Association Between Colonoscopy Rates and Colorectal Cancer Mortality

Linda Rabeneck, MD, MPH, Lawrence F. Paszat, MD, MS, Refik Saskin, MSc and Therese A. Stukel, PhD

OBJECTIVES: Although colonoscopy use has increased in the United States and Canada since the early 1990s, it is unclear whether this has been associated with benefit at the population level. Our objective was to evaluate the association between regional colonoscopy rates and death from colorectal cancer (CRC).

METHODS: We conducted a natural experiment involving a 14-year follow-up of a cohort of all men and women 50–90 years of age living in Ontario on 1 January 1993 exposed to different intensities of colonoscopy use. Each member of the study cohort was assigned to a region each year, on the basis of his/her residence. Each individual was followed up through 31 December 2006; age- and sex-standardized CRC incidence rates were calculated and all CRC deaths were identified. Each year, for each region, the rate of colonoscopies performed on persons 50–90 years of age, per 1,000 population 50–90 years of age, living in the region, was calculated. Multivariable cox proportional hazards models were used to evaluate the association between colonoscopy rate and death from CRC, adjusting for age, sex, comorbidity, income, and location of residence (urban/rural).

RESULTS: The study cohort comprised 2,412,077 persons 50–90 years of age. The mean age was 64 years, and 53.7% were women. Colonoscopy rates increased in all regions during 1993–2006. The increased rate of complete colonoscopy was inversely associated with death from CRC. For every 1% increase in complete colonoscopy rate, the hazard of death decreased by 3%.

CONCLUSIONS: Increased colonoscopy use was associated with mortality reduction from CRC at the population level.
Revised Clinical Modification (ICD-9-CM) from 1 April 1988 to 31 March 2002 and the International Classification of Diseases 10th Revision from 1 April 2002 onward (11,12). The OHIP database contains information about all claims for physicians’ services provided to Ontario residents since 1 July 1991. The RPDB is a roster of all permanent residents with a valid OHIP health card in Ontario and includes age, sex, location of residence, and vital status. The OCR records all cancer diagnoses in Ontario residents since 1964.

Defining the study cohort
We identified a fixed cohort of all individuals 50–90 years of age on 1 January 1993 in Ontario. We excluded those who had a previous diagnosis of CRC based on ICD-9 codes recorded in the OCR (Table 1) and those who had a previous diagnosis of ulcerative colitis (ICD-9-CM codes 556.x) or Crohn’s disease (ICD-9-CM codes 555.x) recorded in CIHI. We also excluded those who, during the study period, had their residence in the South East Local Health Integration Network, a region of Ontario where physicians are reimbursed through an alternative funding plan, and thus claims for services are not recorded in OHIP. The remaining persons comprise the study cohort.

CRC incidence and mortality
We followed each cohort member from 1 January 1993 to 31 December 2006 and used the OCR to identify those who were diagnosed with CRC (Table 1). We computed annual age- and sex-standardized CRC incidence for the study cohort for each year. The 1993 cohort was used as the standard population. We identified deaths from the RPDB. We identified CRC deaths in the study cohort to one of 13 regions, based on his/her residence. We reasoned that each year, the members of the study cohort were exposed to the colonoscopy rate for the region in which they lived. Each year, from 1 January 1993 to 31 December 2006, for each region, we computed the rate of complete colonoscopies (Z555 plus E747) (Table 2) performed on persons 50–90 years of age, per 1,000 population 50–90 years of age living in the region.

Evaluating factors associated with death
We examined patient age, sex, comorbidity, income quintile, and location of residence. We had previously reported these variables to be associated with receipt of colonoscopy in Ontario (13). Using the validated approach published by Deyo et al. (14), a comorbidity score of 0–17 was assigned to each person on 1 January 1993 on the basis of the presence of predefined comorbid illnesses. The scores were determined using ICD-9-CM diagnosis codes other than CRC recorded in CIHI for 5 years before 1 January 1993 (14). Income quintile, which was measured relative to neighborhood income, was used to indicate socioeconomic status. Statistics Canada Census data were used to ascertain the neighborhood income per person equivalent, which is a household size-adjusted measure of household income based on (1991 census) data at the enumeration area level. An enumeration area is the geographical area canvassed by one census representative. Within each census metropolitan area, the enumeration area average income per person equivalent was used to rank all enumeration areas, and the population was divided into approximate fifths. This creates community-specific income quintiles based on income per person equivalent, where 1 = lowest income quintile and 5 = highest income quintile. Location of residence was classified as urban vs. rural using 1991 Statistics Canada Census definitions applied to the postal code of the primary address of the cohort member.

