Diabetes and Sex-specific Colorectal Cancer Risks in Newfoundland and Labrador: A Population-based Retrospective Cohort Study

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ABSTRACT

OBJECTIVE: Studies on the relationship between diabetes and colorectal cancer (CRC) are inconsistent. It is also unclear whether CRC risk elevation for individuals with diabetes is similar for males and females. Using data from Newfoundland and Labrador (NL), the province with the highest CRC incidence and diabetes prevalence in Canada, we assessed and compared the risk elevation of CRC for males and females with diabetes, overall and by anatomic subsite.

METHODS: A population-based retrospective cohort study including a study sample of 122,228 individuals aged ≥30 years was conducted using administrative health databases over a 10.5-year period (October 1, 1996 to March 31, 2007). Hazard ratios were estimated using Cox proportional hazard models.

RESULTS: In comparison with non-diabetes counterparts, both males and females with diabetes were at a significantly elevated risk of overall CRC, with corresponding hazard ratios of 1.38 and 1.52, respectively. For males, diabetes significantly increased the risk of proximal and distal colon cancers, but not of rectal cancer. For females, diabetes significantly increased the risk of proximal colon and rectal cancers, but not of distal colon cancer. The results suggest that there is a stronger association between diabetes and CRC for females than for males, and the association did not change after adjusting for overweight/obesity.

CONCLUSIONS: Diabetes led to a greater risk of CRC in both the male and female population in NL. Risk was subsite-specific and varied by sex. Future research should examine reasons for the observed diabetes-associated CRC risk to support CRC prevention strategies among the diabetes population.

KEY WORDS: Colorectal cancer; diabetes mellitus; cohort study; hazard ratio; risk elevation

La traduction du résumé se trouve à la fin de l'article.

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Type 2 diabetes and colorectal cancer (CRC) are major causes of morbidity and mortality in Canada and the burden of these diseases is rapidly growing.[1,2] In 2008/09, almost 2 million Canadians (about 1 in 15) aged ≥1 year had been diagnosed with diabetes and this number is predicted to reach 3.7 million in 2018/19. Rates are consistently highest in Aboriginal communities and the Atlantic Provinces.[1] Currently, Newfoundland and Labrador (NL) has the highest age-standardized prevalence of diabetes in Canada.[1] Likewise, the number of new CRC cases in Canada has risen by 35% in the past decade, from an estimated 17,200 new cases in 2001 to an estimated 23,300 cases in 2012.[2,3] CRC is the second leading cause of cancer mortality in Canada; an estimated 9,200 Canadians died of CRC in 2012.[2] The province of NL has the highest incidence of CRC in the world.[4]

Previous studies exploring the relationship between diabetes and CRC have not been consistent. Some studies report a lack of association,[5,6] some have found that diabetes increases the risk of CRC,[7-11] while others have found that the relationship between diabetes and CRC is subsite-specific, for example, a stronger association for colon cancer than for rectal cancer.[12-14] The literature in relation to sex-specific association between diabetes and CRC revealed inconsistent results; a meta-analysis-based study found a strong relationship between diabetes and increased risk of CRC in both males and females,[10] while others have reported the association in women only.[12,15] Other work has shown that different types of CRC have different etiologies,[16] which are differentially affected by sex. Thus, it is plausible that diabetes may affect subsite-specific CRCs differently for males compared to females.

To further assess the relationship between diabetes and the risk of CRC (overall and subsite-specific) for males and females, we conducted a population-based study in NL.

METHODS

This was a population-based retrospective cohort study that used health administrative databases in NL, a province with a population of 509,000 (in 2012). This study protocol was approved by the Health Research Ethics Authority of NL.

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Conflict of Interest: None to declare.

