Risk of colorectal cancer after a negative colonoscopy in low-to-moderate risk individuals: impact of a 10-year colonoscopy

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ABSTRACT

Background and study aims National societies recommend colorectal cancer (CRC) screening 10 years after a normal (“negative”) colonoscopy in low-risk individuals. We studied the impact of a 10-year repeat colonoscopy on the risk of early incident CRC.

Patients and methods We used health administrative data from Ontario, Canada, to conduct a population-based retrospective cohort study in 50–74-year-old individuals at low-to-moderate risk of CRC who had a negative colonoscopy between 1996 and 2001. We approximated exposure to repeat colonoscopy using an 8–12-year window. We excluded individuals who underwent lower endoscopy or colectomy, developed CRC, or were lost to follow-up between the baseline and repeat colonoscopies. We matched exposed individuals 1:1 to individuals who did not undergo lower endoscopy within 12 years for age, sex, and calendar year of baseline colonoscopy, and followed matched pairs for incident CRC. The primary analysis was multivariable hazards regression, adjusting for competing risks.

Results A total of 13 350 matched pairs were observed for a median of 4.5 years (interquartile range 3.2–5.9 years). The cumulative probability of CRC following the matching date was 0.70% (95% confidence interval [CI] 0.42%–1.11%) in individuals who underwent repeat colonoscopy and 0.77% (95% CI 0.48%–1.2%) in individuals who did not undergo repeat colonoscopy. The adjusted hazard ratio for CRC was 0.91 (95% CI 0.68–1.22).

Conclusions We did not find an association between a second colonoscopy performed 10 years after a negative colonoscopy and early incident CRC. Our findings support the need for further studies on the utility of 10-year rescreening with colonoscopy in this setting.
Introduction

Colonoscopy reduces the risk of colorectal cancer (CRC) and CRC-related death [1–5], and is recommended by North American societies as a modality for CRC screening and prevention in individuals over the age of 50 years [6–8]. For individuals who do not have CRC or adenomas detected during colonoscopy ("negative colonoscopy") or major risk factors for developing CRC, re-screening for CRC is recommended after 10 years [7–9]. This recommendation is supported by several indirect lines of evidence: 1) Cohort and case–control studies have reported that a negative colonoscopy is associated with a substantially reduced risk of developing CRC for 10 years or longer among low-to-moderate risk individuals [4, 10–12]; 2) randomized controlled trials in screening cohorts have shown a protective benefit of flexible sigmoidoscopy against CRC and CRC-related death for more than 10 years [13, 14]; and 3) natural history and "portrait" studies suggest that the time to progression of low-risk adenomas to CRC is greater than 10 years [15, 16].

While these studies justify a re-screening interval no shorter than 10 years, few studies have evaluated whether 10-year colonoscopy in this setting further reduces the risks of CRC or CRC-related death. The very low rates of CRC observed for up to 10 years in negative colonoscopy cohorts cast doubt on the utility of this intervention at a population level [4, 10–12]. A modeling study based on a German screening cohort estimated the 10-year probability of developing CRC following a negative colonoscopy to be less than 0.5% [17]. Recent studies have also reported very low rates of CRC [18] and advanced adenomas [19] during screening colonoscopy performed close to 10 years after a negative screening colonoscopy.

Given the uncertainty about the utility of 10-year re-screening with colonoscopy, we used population-level data to study the real-world association between performance of a second colonoscopy 10 years following a negative colonoscopy and the risk of subsequent incident CRC in low-to-moderate risk screen-eligible individuals.

Patients and methods

Study setting and data sources

We used health administrative data from Ontario, Canada, to conduct this study. Ontario is a geographically and ethnically diverse province comprising more than 13 million inhabitants. Ontario health care is covered under a single public payer system for all legal long-term residents (>99% of the population) through the Ontario Health Insurance Plan (OHIP). All health care encounters and claims for drugs and services are recorded by the Ontario government and made available for research purposes. These unique features of health care delivery and data capture allow for comprehensive study of individual health care utilization and health outcomes at a population level.

