

The risk of colorectal cancer is not increased after a diagnosis of urothelial cancer: a population-based study

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ABSTRACT

Background The data about whether patients with a prior urothelial cancer (uca) are at increased risk of colorectal cancer (CRC) are conflicting. We used a competing risks analysis to determine the risk of CRC after uca.

Methods Historical cohorts were assembled by record linkage of Manitoba Cancer Registry and Manitoba Health databases. The incidence of CRC for individuals with uca as their first cancer between 1987 and 2009 was compared with the incidence for randomly selected age- and sex-matched individuals without a cancer diagnosis at the index date (uca diagnosis date). Three competing outcomes (CRC, another primary cancer, and death) were evaluated by competing risks proportional hazards models with adjustment for relevant confounders.

Results The cohorts of 4591 patients with uca and 22,312 without uca were followed for a total of 179,287 person-years (py). After uca, the rate of subsequent colon cancer in uca patients was 4.5 per 1000 py compared with 3.6 per 1000 py in the non-cancer cohort. In the multivariable analysis, no overall increase in CRC risk was observed for patients first diagnosed with uca (hazard ratio: 0.88; 95% confidence interval: 0.70 to 1.1; $p = 0.26$).

Conclusions Because of similar CRC risk, a similar CRC screening strategy should be applied for individuals with and without uca.

Key Words Colorectal neoplasms, urinary bladder neoplasms, ureteric neoplasms, second primary neoplasms, survivorship, competing risks analyses

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INTRODUCTION

Colorectal cancer (CRC) is the 2nd most common cause of cancer-related death among Canadian men and the 3rd most common cause of cancer related death among Canadian women¹. The death rate in CRC has been declining since 2004 for men and since 2001 for women¹, at least in part because of screening for CRC and its precursor lesions, which is known to reduce CRC-related mortality²⁻⁵. Identifying individuals at higher risk of CRC is essential for determining the groups that should be targeted for CRC screening and the optimal timing and frequency of screening⁶⁻⁸.

Urothelial cancer (uca) originates from the transitional cell epithelium found in the renal pelvis, ureters, bladder,

and proximal urethra. It often presents multifocally and can recur in other parts of the urothelium over time. It is the 12th most common cancer diagnosis in women, but the 4th most common in men¹. There are several common risk factors for CRC and uca, including diabetes⁹⁻¹¹ and smoking^{12,13}. Lynch syndrome is also associated with an increased risk of both CRC and uca^{14,15}. Although consumption of red and processed meats has been linked with an increased risk of CRC¹⁶, studies of their association with uca have yielded mixed results^{17,18}.

Several studies have demonstrated an increased risk of secondary cancers after a diagnosis of uca. Data about the incidence of CRC after a diagnosis of uca are mixed, with some studies demonstrating no increased incidence¹⁹⁻²¹, and one study demonstrating an increased incidence

[standardized incidence ratio (SIR) for colon cancer in women: 1.76; 95% confidence interval (CI): 1.44 to 2.15; SIR for colon cancer in men: 1.21; 95% CI: 1.09 to 1.34; SIR for rectal cancer in women: 1.67; 95% CI: 1.25 to 2.24; SIR for rectal cancer in men: 1.22; 95% CI: 1.06 to 1.41]²². All prior studies, including one from our own institution²¹ are limited, given that they have not adjusted the risk estimates for competing events such as other cancer diagnoses and death. In addition, the studies from cancer registries alone are unable to adjust for other confounding factors such as increased exposure to lower gastrointestinal endoscopy and health care visits by cancer survivors. Increased rates of endoscopy and health care contact for patients who have been diagnosed with uca could alter the incidence of CRC, either by increasing the rate of detection or by identifying and removing early precancerous lesions during endoscopy. Increased health care contacts could increase the chances of earlier detection because of increased diagnostic work-up of minor symptoms.

An increased risk of CRC in patients with a diagnosis of uca could alter the CRC screening recommendations for this population. We therefore undertook a population-based cohort study to rigorously investigate the risk of CRC after a uca diagnosis.

METHODS

A historical cohort was assembled by record linkage of several large longitudinal databases of health data collected by the Manitoba Cancer Registry (MCR) and Manitoba Health.

Data Sources

Manitoba is a central Canadian province with a relatively stable population (1.3 million in 2012)²³. Manitoba has a comprehensive universal health care system, with Manitoba Health being the publicly funded health agency that provides funding for the health care delivered to the Manitobans. Centralized electronic databases maintained by Manitoba Health include data about physician claims, hospital discharges, and drug prescriptions. A personal health identification number has been assigned to each Manitoban since 1984. That number can be used to link patient records over time and across databases.

