Risk of Developing Proximal Versus Distal Colorectal Cancer After a Negative Colonoscopy: A Population-Based Study

JOSH LAKOFF,* LAWRENCE F. PASZAT,[‡,§,‖] REFIK SASKIN,[‖] and LINDA RABENECK*[,§,‖]

*Department of Medicine, [‡]Department of Radiation Oncology, and [§]Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; and the [‖]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada

See Lieberman DA et al on page 1100 for the companion article in the October 2008 issue of *Gastroenterology*.

See CME exam on page 1064; see editorial on page 1068.

Background & Aims: **The incidence of colorectal cancer (CRC) overall is reduced for up to 10 years after a negative colonoscopy. The objective of this research was to determine the incidence of proximal and distal CRC after a negative complete colonoscopy.** *Methods:* **A cohort of Ontario residents aged 50 to 80 years who had a negative complete colonoscopy between January 1, 1992, and December 31, 1997, was identified by using linked administrative databases. Cohort members had no prior history of CRC, inflammatory bowel disease, or recent colonic resection. Each individual was followed up through December 31, 2005, and the relative rate (RR) of overall CRC, distal CRC, and proximal CRC was compared with the remaining Ontario population.** *Results:* **A cohort of 110,402 individuals with a negative complete colonoscopy was identified. The RR of CRC overall and the RR of distal CRC remained significantly lower than the Ontario population. For example, at year 14 the RR of distal CRC was 0.21 (95% confidence interval, 0.05–0.36). The RR of proximal CRC was significantly lower than the Ontario population in half of the follow-up years, mainly after 7 years of follow-up.** *Conclusions:* **Over a 14-year follow-up period, negative complete colonoscopy was associated with a subsequent reduced incidence of CRC overall, and of incident CRC in the distal colon. However, the reduction in incidence of proximal CRC differed in magnitude and timing, and occurred in half the follow-up years, mainly after 7 years of follow-up. These results highlight an important limitation of colonoscopy in usual clinical practice.**

In Canada, colorectal cancer (CRC) is second only to lung cancer as the leading cause of cancer death.[1] In 2007, an estimated 20,800 Canadians were diagnosed with CRC and 8700 died from the disease.[1] CRC screening rates in Canada remain low.[2–4]

Colonoscopy is endorsed as an option for CRC screening by multiple professional societies including the Canadian Association of Gastroenterology and the American Gastroenterological Association.[5,6] Colonoscopy is considered to be the gold standard for detecting and removing adenomas and colonoscopic polypectomy is associated with a reduced incidence of CRC.[7] A recent population-based study from Manitoba reported that the risk of incident CRC after a negative colonoscopy was reduced for up to 10 years.[8] However, the magnitude and duration of risk for incident proximal versus distal CRC after negative colonoscopy remains unclear. This is an important question because proximal and distal CRC may be different. Proximal and distal lesions display differences in gene expression and tumor phenotype,[9,10] which may be the basis for different mechanisms of tumor development and growth. In addition, the proximal colon tends to give rise to lesions of smaller size,[11] which may be more likely than distal lesions to be missed without the use of special techniques for their recognition.

The objective of this research was to determine the incidence of proximal and distal CRC after a negative colonoscopy in usual clinical practice.

Methods

Data Sources

Four data sources were used in this study.

First, the Canadian Institute for Health Information—Discharge Abstract Database (CIHI-DAD) contains information about all diagnoses and procedures for patients discharged from acute care hospitals and hospital-based, same-day surgery units for residents of Ontario since April 1, 1988. All diagnostic codes are recorded according to the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM)[12] from April 1, 1988, to March 31, 2002.

Second, the Ontario Health Insurance Plan (OHIP) database contains information on all claims for physicians' services provided to Ontario residents since January 1, 1991.

Third, the Registered Persons Database 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.

Fourth, the Ontario Cancer Registry records all cancer diagnoses in Ontario residents since 1964. More than 95% of pa-

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; ICD-9-CM, International Classification of Diseases, 9th revision, clinical modification; OHIP, Ontario Health Insurance Plan; RR, relative rate.

1542-3565/08/$34.00
doi:10.1016/j.cgh.2008.05.016

thology reports relating to cancer in Ontario are received by the Ontario Cancer Registry.[13]

Data from these databases for each patient were linked using encrypted numeric identifiers. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre in Toronto, Ontario.