Data analysis
Data analysis was conducted using SAS Version 9.13 (SAS Institute, Cary, NC). Cox proportional hazards models with 95% CIs were used to evaluate the association

| Table 1. ICD-9-CM diagnosis codes used to identify colorectal cancer |
|-------------------------|------------------|
| ICD-9-CM code   | ICD-9-CM diagnosis                  |
| 153.0          | CRC hepatic flexure                  |
| 153.1          | CRC transverse colon                 |
| 153.2          | CRC descending colon                 |
| 153.3          | CRC sigmoid colon                    |
| 153.4          | CRC cecum (ileocecal valve)          |
| 153.6          | CRC ascending colon                  |
| 153.7          | CRC splenic flexure                  |
| 153.8          | CRC other specific site              |
| 153.9          | CRC colon unspecified                |
| 154.0          | CRC rectosigmoid junction            |
| 154.1          | CRC rectum                           |

Table 2. OHIP procedure codes

<table>
<thead>
<tr>
<th>OHIP procedure code</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z555</td>
<td>Colonoscopy to descending colon</td>
</tr>
<tr>
<td>Z555+E740</td>
<td>Colonoscopy to splenic flexure</td>
</tr>
<tr>
<td>Z555+E740+E741</td>
<td>Colonoscopy to hepatic flexure</td>
</tr>
<tr>
<td>Z555+E740+E741+E747</td>
<td>Colonoscopy to cecum</td>
</tr>
<tr>
<td>Z555+E740+E741+E747+E705</td>
<td>Colonoscopy to terminal ileum</td>
</tr>
<tr>
<td>OHIP, Ontario Health Insurance Plan.</td>
<td></td>
</tr>
</tbody>
</table>
between colonoscopy rate and death from CRC, adjusting for age, sex, comorbidity, income quintile, and location of residence. Colonoscopy rate was a time-varying covariate in the models, and the unit of analysis was the individual.

RESULTS
Study cohort
The study cohort comprised 2,412,077 persons who were 50–90 years of age on 1 January 1993 and met the inclusion criteria. Table 3 shows the baseline characteristics. The mean age (s.d.) was 64 (9.8) years and 1,294,740 (53.7%) were women. The majority (86.5%) had a comorbidity score of 0 and lived in an urban area (84.2%).

During the 14-year follow-up, 62,819 persons (2.6%) were diagnosed with CRC, 773,677 (32.1%) died from all causes, and 23,743 (0.98%) died from CRC.

Colonoscopy rates and incident CRC
Figure 1 shows the regional rates of complete colonoscopy by year. During 1993–2006, the rates increased in all regions; rates varied across the regions.

Figure 2 shows CRC incidence in the study cohort plotted against the regional complete colonoscopy rate. Each data point plots the CRC incidence rate in the study cohort against the regional complete colonoscopy rate for each calendar year, from 1993 to 2006. The incidence rates were lower in the younger age group (50–69 years), and within each age group, the rates were lower for women than for
men. The range of complete colonoscopy rates was similar for both men and women among those 50–69 years of age. In those 70 years and older, the rates were lower for women (13.9/1,000–44.8/1,000) compared with men (21.4/1,000–60.7/1,000). The CRC incidence rate increased with age for those in the younger age groups, because as the cohort ages, more persons are diagnosed with CRC. For those in the older age group, there is no appreciable increase in CRC incidence, because those persons who have been diagnosed with CRC and those who have died have been censored.

**Figure 3** shows CRC mortality in the study cohort plotted against the regional complete colonoscopy rate, incorporating a 5-year time lag. Each data point plots the CRC mortality rate in the study cohort against the regional complete colonoscopy rate 5 years earlier for each calendar year, from 1993 to 2002. The CRC mortality rates were lower in the younger age group (50–69 years), and within each age group, the rates were lower for women than for men.

### Colonoscopy rate and death from CRC

Table 4 shows the results of the multivariable model evaluating the association between regional rate of complete colonoscopy and death from CRC. Increased age, lower income, and living in a rural location were associated with an increased risk of death from CRC. The association with comorbidity was attenuated at higher comorbidity scores. Female sex was associated with a decreased risk of death from CRC. After adjustment for age, sex, comorbidity, income quintile, and location of residence, increased complete colonoscopy rate was associated with a decreased risk of death from CRC. The hazard ratio of 0.970 (95% CI: 0.949–0.991) indicates that for every increase in colonoscopy rate of 10/1,000 or 1% in the region of residence of the study cohort member, the hazard of death decreased by 3%.

**Table 4. Association between regional rate of complete colonoscopy and death from CRC in Ontario (n=2,412,077)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.860 (1.835–1.885)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.626 (0.610–0.643)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.067 (1.016–1.121)</td>
<td>0.0096</td>
</tr>
<tr>
<td>2</td>
<td>0.922 (0.858–0.991)</td>
<td>0.0269</td>
</tr>
<tr>
<td>≥3</td>
<td>0.901 (0.810–1.001)</td>
<td>0.0517</td>
</tr>
<tr>
<td>Income quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Lowest)</td>
<td>1.170 (1.124–1.217)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>1.120 (1.075–1.166)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>1.099 (1.055–1.145)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>1.060 (1.017–1.104)</td>
<td>0.0058</td>
</tr>
<tr>
<td>5</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Location of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1.066 (1.030–1.104)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Colonoscopy rate (per 10/1,000)</td>
<td>0.970 (0.949–0.991)</td>
<td>0.0055</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; HR, hazard ratio.
DISCUSSION

We report here that in a population-based cohort of 2,412,077 individuals 50–90 years of age followed over 14 years, living in a region of higher colonoscopy use was associated with a decreased risk of death from CRC.

