Duration of risk reduction in colorectal cancer incidence and mortality after a complete colonoscopy in Ontario, Canada: a population-based cohort study

Arlinda Ruco, Rahim Moineddin, Rinku Sutradhar, Jill Tinmouth, Qing Li, Linda Rabeneck, M Elisabetta Del Giudice, Catherine Dubé, Nancy N Baxter

Summary

Background Colorectal cancer guidelines recommend screening colonoscopy every 10 years after a negative procedure. If risk reduction extends past 10 years, the recommended interval could be extended, reducing the burden on the individual and health-care system. We aimed to estimate the duration that patients remain at reduced risk of colorectal cancer incidence and mortality after a complete colonoscopy.

Methods We did a population-based cohort study of individuals aged 50–65 years between Jan 1, 1994, to Dec 31, 2017. We excluded individuals with previous exposure to colonoscopy or colorectal surgery, those previously diagnosed with colorectal cancer, or a history of hereditary or other bowel disorders. We followed up participants until Dec 31, 2018, and identified all colonoscopies performed in this time period. We used a 9-level time-varying measure of exposure, capturing time since last complete colonoscopy (no complete colonoscopy, ≤5 years, >5–10 years, >10–15 years, and >15 years) and whether an intervention was performed (biopsy or polypectomy). A Cox proportional hazards regression model adjusting for age, sex, comorbidity, residential income quintile, and immigration status was used to estimate the association between exposure to a complete colonoscopy and colorectal cancer incidence and mortality.

Findings 5 298 033 individuals (2 609 060 [49·2%] female and 2 688 973 [50·8%] male; no data on ethnicity were available) were included in the cohort, with a median follow-up of 12·56 years (IQR 6·26–20·13). 90 532 (1·7%) individuals were diagnosed with colorectal cancer and 44 088 (0·8%) died from colorectal cancer. Compared with those who did not have a colonoscopy, the risk of colorectal cancer in those who had a complete negative colonoscopy was reduced at all timepoints, including when the procedure occurred more than 15 years earlier (hazard ratio [HR] 0·62 [95% CI 0·51–0·77] for female individuals and 0·57 [0·46–0·70] for male individuals. A similar finding was observed for colorectal cancer mortality, with lower risk at all timepoints, including when the procedure occurred more than 15 years earlier (HR 0·64 [95% CI 0·49–0·83] for female participants and 0·65 [0·50–0·83] for male participants). Those who had a colonoscopy with intervention had a significantly lower colorectal cancer incidence than those who did not undergo colonoscopy if the procedure occurred within 10 years for females (HR 0·70 [95% CI 0·63–0·77]) and up to 15 years for males (0·62 [(0·53–0·72]).

Interpretation Compared with those who do not receive colonoscopy, individuals who have a negative colonoscopy result remain at lower risk for colorectal cancer incidence and mortality more than 15 years after the procedure. The current recommendation of repeat screening at 10 years in these individuals should be reassessed.

Funding Canadian Institutes of Health Research.

Introduction

Average-risk screening for colorectal cancer with colonoscopy is common[1–5] and recommended by a number of screening guidelines.[6–11] After a negative procedure (ie, with no findings of colorectal neoplasia), it is recommended by screening guidelines that a follow-up screening occurs after 10 years,[6–12] although this recommendation is based on scarce evidence and modelling studies.[13–16] Some previously published literature suggest that this re-screening interval might be potentially extended beyond 10 years.[17–24] For example, a recent study of 120 298 individuals who received repeated screening colonoscopy 10 years after a negative colonoscopy reported a reduced prevalence of advanced colorectal neoplasia compared with those who received an initial screening procedure, suggesting that longer intervals might be warranted.[18]

In a 2019 systematic review and meta-analysis examining longer term outcomes for individuals with negative colonoscopy, only three studies included intervals of more than 10 years.[25] The authors concluded more evidence, including higher quality studies, were needed for durations of longer than 10 years to further inform recommended intervals for repeat screening.[25]

Developing a better understanding of the duration of the reduction in risk of colorectal cancer incidence and

Lancet Gastroenterol Hepatol 2024

Published Online May 15, 2024 https://doi.org/10.1016/S2468-1253(24)00084-0

See Online/Comment https://doi.org/10.1016/S2468-1253(24)00115-8

Interdisciplinary Health Program, St Francis Xavier University, Antigonish, NS, Canada (A Ruco PhD); **Peter Gilgan Centre for Women's Cancers, Women's College Hospital, Toronto, ON, Canada** (A Ruco); **Beatrice Hunter Cancer Research Institute, Halifax, NS, Canada** (A Ruco); **VHA Home HealthCare, Toronto, ON, Canada** (A Ruco); **Department of Family and Community Medicine** (Prof R Moineddin PhD, Prof L Rabeneck MD MPH, M E Del Giudice MD MSc) **and Department of Surgery** (Prof N N Baxter MD PhD), **Dalla Lana School of Public Health** (Prof R Sutradhar PhD, J Tinmouth MD PhD, Prof L Rabeneck, Prof N N Baxter), **University of Toronto, Toronto, ON, Canada; ICES, Toronto, ON, Canada** (Prof R Sutradhar, Q Li MMath, Prof L Rabeneck, Prof N N Baxter); **Prevention & Cancer Control, Ontario Health (Cancer Care Ontario), Toronto, ON, Canada** (J Tinmouth); **Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (J Tinmouth); **Department of Family and Community Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (M E Del Giudice); **Department of Medicine, The Ottawa Hospital–University of Ottawa, Ottawa, ON, Canada** (C Dubé MD MSc); **Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada** (Prof N N Baxter); **School of Population and**

