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

C.H. Harlos MD,† H. Singh MD MPH,‡§ Z. Nugent PhD,|| A. Demers PhD,‡|| S.M. Mahmud MD PhD,§ and P.M. Czaykowski MD MSc*‡§

ABSTRACT

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

Methods  Historical cohorts were assembled by record linkage of Manitoba Cancer Registry and Manitoba Health databases. The incidence of crc for individuals with uc 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 (uc 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 uc and 22,312 without uc were followed for a total of 179,287 person–years (py). After uc, the rate of subsequent colon cancer in uc 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 uc (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 uc.

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

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 women. The death rate in crc has been declining since 2004 for men and since 2001 for women, at least in part because of screening for crc and its precursor lesions, which is known to reduce crc-related mortality. 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 screening.

Urothelial cancer (uc) 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 men. There are several common risk factors for crc and uc, including diabetes and smoking. Lynch syndrome is also associated with an increased risk of both crc and uc. Although consumption of red and processed meats has been linked with an increased risk of crc, studies of their association with uc have yielded mixed results.

Several studies have demonstrated an increased risk of secondary cancers after a diagnosis of uc. Data about the incidence of crc after a diagnosis of uc are mixed, with some studies demonstrating no increased incidence, 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 institution 21 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 crc 15 as well as for uca 3,10.

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 analysis. Instead, cumulative incidence curves of the probability of failing from each competing event were produced. Competing risks proportional hazards models, as modified by Fine and Gray, 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, Socioeconomic Factor Index score, presence of diabetes, 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. The analysis was stratified by age and time since the diagnosis of uca. Right sided ccrCs were also analyzed separately because of their known association with Lynch syndrome.

RESULTS

The final cohorts of 4591 subjects with uca and 22,312 without uca (Table II) 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 ccrC among patients with uca was 4.5 per 1000 py (Table I). In the non-cancer cohort, the rate of ccrC 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-ccrC 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 ccrC was not significantly different between subjects with a history of uca and the non-cancer subjects (Figure I). In the multivariable models that included all potential confounders, a prior diagnosis of uca was not associated with an increased risk of subsequent ccrC (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 ccrC.

In an analysis stratified by follow-up time, an increased risk of a diagnosis of ccrC 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 ccrC 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 ccrCs (HR: 0.5; p = 0.009) and of right-sided ccrCs (HR: 0.3; p = 0.04) was observed in 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 ccrC cases (exact number suppressed for confidentiality per Manitoba Health protocol) were identified among subjects with uca and 32 cases of ccrC 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-ccrC 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 ccrC. Those results agree with findings in some earlier studies, including one from our institution, and contrast with the findings in a U.S. Surveillance, Epidemiology, and End Results database study demonstrating an increase in ccrC incidence after a...
None of the earlier studies used a competing risks analysis. Moreover, the potentially confounding factors of lower gastrointestinal 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 syndrome. Most evidence suggests that the increased risk is predominantly for uca of the upper urinary tract, including the renal pelvis and ureter. However, some studies indicate that, in Lynch syndrome, the risk of bladder cancer is increased as well. In the present study, we observed no increased risk of ccc 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 ccc. We did not find, in stratified analysis, an increased risk for those less than 60 years of age at time of uca diagnosis.

The most common malignancies associated with Lynch syndrome are ccc and endometrial cancer. The average age of onset of ccc in the setting of Lynch syndrome varies between studies, but it is generally considered to be the mid-40s. In a series of 125 women with Lynch syndrome and endometrial cancer, the median age of diagnosis was 48 years. 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 II

| Event                  | Urothelial cancer (n=4,591) | Patient cohort | Non-cancer (n=22,312) |
|------------------------|-----------------------------|----------------|-----------------------|
| CRC diagnosis          | 89                          | 4.5            | 3.5 to 5.4            |
| Other invasive cancer  | 850                         | 42.7           | 39.8 to 45.6          |
| Death                  | 1921                        | 96.6           | 92.8 to 100.3         |

*Per 1000 patient–years.
CI = confidence interval; CRC = colorectal cancer.

### Table III

| Variable                                | Comparator   | HR  | 95% CI   | p Value |
|-----------------------------------------|--------------|-----|----------|---------|
| Age at index date (years)               | Reference    |     |          |         |
| Q1 (lowest)                             |              |     |          |         |
| 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                      | Reference    |     |          |         |
| Yes                                    | 0.81         | 0.64 to 1.01 | 0.061 |
| No                                     | Reference    |     |          |         |
| Diabetes                                | Yes          | 0.88 | 0.72 to 1.08 | 0.23 |
|                                          | No           |     |          |         |
| Socioeconomic factor index              | Reference    |     |          |         |
| Per unit increase                       | 1.00         | 0.94 to 1.05 | 0.88    |
| Average annual ambulatory care visits   | Reference    |     |          |         |
| Q1 (lowest)                             |              |     |          |         |
| 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           |     |          |         |

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

| Variable          | All CRC          | Right-sided CRC       |
|-------------------|------------------|-----------------------|
|                   | (n)   | HR    | 95% CI | pValue | (n)   | HR    | 95% CI | pValue |
| Time since diagnosis |       |       |       |        |       |       |       |       |        |
| 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 |
| Age at diagnosis  |       |       |       |        |       |       |       |       |        |
| <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.

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, 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 care visits with health care providers were included as covariates 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 cancer 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 cancer 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.

ACKNOWLEDGMENTS

This study was funded by an operating research grant from the Manitoba Medical Services Foundation. The funding agency had no role in the conduct of the study or the reporting of its findings. All of the authors were involved in the analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. PMC, ZN, AD, SMM, and HS were involved in the study concept and design, obtaining funding, and acquiring data. The results and conclusions are those of the authors, and no
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: SMH 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.