Table 1. Characteristics of the Study Sample by Diabetes Status and Sex

	Diabetes			No Diabetes		
	Males (n=12,667)	Females (n=12,637)	p-value	Males (n=48,489)	Females (n=48,435)	p-value
Mean age* (yr) (SD)	56.3 (12.8)	58.7 (14.3)	<0.01	55.9 (12.8)	58.3 (14.3)	<0.01
Age at baseline† (yr) (%)						
30-44	2644 (20.9)	2467 (19.5)	<0.01	10,478 (21.6)	9734 (20.1)	<0.01
45-54	3494 (27.6)	2863 (22.7)		13,596 (28.0)	11,128 (23.0)	
55-64	3137 (24.8)	2782 (22.0)		11,940 (24.6)	10,614 (21.9)	
65-74	2315 (18.3)	2650 (21.0)		8637 (17.8)	10,011 (20.7)	
75+	1077 (8.5)	1875 (14.8)		3838 (7.9)	6948 (14.3)	
Co-morbidities at baseline†‡ (%)						
AMI	460 (3.6)	276 (2.2)	<0.01	828 (1.7)	432 (0.9)	<0.01
CHF	576 (4.6)	577 (4.6)	0.94	895 (1.9)	840 (1.7)	0.19
PVD	395 (3.1)	300 (2.4)	<0.01	770 (1.6)	527 (1.1)	<0.01
CVD	391 (3.1)	333 (2.6)	<0.05	712 (1.5)	657 (1.4)	<0.14
Dementia	99 (0.8)	170 (1.4)	<0.01	234 (0.5)	497 (1.0)	<0.01
PD	1187 (9.4)	1369 (10.8)	<0.01	2874 (5.9)	2909 (6.0)	<0.60
CTD	688 (5.4)	1060 (8.4)	<0.01	1924 (4.0)	2778 (5.7)	<0.01
Peptic ulcer	292 (2.3)	265 (2.1)	0.26	824 (1.7)	727 (1.5)	<0.05
Liver disease	88 (0.7)	53 (0.4)	<0.01	97 (0.2)	78 (0.2)	0.15
Paraplegia	52 (0.4)	44 (0.4)	0.42	111 (0.2)	95 (0.2)	0.27
Renal disease	202 (1.6)	191 (0.5)	0.59	367 (0.8)	229 (0.5)	<0.01
SLD	14 (0.1)	4 (0.0)	<0.05	21 (0.0)	15 (0.0)	0.32
Mean CCI score * (SD)	0.4 (0.7)	0.4 (0.7)	0.15	0.2 (0.6)	0.2 (0.5)	0.87
Severity of illness†§						
Not severe (%)	9,331 (73.7)	9135 (72.3)	<0.05	40,924 (84.4)	40,556 (83.7)	0.01
Severe (%)	3,336 (26.3)	3502 (27.7)		7565 (15.6)	7879 (16.3)	

AMI = acute myocardial infarction, CHF = congestive heart failure, PVD = peripheral vascular disease, CVD = cerebral vascular disease, PD = pulmonary disease, CTD = connective tissue disorder, SLD = severe liver disease, CRC = colorectal cancer, CCI = Charlson Comorbidity Index.
* Comparisons of demographic and clinical characteristics between males and females were performed using Student's t-tests.
† Comparisons of demographic and clinical characteristics between males and females were performed using χ^2 tests.
‡ HIV (Human Immunodeficiency Virus) was excluded from individual co-morbidities due to low numbers of incident cases.
§ Not severe: 0; severe: 1+.

Data sources

Individuals eligible to be included in the study were residents of NL aged ≥30 years at study entry. The study population was obtained from the Cancer and Chronic Disease Research Database (CCDRD), which was built for ongoing research related to the association between cancer and chronic diseases. The patient population in the CCDRD was assembled by linking two databases: the NL component of the Canadian Chronic Disease Surveillance System (CCDSS) and the provincial Oncology Patient Information System (OPIS). The CCDSS compiles administrative health care data relating to several chronic conditions, including diabetes. The information from which the CCDSS is composed includes the provincial health insurance registry, hospital discharge records, and fee-for-service physician claims. The OPIS is a province-wide cancer surveillance system and contains information on new histology-confirmed cancer cases in the province.

Formation of the Diabetes Inception Cohort

The diabetes cohort consisted of individuals with a new diabetes diagnosis between October 1, 1995 and March 31, 2004. The diabetes cases were previously extracted using a nationally validated case definition for diabetes: one or more hospitalizations or two or more fee-for-service physician claims with a diagnosis of diabetes within a two-year period.[1] This case criterion was shown to have a high sensitivity (79.5% to 91%), and specificity (~99%).[17] While we were unable to distinguish between type 1 and type 2 diabetes, the vast majority of individuals aged ≥30 years are expected to have type 2 diabetes.[10] In order to minimize the inclusion of individuals having diabetes before the study entry date, a six-month wash-out period from April 1, 1995 to October 1, 1995 was used. The study entry date for those with diabetes was the date of their initial diabetes diagnosis.

Selection of the Comparison Group

Individuals without any evidence of diabetes at baseline were eligible to be included in the comparison group. Using frequency matching by 5-year age groups and sex, four non-diabetes individuals were selected for each diabetes case. Non-diabetes individuals were assigned the same entry date as their matched diabetes counterparts. Those who died prior to their assigned study entry date were excluded.