Global Health, University of Melbourne, Melbourne, VIC, Australia (Prof N N Baxter)

Correspondence to: Prof Nancy N Baxter, School of Population and Global Health, University of Melbourne, Melbourne, VIC 3010, Australia
baxtern@smh.ca

Research in context

Evidence before this study

Colorectal cancer guidelines recommend screening colonoscopy every 10 years after a negative procedure. We searched Ovid MEDLINE without date or language restrictions for articles exploring the association between receipt of colonoscopy and colorectal cancer incidence and related mortality, using terms such as "colonoscopy", "colorectal neoplasms", "colon cancer", and "early detection of cancer". Some studies suggest that individuals who had a negative colonoscopy are at a lower risk of colorectal cancer for a duration that potentially extends beyond the 10-year recommended rescreening interval. However, more evidence is needed for durations of longer than 10 years, including from higher quality studies to refine or further inform recommended intervals for repeat screening.

Added value of this study

In this population-based cohort study based in Ontario, Canada, the risk of colorectal cancer in those who had a complete and negative colonoscopy was reduced at all timepoints, including if the procedure occurred more than 15 years earlier (HR 0·62 [95% CI 0·51–0·77] for female individuals and 0·57 [0·46–0·70] for male individuals) compared with those who did not have a colonoscopy. A similar result was observed for colorectal cancer-related mortality. This study included a median follow-up time of 12·56 years (IQR 6·26–20·13) with over 69 million person-years of follow-up. We had the capacity to track multiple colonoscopies over time in all settings in the province and used a novel time-varying exposure that could account for multiple exposures to colonoscopy, whether or not an intervention was completed, and time since last colonoscopy.

Implications of all the available evidence

Our results showed that reduction in risk after a complete negative colonoscopy extends beyond 10 years, providing evidence that the interval for repeat colonoscopy recommended by various screening guidelines could be extended.

mortality associated with a complete colonoscopy is important—if the duration of risk reduction extends past 10 years for patients with a negative colonoscopy, then the recommended interval for repeat screening colonoscopy could be extended, reducing the burden on individuals and the health-care system. Colonoscopy could, therefore, have an important role for risk stratification of individuals. We aimed to estimate the duration that patients remain at reduced risk of colorectal cancer incidence and mortality after a complete colonoscopy.

Methods

Study design and setting

In this population-based retrospective cohort study done in Ontario, Canada, we used linked health administrative databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse health-care data and demographic data, without consent, for health-care system evaluation and improvement. The study was approved by the Research Ethics Board at the University of Toronto and reporting of the study is consistent with the RECORD statement.[26]

Data sources

The Discharge Abstract Database and the National Ambulatory Care Reporting System contain information for all hospital and ambulatory services in Canada, including day surgeries and colonoscopies, outpatient clinics, and emergency department visits. The Ontario Health Insurance Plan (OHIP) physician claims database contains information on all claims billed by physicians for reimbursement of services in the province since July 1, 1991. The Ontario Cancer Registry contains information on all incident cancers diagnosed and cancer deaths in the province since January 1, 1964. The Office of the Registrar General–Deaths database contains vital mortality statistics from Jan 1, 1990, onwards. The Registered Persons Database contains demographic information on individuals who are OHIP beneficiaries from April 1, 1991, onwards and the Immigration, Refugee and Citizenship Canada database contains information on all permanent residents in the country from Jan 1, 1985, onwards. Race and ethnicity data are not routinely collected in these health administrative databases and therefore were not available.

The datasets were linked using unique encoded identifiers and analysed at ICES. Ontario provides universal insurance coverage for hospital care and physician services and therefore these databases are comprehensive in capturing health care delivered in the province. If individuals moved out of the province, they would be ineligible for the provincial health insurance plan.

Study cohort

We identified all individuals aged 50–65 years who were eligible for OHIP within the study accrual window (Jan 1, 1994, to Dec 31, 2017). To approximate an average risk cohort, we excluded those with any previous exposure to colonoscopy or colorectal surgery, those who had been previously diagnosed with colorectal cancer, those ever diagnosed with inflammatory bowel disease, and those with a history of hereditary or other bowel disorders (eg, familial adenomatous polyposis; appendix pp 1–2). We

See Online for appendix

also excluded those with any previous exposure to stool-based testing (faecal immunochemical test or faecal occult blood test) before or on the study entry date. Individuals were followed up from study entry (ie, study entry was first date of eligibility) until death, last date of eligibility, or if they were not eligible for OHIP for two consecutive quarters during the follow-up period (Jan 1, 1994, to Dec 31, 2018), whichever occurred first. Follow-up was also terminated at the occurrence of a colonoscopy with colon stent, dilatation of stricture, or excision of obstructive tumour or stricture at colonoscopy, since these occurrences are likely to be associated conditions that increase risk of colorectal cancer. These individuals were censored one day before this procedure and not counted as having had colorectal cancer. We also censored individuals if they had an incomplete colonoscopy (ie, one that did not reach the caecum or terminal ileum) or a flexible sigmoidoscopy.