Defining the Study Cohort

We identified all residents of Ontario aged 50 to 80 years who underwent a complete colonoscopy that was negative between January 1, 1992, and December 31, 1997. As we have done in previous research, we defined colonoscopy using OHIP procedure code Z555 (insertion of colonoscope to descending colon) and we defined a complete colonoscopy using OHIP procedure code Z555 plus either E747 (insertion of colonoscope to cecum) or E705 (insertion of colonoscope to terminal ileum).[14,15] We defined the first complete colonoscopy as the index colonoscopy. The index colonoscopy was defined as negative when a colorectal biopsy or a polypectomy was not performed on the date of the colonoscopy, and a second colonoscopy was not performed within 6 months, and the person was not diagnosed with CRC within 6 months. By using the OHIP database we identified the endoscopists' specialty as gastroenterology, general surgery, internal medicine or family physician, or other. Note that in Ontario, before 2000–2001 many gastroenterologists were classified in the internal medicine group.

We excluded those with a prior diagnosis of CRC recorded in the Ontario Cancer Registry. Based on information recorded in the CHI-DAD, we excluded individuals with a prior diagnosis of inflammatory bowel disease (ICD-9-CM codes 555.x and 556.x) and those who had undergone a colonic resection within 5 years before the index colonoscopy. We also excluded individuals who lived in the South East Local Health Integration Network, a geographic region of Ontario in which physician reimbursement is through an alternate funding plan and therefore claims for services are not recorded in OHIP.

Data Analysis

We computed the annual age- and sex-standardized incidence of proximal CRC (cecum [ICD-9-CM code 153.4], ascending colon [ICD-9-CM code 153.6], hepatic flexure [ICD-9-CM code 153.0], transverse colon [ICD-9-CM code 153.1], and splenic flexure [ICD-9-CM code 153.7]), distal CRC (descending colon [ICD-9-CM code 153.2], sigmoid colon [ICD-9-CM code 153.3], rectosigmoid junction [ICD-9-CM code 154.0], and rectum [ICD-9-CM code 154.1]), and CRC overall (all codes listed previously, as well as codes for CRC other specific site [ICD-9-CM code 153.8] and CRC colon unspecified [ICD-9-CM code 153.9]) through December 31, 2005, for the negative complete colonoscopy cohort and for the remaining Ontario population who met the exclusion criteria. Follow-up began on the date of the colonoscopy for the negative complete colonoscopy cohort, and on the date at which the person became age-eligible for the remaining Ontario population. We computed the relative rate (RR) and 95% confidence intervals (CIs) for incident cancers for the negative complete colonoscopy cohort and compared this with the remaining Ontario population during each year of follow-up. During the follow-up period we removed individuals from the study cohort if they developed CRC, moved out of the province, or died. The 1995 Ontario population was used as the standard population and we used 5-year age intervals.

We performed sensitivity analyses by recomputing the RRs of distal and proximal CRC after including all the patients with cancer site classified as CRC other specific site [ICD-9-CM code 153.8] and CRC colon unspecified [ICD-9-CM code 153.9]) (taken together, these sites subsequently are referred to here as "other") and assuming these cancers were either all distal or all proximal.

Table 1. Characteristics of the Negative Complete Colonoscopy Cohort Compared With the Ontario Population

	Negative complete colonoscopy		Controls	
Variable	N	%	N	%
Sex				
Women	60,960	55.2	1,488,441	52.1
Men	49,442	44.8	1,370,646	47.9
Age, *y*				
50–54	21,449	19.4	621,939	21.8
55–59	19,726	17.9	556,260	19.5
60–64	20,005	18.1	533,877	18.7
65–69	19,875	18.0	476,270	16.7
70–74	16,876	15.3	361,055	12.6
75–80	12,471	11.3	309,686	10.8
Endoscopist specialty				
General surgery	44,930	40.7		
Internal medicine/family physician	46,459	42.1		
Gastroenterology	17,718	16.1		
Other	1295	1.2		

NOTE. Data from January 1, 1992, to December 31, 2005. Controls were from the Ontario population.

Results

From January 1, 1992, to December 31, 1997, we identified 110,402 individuals who had a negative complete colonoscopy. In the remaining Ontario population, 2,859,087 met the exclusion criteria and did not have a colonoscopy (controls). Table 1 shows the characteristics of the 2 groups. Compared with the Ontario population (controls), in the negative complete colonoscopy cohort the proportion of women was slightly greater (55.2% vs 52.1%), and the age distribution was somewhat older.

During the 14-year follow-up period, CRC was diagnosed in 1461 persons in the negative complete colonoscopy cohort, in 443 (30%) of whom the cancers were in the distal colon, 610 (42%) were in the proximal colon, and 408 (28%) were classified as other. In the control group CRC was diagnosed in 62,387 persons, in 33,195 (53%) of whom the cancers were in the distal colon, 19,056 (31%) were in the proximal colon, and 10,136 (16%) were classified as other.

In the negative complete colonoscopy cohort, the RR of CRC overall was significantly lower after year 1 (Table 2), and the RR of distal CRC was significantly lower than the control Ontario population in each of the 14 years of follow-up (Table 3). For example, in year 14 the RR of CRC overall was 0.25 (95% CI,