The population-based MCR has tracked all cancers diagnosed in the province of Manitoba since 1956. The registry has repeatedly attained a high standing in evaluations by the North American Association of Central Cancer Registries^{24,25}. The MCR was used to identify all cancers occurring in study subjects.

Information about diabetes, inflammatory bowel disease, counts of ambulatory care visits with physicians, and lower gastrointestinal (GI) endoscopy was obtained by linkage to Manitoba Health's Hospital Discharge Abstract and Medical Claims databases, which respectively include all hospitalizations and physician billings in the province. Earlier studies have validated the accuracy and comprehensiveness of those databases^{26,27}. Diabetes and inflammatory bowel disease were identified using previously validated algorithms^{28,29}.

The socioeconomic status of the study subjects was assigned by applying the Socioeconomic Factor Index, a composite index based on several neighbourhood-level social determinants of wealth, to each individual's area of residence^{30–32}.

Study Cohorts

Patients diagnosed with a first primary uca between 1987 and 2009 ("cancer cohort") were age- and sex-matched to as many as 5 individuals without an invasive cancer diagnosis at the date of diagnosis of the matched case ("non-cancer cohort"). The non-cancer cohort was assembled by using the Manitoba Population Registry (an actively maintained comprehensive registry of all residents of Manitoba) to random select individuals from among the entire Manitoba population. "Index date" refers to the date of uca diagnosis for individuals with uca and for their respective matched subjects without uca.

To be eligible for inclusion in the study, individuals had to be residents of Manitoba and to be registered with Manitoba Health for at least 3 years before the index date. The minimum 3-year cut-off was used to ensure sufficient follow-up time for the identification of prior procedures and pre-existing medical conditions. Individuals who were diagnosed with any cancer (aside from non-melanoma skin cancer) before the index date or with inflammatory bowel disease at any time were excluded.

Study Outcomes

The primary outcome of interest was a diagnosis of first primary CRC. Secondary outcomes were right-sided CRC (occurring at and proximal to the hepatic flexure) and left-sided CRC (occurring in the transverse and more distal colon).

Potential Confounders

Age at diagnosis of uca, history of diabetes, exposure to lower GI endoscopy, number of ambulatory care physician visits annually (divided into quartiles), and Socioeconomic Factor Index score were included as potential confounders in the study. Diabetes has been reported as a risk factor for CRC¹¹ as well as for uca^{9,10}.

Medical conditions, procedures, and physician visits must have occurred a minimum of 6 months before the end of follow-up, including date of CRC diagnosis. Lower GI endoscopy is the most common test used to diagnose CRC, and its use within the 6 months preceding a cancer diagnosis would therefore be strongly correlated with the diagnosis of CRC, the outcome of interest in our study.

Statistical Analysis

Study subjects were followed from the index date to the earliest of the date of diagnosis of CRC or another primary invasive cancer of any type, death, migration, or study end date (31 December 2009). Three mutually exclusive and competing outcomes were included in the analysis:

- Diagnosis of CRC
- Diagnosis of a different primary invasive cancer
- Death

The occurrence of a competing event precludes or modifies the probability of the other events occurring. For that reason, Kaplan–Meier and Cox regression models, which are standard time-to-event analysis methods that assume all events are independent, were not used for the analysis³³. Instead, cumulative incidence curves of the probability of failing from each competing event were produced³⁴. Competing risks proportional hazards models, as modified by Fine and Gray³⁵, were used to calculate the relative risk as estimated by hazard ratio (HR) and 95% CI. Censoring occurred if the subjects were still living by the study end date or were lost to follow-up because of emigration.

Models were adjusted for the potential confounding factors already mentioned: age at uca diagnosis, Socio-economic Factor Index score, presence of diabetes¹¹, number of ambulatory care visits, and history of lower GI endoscopy more than 6 months before the end of follow-up. A separate exploratory analysis was conducted for ureteric and renal pelvis cancers, recognizing their possible link with Lynch syndrome^{14,36}. The analysis was stratified by age and time since the diagnosis of uca. Right sided CRCs were also analyzed separately because of their known association with Lynch syndrome¹⁵.

RESULTS

The final cohorts of 4591 subjects with uca and 22,312 without uca (Table I) were followed for a total of 179,287 person–years (py). Median follow-up duration was 5.2 years. Most uca patients (73.7%) were men, and median age at the index date was 72 years. Cancers within the bladder constituted 92% of the ucas.