Outcome and follow-up

The outcome of interest was CRC incidence overall and by anatomic subsite based on a new diagnosis of CRC, for which we adopted a definition from previous research.[2,9,12] According to the International Classification of Disease – Oncology, version three (ICD-O-3) diagnosis codes, cases of CRC comprised codes C18-C21 and C26. Colon cancers comprised ICD-O-3 codes C18.0-C18.9, with specification as to whether the diagnosis was in proximal or distal colon (ICD-O-3 codes C18.0-C18.5 and C18.6-C18.7, respectively). For identification of rectal cancer, ICD-O-3 codes C19 to C21 were employed. For individuals with and without diabetes, the follow-up period started one year after their entry into the study and ended on the earliest of the following events: incident CRC, death, or end of the study (March 31, 2007). Maximum follow-up was 10.5 years (from October 1, 1996 to March 31, 2007). Individuals with previous cancer history or those who developed cancer within the first year of entry were excluded. Individuals identified as having cancer or diabetes at baseline in the hospital discharge abstract or physician billing records, but not in the OPIS or CCDSS, were also excluded.

Covariates

The following covariates were included in the analysis: baseline age, sex, and severity of illness. Severity of illness at baseline was estimated using the Charlson Comorbidity Index (CCI).[18] The CCI

Table 2. Colorectal Cancer Incidence Among Diabetes and Non-Diabetes Groups

	Diabetes				No Diabetes			
	n	PY of Follow-up	CRC Cases	CRC Incidence/ 10,000 PY (95% CI)*	n	PY of Follow-up	CRC Cases	CRC Incidence/ 10,000 PY (95% CI)*
Both sexes								
All individuals	25,304	144,427	414	28.7 (25.9-31.4)	96,924	607,135	1249	20.6 (19.4-21.7)
Age at baseline (years)								
30-44	5111	30,821	21	6.8 (3.9-9.7)	20,212	124,102	56	4.5 (3.3-5.7)
45-54	6357	38,863	78	20.1 (15.6-24.5)	24,724	157,063	202	12.9 (11.1-14.6)
55-64	5919	36,150	125	34.6 (28.5-40.6)	22,554	148,230	356	24.0 (21.5-26.5)
65-74	4965	27,335	130	47.6 (39.4-55.7)	18,648	120,898	434	35.9 (32.5-39.3)
75+	2952	11,258	60	53.3 (39.8-66.8)	10,786	56,843	201	35.4 (30.5-40.2)
Severity of illness†								
Not severe	18,466	110,753	307	27.7 (24.6-30.8)	81,480	521,193	1023	19.6 (18.4-20.8)
Severe	6838	33,675	107	31.8 (25.8-37.8)	15,444	85,942	226	26.3 (22.9-29.7)
Males								
Total	12,667	71,676	241	33.6 (29.4-37.9)	48,489	299,162	749	25.0 (23.2-26.8)
Age at baseline (years)								
30-44	2644	15,665	14	8.9 (4.3-13.6)	10,478	63,482	40	6.3 (4.3-8.3)
45-54	3494	21,449	44	20.5 (14.5-26.6)	13,596	86,549	134	15.5 (12.9-18.1)
55-64	3137	18,778	80	42.6 (33.3-51.9)	11,940	77,094	237	30.7 (26.8-34.7)
65-74	2315	12,061	73	60.5 (46.6-74.4)	8637	53,742	261	48.6 (42.7-54.5)
75+	1077	3724	30	80.6 (51.7-109.4)	3838	18,294	77	42.1 (32.7-51.5)
Severity of illness†								
Not severe	9331	55,650	178	32.0 (27.3-36.7)	40,924	258,178	615	23.8 (21.9-25.7)
Severe	3336	16,026	63	39.3 (29.6-49.0)	7565	40,984	134	32.7 (27.2-38.2)
Females								
Total	12,637	72,751	173	23.8(20.2-27.3)	48,435	307,973	500	16.2 (14.8-17.7)
Age at baseline (years)								
30-44	2467	15,155	7	4.6 (1.2-8.0)	9734	60,619	16	2.6 (1.3-3.9)
45-54	2863	17,414	34	19.5 (13.0-26.1)	11,128	70,514	68	9.6 (7.4-11.9)
55-64	2782	17,372	45	25.9 (18.3-33.5)	10,614	71,135	119	16.7 (13.7-19.7)
65-74	2650	15,274	57	37.3 (27.6-47.0)	10,011	67,156	173	25.8 (21.9-29.6)
75+	1875	7534	30	39.8 (25.6-54.1)	6948	38,549	124	32.2 (26.5-37.8)
Severity of illness†								
Not severe	9135	55,102	129	23.4 (19.4-27.5)	40,556	263,015	408	15.5 (14.0-17.0)
Severe	3502	17,648	44	24.9 (17.6-32.3)	7879	44,958	92	20.5 (16.3-24.6)

