Risk of Developing Colorectal Cancer Following a Negative Colonoscopy Examination

Evidence for a 10-Year Interval Between Colonoscopies

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Context Limited evidence exists to guide the optimal frequency of repeat endoscopic examination for colorectal cancer screening after a negative colonoscopy.

Objective To determine the duration and magnitude of the risk of developing colorectal cancer following performance of a negative colonoscopy.

Design, Setting, and Patients Population-based retrospective analysis of individuals whose colonoscopy evaluations did not result in a diagnosis of colorectal neoplasia. Patients who had been evaluated between April 1, 1989, and December 31, 2003, were identified using Manitoba Health's physician billing claims database (N = 35 975). Standardized incidence ratios (SIRs) were calculated to compare colorectal cancer incidence in our cohort with colorectal cancer incidence in the provincial population. Stratified analysis was performed to determine the duration of the reduced risk. Patients with a history of colorectal cancer prior to the index colonoscopy, inflammatory bowel disease, resective colorectal surgery, and lower gastrointestinal endoscopy within the 5 years before the index colonoscopy were excluded. Cohort members were followed up from the time of the index colonoscopy until diagnosis of colorectal cancer, death, out-migration from Manitoba, or end of the study period on December 31, 2003.

Main Outcome Measure Incidence of colorectal cancer.

Results A negative colonoscopy was associated with SIRs of 0.69 (95% confidence interval [CI], 0.59-0.81) at 6 months, 0.66 (95% CI, 0.56-0.78) at 1 year, 0.59 (95% CI, 0.48-0.72) at 2 years, 0.55 (95% CI, 0.41-0.73) at 5 years, and 0.28 (95% CI, 0.09-0.65) at 10 years. The proportion of colorectal cancer located in the right side of the colon was significantly higher in the colonoscopy cohort than the rate in the Manitoba population (47% vs 28%; $P<.001$).

Conclusions The risk of developing colorectal cancer remains decreased for more than 10 years following the performance of a negative colonoscopy. There is a need to improve the early detection rate of right-sided colorectal neoplasia in usual clinical practice.

JAMA. 2006;295:2366-2373 www.jama.com

COLORECTAL CANCER (CRC) IS the third most commonly diagnosed cancer and the second leading cause of cancer deaths in North America.[1,2] Screening for CRC and its precursor lesions has become an increasingly prevalent practice. Colonoscopy has been recommended as the preferred initial screening test by several medical authorities including the American College of Gastroenterology and is being widely performed in the United States for screening among average-risk individuals.[3] This is based on strong biological arguments and a higher detection rate of neoplastic lesions on colonoscopy compared with the other widely available screening modalities.[4-7] Colonoscopy also allows for removal of most precancerous polyps at the time of detection. A screening interval of 10 years after a normal colonoscopy has been adopted based on the estimate of the time it takes for an adenomatous polyp to transform into carcinoma. However, the duration over which the risk of CRC remains decreased following the performance of a normal colonoscopy remains unknown.[8]

See also pp 2357 and 2411.

To answer some of the outstanding questions about the magnitude and duration of the decreased risk of CRC following the performance of a negative colonoscopy,[9] we have established a population-based cohort of individu-

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als who underwent a colonoscopic evaluation that did not result in the diagnosis of colorectal neoplasia. This report describes the magnitude and duration of the lowered risk of developing CRC in this cohort for up to 15 years following the initial colonoscopy.

METHODS

Description of Databases

Manitoba is a central Canadian province with a population of approximately 1.2 million. The population is ethnically diverse with more than 60% of the residents living in urban areas. Manitoba Health is the region's publicly funded health insurance agency providing comprehensive universal health insurance for residents in the province. Because no requirement for premiums or co-payments exists, participation in the plan by the residents of Manitoba is virtually 100%. All physicians in the province who perform colonoscopy are paid on a fee-for-service basis and submit claims for reimbursement to Manitoba Health. Hence, reporting of colonoscopy is expected to be comprehensive and complete, for physicians would not be paid unless the claim for the colonoscopy visit is submitted to Manitoba Health. Additionally, services can be tracked on an individual patient basis. Since 1984, every resident of Manitoba has a unique personal health identification number (PHIN). Every health system contact with a fee-for-service physician is recorded by the PHIN, date of contact, *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code for diagnosis (reason for visit) and service (tariff) code. Also after each hospital discharge, all Manitoba hospitals submit a hospital discharge abstract to Manitoba Health that codes up to 16 diagnoses and 12 procedures performed during each hospitalization. The accuracy of the various administrative health databases in Manitoba has been previously demonstrated.[10-14]