Covariates

We obtained demographic characteristics for individuals in our cohort, including age (50–59 years, 60–69 years, and ≥70 years) sex (male or female), immigration status (immigrant *vs* long-term resident), socio-economic status based on the median neighbourhood income quintile (Q1, lowest to Q5, highest for urban areas, and rural),[2,3,27] and comorbidities using the Johns Hopkins ACG System Aggregated Diagnosis Groups (ADGs).[3] We used major ADGs from the two previous years and categorised individuals as having 0, 1, or 2 or more major ADGs.[27] Age, neighbourhood income quintile, and comorbidities were updated annually in our dataset and thus could change over time. Confounders were identified a priori using the research literature and clinical judgements, as well as data availability.

Exposure

The primary exposure was having had a complete colonoscopy (procedure reaching the caecum or terminal ileum). A negative colonoscopy was a procedure where no intervention was performed (biopsy, polypectomy, or bleeding on the same day of the procedure indicating an intervention was performed; appendix p 3).

Since we were interested in the risk of colorectal cancer incidence and mortality over time in the population where additional colonoscopy might occur at varying intervals and given that colonoscopies requiring intervention at the procedure can inform risk of disease (and thus rescreening interval), we developed a 9-level time-varying covariate that captured the time since most recent complete colonoscopy (no complete colonoscopy recorded, ≤5 years, >5–10 years, >10–15 years, and >15 years) and whether any intervention had occurred during that episode of care. Multiple colonoscopies occurring within 6 months were considered one episode of care, with the date of the first procedure considered the exposure date, and the exposure was classified according to whether an intervention was done during any colonoscopy. If a colonoscopy was done more than 6 months after the date of exposure, this was considered a new procedure. For individuals who had stool-based testing completed during the study period, we excluded any colonoscopies completed 2 years after their faecal testing because these procedures might be related to diagnostic follow-up rather than primary screening.

The exposure was updated once an individual had a colonoscopy and annually for the entire cohort. In this way, individuals could contribute multiple person-years to various categories of exposure over time. For example, an individual who had a colonoscopy could contribute up to 5 person-years to the first category of exposure (most recent colonoscopy ≤5 years with or without intervention) and then could contribute another 5 person-years of observation to the second category of exposure (most recent colonoscopy within >5–10 years with or without intervention).

Outcomes

The outcomes were incidence of colorectal cancer as determined through the Ontario Cancer Registry and colorectal cancer-related mortality as determined through the Office of the Registrar General–Deaths (appendix p 4).

Statistical analysis

We used descriptive statistics to summarise the distributions of the study cohort and calculated crude rates for colorectal cancer incidence and mortality. Since we were interested in risk of colorectal cancer incidence and mortality over time and because individuals might have multiple colonoscopies, we used time-to-event analysis using Cox proportional hazards regression model, with time-varying covariates updated annually to estimate the association between exposure to a complete colonoscopy on the hazard ratios (HRs) and 95% CIs of colorectal cancer incidence and mortality. The proportional hazards assumption was assessed and satisfied by examining Schoenfeld residuals. The origin and start time for analysis included when individuals were eligible for study entry based on the inclusion criteria until the occurrence of the outcome, death, or until censoring, whichever occurred first. If a colorectal cancer diagnosis occurred within 6 months of a procedure, the individual was considered to have had the outcome and the episode of care was therefore not counted because this diagnosis suggested that the outcome was likely present before the current episode of care.[28] We also present the colorectal cancer incidence per 1000 person-years for each level of our time-varying covariate stratified by sex. We conducted several sensitivity analyses, including not excluding colonoscopies completed within 2 years of a stool test and an analysis with death from other causes as a competing risk for the outcome of colorectal cancer-related mortality. Significance was determined at the p=0·05 level with

two-sided tests and all analyses were sex-stratified. Observations with any missing data were minimal (<1%) and were excluded from the analysis because these were unlikely to skew the results given our large sample size.[29]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

