient and control had more than 42 months of potential exposure to colonoscopy and at least 18 months of potential exposure while of screening-eligible age. We defined 2 exposures: any colonoscopy regardless of completeness (**Appendix Table**, available at www.annals.org) and complete colonoscopy (colonoscopy coded as reaching the cecum). We did not consider flexible sigmoidoscopy to be an exposure. We treated exposure to colonoscopy as a binary variable: Persons who had at least 1 colonoscopy were considered exposed, and if any colonoscopy was complete to the cecum, those persons were considered exposed to complete colonoscopy. For persons who had more than 1 colonoscopy, we included only the first complete colonoscopy. In persons with no complete colonoscopy, we included the first incomplete colonoscopy. From billing codes, we detected polypectomies done during colonoscopy. We ascertained the self-designated specialty of the physician who billed for the included colonoscopy from the Ontario Physicians Human Resources Data Centre.

Diagnostic colonoscopies (those done to evaluate CRC symptoms, confirm the diagnosis, or search for metachronous tumors) would be associated with greater odds of CRC death than screening colonoscopies, which could mask any effect of screening colonoscopy on preventing death from CRC. Because Ontario Health Insurance Plan billing codes do not distinguish between screening and diagnostic colonoscopies (27), we tried to increase the proportion of screening colonoscopies by excluding all colonoscopies done within 6 months before the date of CRC diagnosis (referent date). This strategy assumes that most diagnoses of CRC in the Ontario Cancer Registry would be made within 6 months of a colonoscopy to investigate symptoms, confirm diagnosis, or search for metachronous tumors. Previous investigators have used a 6-month window of exclusion (19), although some chose a shorter period (14). To validate our choice, we recalculated the OR for the association of colonoscopy and CRC death for windows varying from 0 to 12 months.

Determining Comorbid Conditions

We identified comorbid conditions at a hospital discharge occurring within 60 months before the index date. We calculated the Charlson Comorbidity Index score (28) as 0, 1, 2, or 3 or more. We assigned a score of 0 to those who were not hospitalized.

Statistical Analysis

We calculated descriptive statistics for study variables stratified by case–control status. We did conditional logistic regression, adjusting for comorbid conditions to calculate the OR for CRC death and 95% CIs. We repeated the analysis, stratified by sex, age (<70 or ≥70 years at diagnosis), and site of cancer (right-sided, left-sided, or unknown site). In a secondary analysis aimed at understanding how colonoscopy affected CRC mortality rates, we defined 2 exposures: exposure to any colonoscopy 6 to 24 months before diagnosis (referent date) and exposure to any colonoscopy more than 24 months before diagnosis (referent date). We hypothesized that colonoscopy done 6 to 24 months before CRC diagnosis would potentially detect early-stage CRC, whereas colonoscopies done earlier would potentially prevent CRC by detecting and removing polyps.

Sensitivity Analysis

We repeated the analysis, stratified by date of cancer diagnosis and, separately, excluded case patients and controls (and matched controls for excluded case patients) with ulcerative colitis, Crohn disease, or previous bowel resection because they are more likely to undergo colonoscopy and develop CRC (**Appendix Table**, available at www.annals.org).

We analyzed the data by using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). All statistical tests were 2-sided.

Role of the Funding Source

The Canadian Institutes of Health Research provided funding for research for this study. The funding source had no role in the design, conduct, or reporting of this study or in the decision to submit the manuscript for publication.

RESULTS

Patients and Procedures

We identified 10 292 case patients and selected 51 460 matched controls from 3 082 050 potential controls. Median age at diagnosis (referent date) was 73 years, and 46% of case patients and controls were women (**Table 1**). Colonoscopy data were available for 7.8 years (median) before date of diagnosis (referent date). During the observation period, 1 262 729 colonoscopies were done in the Ontario sample. In total, 5750 persons (9.3%) in the study had a colonoscopy, of whom 4522 (79%) had at least 1 complete colonoscopy. Most colonoscopies were done by gastroenterologists (31%) or general surgeons (40%) (**Table 2**). We excluded 260 case patients (2.5%) with a diagnosis of ulcerative colitis, Crohn disease, or bowel resection before CRC diagnosis, as well as 1931 controls (3.8%) who had 1 of these conditions or were matched to a case patient who did. Colorectal cancer developed in 693 controls (1.3%).