The rate of subsequent CRC among patients with uca was 4.5 per 1000 py (Table II). In the non-cancer cohort, the rate of CRC diagnosis was 3.6 per 1000 py. The death rate per 1000 py was 96.6 for patients with uca and 52.9 for the non-cancer cohort. In patients with prior uca, non-CRC cancers occurred at a rate of 42.7 per 1000 py compared with 21.2 per 1000 py in the non-cancer cohort. The increased risk of death and other cancer diagnoses for the uca patients supported our decision to use competing risks analyses. The cumulative incidence for CRC was not significantly different between subjects with a history of uca and the non-cancer subjects (Figure 1).

In the multivariable models that included all potential confounders, a prior diagnosis of uca was not associated with an increased risk of subsequent CRC (HR: 0.88; $p = 0.26$; Table III). As could be expected, age at the index date had the strongest association with a subsequent diagnosis of CRC.

In an analysis stratified by follow-up time, an increased risk of a diagnosis of CRC was observed for those with a diagnosis of uca within 0–30 days after the diagnosis of that uca (HR: 9.4; $p < 0.001$), but not during any other follow-up period (Table IV). An increased incidence of right-sided CRC was observed in the period 30–365 days after the diagnosis of uca (HR: 2.7; $p = 0.039$), but not during other follow-up periods (Table IV).

In an analysis stratified by age at diagnosis of uca, a significantly decreased risk of all CRC (HR: 0.5; $p = 0.009$) and of right-sided CRC (HR: 0.3; $p = 0.04$) was observed in

TABLE I Characteristics of the study cohorts

Characteristic	Patient cohort		<i>p</i> Value
	Urothelial cancer	Non-cancer	
Patients (<i>n</i>)	4,591	22,312	
Sex (% men)	73.7	73.7	(matching variable)
Age at index (years)			
Median	72	72	(matching variable)
IQR	63–79	63–79	
Age group [<i>n</i> (%)]			
<50 Years	300 (7)	1407 (6)	
51–65 Years	1120 (24)	5474 (25)	
>65 Years	3171 (69)	15429 (69)	
Lower GI endoscopy	930 (20)	4334 (19)	0.20
Diabetes [<i>n</i> (%)]	947 (21)	4714 (21)	0.46
Socioeconomic factor index			
Median	–0.21	–0.26	0.86 ^a
IQR	–0.87 to 0.63	–0.89 to 0.65	
Annual ambulatory visits (<i>n</i>)			
Median	9.8	7.5	<0.001 ^a
IQR	6.0–14.1	4.0–11.9	
Duration of follow-up (years)			
Total	23,387	155,900	
Median	3.2	5.7	<0.001 ^a
IQR	0.9–7.8	2.6–10.4	
Range	0–22.7	0–22.8	

^a By Wilcoxon two-sample test.

IQR = interquartile range; GI = gastrointestinal.

subjects diagnosed between the ages of 60 and 69 (Table IV), but not in the other age groups.

In a subgroup analysis, 206 patients with uca of the renal pelvis and 88 patients with uca of the ureter were identified. Five or fewer CRC cases (exact number suppressed for confidentiality per Manitoba Health protocol) were identified among subjects with uca and 32 cases of CRC were identified among their matched controls (HR: 0.73; 95% CI: 0.29 to 1.87; $p = 0.51$).

Compared with subjects in the non-cancer cohort, patients in the uca cohort were at increased risk of developing a second non-CRC malignancy (HR: 1.6; $p < 0.001$; Table V). Malignancies with increased incidence included a second diagnosis of uca (HR: 2.6; $p < 0.001$), lung cancer (HR: 1.6; $p < 0.001$), and prostate cancer (HR: 1.9; $p < 0.001$).

DISCUSSION

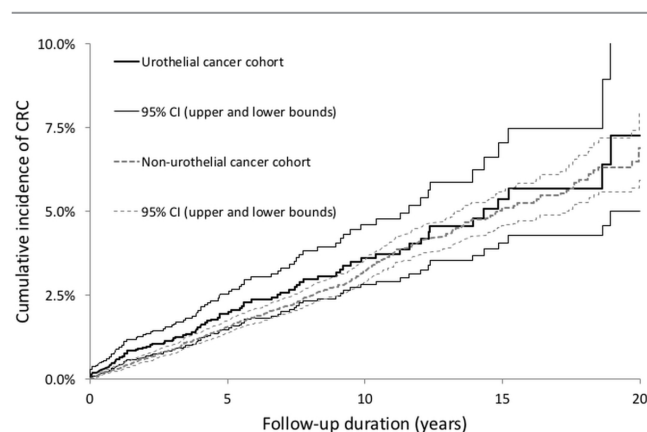
We found that patients with a diagnosis of uca did not have a subsequently increased risk of CRC. Those results agree with findings in some earlier studies^{19,20}, including one from our institution²¹, and contrast with the findings in a U.S. Surveillance, Epidemiology, and End Results database study demonstrating an increase in CRC incidence after a