Longitudinal health service use and outcomes can be determined by linkage of health utilization files and other databases that use PHIN as a key personal identifier. For this study, we were interested in cancer and death outcomes found in the Manitoba Cancer Registry and Manitoba Health Population Registry, respectively. The Manitoba Cancer Registry is a population-based database recording all cancers diagnosed in the residents of the province since 1956. The data from the Manitoba Cancer Registry have been routinely linked to the Manitoba Health's administrative health databases and population registry for events occurring through 2003, using various personal identifiers including PHIN. The Manitoba Health Population Registry captures entry into the plan, migration in and out of the province, and death of all individuals. Of importance when determining cancer rates, the population registry is used as a source of denominators; the registered population closely matches census estimates.[12]

To protect patient confidentiality, the linkage in this study was performed via scrambled PHINs using anonymous versions of the Cancer Registry and Manitoba Health's hospital discharge and physician claims databases. The study was approved by the University of Manitoba's Health Research Ethics Board and Manitoba Health's Health Information and Privacy Committee.

Identification of the Study Cohort

All individuals who had undergone colonoscopy or sigmoidoscopy in Manitoba between April 1, 1984, and December 31, 2003, were identified from Manitoba Health's medical claims database. The cohort of individuals who had a negative colonoscopy result between April 1, 1989, and December 31, 2003, was identified. A *negative colonoscopy* result was defined as a colonoscopy without any extra procedures, such as biopsy or polypectomy (tariff code 3185). There are separate higher-paying tariff codes for colonoscopy with biopsy or polypectomy in the province (tariff codes 3186, 3187, 3188, 3189). There have been no major modifications to these tariff codes since 1984, other than the periodic increments in the amount of reimbursements (and a 1-time decrease in 1995).

It is assumed that endoscopists who submit procedure bills for tariff 3185 have scoped beyond the splenic flexure, for there is a separate tariff (3320, 3323, or 3324) for flexible sigmoidoscopy. However, the billing tariffs are submitted directly by the endoscopists and are based on an honor system. Because of the higher fee paid for colonoscopy tariffs that include biopsy or polypectomy, it is assumed that any colonoscopy submitted with tariff code 3185 did not have any lesions requiring biopsies. It is also possible that some patients who underwent colonoscopy without biopsy (and hence the applied tariff was 3185) were using anticoagulants, and hence biopsy was contraindicated; however, this could not be determined from the database.

Exclusion Criteria

Patients who had a prior diagnosis of colorectal cancer were excluded, as were patients who underwent a lower gastrointestinal endoscopy of any type in the 5 years preceding the index colonoscopy. Cancer Registry data were available back to 1956 and health service utilization data were available from 1984 onward. A run-in period of 5 years (April 1, 1984, and April 1, 1989) provided a lead time to identify individuals who had a prior endoscopy.

Because the goal of the study was to evaluate the risk relative to the general population of developing CRC in average-risk individuals after a negative colonoscopy result, patients with inflammatory bowel disease, and those with a history of resective colorectal surgery prior to the index colonoscopy were excluded from the final cohort. Patients with inflammatory bowel disease were identified using the administrative case definition that has been developed and previously validated for the population in this province.[14] Patients with colorectal surgery prior to endoscopic evaluation were identified through the medical claims database.

Definition of Outcomes

Right-sided colon cancers were defined as those occurring in the cecum,

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Table 1. Characteristics of Colonoscopy Cohort*

	No. (%) of Persons (N = 35 975)
Men	21 116 (59)
Women	14 859 (41)
Age group, y	
0-39	5190 (14)
40-49	6999 (19)
50-59	8057 (22)
60-69	6915 (19)
70-79	6082 (17)
80-89	2478 (7)
≥90	254 (1)
Specialty of the physicians performing the index colonoscopy	
Internists (including gastroenterologists)	13 142 (37)
Surgeons	20 111 (56)
General practitioners	2712 (8)

*Percentages may not sum to 100 due to rounding.

ascending colon, and hepatic flexure. Left-sided cancers included those occurring in the descending and sigmoid colon. We considered transverse colon cancers separately. To evaluate the outcomes after a single negative colonoscopy, a subgroup analysis was performed limited to a subcohort of individuals who did not have a repeat lower gastrointestinal tract endoscopy unless CRC was diagnosed on the follow-up endoscopy. In addition this subgroup analysis was performed to exclude patients who were at higher-than-average risk of developing CRC, including persons with a family history of CRC. These individuals are more likely to undergo multiple colonoscopies for the purpose of intensive screening or surveillance and would thus be excluded in this analysis.