Exposure to Colonoscopy

A total of 719 case patients (7.0%) had colonoscopy before the index date, of whom 523 (73%) had complete colonoscopy. A total of 5031 controls (9.8%) had colonoscopy, of whom 3999 (81%) had complete colonoscopy. Colonoscopy with polypectomy was done in 188 case pa-

Table 1. **Characteristics of Case Patients and Controls**

Characteristic	Case Patients (n = 10 292)	Controls (n = 51 460)
Median age (range), *y*	73 (52–92)	73 (51–91)
Women, %	45.7	45.7
Socioeconomic status, *n (%)**		
Quintile 1	2198 (21.4)	10 990 (21.4)
Quintile 2	2353 (22.9)	11 765 (22.9)
Quintile 3	2052 (19.9)	10 260 (19.9)
Quintile 4	1805 (17.5)	9025 (17.5)
Quintile 5	1884 (18.3)	9420 (18.3)
Charlson Comorbidity Index score, *n (%)*		
0	8075 (78.5)	40 892 (79.5)
1	1153 (11.2)	5248 (10.2)
2	639 (6.2)	3178 (6.2)
>3	425 (4.1)	2142 (4.1)
Potential exclusions, *n (%)*†	260 (2.5)	1931 (3.8)
Median observation period before date of diagnosis (IQR), *mo*	94 (76 111)	94 (76 111)
Underwent any attempted colonoscopy ≥6 mo before date of diagnosis, *n (%)*	7.0 (719)	9.8 (5031)
Median time from colonoscopy to date of diagnosis (IQR), *mo*	28 (15–53)	33 (18–55)
Site of cancer at diagnosis, *n (%)*		
Right side	3343 (32.5)	–
Left side	5310 (51.6)	–
Unknown	1639 (15.9)	–

IQR = interquartile range.
* Socioeconomic status is measured by income quintile, based on the mean household income of the enumeration area of residence. The quintile ranges vary by area of residence, so there are no set boundaries for all regions.
† Based on diagnosis of ulcerative colitis, Crohn disease, or previous bowel resection. The number of controls excluded is the sum of the controls with the relevant diagnoses (n = 631 [1.2%]) and the controls matched to a case patient with these diagnoses (n = 1300 [2.5%]).

tients (1.8% overall; 26% of those who had colonoscopy) and 1043 controls (2.0% overall; 21% of those who had colonoscopy). Case patients were less likely than controls to have undergone any attempted colonoscopy (OR, 0.69 [95% CI, 0.63 to 0.74; $P < 0.001$]) or complete colonoscopy (OR, 0.63 [CI, 0.57 to 0.69; $P < 0.001$]) (**Table 3**). These ORs are mathematically equal to the ORs for death from CRC if colonoscopy is done.

When we varied the exclusion window from 0 to 12 months, the OR for CRC death ranged from 5.92 (CI, 5.63 to 6.14) with no exclusion window to 0.67 (CI, 0.61 to 0.74) with a 12-month exclusion window (**Figure**). The ORs were the same for the 6-month window we chose up to 12 months, suggesting that the inclusion of diagnostic colonoscopies had little effect on our results.

Site of Primary Cancer

We found an inverse association between colonoscopy and CRC death, but the association differed by site of primary CRC. A total of 3343 case patients (32.5%) had right-sided cancer, 5310 (51.6%) had left-sided cancer, and 1639 (15.9%) had cancer of an unknown primary site. The rate of colonoscopy in case patients (those who died of CRC) varied by site of primary CRC (4.1%, 10.6%, and 9.1% of case patients with left-sided cancer, right-sided cancer, and unknown site of cancer, respectively). The rate of colonoscopy in matched controls did not vary by site of primary CRC (9.7%, 9.9%, and 9.8% of controls matched to case patients with left-sided cancer, right-sided cancer, and unknown site of cancer, respectively). The inverse association of death from left-sided CRC with colonoscopy was substantial for attempted colonoscopy (OR, 0.39 [CI, 0.34 to 0.45]) and complete colonoscopy (OR, 0.33 [CI, 0.28 to 0.39]). Colonoscopy was not associated with death from right-sided CRC (OR from any attempted colonoscopy, 1.07 [CI 0.94 to 1.21]; OR from complete colonoscopy, 0.99 [CI, 0.86 to 1.14]) (**Table 3**). For patients with an unknown site of CRC, the findings were similar to those of patients with right-sided cancer. Stratification by age and sex did not alter these findings (**Table 4**), nor did exclusion of case patients and controls with a previous diagnosis of inflammatory bowel disease or bowel resection.