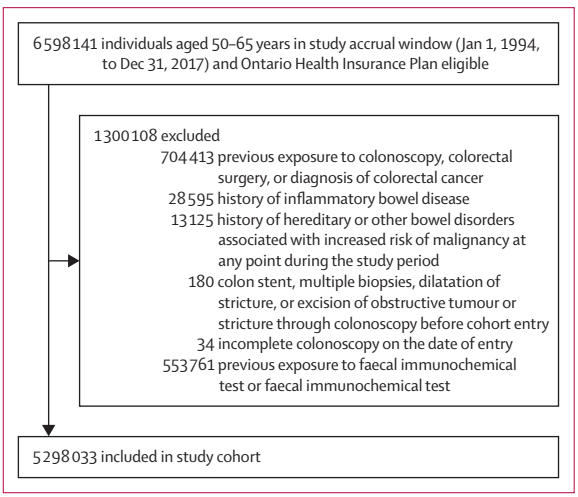

Figure 1: **Study profile**

	Female individuals (n=2 609 060)	Male individuals (n=2 688 973)	Total (N=5 298 033)
Age at cohort entry			
Mean (SD), years	52·42 (4·32)	52·26 (4·17)	52·34 (4·24)
Years of follow-up			
Median (IQR), years	13·02 (6·51–20·72)	12·17 (6·04–19·54)	12·56 (6·26–20·13)
Comorbidity (major ADGs)			
0 ADGs	1 679 107 (64·4%)	1 761 271 (65·5%)	3 440 378 (64·9%)
1 ADG	633 637 (24·3%)	621 861 (23·1%)	1 255 498 (23·7%)
2+ ADGs	296 316 (11·4%)	305 841 (11·4%)	602 157 (11·4%)
Geographical region			
Urban	2 277 201 (87·3%)	2 318 239 (86·2%)	4 595 440 (86·7%)
Rural	327 202 (12·5%)	357 293 (13·3%)	684 495 (12·9%)
Missing	4657 (0·2%)	13 441 (0·5%)	18 098 (0·3%)
Resident status			
Long-term resident	2 202 181 (84·4%)	2 276 589 (84·7%)	4 478 770 (84·5%)
Immigrant	406 879 (15·6%)	412 384 (15·3%)	819 263 (15·5%)
Income quintile			
Missing	10 926 (0·4%)	20 965 (0·8%)	31 891 (0·6%)
1	492 201 (18·9%)	517 607 (19·2%)	1 009 808 (19·1%)
2	510 122 (19·6%)	522 980 (19·4%)	1 033 102 (19·5%)
3	516 315 (19·8%)	528 379 (19·6%)	1 044 694 (19·7%)
4	523 555 (20·1%)	537 168 (20·0%)	1 060 723 (20·0%)
5	555 941 (21·3%)	561 874 (20·9%)	1 117 815 (21·1%)

ADG=aggregated diagnosis group.

Table 1: **Baseline characteristics stratified by sex at study cohort entry**

Results

Between Jan 1, 1994, to Dec 31, 2017, 5 298 033 individuals were included in the study cohort (figure 1). 2 609 060 (49·2%) were female and 2 688 973 were male, and the mean age was 52·34 (SD 4·24) years at entry into the cohort (table 1). Median follow-up was 12·56 (IQR 6·26–20·13) years. Most of the cohort lived in urban areas (4 595 440 [86·7%] individuals) and were long-term residents of Canada (4 478 770 [84·5%] individuals). 1 392 878 (26·3%) individuals had at least one complete colonoscopy (range 0–17). For the outcome of colorectal cancer incidence, we had 58 995 962 person-years of follow-up for those with no complete colonoscopy, 6 803 021 for those who received a procedure without intervention, and 3 921 068 for those who received a procedure with intervention (table 2). For the outcome of colorectal cancer-related mortality, we had 6 822 549 person-years of follow-up for those who received a procedure without intervention and 3 940 933 person-years of follow-up for procedures with intervention. For those who did not receive a complete colonoscopy, we had an additional 59 469 946 person-years of follow-up.

90 532 (1·7%) individuals were diagnosed with colorectal cancer and the crude incidence rate was 13·0 per 10 000 person-years for the overall cohort (15·5 and 10·6 per 10 000 person-years for male and female individuals, respectively). 44 088 individuals died from colorectal cancer, representing 5·9% of all deaths during the study period (n=743 161) with a crude colorectal cancer-related mortality rate of 6·3 per 10 000 person-years. Crude mortality rate was 5·1 per 10 000 person-years (18 200 deaths and 35 435 789 person-years of follow-up) for female individuals and 7·4 per 10 000 (25 888 deaths and 34 797 642 person-years of follow-up) for male individuals. The unadjusted colorectal cancer incidence per 1000 person-years increased with duration of time since colonoscopy. For female individuals who had received a complete and negative colonoscopy, it ranged from 0·47 (last complete colonoscopy ≤5 years ago) to 1·59 (last complete colonoscopy >15 years ago), and for female individuals who had a colonoscopy with intervention it ranged from 0·87 to 2·04 (appendix p 5). Similar trends were observed for male individuals for whom colorectal cancer incidence ranged from 0·53 to 2·18 in those who had received a complete and negative colonoscopy and 1·05 to 3·31 in those with a colonoscopy with intervention. Colorectal cancer incidence per 1000 person-years in those who had not received a colonoscopy was 1·11 for female individuals and 1·66 for male individuals (appendix p 5). 690 048 (13%) of individuals were censored for reasons other than study end or death, if they had a flexible sigmoidoscopy or incomplete colonoscopy, if they lost health insurance coverage for two consecutive quarters, or if they had a colonoscopy associated with colon stent, dilatation of stricture or excision of obstructive tumour, or stricture at colonoscopy.

Those who had received a complete and negative colonoscopy had a lower HR for colorectal cancer incidence compared with those who had not had a procedure at all durations; however, HRs were closer to 1 with longer intervals (figure 2). For example, HRs for those who had a procedure within 5 years were 0·35 (95% CI 0·33–0·37) for female individuals and 0·24 (0·23–0·26) for male individuals, which increased to 0·62 (0·51–0·77) and 0·57 (0·46–0·70), respectively, for those who had a colonoscopy done more than 15 years previously.