TABLE II Outcome rates in the study cohorts

Event	Patient cohort					
	Urothelial cancer (n=4,591)			Non-cancer (n=22,312)		
	(n)	Rate ^a	95% CI	(n)	Rate ^a	95% CI
CRC diagnosis	89	4.5	3.5 to 5.4	478	3.6	3.3 to 4.0
Other invasive cancer	850	42.7	39.8 to 45.6	2791	21.2	20.4 to 22.0
Death	1921	96.6	92.8 to 100.3	8520	52.9	51.8 to 54.0

^a Per 1000 patient-years.

CI = confidence interval; CRC = colorectal cancer.


FIGURE 1 Cumulative incidence of colorectal cancer (CRC) among individuals diagnosed with urothelial cancer and matched controls. CI = confidence interval.

diagnosis of uca²². None of the earlier studies used a competing risks analysis. Moreover, the potentially confounding factors of lower GI endoscopy, diabetes, and number of ambulatory care visits have not been used in earlier analyses, including the earlier analysis from our institution. We therefore believe that the results of the present study are more robust and provide strong evidence that a diagnosis of uca does not increase the risk of CRC.

In our analysis stratified by follow-up time, an increased risk was demonstrated 0–30 days after the diagnosis of uca. That result is likely attributable to detection bias caused by increased exposure to health care providers and consequent diagnostic testing not accounted for in our analysis, such as tumour markers and computed tomography and magnetic resonance imaging.

Increased risk of uca has been associated with Lynch syndrome¹⁴. Most evidence suggests that the increased risk is predominantly for uca of the upper urinary tract, including the renal pelvis and ureter³⁶. However, some studies indicate that, in Lynch syndrome, the risk of bladder cancer is increased as well^{37,38}. In the present study, we observed no increased risk of CRC in all uca survivors or in patients with upper urinary tract tumours. There also did not appear to be an increased risk of right-sided CRC. We did not find, in stratified analysis, an increased risk for those less than 60 years of age at time of uca diagnosis.

TABLE III Multivariable competing risks analysis of the risk of colorectal cancer after a prior diagnosis of urothelial cancer

Variable	Comparator	HR	95% CI	p Value
Age at index date (years)				
Q1 (lowest)		Reference		
Q2		2.32	1.81 to 2.99	<0.001
Q3		2.17	1.67 to 2.81	<0.001
Q4		1.85	1.41 to 2.44	<0.001
Sex				
Male		1.21	1.00 to 1.47	0.050
Female				
Lower GI endoscopy				
Yes		0.81	0.64 to 1.01	0.061
No		Reference		
Diabetes				
Yes		0.88	0.72 to 1.08	0.23
No		Reference		
Socioeconomic factor index				
Per unit increase		1.00	0.94 to 1.05	0.88
Average annual ambulatory care visits				
Q1 (lowest)		Reference		
Q2		0.95	0.76 to 1.19	0.64
Q3		0.80	0.64 to 1.01	0.064
Q4		0.72	0.56 to 0.92	0.008
Urothelial cancer diagnosis				
Yes		0.88	0.70 to 1.1	0.26
No		Reference		

HR = hazard ratio; CI = confidence interval; Qx = quartile x; GI = gastrointestinal.

The most common malignancies associated with Lynch syndrome are CRC and endometrial cancer³⁹. The average age of onset of CRC in the setting of Lynch syndrome varies between studies, but it is generally considered to be the mid-40s¹⁵. In a series of 125 women with Lynch syndrome and endometrial cancer, the median age of diagnosis was 48 years⁴⁰. Given that the patients in the present study were relatively elderly (median age 72 years), it is therefore likely that patients with Lynch syndrome would have developed a first malignancy other than uca at an earlier age and

TABLE IV Risk of all colorectal cancer (CRC) and right-sided CRC among patients with a history of urothelial cancer, by time since diagnosis and age at diagnosis of urothelial cancer^a