Table 2. **Self-designated Specialty of Endoscopist**

Variable	Gastroenterologist	General Surgeon	General Internist	Other
Total colonoscopies, *n*	1808	2303	944	695
Complete colonoscopies, %	83	79	80	66
All colonoscopies, %	31	40	16	12
Case patients, %	30	42	17	11
Controls, %	32	40	16	12

Timing of Colonoscopy Relative to Diagnosis

We found a weaker association between exposure to colonoscopy 6 to 24 months from diagnosis (referent date) and CRC death (OR, 0.84 [CI, 0.75 to 0.94]) than between exposure to colonoscopy more than 24 months from diagnosis (referent date) and CRC death (OR, 0.62 [CI, 0.56 to 0.69]) (**Table 5**). This relationship differed by site

Table 3. **Results of Primary Analysis: Odds Ratio for the Association Between Colonoscopy and Colorectal Cancer Death***

Model	Odds Ratio (95% CI)			
	All Cancer	Right-Sided Cancer	Left-Sided Cancer	Undefined Site of Cancer
Attempted colonoscopy				
None	1.00	1.00	1.00	1.00
Any	0.69 (0.63–0.74)	1.07 (0.94–1.21)	0.39 (0.34–0.45)	0.90 (0.75–1.08)
Completeness of colonoscopy				
None	1.00	1.00	1.00	1.00
Complete	0.63 (0.57–0.69)	0.99 (0.86–1.14)	0.33 (0.28–0.39)	0.90 (0.73–1.10)
Incomplete	0.91 (0.78–1.07)	1.35 (1.07–1.69)	0.63 (0.49–0.81)	0.91 (0.61–1.35)

* Conditional logistic regression, adjusted for Charlson Comorbidity Index score.

of primary CRC. For death from left-sided cancer, the association with colonoscopy 6 to 24 months before diagnosis was similar (OR, 0.46 [CI, 0.36 to 0.57]) to the association with colonoscopy more than 24 months before diagnosis (OR, 0.38 [CI, 0.32 to 0.45]). In contrast, for death from right-sided cancer, the association with colonoscopy 6 to 24 months before diagnosis was stronger (OR, 1.32 [CI, 1.10 to 1.59]) than the association with colonoscopy more than 24 months before diagnosis (OR, 0.92 [CI, 0.79 to 1.08]).

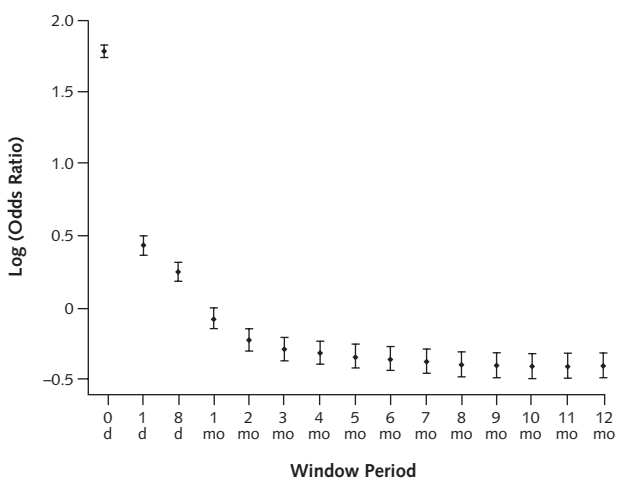
DISCUSSION

This study shows that colonoscopy is associated with lower CRC mortality rates, primarily due to fewer deaths from left-sided cancer. Our estimates of the association of colonoscopy with fewer deaths from left-sided CRC are similar to those of case–control studies of sigmoidoscopy that had strong internal controls (29, 30). Even self-reported complete colonoscopy to the cecum (versus attempted colonoscopy) was not associated with right-sided CRC deaths. This finding was consistent for men and women and for older and younger persons. We searched the literature for relevant research indexed in MEDLINE from 1950 to July 2008, limited to publications in English, using the search terms "exp colonoscopy," "exp screening," "exp colorectal neoplasms," and "exp epidemiologic methods." Two other studies showed that colonoscopy effectiveness differs for right- and left-sided CRC. These case–control studies (16, 17) found that colonoscopy was associated with a much lower incidence of left-sided CRC. The relative risk for left-sided tumors after negative colonoscopy was less than 0.2, whereas the relative proximal cancer risk ranged from 0.40 (17) to 0.67 (16). These studies, together with ours, provide consistent evidence that colonoscopy is less effective for right-sided CRC than left-sided CRC in Canada, United States, and Germany.