Ontario health administrative data are housed at the institute for Clinical Evaluative Sciences (ICES), a nonprofit research institute. ICES enables linkage of individual-level data across datasets and health care encounters [20]. ICES datasets are linked using unique encoded identifiers and analyzed by trained ICES analysts. All diagnostic and procedural information is coded using the International Classification of Diseases and Canadian Classification of Interventions nomenclature, respectively. Lists of the datasets and administrative codes used for cohort derivation and ascertainment of study variables are provided in supplemental ▶Table1 and ▶Table2 (available online). This study was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Study design, subjects, and outcomes

We conducted a population-based retrospective cohort study in low-to-moderate risk individuals aged 50–74 years who underwent a negative complete colonoscopy (colonoscopy to cecum or terminal ileum without polypectomy, polyp fulguration, biopsy, or CRC diagnosis) between 1 July 1996 and 31 December 2001. Colonoscopy completeness can be gauged through physicians’ billing claims, which require a separate claim for each intubated segment. We considered all consecutive lower endoscopies performed within 12 months of one another, wherein at least one of the procedures was complete to the cecum or terminal ileum, as part of a single colonoscopy "episode," as some individuals would have had multiple successive procedures as part of a single planned evaluation, owing to poor bowel preparation [19], uncertainty about the completeness of polyp eradication [19], referral to advanced specialists and/or centers for management of complex lesions, or re-evaluation prior to surgical cancer resection. In such cases, the procedure end date (and observation start date) was the date of the last procedure in the series. We excluded individuals in whom the total duration of an episode exceeded 2 years in order to avoid including individuals who were undergoing frequent surveillance.

To define a low-to-moderate risk cohort, we excluded all individuals with inflammatory bowel disease, a history of CRC (since 1964), or a history of partial or total colectomy or lower endoscopy within 5 years preceding the negative colonoscopy, which is similar to the approach used in previous studies [11, 12]. We also excluded individuals who did not have continuous OHIP coverage for 5 years preceding the negative colonoscopy, as they could have incurred exclusionary events outside of Ontario. We further excluded individuals without a valid OHIP number (which is necessary for deterministic individual linkage) and those residing in areas in which some physicians are salaried by their institutions and do not submit billing claims (which was necessary for ascertaining several study variables). We did not specifically exclude individuals who underwent colonoscopy for evaluation of symptoms or signs (including positive fecal occult blood testing [FOBT] or abnormal laboratory investigations), a family history of CRC or a history of colorectal adenomas.

For this cohort, we ascertained exposure to a 10-year complete colonoscopy by using an 8–12-year window following the negative colonoscopy, allowing for differences in the interpretation of this screening recommendation and exact timing of the procedure in clinical practice. As our objective was to study the protective benefit of a second colonoscopy performed at an appropriate screening interval, we excluded indi-
viduals who underwent lower endoscopy, as well as those who underwent colectomy, developed CRC, or lost health care coverage, between the baseline and repeat colonoscopies. We extended these exclusion criteria to a 6-month period following the date of repeat colonoscopy to account for lag time for formal pathological diagnosis and capture of CRC events within the Ontario Cancer Registry (or events that would preclude ascertainment of CRC diagnosis), which is similar to the approach used in previous studies [1, 11]. The exclusion of individuals who were diagnosed with CRC during repeat colonoscopy was important for two reasons: first, to ensure accurate ascertainment of subsequent incident CRC, which was the primary study outcome; and second, to avoid confounding by indication (because symptomatic and other higher-risk individuals are more likely to have been in the exposed group), which could have led to a spurious association between repeat colonoscopy and CRC diagnosis. Unfortunately, procedure indication is not included in Ontario health administrative data; therefore, we were only able to address this potential issue by excluding detected cancers at the second colonoscopy.

We matched individuals who were not exposed to a lower endoscopy (including colonoscopy or flexible sigmoidoscopy) within 12 years following the baseline negative colonoscopy to exposed individuals for age, sex, and calendar year of baseline colonoscopy. We applied the same exclusion criteria for unexposed individuals as we did for exposed individuals based on the date of matching for each pair. Matched pairs were excluded from the final analysis if either individual had missing data on one or more baseline characteristics, including age, sex, neighborhood income quintile, residential setting (rural vs. urban), co-morbidity burden (based on the Ambulatory Diagnostics Group [ADG] Score), endoscopist specialty at baseline colonoscopy (gastroenterologist vs. nongastroenterologist), and institutional setting at baseline colonoscopy (academic hospital vs. nonacademic hospital vs. community endoscopy clinic). We re-assigned any endoscopist with a designation of internist as a gastroenterologist if they performed more than 200 colonoscopies in the year preceding the baseline colonoscopy. We assigned a colonoscopy to a hospital setting if there was an individual record in the hospital database corresponding to the date of a physician claim for the colonoscopy. We defined academic hospitals as those affiliated with a university.