PY = person-years, CRC = colorectal cancer, CI = confidence intervals.
* 95% CIs for the CRC incidence rates were calculated based on the Poisson distribution.
† Calculated based on the Charlson Comorbidity Index.[31] Not severe: 0; severe: 1+.

measure was used to control for the presence of a number of serious health conditions for the 18 months prior to study entry that may have altered cancer diagnosis rates. After identifying co-morbidities through diagnosis codes in the fee-for-service physician claims and hospital discharge abstracts databases, a co-morbidity score (representing severity of illness) was assigned to each individual based on the presence or absence of 13 specific conditions, identified using ICD-9 (all physician claims, and hospital records prior to April 1, 2001) and ICD-10-CA codes (hospital records, as of April 1, 2001). Given that the aim was to assess the risk of developing CRC for those with diabetes, the two diabetes (diabetes and diabetes with complications) and two cancer (cancer and metastatic cancer) co-morbidities were removed from the CCI.

Statistical analysis

For individuals with and without diabetes, characteristics of the study subjects were compared between males and females using Student's t-tests for continuous variables and χ^2 tests for categorical variables. Severity of illness was categorized as "not severe" (CCI = 0) and "severe" (CCI = ≥1). Overall and sex-specific incidences of CRC were calculated separately for individuals with and without diabetes by dividing the number of incidence cases by category-specific person-years and presented by age group and severity of illness. Sex-specific incidence rates of CRC by anatomic subsite (i.e., colon, proximal colon, distal colon and rectal cancers) were calculated following a similar manner used in calculating CRC incidence. Ninety-five percent confidence intervals (95% CIs) for the CRC incidence rates were calculated assuming a Poisson distribution. To examine unadjusted CRC risk, we compared Kaplan-Meier estimates of survival probabilities between diabetes and non-diabetes groups. Cox proportional hazards regression, adjusted for age and severity of illness, was performed to estimate hazard ratios (HR) with corresponding 95% CIs for overall and subsite-specific CRC associated with diabetes. To investigate whether any observed association of diabetes with CRC was due to a high proportion of overweight and obese individuals in the diabetes group, the relative risk (RR) of diabetes with CRC was calculated after adjusting for overweight and obesity in the population (Appendix A). To do this adjustment, the RR of overweight/obesity with CRC was obtained from a published meta-analysis of 15 cohort studies,[19] and the prevalence of overweight and obese in the NL population aged 30 years and older was derived from the 2005 public use micro data file of the Canadian Community Health Survey (CCHS) Cycle 3.1. These two estimates were used to derive the obesity-attributable CRC cases in our study cohort, which was subsequently subtracted from overall CRC cases to adjust for obesity effect on CRC. All statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) software.

RESULTS

The initial study cohort comprised 130,710 individuals (26,142 with diabetes and 104,568 without diabetes). Following exclusions mentioned above, the analysis cohort consisted of a total of

Figure 1. Sex-specific survival of patients with colorectal cancer, in relation to diabetes status