Indirect clinical evidence and some biological evidence are consistent with these case–control studies. Colorectal cancer developing after colonoscopy is more frequently right-sided than its incidence in the general population (31, 32). In a population-based study of right-sided cancer, at least 6% of patients had colonoscopy 6 to 36 months before diagnosis, suggesting that the endoscopist missed the cancer (19).

Why would colonoscopy be less effective in preventing death from right-sided CRC? First, some "complete" colonoscopies do not evaluate the entire right colon. Second, bowel preparation may be worse in the right colon. Finally, right and left colonic neoplasia may differ biologically. Right-sided colonic adenomas are less often pedunculated (33) and are occasionally flat, which makes them harder to identify and remove. The histology and molecular features of right-sided cancer may differ (34, 35), implicating predominant genetic pathways of carcinogenesis (36–38), which may influence the effectiveness of early detection.

Figure. **Influence of the exclusion window on the conditional odds ratio for the association between attempted colonoscopy and colorectal cancer deaths.**



Values >0 indicate an increased risk with colonoscopy, and values <0 indicate a decreased risk (see Methods section).

Table 4. **Results of Analysis Stratified by Age and Sex: Odds Ratio for the Association Between Colonoscopy and Colorectal Cancer Death***

Variable	Odds Ratio (95% CI)			
	All Cancer	Right-Sided Cancer	Left-Sided Cancer	Undefined Site of Cancer
Stratified by age at diagnosis				
<70 y				
No colonoscopy	1.00	1.00	1.00	1.00
Complete colonoscopy	0.47 (0.39–0.55)	0.92 (0.72–1.18)	0.22 (0.16–0.30)	0.52 (0.33–0.84)
Incomplete colonoscopy	0.78 (0.58–1.05)	1.14 (0.75–1.73)	0.53 (0.33–0.86)	0.92 (0.38–2.21)
≥70 y				
No colonoscopy	1.00	1.00	1.00	1.00
Complete colonoscopy	0.72 (0.64–0.81)	1.03 (0.86–1.22)	0.41 (0.33–0.50)	1.06 (0.84–1.33)
Incomplete colonoscopy	0.98 (0.81–1.17)	1.46 (1.11–1.93)	0.68 (0.51–0.92)	0.92 (0.59–1.43)
Stratified by sex				
Men				
No colonoscopy	1.00	1.00	1.00	1.00
Complete colonoscopy	0.59 (0.52–0.67)	1.02 (0.84–1.25)	0.33 (0.26–0.41)	0.80 (0.60–1.07)
Incomplete colonoscopy	0.75 (0.58–0.96)	1.01 (0.67–1.51)	0.56 (0.39–0.081)	1.00 (0.55–1.84)
Women				
No colonoscopy	1.00	1.00	1.00	1.00
Complete colonoscopy	0.68 (0.59–0.78)	0.96 (0.79–1.17)	0.33 (0.25–0.44)	1.03 (0.76–1.38)
Incomplete colonoscopy	1.05 (0.86–1.29)	1.57 (1.19–2.08)	0.71 (0.50–1.00)	0.85 (0.50–1.44)

* Conditional logistic regression, adjusted for Charlson Comorbidity Index score.

Our study has several limitations. First, we did not know the indication for colonoscopies and had to include both diagnostic and screening procedures. Screening colonoscopy was probably in the minority. In a study of indications for colonoscopy in Ontario in 2000, 26% of 175 randomly selected persons undergoing first-time colonoscopy did so purely for screening (39). However, screening colonoscopy was reimbursable in Ontario throughout this study, and therefore the proportion of screening colonoscopies may have actually been higher than that in the United States (40). To minimize this limitation, we excluded colonoscopy done within 6 months of CRC diagnosis, which means that, along with diagnostic colonoscopies, we excluded screening colonoscopies that led to an immediate diagnosis of cancer. Because all case patients died of CRC, the excluded screening examinations did not prevent CRC deaths. Because we did not include them in the analysis, we may have overestimated the strength of the inverse association between colonoscopy and CRC death.