A similar finding was observed for a colonoscopy with intervention. Female individuals who had received a colonoscopy with intervention had a lower risk of colorectal cancer than those who did not undergo colonoscopy, although only durations from colonoscopy within 10 years were statistically significant (HR 0·70 [95% CI 0·63–0·77). Male individuals who had a colonoscopy with intervention were at a lower risk for longer durations, with statistically significant effects up to 15 years after colonoscopy (HR 0·62 [95% CI 0·53–0·72]). Overall, the risk reduction from receiving a complete colonoscopy was more pronounced in male individuals. The results for colorectal cancer incidence remained consistent in the sensitivity analysis when colonoscopy within 2 years of a stool test were included (data not shown).

A similar finding was observed for colorectal cancer-related mortality in individuals who had a complete negative colonoscopy, with lower HRs at all durations for both female and male individuals and HRs increased with longer durations (figure 3). For example, female individuals who received a complete and negative colonoscopy more than 15 years earlier had a HR of 0·64 (95% CI 0·49–0·83) and male individuals had a HR of 0·65 (0·50–0·83) compared with those who did not undergo a colonoscopy. A similar finding was observed for colorectal cancer-related mortality after colonoscopy with intervention for up to 15 years. Similar findings were observed in the sensitivity analysis for colorectal cancer-related mortality when colonoscopy withing 2 years of a stool test were included (data not shown). These results remained consistent in the sensitivity analysis when death from other causes was treated as a competing risk (appendix p 6).

	Person-years of follow-up without intervention	Person-years of follow-up with intervention
Exposure of interest for colorectal cancer incidence		
Last complete colonoscopy ≤5 years ago	4 531 311	3 030 356
Last complete colonoscopy >5–10 years ago	1 739 819	698 217
Last complete colonoscopy >10–15 years ago	434 202	156 454
Last complete colonoscopy >15 years ago	97 689	36 041
No complete colonoscopy	58 995 962	NA
Total	69 720 052	..
Exposure of interest for colorectal cancer-related mortality		
Last complete colonoscopy ≤5 years ago	4 535 050	3 036 378
Last complete colonoscopy >5–10 years ago	1 747 989	706 370
Last complete colonoscopy >10–15 years ago	439 534	160 639
Last complete colonoscopy >15 years ago	99 976	37 546
No complete colonoscopy	59 469 946	NA
Total	70 233 431	..

NA=not applicable.

Table 2: **Total person-years of follow-up for colorectal cancer incidence and colorectal cancer-related mortality by exposure of interest**

Discussion

The results of our study show that having a complete negative colonoscopy was associated with a lower risk of colorectal cancer incidence and colorectal cancer-related mortality for more than 15 years compared with those who did not receive a colonoscopy. The risk reduction changed over time, diminishing with longer duration since the procedure; however, the risk of colorectal cancer incidence and colorectal cancer-related mortality in those who had a complete negative colonoscopy never returned to the risk in unexposed individuals. For those who received a complete colonoscopy with intervention, the risk reduction was not as great and was of more limited duration. For both colorectal cancer incidence and colorectal cancer-related mortality, our findings show that male individuals have a greater risk reduction associated with exposure to a complete colonoscopy than female individuals. The unadjusted colorectal cancer incidence per 1000 person-years increased with time since colonoscopy for both sexes. Paradoxically, the risk in those without colonoscopy was lower than in those with colonoscopy for some durations since the procedure. However, this analysis did not adjust for age. The colonoscopy group, especially those who had gone more than 15 years after the procedure, would be substantially older on average than the group who did not have a colonoscopy, explaining their higher colorectal cancer incidence.

Although many studies have evaluated the shorter term risk reduction in colorectal cancer incidence and colorectal cancer-related mortality associated with colonoscopy, our findings are consistent with the small number of studies that have evaluated exposure occurring more than 15 years earlier.[17,18,20,21] Pilonis and colleagues[21] found that, among their cohort of 165 887 individuals, those with a single negative colonoscopy had reduced colorectal cancer incidence (standardised incidence ratio 0·34 [95% CI 0·27–0·41]) and mortality (standardised mortality ratio 0·28 [95% CI 0·20–0·37]) compared with the general population for 10·1 to 17·4 years after the procedure. In another study that included 1945 patients with colorectal cancer and 2399 controls,[20] the risk of colorectal cancer after complete negative colonoscopy was lower for over 20 years (odd ratio 0·40 [95% CI 0·24–0·66]). However, Nishihari and colleagues[15]