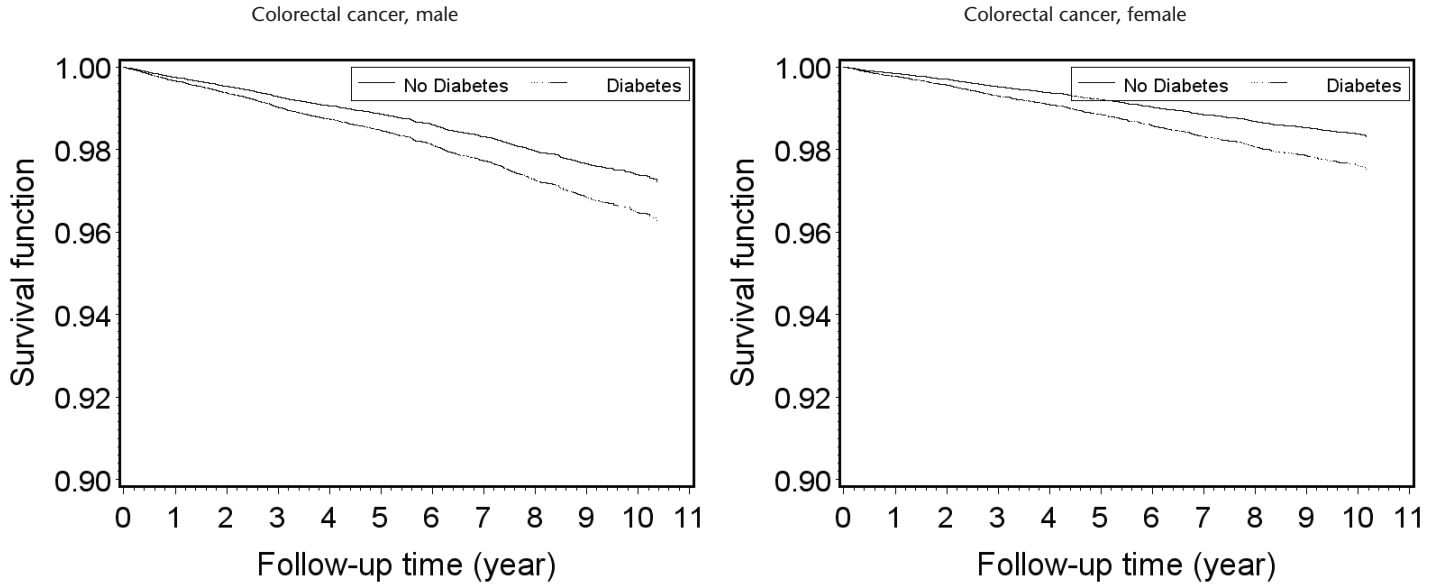

Table 3. Diabetes and HRs of Incident Colorectal Cancer Overall and by Cancer Subsite

	Males			Females		
	Diabetes	**No Diabetes**	**p-value**	**Diabetes**	**No Diabetes**	**p-value**
Colorectal cancer						
n *	241	749		173	500	
Person-years	71,676	299,162		72,751	307,973	
Incidence/10,000 (95% CI)†	33.6 (29.4-37.8)	25.0 (23.2-26.8)		23.8 (20.3-27.3)	16.2 (14.8-17.6)	
Multivariate HR‡ (95% CI)†	1.38 (1.19-1.60)	1.00 (reference)	<0.0001	1.52 (1.27-1.80)	1.00 (reference)	<0.0001
Colon cancer						
n*	161	464		127	379	
Person-years	71,868	299,829		72,888	308,286	
Incidence/10,000 (95% CI)†	22.4 (18.9-25.9)	15.5 (14.1-16.9)		17.4 (14.4-20.5)	12.3 (11.1-13.5)	
Multivariate HR‡ (95% CI)†	1.49 (1.24-1.78)	1.00 (reference)	<0.0001	1.47 (1.20-1.80)	1.00 (reference)	0.0002
Proximal colon cancer						
n	78	246		84	237	
Person-years	72,078	300,346		72,967	308,622	
Incidence/10,000 (95% CI)†	10.8 (8.4-13.2)	8.2 (7.2-9.2)		11.5 (9.1-14.0)	7.7 (6.7-8.7)	
Multivariate HR‡ (95% CI)†	1.35 (1.05-1.78)	1.00 (reference)	0.023	1.58 (1.22-2.02)	1.00 (reference)	0.0004
Distal colon cancer						
n	66	174		30	109	
Person-years	72,119	300,495		73,072	308,952	
Incidence/10,000 (95% CI)†	9.2 (6.9-11.4)	5.8 (4.9-6.7)		4.1 (2.6-5.6)	3.5 (2.9-4.2)	
Multivariate HR‡ (95% CI)†	1.61 (1.21-2.15)	1.00 (reference)	0.001	1.19 (0.79-1.79)	1.00 (reference)	0.398
Rectal cancer						
n	79	281		43	120	
Person-years	72,101	300,253		73,011	308,916	
Incidence/10,000 (95% CI)†	11.0 (8.5-13.4)	9.5 (8.3-10.5)		5.9 (4.1-7.6)	3.9 (3.2-4.6)	
Multivariate HR‡ (95% CI)†	1.19 (0.93-1.53)	1.00 (reference)	0.165	1.56 (1.10-2.22)	1.00 (reference)	0.012

HR = hazard ratio; CI = confidence intervals.
* The numbers of proximal colon, distal colon, and rectal cancers do not add up to the total number of CRCs, and the numbers of proximal colon and distal colon cancers do not add to the total number of colon cancers, because, in some cases, information on the specific site was unknown.
† 95% CIs for the CRC incidence rates were calculated based on the Poisson distribution.
‡ Adjusted for age (in years), and severity of co-morbid illness.