Second, case–control studies are subject to confounding by factors inadequately controlled for by matching or adjustment. Although we matched for age, sex, and geographic location, unmeasured factors associated with colonoscopy and with CRC incidence or death may bias our results. Although we excluded patients with a history of inflammatory bowel disease or bowel surgery, we could not measure other important confounders, such as persons living a healthy lifestyle who may be more likely to undergo colonoscopy and less likely to die of CRC. However, lifestyle factors are not likely to affect the outcome of left-sided cancer more than right-sided cancer and, in fact,

Table 5. **Results of Analysis Stratified by Date of Exposure: Odds Ratio for the Association Between Colonoscopy and Colorectal Cancer Death***

Variable	Odds Ratio (95% CI)			
	All Cancer	Right-Sided Cancer	Left-Sided Cancer	Undefined Site of Cancer
Exposure to colonoscopy 6–24 mo before diagnosis				
No colonoscopy (referent date)	1.00	1.00	1.00	1.00
Colonoscopy (referent date)	0.84 (0.74–0.95)	1.32 (1.10–1.59)	0.46 (0.36–0.57)	1.08 (0.82–1.43)
Exposure to colonoscopy >24 mo before diagnosis				
No colonoscopy (referent date)	1.00	1.00	1.00	1.00
Colonoscopy (referent date)	0.62 (0.56–0.69)	0.92 (0.79–1.08)	0.38 (0.32–0.45)	0.80 (0.63–1.02)

* Conditional logistic regression, adjusted for Charlson Comorbidity Index score.

seem to affect proximal cancer more than distal cancer (41). More important, we could not assess family history. Persons with a family history of CRC may be more likely to die of CRC and undergo colonoscopy, which should cause us to underestimate an inverse association of colonoscopy and CRC death.

Third, we could not detect exposure to colonoscopy before 1991, which could bias the study in either direction. However, colonoscopy was comparatively uncommon before 1992 (42). Fourth, the overall rate of colonoscopy was low in case patients and controls, and the overall rate difference was small (7.0% vs. 9.8%). However, for left-sided cancer, the difference in the crude rate of colonoscopy between case patients and controls was greater (4.1% vs. 9.7%) and similar to results in previous case–control studies of sigmoidoscopy and colonoscopy (14).

The strong inverse association between colonoscopy and death from left-sided but not right-sided CRC may be due in part to inadequate colonoscopy, whose quality reflects the Ontario-wide community standard from 1992 to 2001. Although plausible as a partial explanation, inadequate colonoscopy is unlikely to fully explain this finding because the associations of colonoscopy and death from right- and left-sided CRC were the same for complete colonoscopy and any attempted colonoscopy. Of note, the rates of cecal intubation in Ontario were similar to those reported in studies from the United Kingdom and Europe (43–46).

The inverse association between colonoscopy and death from left-sided CRC was the same for colonoscopy done soon before CRC diagnosis or earlier, which may mean that both early detection of CRC (colonoscopy within 24 months) and its prevention (colonoscopy before 24 months) underlie the association. For right-sided CRC, colonoscopy done more than 24 months before diagnosis was not associated with CRC death, whereas colonoscopy done within 6 to 24 months of diagnosis was associated with an increased risk for right-sided CRC death (OR, 1.32 [CI, 1.10 to 1.59]). The mechanism of this finding is clearly speculative, but false-negative colonoscopy may be 1 factor, because colonoscopy is more likely to miss right-sided cancer (19) and delay in diagnosis after a false-negative result might lead to worse outcomes.

Imperiale and colleagues (47) recently reported that repeated colonoscopic screening within 5 years of a negative screening examination found advanced adenoma in 1.3% of 1256 persons and no cancer. These findings seem to contrast with our findings that a colonoscopy provides imperfect protection against death from CRC. However, the findings are just as expected in the small study sample used, which was at low risk for CRC (asymptomatic; relatively young; no history of polyps, CRC, or inflammatory bowel disease; and negative initial colonoscopy). We studied more than 1.2 million colonoscopies and their association with 719 deaths from CRC. As a proportion of all procedures done, failure of colonoscopy to prevent a CRC death is rare even in a sample at higher risk for CRC than the cohort in Imperiale and colleagues' study.