AUTHOR AFFILIATIONS
1. Section of Hematology/Oncology, Department of Internal Medicine, University of Manitoba, 2. Department of Medical Oncology and Hematology, CancerCare Manitoba, 3. Section of Gastroenterology, Department of Internal Medicine, University of Manitoba, 4. Community Health Sciences, University of Manitoba, and 5. Department of Epidemiology and Cancer Registry, CancerCare Manitoba, Winnipeg, MB.

REFERENCES
1. Canadian Cancer Society’s Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015. Toronto, ON: Canadian Cancer Society; 2015.
2. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013;369:1106–14.
3. 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.
4. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemocult. Cochrane Database Syst Rev 2007;:CD000216.
5. Holme Ø, Brethauer M, Fretheim A, Ogaard-Jensen J, Hoff G. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database Syst Rev 2013;:CD009259.
6. Desch CE, Benson AB 3rd, Sommerfield MR, et al. on behalf of the American Society of Clinical Oncology. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005;23:8512–19.
7. Leddin D, Hunt R, Champion M, et al. on behalf of the Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation. Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: guidelines on colon cancer screening. Can J Gastroenterol 2004;18:93–9.
8. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM on behalf of the American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739–50. [Erratum in: Am J Gastroenterol 2009;104:1613]
9. Woolcott CG, Maskarinec G, Haiman CA, Henderson BE, Kolonel LN. Diabetes and uterine cancer risk: the Multi-ethnic Cohort Study. Cancer Epidemiol 2011;35:551–4.
10. Fang H, Yao B, Yan Y, et al. Diabetes mellitus increases the risk of bladder cancer: an updated meta-analysis of observational studies. Diabetes Technol Ther 2013;15:914–22.
11. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–87.
12. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013;63:234–41.
13. Botteri E, Iodice S, Bagnardi S, Raimondi AB, Lowenfels M, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300:2765–78.
14. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123:444–9.
15. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919–32.
16. Chan DS, Lau R, Aune D, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6:e20456.
17. Jakszyn P, González CA, Luján-Barroso L, et al. Red meat, dietary nitrosamines, and heme iron and risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Epidemiol Biomarkers Prev 2011;20:555–9.
18. Ronco AL, Mendilaharsu M, Boffetta P, Deneo-Pellegrini H, De Stefani E. Meat consumption, animal products, and the risk of bladder cancer: a case–control study in Uruguayan men. Asian Pac J Cancer Prev 2014;15:5805–9.
19. Heard A, Roder D, Luke C. Multiple primary cancers of separate organ sites: implications for research and cancer control (Australia). Cancer Causes Control 2005;16:475–81.
20. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 2007;12:20–37.
21. Pruthi DK, Nugent Z, Czaykowski P, Demers AA. Urothelial cancer and the diagnosis of subsequent malignancies. Can Urol Assoc J 2013;7:57–64.
22. Bermejo JL, Sundquist J, Hemminki K. Bladder cancer in cancer patients: population-based estimates from a large Swedish study. Br J Cancer 2009;101:1091–9.
23. Manitoba Health, Health Information Management Branch. Manitoba Health Population Report: June 1, 2012, Winnipeg, MB: Manitoba Health; 2012. [Available online at: http://www.gov.mb.ca/health/population/2012/pr2012.pdf; cited 24 October 2016]
24. Andrews PA, Chen VW, Wu XC, eds. Cancer in North America, 1991–1995. Vol. 1: Incidence. Sacramento, CA: North American Association of Central Cancer Registries; 1999.
25. Hotes EJ, Wu XC, McLaughlin CC, et al., eds. Cancer in North America: 1996–2000. Vol. 1: Incidence, Sacramento, CA: North American Association of Central Cancer Registries; 2003.
26. Roos LL, Mustard CA, Nicol JP, et al. Registries and administrative data: organization and accuracy. Med Care 1993;31:201–12.
27. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. Med Care 1997;35:932–47.
28. Blanchard JF, Ludwig S, Wajda A, et al. Incidence and prevalence of diabetes in Manitoba, 1986–1991. Diabetes Care 1996;19:807–11.
29. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn’s disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999;149:916–24.
30. Martens PJ, Frohlich N, Carriere KC, Derksen S, Brownell M. Embedding child health within a framework of regional health: population health status and sociodemographic indicators. Can J Public Health 2002;93(suppl 2):S15–20.
31. Martens PJ, Derksen S, Gupta S. Predictors of hospital readmission of Manitoba newborns within six weeks postbirth discharge: a population-based study. Pediatrics 2004;114:708–13.
32. Frohlich N, Mustard C. A regional comparison of socioeconomic and health indices in a Canadian province. Soc Sci Med 1996;42:1273–81.
33. Tai BC, White IR, Gebski V, Machin D. On the issue of “multiple” first failures in competing risks analysis. Stat Med 2002;21:2243–55.
34. Coviello V, Bogess M. Cumulative incidence estimation in the presence of competing risks. Stata J 2004;4:103–12.
35. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
36. Rouprêt M, Yates DR, Comperat E, Cussenot O. Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (Lynch syndrome) tumor spectrum. Eur Urol 2008;54:1226–36.
37. van der Post RS, Kiemeneij LA, Ligtenberg MJ, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet 2010;47:464–70.
38. Skeldon SC, Semotiuk K, Aronson M, et al. Patients with Lynch syndrome mismatch repair gene mutations are at higher risk for not only upper tract urothelial cancer but also bladder cancer. Eur Urol 2013;63:379–85.
39. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 2009;76:1–18.
40. Meyer LA, Broaddus RB, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 2009;16:14–22.