122,228 individuals (25,304 with diabetes and 96, 924 without diabetes). Characteristics of the study subjects are presented in Table 1. There were almost equal numbers of males and females, 61,156 (50%) and 61,072 (50%), respectively. Females were older than males (mean age 58.4 versus 55.9 years, p<0.01). Females with diabetes were also older than males with diabetes (58.7 versus 56.3 years, p<0.01) as were females without diabetes compared to males without diabetes (58.3 versus 55.9 years, p<0.01).

During 751,562 person-years of follow-up, a total of 1,663 newly diagnosed CRC cases (414 for diabetes and 1,249 for non-diabetes) were identified (Table 2). The incidence of CRC was higher for individuals with diabetes compared to those without diabetes (28.7, 95% CI 25.9-31.4 versus 20.6, 95% CI 19.4-21.7 per 10,000 person-years) and increased with age. The same pattern was observed when the analysis was stratified by sex. As shown in Figure 1, diabetes negatively affected survival of patients with CRC in both sexes.

Incidence rates of CRC by anatomic subsite and hazard ratios stratified by sex are presented in Table 3. Among males, incidences of specific CRC were higher for individuals with diabetes compared to those without diabetes for colon (22.4, 95% CI 18.9-25.9 versus 15.5, 95% CI 14.1-16.9 per 10,000 person-years) and distal colon (9.2, 95% CI 6.9-11.4 versus 5.8, 95% CI 4.9-6.7 per 10,000 person-years). Among females, a higher incidence of colon (17.4, 95% CI 14.4-20.5 versus 12.3, 95% CI 11.1-13.5 per 10,000 person-years) and proximal colon cancer (11.5, 95% CI 9.1-14.0 versus 7.7, 95% CI 6.7-8.7

per 10,000 person-years) was found for those with diabetes compared to those without diabetes, respectively. Overlapping confidence intervals indicated that incidences of proximal colon cancer in males with and without diabetes were similar, and incidences of distal colon cancer in the two groups for females were similar. For both sexes, rectal cancer incidence rates were not significantly different for those with and without diabetes.

As shown in Table 3, after adjusting for age and severity of illness, CRC risk was increased by 38% (HR=1.38, 95% CI 1.19-1.60) among males with diabetes and by 52% (HR=1.52, 95% CI 1.27-1.80) among females with diabetes, compared to males and females without diabetes. Subsite-specific stratified analyses indicated that among males, diabetes was positively associated with overall colon cancer risk (HR=1.49, 95% CI 1.24-1.78), proximal colon cancer risk (HR =1.35, 95% CI 1.05-1.78) and distal colon cancer risk (HR=1.61, 95% CI 1.21-2.15). Among females, diabetes was significantly associated with increased risk of overall colon cancer (HR =1.47, 95% CI 1.20-1.80), proximal colon cancer (HR=1.58, 95% CI 1.22-2.02) and rectal cancer (HR=1.56, 95% CI 1.10-2.22). No significant association was observed for diabetes and the risk of rectal cancer in males, nor for diabetes and the risk of distal colon cancer in females.

Obesity-adjusted RR of CRC on diabetes estimated separately for males and females demonstrates that controlling for obesity did not substantially alter the degree of CRC risk on diabetes. Following this adjustment, the RR of diabetes with CRC was 1.30 (95% CI 1.28-1.32) among males and 1.44 (95% CI 1.40-1.48) among females. These results did not differ from the HR (1.38, 95% CI 1.19-1.60 for males and 1.52, 95% CI 1.27-1.80 for females) when obesity-attributable CRC cases were included in the analysis.

DISCUSSION

This is the first population-based cohort study that employed population-based administrative data to examine the relationship between diabetes and CRC incidence in Canada. We found that diabetes was associated with a 38% increased risk of CRC among males and a 52% increased risk of CRC among females. Adjusting for obesity effect did not alter the diabetes-associated risk of CRC. Findings from this study support those of other cohort studies that have demonstrated a significant increase in CRC incidence among individuals with diabetes.[8-11] The CRC incidence rates in this study are notably higher than those of other studies. For example, one population-based cohort study from Singapore reported 208.9 and 140.2 incidence per 100,000 person-years for those with diabetes and those without diabetes, respectively,[20] which is considerably lower than the 287 and 206 per 100,000 person-years, respectively, found in the current study. The higher rates in this study likely reflect the added influence of Western lifestyle factors.