We observed matched pairs from 6 months following a repeat complete colonoscopy until the development of CRC (primary outcome), a competing event (colectomy or death not attributable to CRC), loss-to-follow-up (based on OHIP coverage) or the end of the study period (31 December 2014). As a secondary evaluation, we describe the distribution of CRC stage (based on the Tumor, Node and Metastasis system), as well as the proportion of individuals who died from CRC among individuals who had CRC diagnosed during repeat colonoscopy, those who had CRC diagnosed following repeat colonoscopy and those who did not undergo 10-year repeat colonoscopy. Owing to incomplete cancer stage data in the Ontario Cancer Registry prior to 2007 and limited observation time for ascertaining deaths following a repeat colonoscopy, we did not perform statistical analyses of these outcomes. Reliable information on cause-specific death could only be ascertained until 31 December 2012.

Statistical methods
We assessed standardized differences in baseline characteristics between exposure groups. Variables with a standardized difference of 0.1 or greater were considered to be statistically unbalanced and were included as covariates in the multivariable models. We used the cumulative incidence function approach to estimate the probability of developing CRC over time while accounting for competing risks (death or colectomy not attributable to CRC). This was done for the overall cohort, and for the exposed and unexposed groups separately. We used two proportional hazards regression functions to model future CRC events. The primary analysis used a conditional sub-distribution hazard function, which models the cumulative risk of developing CRC and accounts for competing risks through informative censoring. A secondary analysis used a conditional cause-specific hazard function, which models the average instantaneous rate of developing CRC over the follow-up period and deals with competing risks through noninformative censoring. Individuals were censored at the time of loss-to-follow-up or at the end of the study observation period (31 December 2014) in all models.

We used two-tailed testing at a 5% level of significance for all statistical comparisons, and report 95% confidence intervals (CI) for all point estimates. All statistical analyses were conducted using SAS Enterprise Guide 6.1 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

Study cohort
Of 104 830 average-risk screen-eligible individuals who underwent a complete negative colonoscopy, 13 350 matched pairs were included in the final analysis (▶ Fig. 1). ADG score was the only baseline characteristic that differed significantly between the two exposure groups (▶ Table 3). Individuals who underwent repeat colonoscopy during the 8 – 12-year exposure window were not different with respect to baseline characteristics compared with individuals who underwent repeat lower endoscopy within 8 years of the baseline colonoscopy (who were excluded from the study), aside from having a slightly lower prevalence of baseline colonoscopies performed at community clinics (10.7% vs. 16.8%) and by nongastroenterologists (50.0% vs. 53.2%) (supplemental ▶ Table 4, available online). The demographics of our exposure group of interest were thus reasonably representative of all individuals undergoing repeat colonoscopy within 12 years of baseline colonoscopy.

Single- vs. multi-procedure repeat colonoscopy
Of the 13 350 included individuals who underwent repeat colonoscopy, 766 (5.7%) had a multi-procedure episode (median 2 procedures, interquartile range [IQR] 2 – 3), and these procedures accounted for 43.6% of all CRC diagnosed during repeat colonoscopy. Of these, 98% were diagnosed within 6 months of
the first lower endoscopic procedure in the series, while one CRC was diagnosed in the seventh month following the first procedure in the series.

**Cumulative probability of CRC**

The cumulative probability of developing CRC over 3, 5, and 8 years following the baseline negative colonoscopy were 0.16% (95% CI 0.14% – 0.19%), 0.30% (95% CI 0.27% – 0.34%), and 0.54% (95% CI 0.49% – 0.58%), respectively (Fig. 2). We also observed 117 CRCs (0.84%) among 14,001 individuals who underwent repeat complete colonoscopy between 8 and 12 years following negative colonoscopy.