Statistical Analysis

Data analysis was performed using the statistical software package SAS version 9.1 (SAS Institute Inc, Cary, NC). χ^2 Tests were used to compare proportions. Significance was determined at the $P = .05$ level. P values were 2-sided. We calculated 95% confidence intervals using the method proposed by Bailar and Ederer,[15] assuming a Poisson distribution.

The cohort was followed up to December 31, 2003; follow-up was truncated at diagnosis of CRC or death or migration using information recorded in the Manitoba Cancer Registry and the Manitoba Health Population Registry. Colorectal cancer incidence in the cohort was compared with the age-, sex-, and calendar-year–adjusted CRC incidence rates in Manitoba and expressed as standardized incidence ratios (SIRs), using the indirect method of standardization.[16] The observed number of cases was determined by enumerating the cases of CRC in the negative colonoscopy cohort. The expected number of cases was calculated by multiplying the person-years at risk accumulated by the negative colonoscopy cohort by the colorectal cancer rate in Manitoba. Person-years at risk were accrued from the date of the performance of the index colonoscopy until the date of diagnosis of CRC, death or migration from the province, or until December 31, 2003. Person-years at risk were stored in a matrix that specified the accrual by calendar year, sex, and 5-year age groups. These were then multiplied by a similarly constructed matrix of CRC rates calculated using data from the Manitoba Cancer Registry and Manitoba Health's Population Registry.

Stratified analysis of SIRs by time since initial colonoscopy was performed to determine the duration of the interval of decreased CRC risk following performance of a negative colonoscopy. We focused on the SIRs after 6 months of the index colonoscopy for our primary analysis so as to exclude cases of CRC diagnosed due to the initial diagnostic evaluation.

Power Calculation

Using CRC incidence in Canada Cancer Statistics 2003 and the Manitoba population projections 2000, we estimated a 2% CRC event rate in 10 years for the general population in Manitoba. Using a conservative estimate of 20% reduction in CRC incidence for those who had colonoscopy, power of 80% at a significance level of 5%, we estimated that we would need 11 460 people in the study cohort. Preliminary data from Manitoba Health on colonoscopy had shown that 46 000 colonoscopies without biopsies were performed between 1986 and 2002.

RESULTS

In the province of Manitoba 170 933 individuals had 331 082 lower gastrointestinal endoscopies between April 1, 1984, and December 31, 2003. Focusing on data from April 1, 1989, onward, we identified 35 975 individuals who had a colonoscopy without biopsy or polypectomy who also did not undergo a lower endoscopy in the preceding 5 years. The characteristics of the colonoscopy cohort are shown in TABLE 1.

There were 32 203 individuals who contributed 147 781 person-years of follow-up beyond 6 months. In this cohort, the incidence of CRC was 1.1 cancers per 1000 person-years of follow-up, which was 31% lower than expected and remained reduced beyond 10 years (TABLE 2). Because SIRs are age standardized, restriction to individuals older than age 50 years did not alter the rates.

The subcohort had an even lower rate of development of CRC (0.7 cancers/1000 person-years) and the effect again persisted beyond 10 years (TABLE 3). TABLE 4 provides the SIRs for individuals who did not undergo a repeat endoscopy for 2, 5, or 10 years following the initial negative colonoscopy result.

The proportion of cancers located in the right side of the colon was higher in individuals with an initially negative colonoscopy than in the general population (76 [47%] of 163 vs 2884 [28%] of 10 197; $P < .001$; TABLE 5 and TABLE 6). Colorectal cancer cases were more likely to be right-sided in patients who were diagnosed with CRC in the initial 2 years following the index colonoscopy (33 [56%] of 59) compared with those diagnosed more than 5 years following the initial colonoscopy (19 [38%] of 50); though the difference did not reach statistical significance ($P = .06$). No physician specialty was found to have disproportionately more CRC cases diagnosed following the index colonoscopy, although there was a nonsignificant trend toward gen-

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Table 2. Standardized Incidence Ratio in Negative Colonoscopy Result Cohort*