The findings of this study are consistent with the hypothesis that the relationship between diabetes and CRC is subsite-specific[12,13] and, furthermore, that the patterns of subsite-specific associations differ for males and females. For males, diabetes significantly increases the risk of overall CRC, as well as proximal, distal, and overall colon cancers. Diabetes does not significantly increase the risk of rectal cancer in males. For females, diabetes significantly increases the risk of overall CRC, as well as proximal and overall colon and rectal cancers, but not of distal colon cancer. The results suggest that there is a stronger association between diabetes and CRC for females than for males; however, this trend was not significant. This finding may be due primarily to the contributions of proximal colon and rectal cancers.

The findings of the current study also support those of studies that have shown that diabetes increases the risk of proximal colon cancer, but not distal colon cancer, in females.[12,14] There are several plausible reasons for why the association between diabetes and distal CRC was observed in males only. Previous studies have demonstrated that smoking significantly increases insulin resistance,[21] which is thought to increase CRC risk;[22,23] it is possible that the distal colon may be especially sensitive to increased insulin and insulin-like growth factors.[24] One study which reported a similar result also found a significantly higher proportion of smokers among males with diabetes than among females with diabetes.[8] In the current study, smoking status was unknown. Another possible explanation for sex differences may be the differential moderating effect of estrogen on levels of insulin and IGFs, as estrogen has been linked to reduced serum IGF levels.[24,25] There is also evidence to suggest that different genetic pathways to CRC dominate in the proximal and distal colon, which are influenced by different sex-related factors;[26] these pathways may differentially interact with diabetes status.

The results of this study should be interpreted in the context of the limitations of the available data. Primarily, the magnitude of the association between type 2 diabetes and CRC risk may be underestimated for several reasons. First, it was not possible to distinguish between type 1 and type 2 diabetes. This is important as type 1 diabetes (which accounts for about 5-10% of the total population living with diabetes)[1] may not be related to CRC.[12] Second, this study included only diabetes cases identified using a validated case definition applied to administrative data. Those with diabetes or its precursors who did not meet the criteria for the CCDSS definition (e.g., they had only one physician claim with a diabetes diagnosis) may have been included in the comparison group as an individual without diabetes. Third, in later stages of diabetes, insulin levels might decline, which may result in variable associations between diabetes and cancer risk, if the hyperinsulinemia hypothesis holds true.[22] Previous work has shown that the risk of CRC may decrease with increased follow-up time.[27] Future work should include all diagnoses of pre-diabetes, hyperinsulinemia, hyperglycemia, and other factors related to insulin resistance, as well as a more in-depth analysis by follow-up time.

A further limitation of the current study is that, since type 2 diabetes and CRC share common risk factors such as smoking, physical inactivity, Western diet, and obesity, the observed increased risk of CRC associated with a history of diabetes may be confounded by these factors. However, as we have shown, controlling for obesity did not alter the association. Also, a meta-analysis found a positive association between diabetes and CRC when the analysis was limited to studies that controlled for activity level and BMI.[10] In future work, controlling for lifestyle factors would reduce error variation and provide a more precise estimate of the strength of the relationship between diabetes and CRC. Similarly, data on insulin use and other medications may be another contributing factor to be included in future investigations, as insulin therapy has also been found to increase CRC risk.[7,28,29]

While the data used in this study posed some minor problems in terms of missing information and other discrepancies, using population-based and large-size administrative datasets along

Appendix A. Approach to the estimation of diabetes-attributable risk for colorectal cancer after adjusting for overweight/obesity; where colorectal cancer (CRC) is the outcome, diabetes is an exposure and overweight/obesity (OB) is a known confounder.

The formulae for attributable risk percent (AR%) and population attributable risk percent (PAR%) were the modified version of the previously used formulae.[31,32]

Formula 1a
AR% was calculated using the overweight/obesity-associated relative risk (RR_{ob}) of colorectal cancer

$$\mathbf{AR\%} = \frac{\mathbf{RR_{ob} - 1}}{\mathbf{RR_{ob}}}$$

where $\mathbf{RR_{ob}}$ is the relative risk of CRC associated with overweight/obesity, obtained from Dai et al.;[19] $\mathbf{RR_{ob} - 1}$ indicates excess relative risk of CRC for overweight/obesity.

Formula 1b
PAR% was calculated separately for diabetes and non-diabetes group according to the formula

$$\mathbf{PAR\% = AR\% * p\ ,}$$

where p is the proportion of population overweight/obese in diabetes and non-diabetes groups, obtained from the Canadian Community Health Survey Cycle 3.1.

Formula 2a
The overweight/obesity attributable CRC cases (x_{ob}) were estimated separately for diabetes and non-diabetes groups

$$\mathbf{x_{ob} = x * PAR\%\ ,}$$

where x is the number of CRC cases obtained from the study sample in each of the diabetes and non-diabetes groups.