Among matched individuals, there were 46 incident CRCs diagnosed in those who underwent 10-year repeat colonoscopy (excluding individuals diagnosed with CRC during repeat colonoscopy) and 52 CRC diagnosed in those who did not undergo 10-year repeat colonoscopy, over a median observation time of 4.5 years (IQR 3.2 – 5.9 years). The cumulative probability of developing CRC, accounting for competing risks, was 0.70% (95% CI 0.42% – 1.11%) among exposed individuals and 0.77% (95% CI 0.48% – 1.2%) among unexposed individuals (Fig. 3). The analysis was truncated at 8 years of observation, as the estimates of CRC incidence were unstable beyond this time.

**Sub-distribution and cause-specific hazard ratios for CRC**

Over a median of 4.5 years of observation (IQR 3.2 – 5.9 years), the univariate sub-distribution hazard ratio (HR) for CRC was 0.94 (95% CI 0.70 – 1.3) and the univariate cause-specific HR for CRC was 0.87 (95% CI 0.57 – 1.3) for individuals exposed to a 10-year repeat colonoscopy. After adjusting for ADG score, the sub-distribution HR for CRC was 0.91 (95% CI 0.68 – 1.22) and the cause-specific HR for CRC was 0.83 (95% CI 0.54 – 1.28) (Table 5).
Table 3  Characteristics of age- and sex-matched study patients.1

<table>
<thead>
<tr>
<th></th>
<th>Repeat colonoscopy (n= 13 350)</th>
<th>No repeat colonoscopy (n= 13 350)</th>
<th>Standardized difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>68 (63 – 74)</td>
<td>68 (63 – 74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Male</td>
<td>5 858 (43.9)</td>
<td>5 858 (43.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>▪ Female</td>
<td>7 492 (56.1)</td>
<td>7 492 (56.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neighborhood household income quintile, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ 0 – 20%</td>
<td>1 898 (14.2)</td>
<td>2 357 (17.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>▪ 21% – 40%</td>
<td>2 298 (17.2)</td>
<td>2 687 (20.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>▪ 41% – 60%</td>
<td>2 586 (19.4)</td>
<td>2 600 (19.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>▪ 61% – 80%</td>
<td>2 852 (21.4)</td>
<td>2 636 (19.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>▪ 81% – 100%</td>
<td>3 716 (27.8)</td>
<td>3 070 (23.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Residential setting, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Rural</td>
<td>1 613 (12.1)</td>
<td>1 889 (14.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>▪ Urban</td>
<td>11 737 (87.9)</td>
<td>11 461 (85.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>ADG score, median (IQR)</td>
<td>14 (5 – 22)</td>
<td>10 (3 – 19)</td>
<td>0.25</td>
</tr>
<tr>
<td>▪ Endoscopist specialty 2, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Gastroenterologist</td>
<td>6 690 (50.1)</td>
<td>6 120 (45.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>▪ Nongastroenterologist</td>
<td>6 660 (49.9)</td>
<td>7 230 (54.2)</td>
<td></td>
</tr>
<tr>
<td>Institutional setting 2, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Academic hospital</td>
<td>2 148 (16.1)</td>
<td>2 205 (16.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>▪ Nonacademic hospital</td>
<td>9 758 (73.1)</td>
<td>9 853 (73.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>▪ Community clinic</td>
<td>1 444 (10.8)</td>
<td>1 292 (9.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IQR, interquartile range; ADG, Ambulatory Diagnostics Group.

1 At 8 years following baseline negative colonoscopy.

2 Corresponds to baseline negative colonoscopy.

Fig. 2  Cumulative incidence function for colorectal cancer (CRC) beginning 6 months following a negative colonoscopy in low-to-moderate risk 50–74-year-old individuals. Competing risks include death or colectomy not attributable to CRC. Shaded bars represent 95% confidence limits.

Fig. 3  Cumulative incidence functions for colorectal cancer (CRC) among matched pairs of low-to-moderate risk 50–74-year-old individuals, stratified by exposure to 10-year repeat colonoscopy. Observation begins 6 months following matching date. Competing risks include death or colectomy not attributable to CRC. Shaded bars represent 95% confidence limits.
Table 5  Hazard ratios from multivariable proportional hazards regression analyses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sub-distribution HR (95%CI)</th>
<th>Cause-specific HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat colonoscopy</td>
<td>0.91 (0.68–1.22)</td>
<td>0.83 (0.54–1.28)</td>
</tr>
<tr>
<td>ADG score (per 1 point increase)</td>
<td>1.01 (0.99–1.04)</td>
<td>1.02 (0.99–1.05)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; ADG, Ambulatory Diagnostics Group.