	Induction Years				
	0.5	1	2	5	10
Cohort					
No. of individuals	32 203	29 357	24 426	13 282	4375
Person-years at risk	147 781.04	132 426.91	105 591.26	50 297.78	9093.72
No. of individuals with colorectal cancer					
Observed	163	142	104	50	5
Expected	235.78	214.29	175.50	90.45	17.78
SIR (95% CI)	0.69 (0.59-0.81)	0.66 (0.56-0.78)	0.59 (0.48-0.72)	0.55 (0.41-0.73)	0.28 (0.09-0.65)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.
*Identified as colonoscopy billed by tariff 3185, which is colonoscopy alone without biopsy or polypectomy. Patients in this cohort underwent a colonoscopy with negative results and included those with subsequent endoscopies of any type and those who had only a single negative colonoscopy result.

Table 3. Standardized Incidence Ratio for Those Who Had a Single Negative Colonoscopy Result*

	Induction Years				
	0.5	1	2	5	10
Cohort					
No. of individuals	25 041	22 303	17 668	8130	2377
Person-years at risk	97 574.37	85 763.22	65 838.20	28 629.56	4801.19
No. of individuals with colorectal cancer					
Observed	73	58	38	12	0
Expected	150.34	133.98	105.46	49.39	8.81
SIR (95% CI)	0.49 (0.38-0.62)	0.43 (0.33-0.57)	0.36 (0.26-0.49)	0.24 (0.12-0.42)	0

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.
*Identified as colonoscopy billed by tariff 3185, which is colonoscopy alone without biopsy or polypectomy and who never underwent any subsequent colonoscopy or sigmoidoscopy, other than diagnostic endoscopic examinations at which colorectal cancer was found and endoscopies for surveillance after colorectal cancer diagnosis.

eral practitioners performing a higher proportion of the index colonoscopies in individuals who subsequently developed CRC than the overall proportion of colonoscopies in the province performed by general practitioners (18 [11%] of 163 vs 10 875 [7%] of 147 281; $P = .07$).

COMMENT

This study demonstrates that following a negative result from a colonoscopy performed in the usual clinical practice, the risk of developing CRC is at most 60% to 70% of the risk of developing CRC in the general population and the duration of the interval of decreased CRC risk persists for more than 10 years. Furthermore, if an individual undergoes a single negative colonoscopy, excepting any follow-up endoscopies at which CRC is diagnosed, the risk of developing CRC is even lower and the duration of the interval of decreased risk again exceeds the 10-year interval currently recommended between screening colonoscopies. Our findings suggest that screening colonoscopies do not need to be performed at intervals shorter than 10 years.

Table 4. Standardized Incidence Ratio for Individuals Who Did Not Have a Repeat Endoscopy for 2, 5, or 10 Years After an Initial Negative Colonoscopy Result

	Duration in Which No Endoscopy Was Performed, y		
	2	5	10
Cohort			
No. of individuals	22 387	10 154	2623
Person-years at risk	96 373.23	38 859.46	5484.47
No. of individuals with colorectal cancer			
Observed	85	32	2
Expected	156.96	66.77	10.05
SIR (95% CI)	0.54 (0.44-0.66)	0.50 (0.34-0.71)	0.20 (0.02-0.72)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

There are no previous data from long-term follow-up studies on the risk of developing CRC after a negative colonoscopy, with which we can directly compare our CRC incidence data. The closest comparative data would be from cohort studies with follow-up after removal of all colonic polyps (ie, clearing colonoscopies) and case-control studies evaluating the risk of CRC after any lower gastrointestinal endoscopy (which includes endoscopies with polypectomies). The magnitude of the reduction in the incidence of CRC after a negative colonoscopy result seen in our study is similar to what has been reported in several case-control studies. Large case-control studies have shown that sigmoidoscopy or colonoscopy results in a 50% reduction in the incidence of the CRC in the portion of the bowel examined.[17,18] A recent Canadian population-based case-control study demonstrated a 30% to 40% re-

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Table 5. Colorectal Cancer Cases at Each Site After Index Colonoscopy vs Site Distribution Among All Colorectal Cancer Cases, Between 1989 and 2003

	No. (%) of Patients With CRC					
	After Index Colonoscopy					
	0.5 to 2 y	2 to 5 y	≥5 y	Any Time	All CRC Cases	*P* Value*
Right colon	33 (56)	24 (44)	19 (38)	76 (47)	2884 (28)	<.001
Transverse colon	4 (7)	2 (4)	2 (4)	8 (5)	566 (5)	.72
Left colon	7 (12)	13 (24)	11 (22)	31 (19)	2878 (29)	.01
Rectosigmoid and rectum	10 (17)	12 (22)	11 (22)	33 (20)	3227 (32)	.002
Other (unspecified/overlapping)	5 (8)	3 (6)	7 (14)	15 (9)	642 (6)	.13
Total	**59 (100)**	**54 (100)**	**50 (100)**	**163 (100)**	**10 197 (100)**	

*Colorectal cancer (CRC) after index colonoscopy vs all CRC cases in province.