Then $\mathbf{x}$ **and** $\mathbf{x_{ob}}$ were used to estimate the CRC cases ($\mathbf{x_{adj}}$) in diabetes and non-diabetes groups after adjusting for overweight/obesity

$$\mathbf{x_{adj} = x - x_{ob}}$$

Formula 2b
The final step is the calculation of diabetes associated relative risk (RR_{adj}) of colorectal cancer after adjusting for overweight/obesity using the following formula

$$RR_{adj} = \frac{\text{Incidence of CRC in diabetes group after adjusting for } \frac{\text{overweight}}{\text{obesity}}}{\text{Incidence of CRC in non-diabetes group after adjusting for } \frac{\text{overweight}}{\text{obesity}}}$$

$$RR_{adj} = \frac{\frac{x_{adj} \text{ in diabetes group}}{\text{Person-years in diabetes group}}}{\frac{x_{adj} \text{ in non-diabetes group}}{\text{Person-years in non-diabetes group}}}$$

with a cohort design is a major strength which has the ability to provide the reliable estimates for diabetes and cancer incidence available at this time for NL and many other provinces. This design allowed us to identify the cases of CRC and carry out successful record linkage of patients via a unique health care number. The cohort design and record linkage of population-based historical data enable us to alleviate issues related to selection and recall bias. Also, exclusion of individuals who developed CRC within the first year of diabetes diagnosis was a thoughtful measure that allowed us to mitigate detection bias or overestimation of the risk. Because of the large datasets and long follow-up period, we were able to identify a relatively large number of CRC cases and, thus, examine the association with diabetes by subsite and stratify the analysis by sex.

In summary, the results of this study have important clinical and public health implications as an association between diabetes and increased risk of CRC in both males and females was found. These findings also provide indirect epidemiological evidence for the hypothesis that either hyperinsulinemia or factors related to insulin resistance may play a role in increasing the risk of CRC by promoting growth of colon tumours, stimulating insulin-like growth factor receptors and acting as cell mitogen.[30] Given the evidence of shared etiologies, along with the increasing burden of both diabetes and CRC in Canada, these findings have implications for screening protocols and preventive initiatives. Also, preventive initiatives should directly address the shared risk factors (smoking, Western diet, obesity, and sedentary lifestyle). Future studies will be necessary to demonstrate whether lessening the burden of hyperinsulinemia and factors related to insulin resistance will be an effective strategy in the prevention of both type 2 diabetes and CRC incidence.

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RÉSUMÉ

OBJECTIF : Les études de la relation entre le diabète et le cancer colorectal (CCR) sont contradictoires. Il n'est pas clair non plus si l'élévation du risque de CCR chez les sujets diabétiques est semblable chez les hommes et les femmes. À l'aide de données de Terre-Neuve-et-Labrador (T.-N.-L.), la province du Canada où l'incidence du CCR et la prévalence du diabète sont les plus élevées, nous avons estimé et comparé l'élévation du risque de CCR pour les hommes et les femmes diabétiques, globalement et par sous-site anatomique.

MÉTHODE : Nous avons mené une étude de cohorte rétrospective populationnelle sur un échantillon de 122 228 sujets de ≥30 ans puisé dans les bases de données administratives sur la santé sur une période de 10,5 ans (1er octobre 1996 au 31 mars 2007). Les coefficients de danger ont été estimés à l'aide des modèles de régression à effet proportionnel de Cox.

RÉSULTATS : Par comparaison avec les sujets non diabétiques, les hommes et les femmes diabétiques présentaient un risque global de CCR significativement élevé, avec des coefficients de danger de 1,38 et de 1,52, respectivement. Chez les hommes, le diabète augmentait significativement le risque de cancers du côlon proximal et distal, mais pas le risque de cancer rectal. Chez les femmes, le diabète augmentait significativement le risque de cancer du côlon proximal et de cancer rectal, mais pas le risque de cancer du côlon distal. Ces résultats montrent que l'association entre le diabète et le CCR est plus forte chez les femmes que chez les hommes; cette association reste inchangée après la prise en considération du surpoids et de l'obésité.

CONCLUSIONS : Le diabète entraîne un plus grand risque de CCR tant chez les hommes que chez les femmes à T.-N.-L. Le risque est propre au sous-site et varie selon le sexe. Les études futures devraient porter sur les raisons du risque observé de CCR associé au diabète pour appuyer des stratégies de prévention du CCR dans la population diabétique.

MOTS CLÉS : cancer colorectal; diabète; études de cohortes; coefficient de danger; élévation du risque