How do our results compare with previous findings? Most of the earlier studies have focused on describing temporal trends and regional variation in rates of colonoscopy use. Studies from the United States (7) and Canada (8–10) show that rates of colonoscopy use have increased. For example, a US study of Medicare beneficiaries 66 years or older reported an increase in colonoscopy rates during 1991–2002 (7). A US study of Medicare beneficiaries and persons included in an endoscopic database (referred to as CORI) of a sample of gastroenterology practices during 1999–2003 showed that colonoscopy has become the most common endoscopic procedure performed (15). An earlier analysis of data from 1998 to 2002 from the CORI database showed a marked increase (from 4.5% to 14.2%) in the proportion of colonoscopies performed for screening among persons at average risk for CRC (16). A study from Alberta, Canada (9) reported an increase in rates of colonoscopy use among all age groups during 1994–2002. Similarly, a study from Ontario, Canada (8) reported an increase in the rates of colonoscopy among those 20–74 years of age during 1992–2001. In addition, a study from Manitoba, Canada (10) of persons of all ages reported an increase in colonoscopy rates during 1984–2003. Regional variation in rates of colonoscopy use has also been reported in the United States (17) and Canada (8,9). However, few studies have evaluated whether the marked increase in colonoscopy use observed in the United States and Canada was associated with CRC mortality reduction at the population level.

Recently, however, a US study of 44,924 Medicare beneficiaries 67 years of age or older with a diagnosis of CRC during 1992–2002 in the SEER regions evaluated the relation between colonoscopy use and CRC stage at diagnosis (7). The investigators found an association between increased colonoscopy use in the SEER regions, and, for those who were diagnosed with CRC, an increased probability of being diagnosed at an early stage. In addition, a cohort study of 715 average-risk individuals followed for a median of 8 years after screening colonoscopy reported that CRC mortality was lower than expected compared with estimates from SEER data (18). In that study, the reported standardized mortality ratio was 0.35 (95% CI 0.0–1.06); this estimate was not statistically significant, although the number of deaths was relatively small given the cohort size. The findings from these two US studies taken together with the present findings indicate that increased colonoscopy is associated with clinical benefit at the population level.

Colonoscopy could lead to a decrease in CRC mortality in two ways. First, according to the adenoma–carcinoma sequence, the detection and removal of adenomatous polyps—before they become cancers—should lead to a reduction in CRC incidence, and subsequently to a reduction in CRC deaths. Second, in persons who have a CRC but who are asymptomatic, colonoscopy should detect the cancer at an earlier stage when the potential for cure is greater, than if the cancer had been detected at a more advanced stage.

The results reported here must be interpreted in light of the strengths and weaknesses of the study. First, a population-based study reduces the selection bias that can occur when patients are enrolled only from centers with specialists in endoscopy. Second, the codes for colonoscopy in the administrative databases allowed us to determine the extent of the colonoscopy performed, so that we were able to study a cohort of persons with a complete colonoscopy. Because this is an ecological study—we evaluated the association between regional colonoscopy rates and death from CRC—the relationship may not be causal in nature. It is possible that those persons who were less likely to die from CRC lived in regions of greater colonoscopy use and may not have undergone the procedure. However, this seems unlikely, given that the distribution of baseline characteristics of the study cohort was similar across colonoscopy rate tertiles. Similar to the US studies that used Medicare data (7), we were unable to reliably distinguish screening from diagnostic colonoscopy. We were therefore unable to disentangle the relative contributions of screening vs. diagnostic colonoscopy to the observed association with CRC mortality benefit.

In conclusion, more intensive use of colonoscopy was associated with a decreased risk of death from CRC in men and women 50–90 years of age in Ontario during 1993–2006. Increased colonoscopy use is associated with mortality reduction from CRC at the population level.

CONFLICT OF INTEREST

Guarantor of the article: Linda Rabeneck, MD, MPH. Specific author contributions: All authors participated in the conception and design, acquisition of data, and analysis and interpretation of data. Rabeneck drafted the paper and all authors participated in its critical revision for important intellectual content, and gave final approval of the submitted paper. Rabeneck has had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data. Financial support: None. Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Rates of colonoscopy use increased dramatically during the 1990s, coupled with a shift to greater use for colorectal cancer (CRC) screening.
- Despite this, it is unclear whether increased colonoscopy use has been associated with benefit at the population level.

WHAT IS NEW HERE

- In men and women 50–90 years of age in Ontario, living in a region with a higher colonoscopy rate was associated with a decreased risk of death from CRC, after taking into account age, sex, income, and location of residence (urban/rural).
- For every 1% increase in colonoscopy rate, the risk of death from CRC decreased by 3%.
- Increased colonoscopy use was associated with mortality reduction from CRC at the population level.
REFERENCES