Table 6. Colorectal Cancer Proximal to Splenic Flexure by Time of Diagnosis After the Index Colonoscopy

	No. (%) of CRC Cases Proximal to the Splenic Flexure		
	Negative Colonoscopy Cohort	All CRC Cases*	*P* Value
Overall	84 (51)	3450 (34)	<.001
Diagnosed, y			
0.5-2.0	37 (63)	3450 (34)	<.001
>2.0-5.0	26 (49)	3450 (34)	.01
>5	21 (42)	3450 (34)	.20

Abbreviation: CRC, colorectal cancer.
*All the CRC cases diagnosed in the province between 1989 and 2003.

duction in CRC risk in patients who underwent screening lower gastrointestinal endoscopy.[19]

Risk of developing CRC following colonoscopy with polypectomy varies widely between different studies. A recent analysis of pooled data from 3 polyp prevention trials suggests that the reduction in colorectal cancer incidence after polypectomy and clearing colonoscopy may be lower in real-world practice than what had been previously documented in controlled trials.[20,21] In the pooled analysis from 3 adenoma chemoprevention trials, the rate of CRC diagnosed following performance of the index colonoscopy was 1.7 cancers per 1000 person-years, which was equivalent to the expected rate based on the US population-based Surveillance, Epidemiology, and End Results (SEER) program (SIR, 0.98).[20] Other surveillance studies with follow-up after clearing colonoscopies have also found higher rates of incident CRC (2.2-2.4/1000 person-years).[22,23] In contrast in the National Polyp Study, in which colonoscopies were performed by a select group of endoscopists, the CRC rate was markedly reduced compared with the SEER population (0.6 cancers/1000 person-years; SIR, 0.24).[21] In an Italian study, a similarly low rate of CRC incidence was found after colonoscopic polypectomy (0.42 cancers/1000 person-years; SIR, 0.34). The CRC incidence in our cohort (1.1 cancers/1000 person-years; SIR, 0.69) and subcohort (0.7/1000 person-years; SIR, 0.49) is intermediate between the rates in these postpolypectomy follow-up studies. However, the postpolypectomy follow-up may not be directly comparable with follow-up of our study cohort with negative colonoscopies. Individuals who have formed polyps once are likely to be at a higher risk of forming polyps again, compared with individuals who have not formed polyps (our cohort) and therefore even after a clearing colonoscopy, the risk of CRC may be higher in the individuals who have formed polyps at least once. Conversely, endoscopists may be more meticulous in the endoscopic examination of individuals found to be harboring polyps and thus less likely to miss lesions in persons in whom synchronous polyps have been detected. Until now, there have been no large studies with follow-up of individuals with negative colonoscopy and no prior history of colorectal adenoma.

We believe there are several potential explanations for the apparent stepwise decline in SIRs in our study. First, the apparent decline is not significant with overlapping confidence intervals. Second, the mean length of follow-up beyond 10 years was only 2.1 additional years, which may contribute to low SIRS at 10 years. Third, a stepwise decline in the SIRs may be expected with follow-up of a negative colonoscopy cohort, due to the effect of missed lesions. Colorectal cancers that are missed at initial endoscopy will manifest in the first few years. Subsequently missed advanced adenomatous polyps will progress to CRC and manifest. The individuals who do not develop CRC even after many years are likely the individuals who had a true negative colonoscopy result.