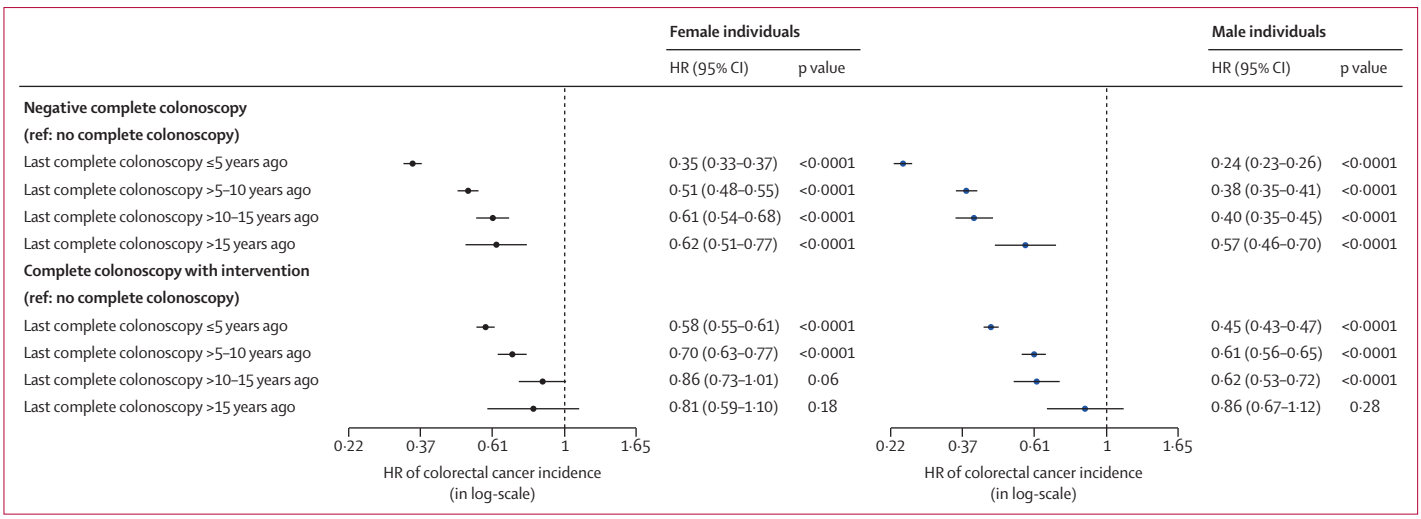

Figure 2: **Multivariable analysis of complete colonoscopy exposure associated with incidence of colorectal cancer stratified by sex**
Model has been adjusted for age, comorbidities, neighbourhood income quintile, and resident status. HR=hazard ratio.

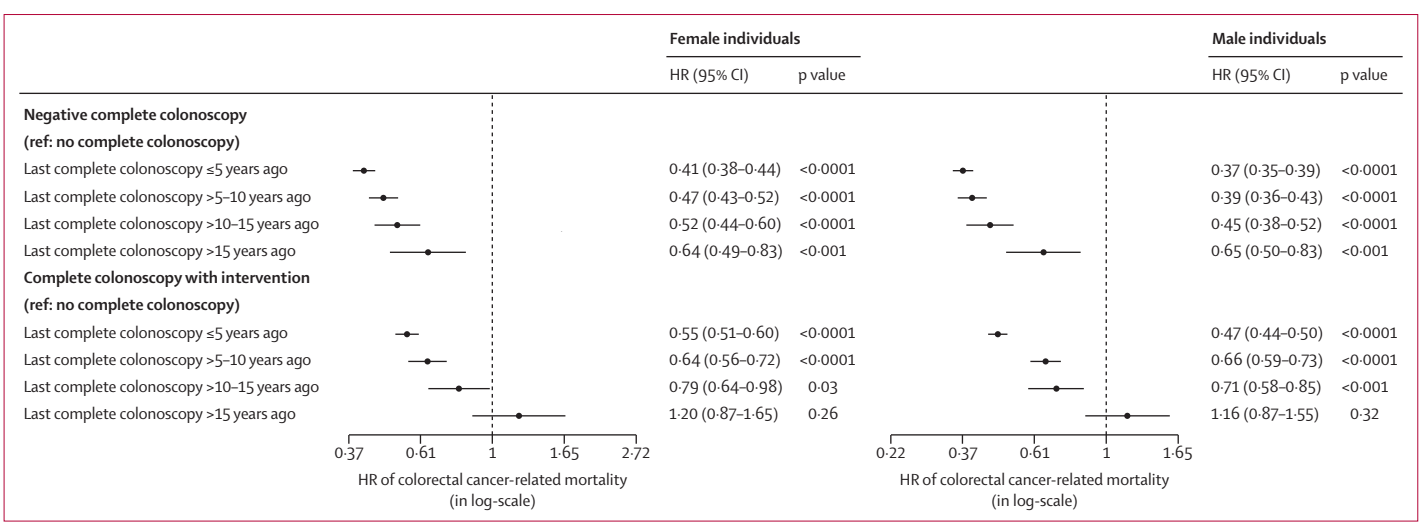

Figure 3: **Multivariable analysis of complete colonoscopy exposure associated with colorectal cancer-related mortality stratified by sex**
Model has been adjusted for age, comorbidities, neighbourhood income quintile, and resident status. HR=hazard ratio.

did not find that risk of colorectal cancer was lower in those who received a negative colonoscopy more than 15 years earlier, but lower risk of colorectal cancer was observed for those with a procedure from 10 years to less than 15 years in their cohort of 88 902 participants. A recent study examined the prevalence of colorectal cancer after a negative screening colonoscopy in the German screening colonoscopy registry and found that the standardised prevalence ratio was lower for both male and female individuals who had a repeat screening colonoscopy more than 10 years earlier and up to 16 years earlier in comparison with all screening colonoscopies done on those aged 65 years and older (standardised prevalence ratio 0·21 [95% CI 0·17–0·26]) for male individuals and 0·35 [0·29–0·41] for female individuals).[18] The NordICC trial[30] found limited effectiveness of colonoscopy as a primary screening method for colorectal cancer in their intention-to-screen analysis. Although our study findings of a lower risk reduction for more than 10 years after exposure to a complete colonoscopy are consistent with the adjusted per-protocol analyses of the NordICC trial,[30] we highlight the role of colonoscopy in risk stratification of individuals in jurisdictions where primary screening with colonoscopy in average risk persons is occurring and suggest that the length of the risk stratification endures more than 10 years.