1 Evaluates risk ratio and treats death or colectomy not attributable to CRC as competing events.
2 Evaluates rate ratio and treats death or colectomy not attributable to CRC as censor events.

CRC stage and CRC-specific deaths

Reliable information regarding CRC stage was available for 98 of 117 CRCs diagnosed during repeat colonoscopy, 38 of 47 CRCs diagnosed after repeat colonoscopy, and 97 of 109 CRC diagnosed in individuals who did not undergo repeat colonoscopy between 8 and 12 years following negative colonoscopy (including all 25,496 unexposed individuals who were included and excluded from the primary analysis). In these groups, the proportion of CRC diagnosed as Stage III or IV cancers was 38.8%, 34.2%, and 50.5%, respectively, while the proportion of CRC diagnosed as Stage I cancers was 31.6%, 32.4%, and 19.6%, respectively.

There were eight CRC-related deaths among the 14,001 individuals (0.06%) who underwent repeat colonoscopy (including CRC that were diagnosed during and after repeat colonoscopy), and nine CRC-related deaths among the 25,496 individuals (0.04%) who did not undergo repeat colonoscopy between 8 and 12 years following negative colonoscopy.

Discussion

In this population-based study of 50–74-year-old low-to-moderate risk individuals who had a negative colonoscopy in Ontario, we did not observe a difference in the risk of incident CRC over a median observation time of 4.5 years (IQR 3.2–5.9 years) between individuals who did or did not have a second colonoscopy performed 8–12 years following the baseline colonoscopy. The probability of developing CRC was very low for both groups of individuals (0.70% and 0.77%, respectively). Notably, as we did not study a true screening cohort and had limited observation time to detect a difference in CRC rates, our findings require confirmation in future studies.

We also observed a low (0.54%) cumulative probability of being diagnosed with CRC within 8 years of a negative colonoscopy, suggesting that a 10-year interval may be too late for some individuals. However, a substantial proportion of these individuals probably had cancers or advanced adenomas that were missed or inadequately treated at the time colonoscopy. Improving baseline colonoscopy quality may be more effective in reducing the risk of post-colonoscopy CRC than repeating a colonoscopy earlier than 10 years in this setting.

Notably, we were unable to study the value of repeating colonoscopy at 10 years to detect early and potentially curable CRC, because of incomplete information on CRC stage and insufficient statistical power to assess the impact of a second colonoscopy on the risk of CRC-related death. As diagnosing early asymptomatic CRC may be an equally justifiable reason to perform a 10-year screening colonoscopy, further studies are required to assess the utility of the practice for this specific indication. Nonetheless, we observed a low rate of CRC (0.84%) detected during opportunistic 10-year colonoscopies in our cohort. Moreover, a substantial proportion of these individuals would have likely undergone repeat colonoscopy to evaluate relevant signs or symptoms, which would not be affected by a screening recommendation.

Our findings add to those of previous studies reporting that a negative colonoscopy selects for a group of individuals who are at much lower risk of developing CRC than the general population for 10 years or longer [10–12]. They also complement those of recent studies demonstrating a low rate (3%–4%) of advanced adenomas [18, 19], as well as one study reporting no detectable CRC [18] among low-to-moderate risk individuals who underwent repeat screening colonoscopy close to 10 years following a negative screening colonoscopy.

Conversely, a microsimulation modeling study found that rescreening in accordance with current guidelines could reduce the risk of CRC compared with no re-screening following a negative colonoscopy among 50-year-old individuals [21]. However, in this study, rescreening with annual FOBT or computed tomographic colonography every 5 years, provided roughly the same survival benefit with fewer complications and at a lower cost compared with repeating colonoscopy every 10 years.