There were disproportionately more right-sided CRC cases in our negative colonoscopy cohort than there were in the general population during the study period. Failure of endoscopists to intubate the cecum, even when they believe they have reached the cecum, or the likelihood that inadequate bowel preparations affect the right side more than the rest of the colon may explain this higher rate of right-sided cancers diagnosed after performance of a seem-

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ingly negative colonoscopy. Furthermore, there are differences in gene expression and molecular characteristics between right-sided and left-sided CRCs[24] with microsatellite instability and CpG island methylator phenotypes being more common in right-sided tumors and chromosomal instability in left-sided tumors.[25,26] Moreover, depressed adenomatous lesions, which are more difficult to detect endoscopically, may occur more often in the right side of the colon,[27,28] and these lesions may be more likely to rapidly progress to adenocarcinoma.[29]

There are several other potential explanations for the development of CRC following an initial negative colonoscopy.[22] Some of the interval colon cancers are likely prevalent cancers that were missed on the initial colonoscopy. Back-to-back examinations of the colon have demonstrated missed lesion rates of 6% to 12% for lesions greater than 1 cm.[30,31] Lesions located on the backside of colonic folds or in close proximity to the anal verge are more likely to be missed on endoscopy.[32] An additional explanation for the development and presentation of new growths soon after the index endoscopy may be related to the biological factors that lead to rapid tumor progression.[33]

In our study, there was a trend toward a higher proportion of the index colonoscopies in individuals who subsequently were diagnosed with CRC to be performed by general practitioners. There is a wide range in the number of polyps and other lesions detected by endoscopists during routine endoscopy, which likely represents differences in the quality of the procedures performed. These differences may be related to the prior training of the physicians performing the procedure and the number of procedures being performed by them on a regular basis. More adenomas are detected by endoscopists who spent longer time examining the bowel during colonoscopy withdrawal and have a more meticulous colonoscopic withdrawal technique.[34,35] Better quality control may lead to improvement in the effectiveness of CRC prevention programs. Indeed it has been estimated that more than 50% of prevalent cancers in the dietary Polyp Prevention Trial could have been prevented or detected earlier if there had been better performance of colonoscopy in the trial.[22]

The most common indications for repeat endoscopies are the development of new symptoms among patients believed to be secondary to colonic disease or the physician believing a particular patient to be at higher-than-average risk of developing CRC. We tried to exclude individuals who may be at higher-than-average risk of developing CRC by excluding patients with either inflammatory bowel disease or a prior history of CRC and by performing a subgroup analysis limited to individuals who had only a single negative colonoscopy result. In this subgroup analysis, there was a 50% to 75% reduction in the incidence of CRC, compared with the general population. We believe this suggests that the incidence of CRC in individuals who do not have a clinical indication for repeat endoscopy is quite low and is similar to that seen in the National Polyp Study.

We used administrative data as our primary source of endoscopy data. There are several factors that improve the accuracy and robustness of administrative databases in Manitoba. Unlike some other Canadian provinces and the United States, there is no requirement for residents in Manitoba to pay health premiums. This contributes to inclusion of almost all residents in the province in the databases; only a small proportion (<1%) are covered by other (usually federal) programs. Although in some other Canadian provinces endoscopists are paid through alternative funding arrangements or on a salary basis, in Manitoba all are reimbursed for care provided on a fee-for-service basis. Fee-for-service physicians are more likely to ensure billing for their services than are the salaried physicians because their income depends on claim submissions. Furthermore, the ability to follow up patients longitudinally in our databases, the relatively low levels of migration into or out of Manitoba, and the large size of the cohort enhance the robustness of our findings. Thus the comprehensiveness of our data collection is an important advantage of our study.

One important disadvantage of our study methods, however, is that we could not absolutely ascertain the indications for the colonoscopy, the findings at the colonoscopy, the extent of the colonoscopy, or the quality of the bowel preparation at the time of the endoscopy. The diagnosis code in tariff submissions is often reflective of either the indication of the procedure or findings noted during the procedure and may not be accurate because there is limited incentive for its accuracy. We can only infer that individuals with a negative colonoscopy billed as a 3185, meaning colonoscopic evaluation with no concurrent biopsy or polypectomy, had a truly negative examination. We have indicated earlier that CRCs diagnosed between 6 months and 5 years from the date of the index negative colonoscopy result might have been partially accounted for by incomplete colonoscopies because there was a relative increase in right-sided colon cancers in the colonoscopy cohort compared with the general population of Manitobans with CRC, but we have no direct evidence documenting the procedural quality.