Variable	All CRC				Right-sided CRC			
	(n)	HR	95% CI	p Value	(n)	HR	95% CI	p Value
<i>Time since diagnosis</i>								
All follow-up	89	0.88	0.70 to 1.10	0.26	35	1.05	0.73 to 1.51	0.79
0–30 Days	8	9.40	2.81 to 31.5	<0.001	Insufficient data			
30 Days to 1 year	15	1.28	0.72 to 2.26	0.40	7	2.67	1.05 to 6.76	0.039
1–5 Years	33	1.02	0.70 to 1.50	0.92	14	1.60	0.87 to 2.95	0.13
>5 Years	33	1.02	0.69 to 1.50	0.93	12	1.00	0.53 to 1.89	0.995
<i>Age at diagnosis</i>								
<60 Years	9	1.33	0.64 to 2.77	0.45	9	1.65	0.52 to 5.28	0.40
60–69 Years	15	0.50	0.29 to 0.84	0.009	<6	0.30	0.09 to 0.97	0.04
70–79 Years	45	1.07	0.78 to 1.48	0.68	18	1.34	0.80 to 2.25	0.27
≥80 Years	20	0.88	0.55 to 1.42	0.61	10	1.32	0.65 to 2.66	0.43

^a Comparison group: matched controls. Multivariate analysis used Fine and Gray's competing-risks regression models adjusted for age at index date, exposure to lower gastrointestinal endoscopy, diabetes, score on the socioeconomic factor index, and average annual number of ambulatory care visits (see text).

HR = hazard ratio; CI = confidence interval.

TABLE V Risk of selected second malignancies for the entire follow-up duration in patients with a history of urothelial cancer^a

Site of second malignancy	(n)	HR	95% CI	p Value
All cancers	850	1.56	1.44 to 1.69	<0.001
Second urothelial cancer	132	2.64	2.14 to 3.28	<0.001
Lung cancer	167	1.59	1.34 to 1.90	<0.001
Prostate cancer	288	1.85	1.61 to 2.12	<0.001

^a Comparison group: matched controls. Multivariate analysis used Fine and Gray's competing-risks regression models adjusted for age at index date, exposure to lower gastrointestinal endoscopy, diabetes, score on the socioeconomic factor index, and average annual number of ambulatory care visits (see text).

HR = hazard ratio; CI = confidence interval.

would therefore have been excluded from the study. Our findings support the understanding that Lynch syndrome does not commonly present with uca as the first cancer and that individuals with uca as their only cancer do not need a work-up for Lynch syndrome.

We found a significantly increased risk of non-CRC cancers diagnosed after a uca diagnosis. Specific sites with an increased incidence after uca included lung, prostate, and second uca. That observation is in keeping with earlier data from our institution²¹ and with data from other studies^{19,20}. Although it was not the primary goal of the present study to examine the risk of all cancers after a diagnosis of uca, the fact that the results of our analysis are congruent with findings in earlier studies provides confidence about the validity of our results.

The strengths and limitations of our study must be considered. Its strengths include the use of validated and high-quality population-based databases, which reduce the chance of information and selection biases. The MCR

has high levels of registration completeness, accuracy of cancer diagnosis, and pathologic verification^{24,25}, plus a large sample size. We were able to link the MCR and the Manitoba Health population registration file, providing accurate information about migration status and vital status. Lower GI endoscopy and number of ambulatory care visits with health care providers were included as co-variables as a means to account for screening and detection biases. Limitations of the study include a lack of accurate information about lifestyle (particularly smoking status and occupational exposures) and family history. Given the observational nature of the study design, residual confounding biases could exist, as is typical in observational studies. In addition, the subgroup analyses were limited by small sample size.

CONCLUSIONS

Our study suggests that there is no increased risk of CRC after a diagnosis of uca, including among patients with upper urinary tract tumours (cancer of the renal pelvis and ureter). Patients with a prior diagnosis of uca should undergo the same age-appropriate CRC screening protocols recommended for individuals without a uca diagnosis. The risk of second malignancies such as recurrent uca, lung cancer, and prostate cancer is higher after a diagnosis of uca.

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official endorsement by Manitoba Health is intended or should be inferred.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: SMM holds a Canada Research Chair in Pharmacoepidemiology and Vaccine Research and was supported by an establishment grant from the Manitoba Health Research Council and by Great-West Life, London Life, and a Canada Life Junior Investigator Award from the Canadian Cancer Society (grant no. 2011-700644). HS has consulted for Medial Cancer Screening Ltd. and has served on the advisory board of Pendopharm.

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