Taken collectively, the data suggest that it may be reasonable to consider less-invasive methods to risk stratify individuals for colonoscopy 10 years after a negative colonoscopy. Although the overall value of 10-year re-screening remains questionable, using less-invasive and less-costly methods may strike a better balance between clinical effectiveness, individual risk, and cost of re-screening until more data become available to identify those who stand to benefit the greatest from repeat colonoscopy, as well as the optimal timing of this intervention. Reducing the colonoscopy frequency in low-risk individuals would also improve access to colonoscopy for higher-risk individuals. In Ontario, more than half of individuals aged 50–74 years who undergo colonoscopy have a negative colonoscopy (unpublished data); further screening in this subgroup can thus have a major impact on colonoscopy burden in society.

We applied multiple exclusion criteria to a population-level cohort undergoing colonoscopy for diagnostic and screening indications to approximate a low-to-moderate risk cohort and a 10-year re-screening paradigm, accepting that there would be some limitations with this approach. Given the immense challenges in conducting a pragmatic randomized controlled trial to answer our study question, this was the most feasible approach to gain some insight into this area. The availability of continuous, comprehensive, linkable health care data spanning multiple decades and the application of rigorous methods, in-
cluding strict eligibility criteria, individual matching, and competing risks analysis, were major strengths of this study.

A significant limitation of our data was the inability to differentiate symptomatic and slightly higher-risk individuals (such as those with a family history of CRC) from low-risk asymptomatic individuals, for whom the 10-year re-screening recommendation is intended. The former group of individuals would have had a greater tendency to be referred for repeat colonoscopy and would have also been at higher risk of harboring prevalent cancers, which could have led to a spurious association between colonoscopy and CRC. To compensate for this, we specifically excluded individuals who were diagnosed with CRC during repeat colonoscopy. However, there could have still been residual bias favoring a higher risk of incident CRC among individuals who underwent repeat colonoscopy, particularly if individuals with environmental risk factors for CRC, such as smoking history or obesity, were more likely to undergo colonoscopy. Furthermore, we were unable to exclude prevalent cancers among those who did not have a repeat 10-year colonoscopy; however, this would have had the effect of underestimating the hazard ratio and its correction would not have changed the interpretation of our findings.

Another potential limitation is the possibility that we isolated a residual cohort comprising largely symptomatic individuals or otherwise very low-risk asymptomatic individuals, who were less representative of individuals undergoing 10-year screening nowadays. Until the past decade, the acceptable timeframe for repeating a colonoscopy in low-to-moderate risk asymptomatic individuals in Canada was closer to 5 years. Notably, close to half of our starting cohort underwent lower endoscopy within 8 years of negative colonoscopy. We did not observe any major differences in characteristics between these individuals and those who underwent colonoscopy between 8 and 12 years following negative colonoscopy. However, we were not able to measure all important characteristics, particularly indication for colonoscopy or individual recalcitrance.

Relatively short observation time could have also attenuated the association between 10-year repeat colonoscopy and risk of incident CRC in this study. However, this still poses the question as to whether a longer re-screening interval would confer a similar benefit as a 10-year interval, which would still have significant implications to costs of screening and individual wait times for colonoscopy. Unfortunately, we did not have sufficient data to describe the impact of colonoscopy performed at longer intervals following a negative colonoscopy. Low rates of incident CRC could have further caused the study to be underpowered; however, we are unable to accurately determine statistical power in this study as a minimal clinically important difference in CRC rates has not been established in this context. Nevertheless, the low rate of incident CRC resulted in fairly wide confidence intervals for measures of CRC rates and hazard ratios, lending some uncertainty to the true CRC risk with or without repeat colonoscopy.

In summary, using population-level data to approximate a low-to-moderate risk screen-eligible cohort, we did not observe an association between a second colonoscopy performed 10 years after a negative colonoscopy and risk of subsequent incident CRC. Our findings add to a growing body of literature questioning the merits of a 10-year repeat colonoscopy in this setting. Prospective studies in screening cohorts followed for longer periods of time are needed to further address the overall impact of this intervention and to identify the optimal timing for re-screening in this setting.

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Competing interests

Dr. S. Murthy has received honoraria for participation in advisory board meetings for Abbvie, Takeda, Shire, Ferring and Pfizer in the past 3 years. None of the other authors have any conflicts to declare. None of the authors have any conflicts directly relevant to the present work.

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