We were also unable to identify individuals at a higher risk of developing CRC due to a family history of CRC. However, inclusion of these individuals would lead to a more conservative estimate of the benefits of colonoscopy. Individuals with a positive family history of CRC are more likely to be classified as being at higher risk for CRC and as a result receive endoscopic evaluations at frequent intervals. Therefore, our subgroup analysis, for which we limited the analysis to individuals who had a single negative colonoscopy, likely excluded most of these individuals and provided a more accurate estimate

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of the benefit of colonoscopy in average-risk individuals. Furthermore, we are unable to determine whether our cohort members were at a lower baseline risk of developing CRC than the reference group (the general population of Manitoba) due to patients who sought colonoscopy possibly having healthier lifestyles or better access to health care than those who did not undergo colonoscopy. Although it can be speculated that people of a higher socioeconomic status are more likely to have colonoscopy performed, this bias is minimized in Manitoba because there is universal access to health care in Manitoba and no direct financial impediments to accessing health care.

An assumption made in our study is that any polyps or cancers visualized at the index colonoscopy would have been biopsied or removed. There is physician incentive to submit claims for the biopsies since there is an extra premium paid for taking biopsies. There is also an additional premium for performing polypectomies. However, it is possible that sometimes a 3186 or a 3187 (tariff codes for colonoscopy with biopsy and colonoscopy with polypectomy using a snare, respectively) could have been erroneously billed as 3185 due to clerical errors in coding. Furthermore, a colonoscopy billed with tariff code 3185 may not necessarily be a normal colonoscopy, because there may have been abnormalities present that did not require biopsy (such as melanosis coli or diverticulosis), or the endoscopists may have believed that performing an endoscopic biopsy was unsafe due to antiplatelet agents or anticoagulant medication that a patient may have been taking.

Another assumption in our study is that we assumed all CRCs that were diagnosed due to the initial diagnostic evaluation would have been diagnosed within 6 months of the initial procedure. For instance, it is possible that a patient underwent a colonoscopy and a cancer was identified but no biopsies were taken and the endoscopist submitted a 3185 tariff. We assumed that in that instance the individual would have either had a repeat colonoscopy with biopsy or surgery within 6 months or would have died. In such cases, as per the Manitoba Cancer Registry protocol, the date of CRC diagnosis would have been recorded as the date when tissue sample was obtained, rather than when CRC was suspected (ie, initial colonoscopy).

At the end of the follow-up period in our study, it is possible that some of the patients were harboring asymptomatic CRC (since these individuals had no endoscopic examination at the end of the study). However our strategy of evaluating CRC incidence in terms of evident or symptomatic cancers is similar to that used in the large fecal occult blood testing trials.[36,37] Moreover, we compared CRC incidence in a colonoscopy cohort with CRC incidence in all residents of Manitoba, some of who may also be harboring asymptomatic CRC.

In conclusion, our data are reassuring that the likelihood of developing CRC after a negative colonoscopy result remains low for more than 10 years after the index procedure. The magnitude of the reduction in CRC incidence in the overall population after a negative colonoscopy result may not be as great as previously suspected. However, if a patient has a single negative colonoscopy result and does not require further colonoscopy for a particular clinical indication, the likelihood of developing CRC is extremely low and for this group a screening interval between colonoscopies can be reasonably set at more than 10 years. Further study is required to determine the true duration of the decreased-risk interval following performance of a negative colonoscopy. Measures to improve the effectiveness of colonoscopy, including improvement in standards of colonoscopy, need to be developed.

Author Contributions: Dr Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Singh, Turner, Bernstein.
Acquisition of data: Singh, Turner, Xue.
Analysis and interpretation of data: Singh, Turner, Xue, Targownik, Bernstein.
Drafting of the manuscript: Singh.
Critical revision of the manuscript for important intellectual content: Singh, Turner, Xue, Targownik, Bernstein.
Statistical analysis: Singh, Turner, Xue.
Obtained funding: Turner, Bernstein.
Administrative, technical, or material support: Turner.
Study supervision: Turner, Bernstein.
Financial Disclosures: None reported.
Funding/Support: This work was supported in part by an unrestricted educational grant from AstraZeneca Canada. Dr Bernstein is supported in part by a Canadian Institutes of Health Research Investigator Award and by a Crohn's and Colitis Foundation of Canada Research Scientist Award. Dr Targownik is supported by the Rudy Falk Clinician Scientist Award.
Role of the Sponsors: AstraZeneca Canada had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Acknowledgment: We thank David Lieberman, MD, Division of Gastroenterology, Oregon Health and Science University and Portland VA Medical Center, Portland, for his thoughtful review of this article.

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—Gilbert Highet (1906-1978)

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