Our study extends on earlier work in several ways. Previous studies have included participants from a small number of centres[20] and thus colonoscopies were done by a select group of endoscopists, which might not reflect colonoscopy performance and risk reduction in usual

practice. This explanation might also help to clarify the difference in the magnitude of risk reduction reported in other studies compared with ours. Moreover, other studies compared risk with the general population,[21] which would include individuals at increased risk of disease. Our results also extend prior work as, due to our large sample size and long follow-up, we were able to explore risk at both more than 10–15 years and more than 15 years of duration. Estimates reported by Pilonis and colleagues[21] for their longest duration (10·1–17·4 years) are based on a small sample of 86 365 individuals contributing only 197 304 person-years of follow-up. Our estimates following a negative complete colonoscopy are based on 434 202 person-years of follow-up for the duration of more than 10–15 years and 97 689 person-years for the duration of more than 15 years for the outcome of colorectal cancer incidence, with person-years of follow-up for colorectal cancer-related mortality being even higher.

Screening and rescreening intervals for colonoscopy have been largely informed by several cohort and case-control studies or based on trials of flexible sigmoidoscopy.[7,10,12] Our results, examining one of the largest population-based cohorts to date, show that those who receive a complete negative colonoscopy have a lower risk of colorectal cancer incidence and mortality that extends beyond 10 years compared with those who do not have a complete colonoscopy. In addition to the need to consider more prolonged rescreening intervals, our results also suggest that risk reduction after a complete negative colonoscopy was more pronounced in male individuals than female individuals, which might suggest different strategies are needed by sex.[20] Although our study had no details about the pathology of removed polyps in those who received a procedure with intervention, our findings still showed a consistent trend in risk reduction for these persons. Risk was still reduced for considerable periods of time even for those who are likely to be at higher risk for colorectal cancer because of polyps found at their colonoscopy. Failure to find statistically significant differences for the longer durations might reflect inadequate power rather than actual effects.

Our study included a large population-based cohort of over 5·2 million individuals, which would be generalisable to usual clinical practice. Our study also includes a median follow-up time of 12·56 (IQR 6·26–20·13) years with over 69 million person-years, including over 590 656 years in those with a complete colonoscopy more than 10–15 years earlier and 133 730 person-years of follow-up in those with a procedure completed more than 15 years earlier. We had the capacity to track multiple colonoscopies over time in all settings in the province and used a novel time-varying exposure that could account for multiple exposures to colonoscopy, whether an intervention was completed or not, and time since last colonoscopy. However, our study has limitations. The cause-specific method relies on assumptions, including intervention and conditional exchangeability of censoring that might not hold for observational data. We were unable to identify all those at increased risk of disease and did not know the indication for colonoscopy. However, we approximated an average risk cohort by excluding those with previous exposure to colonoscopy, a previous diagnosis of colorectal cancer, and those with history of hereditary or other bowel disorders associated with an increased risk of malignancy. We also excluded those diagnosed with colorectal cancer within 6 months of a colonoscopy as this might be an indication that the colonoscopy was done to evaluate symptoms, which in turn would influence the estimated risk reduction. We also did not have information on pathology findings for procedures with intervention and therefore were not able to present estimates for those with low-risk polyps versus high-risk polyps. We also did not have any information about other quality parameters of the colonoscopy or about quality performing indicators of the endoscopists. Individuals were young at inclusion in our study and thus results might be different for an older cohort. There also remains a chance for measurement error in covariates such as income given that data were available only at the residential neighbourhood quintile level and the potential for unmeasured confounders. Lastly, we recognise the built-in selection bias associated in HR estimates, which might be partly addressed by presenting HRs for multiple durations since an individual's colonoscopy to address the potential built-in selection bias in average HRs, which could be potentially time varying.[31]

Our findings show that, compared with those who do not receive colonoscopy, individuals who have a negative complete colonoscopy remain at lower risk for colorectal cancer incidence and mortality more than 15 years after the procedure. In conclusion, our findings support extending the recommended interval to repeat screening colonoscopy.

Contributors

NNB, AR, RM, RS, and JT conceptualised and designed the study. NNB and AR acquired funding. AR, NNB, RM, RS, QL, and JT curated data and methodology. QL and AR completed data analysis. NNB supervised the study. All authors reviewed and interpreted the data. AR and NNB drafted the article and all authors reviewed and edited the article. QL and AR directly accessed and verified the underlying data reported in the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

CD is contracted as Clinical Lead of the ColonCancerCheck programme, Ontario's organised colorectal cancer screening programme. All other authors declared no competing interests.

Data sharing

No additional data other than what were presented in the manuscript will be made available to others.