Although randomized, controlled trials with cancer death as the outcome are the gold standard for evaluating cancer screening, no such trial of screening colonoscopy is currently under way. Our study and others like it provide unique insight into colonoscopic approaches to prevent CRC death. In an Ontario-wide sample, colonoscopy is associated with a reduced risk for death from CRC arising from the left colon but not from the right colon. Although improvements in the quality of screening colonoscopy may narrow this difference, differences in tumor biology may limit the potential to prevent right-sided colon cancer deaths with current endoscopic technology.

From Li Ka Shing Knowledge Institute, St. Michael's Hospital; University Health Network and University of Toronto; Institute for Clinical Evaluative Sciences; and Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

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Requests for Single Reprints: Nancy Baxter, MD, PhD, Division of General Surgery, St. Michael's Hospital, University of Toronto, 30 Bond Street 16CC-40, Toronto Ontario, M5B 1W8, Canada; e-mail, baxtern@smh.toronto.on.ca.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Baxter: Division of General Surgery, St. Michael's Hospital, University of Toronto, 30 Bond Street 16CC-40, Toronto, Ontario M5B 1W8, Canada.
Drs. Goldwasser and Paszat and Mr. Saskin: Institute for Clinical Evaluative Sciences, G1-06, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.
Dr. Urbach: University of Toronto, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada.
Dr. Rabeneck: Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room T2 025, Toronto, Ontario M4N 3M5, Canada.

Author Contributions: Conception and design: N.N. Baxter, M.A. Goldwasser, L.F. Paszat, D.R. Urbach, L. Rabeneck.
Analysis and interpretation of the data: N.N. Baxter, M.A. Goldwasser, L.F. Paszat, R. Saskin, D.R. Urbach, L. Rabeneck.
Drafting of the article: N.N. Baxter, R. Saskin.
Critical revision of the article for important intellectual content: N.N. Baxter.
Final approval of the article: N.N. Baxter, M.A. Goldwasser, L.F. Paszat, D.R. Urbach, L. Rabeneck.
Statistical expertise: N.N. Baxter.
Obtaining of funding: N.N. Baxter.
Collection and assembly of data: R. Saskin.

Appendix Table. Diagnostic and Procedure Codes

Variable	Diagnostic and Procedure Codes
Diagnosis	
Colorectal cancer	ICD-9 codes 153.0–153.4, 153.6–154.1
Death from colorectal cancer	ICD-9 codes 153.0–153.4, 153.6–154.1, 159, 197, or 199
Inflammatory bowel disease	ICD-9 codes 556.0–556.9, 555.0–555.9; ICD-10 codes K50.0–K50.9, K51.0–K51.9
Site of diagnosis	
Right-sided cancer	ICD-9 codes 153.4, 153.6, 153.0, 153.1 (cecum to transverse colon)
Left-sided cancer	ICD-9 codes 154.1, 154.0, 153.3, 153.2, 153.7 (splenic flexure to rectum)
Unknown site of cancer	ICD-9 codes 153.8, 153.9 (overlapping or unspecified site)
Procedure	
Any attempted colonoscopy	OHIP billing code Z555 (colonoscopy to descending colon)
Complete colonoscopy	OHIP billing code Z555 with accompanying codes E747 (colonoscopy to cecum) or E705 (colonoscopy to terminal ileum)
Polypectomy	OHIP billing code Z571 (excision of polyp >3 mm)
Previous colorectal resection	OHIP billing code S162, S166, S167, S169, S172, S171, S168, S170, S173, S174, S188, S177, S213, S214, S215, S216, S217; ICD-9 procedure codes 57.5x, 57.6x, 60.4x, 60.5x; procedure codes* 1.NM.87x, 1.NM.89x, 1.NM.91x, 1.NQ.87x, 1.NQ.89x, 1.NQ.90x

ICD-9 = International Classification of Diseases, Ninth Revision; OHIP = Ontario Health Insurance Plan.
* Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedure codes used by the Canadian Institute for Health Information.