Acknowledgments

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care. This study also received funding from the Canadian Institutes of Health Research (FRN-162509 and FDN-148470). Parts of this material are based on data and information compiled and provided by Canadian Institute for

Health Information, Ontario Health, Ontario Ministry of Health, Immigration, Refugees and Citizenship Canada (from May 2017 to currently), and Ontario Registrar General information on deaths, the original source of which is ServiceOntario. The analyses, conclusions, opinions, and statements herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. This study was not funded by the National Institutes of Health and no author is in receipt of a National Institutes of Health grant. This document used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from Canada Post Corporation and Statistics Canada. The views expressed herein are those of the author and do not necessarily reflect those of Ontario Registrar General or the Ministry of Public and Business Service Delivery.

References

1 Schultz SE, Vinden C, Rabeneck L. Colonoscopy and flexible sigmoidoscopy practice patterns in Ontario: a population-based study. *Can J Gastroenterol* 2007; **21:** 431–34.

2 Hol L, Sutradhar R, Gu S, et al. Repeat colonoscopy after a colonoscopy with a negative result in Ontario: a population-based cohort study. *CMAJ Open* 2015; **3:** E244–50.

3 Paszat L, Sutradhar R, Baxter NN, Tinmouth J, Rabeneck L. Repeat colonoscopy within 6 months after initial outpatient colonoscopy in Ontario: a population-based cross-sectional study. *Can J Gastroenterol Hepatol* 2017; **2017:** 5917057.

4 Murthy SK, Dubé C, Rostom A, et al. Risk of colorectal cancer after a negative colonoscopy in low-to-moderate risk individuals: impact of a 10-year colonoscopy. *Endoscopy* 2017; **49:** 1229–36.

5 Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. *Clin Gastroenterol Hepatol* 2008; **6:** 1117–21; quiz 1064.

6 Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA* 2016; **315:** 2564–75.

7 Rex DK, Boland CR, Dominitz JA, et al. colorectal cancer screening: recommendations for physicians and patients from the U.S. multi-society task force on colorectal cancer. *Am J Gastroenterol* 2017; **112:** 1016–30.

8 Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA* 2021; **325:** 1965–77.

9 Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018; **68:** 250–81.

10 von Karsa L, Patnick J, Segnan N, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. *Endoscopy* 2013; **45:** 51–59.

11 European Commission, Directorate-General for Health, Consumers Executive Agency for Health and Consumers, World Health Organization. European guidelines for quality assurance in colorectal cancer screening and diagnosis. Publications Office, 2010.

12 Tinmouth J, Vella ET, Baxter NN, et al. Colorectal cancer screening in average risk populations: evidence summary. *Can J Gastroenterol Hepatol* 2016; **2016:** 2878149.

13 Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2021; **325:** 1978–98.

14 García-Albéniz X, Hsu J, Bretthauer M, Hernán MA. Effectiveness of screening colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to 79 years. *Ann Intern Med* 2016; **166:** 18–26.

15 Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369:** 1095–105.

16 Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal cancer screening: an updated modeling study for the US preventive services task force. *JAMA* 2021; **325:** 1998–2011.

17 Duvvuri A, Chandrasekar VT, Srinivasan S, et al. Risk of colorectal cancer and cancer related mortality after detection of low-risk or high-risk adenomas, compared with no adenoma, at index colonoscopy: a systematic review and meta-analysis. *Gastroenterology* 2021; **160:** 1986–96.

18 Heisser T, Kretschmann J, Hagen B, Niedermaier T, Hoffmeister M, Brenner H. Prevalence of colorectal neoplasia 10 or more years after a negative screening colonoscopy in 120 000 repeated screening colonoscopies. *JAMA Intern Med* 2023; **183:** 183–90.

19 Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* 2014; **348:** g2467.

20 Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Long-term risk of colorectal cancer after negative colonoscopy. *J Clin Oncol* 2011; **29:** 3761–67.

21 Pilonis ND, Bugajski M, Wieszczy P, et al. Long-term colorectal cancer incidence and mortality after a single negative screening colonoscopy. *Ann Intern Med* 2020; **173:** 81–91.

22 Rex DK, Ponugoti PL, Johnson CS, Kittner L, Yanda RJ. Neoplasia at 10-year follow-up screening colonoscopy in a private U.S. practice: comparison of yield to first-time examinations. *Gastrointest Endosc* 2018; **87:** 254–59.

23 Ponugoti PL, Rex DK. Yield of a second screening colonoscopy 10 years after an initial negative examination in average-risk individuals. *Gastrointest Endosc* 2017; **85:** 221–24.

24 Lee JK, Jensen CD, Levin TR, et al. Long-term risk of colorectal cancer and related deaths after a colonoscopy with normal findings. *JAMA Intern Med* 2019; **179:** 153–60.

25 Heisser T, Peng L, Weigl K, Hoffmeister M, Brenner H. Outcomes at follow-up of negative colonoscopy in average risk population: systematic review and meta-analysis. *BMJ* 2019; **367:** l6109.

26 Benchimol EI, Smeeth L, Guttmann A, et al. the reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med* 2015; **12:** e1001885.

27 Tinmouth J, Patel J, Austin PC, et al. Directly Mailing gFOBT kits to previous responders being recalled for colorectal cancer screening increases participation. *J Can Assoc Gastroenterol* 2020; **3:** 197–203.

28 Rabeneck L, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. *Clin Gastroenterol Hepatol* 2010; **8:** 275–79.

29 Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol* 2013; **64:** 402–06.

30 Bretthauer M, Løberg M, Wieszczy P, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med* 2022; **387:** 1547–56.

31 Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; **21:** 13–15.