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Association between chronic bladder catheterisation and bladder cancer incidence and mortality: a population-based retrospective cohort study in Ontario, Canada

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ABSTRACT

Objectives To compare the risk of bladder cancer and bladder cancer mortality among patients with chronic bladder catheterisation (indwelling or intermittent) to patients from the general population.

Design Retrospective cohort study.

Setting Population-based study in Ontario, Canada between 2003 and 2018.

Participants Adult patients 18–90 years of age with chronic bladder catheterisation were hard matched to patients from the general population without a history of bladder catheterisation.

Interventions The presence of a chronic catheter was defined as a minimum of two physician encounters for bladder catheterisation, suprapubic tube insertion or home care for catheter care separated by at least 28 days. Urinary tract infection (UTI) rates were collected.

Main outcome measures Bladder cancer and bladder cancer-specific mortality after a 1-year lag period were compared between groups.

Results We identified 36 903 patients with chronic catheterisation matched to 110 709 patients without a history of catheterisation. Patients were followed for a median of 8.8 years (IQR: 5.2–11.9 years). The median age was 62 years (IQR: 50–71) and 52% were female. More patients in the catheter group developed bladder cancer (393 (1.1%) vs 304 (0.3%),p<0.001). There were 106 (0.3%) bladder cancer deaths in the catheter group and 59 (0.1%) in the comparison group (p<0.001). Chronic catheterisation (adjusted subdistribution HR (sdHR)=4.80, 95% CI: 4.26 to 5.42,p<0.001) and the number of UTIs (adjusted sdHR=1.04 per UTI, 95% CI: 1.04 to 1.05,p<0.001) were independent predictors of bladder cancer. The relative rate of bladder cancer-specific death was more than eightfold higher among patients with chronic catheterisation (adjusted sdHR=8.68, 95% CI: 6.97 to 10.81,p<0.001). Subgroup analysis among patients with neurogenic bladder and bladder calculi similarly revealed an increased risk of bladder cancer diagnosis and mortality. Bladder cancer risk was highest among patients in the two longest catheter duration quintiles (2.9–5.9 and 5.9–15.5 years).

Conclusions This is the first study to quantify the increase in bladder cancer incidence and mortality in a large, diverse cohort of patients with chronic indwelling or intermittent bladder catheterisation. The risk was highest among patients with a chronic catheter beyond 2.9 years.

Strengths and limitations of this study

- This is the first study to quantify the increase in risk of bladder cancer and to explore the impact on bladder cancer mortality among a large, diverse group of patients with chronic bladder catheterisation.
- Our study findings remained robust on sensitivity analysis accounting for potential verification bias using a second comparison group of patients who would have had access to regular urological care during the study period.
- The definition of chronic catherisation using administrative data is unvalidated and it is not possible to differentiate indwelling catheter versus intermittent catheterisation in the absence of individual patient-level data.
- With all administrative studies, there is potential for misclassification bias.
- There is also potential for bias secondary to unmeasured confounding, including ethnicity, genetic factors, occupational exposures and smoking history, which are not captured using population-level data in Ontario.

INTRODUCTION

Patients who develop non-metastatic invasive bladder cancer require radical surgery, radiation or chemotherapy.[1] Despite aggressive multimodality treatment, 5-year patient survival is approximately 50%,[1] and these patients continue to be a clinical challenge for primary care physicians, urologists and oncologists to manage.

Many cases of bladder cancer are preventable as there are several known environmental risk factors. Smoking is the most common cause and widespread smoking cessation has shown a reduction in the incidence of bladder cancer.[2] Another risk factor that can be mitigated to prevent bladder cancer is the presence of chronic inflammation of the bladder,[1] which can be caused by several conditions including the use of chronic urinary catheters and recurring urinary tract infections (UTIs).

The need for chronic bladder catheterisation (indwelling suprapubic or urethral catheter or patients preforming clean intermittent catheterisation) is common and can be necessary for patients with urinary retention due to various anatomic and neurological conditions. Although the overall prevalence of long-term bladder catheterisation is unknown, the prevalence of urinary catheter use among residents in long-term care facilities in the USA is on the order of 5%–15%, representing as many as 225 000 residents with catheters at any given time.[3]

Currently, the risk of bladder cancer among patients requiring chronic bladder catheterisation has been poorly characterised. Observational studies have been limited to specific patient groups, primarily patients with spinal cord injury,[4] who represent only a fraction of patients who require a chronic catheter. Further, there are data to suggest an increased risk of variant bladder cancer histology with chronic bladder inflammation,[5] which may confer an increased risk of cancer-specific mortality. No large-scale studies have explored the relationship between catheter duration and bladder cancer diagnosis and mortality risk. It would be important to obtain a better understanding of the relative risk and exposure time in a large group of patients who require chronic catheterisation in order to develop appropriate prevention and screening strategies.

Thus, we examined a population-based cohort of 36 903 patients requiring chronic bladder catheterisation (indwelling suprapubic or urethral catheter or patients preforming clean intermittent catheterisation) and examined their risk of bladder cancer and mortality compared with a matched cohort of patients from the general population.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective cohort study using population-based administrative data examining bladder cancer incidence and mortality among patients with chronic bladder catheterisation between 1 April 2003 and October 2017. We chose April 2003 as a start date to use contemporary coding systems to ascertain our covariates and outcomes of interest. Patients were followed from index date until bladder cancer diagnosis, death or 31 October 2018.

Data were extracted through the Institute of Clinical and Evaluative Sciences (ICES). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. All datasets were anonymised and linked using unique encoded identifiers and analysed at ICES. The study was designed and conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[6]

Study subjects

We included adult patients between the ages of 18 and 90 years with chronic bladder catheterisation. All medical procedures in Ontario are reimbursed by a government-operated health insurance system (Ontario Health Insurance Plan (OHIP)). OHIP fee codes are listed for specific procedures. We used OHIP fee codes, Canadian Classification of Health Intervention (CCI) codes, and home care codes through the Home Care Resident Assessment Instrument and Continuing Care Reporting System to identify patients who underwent bladder catheterisation. To identify patients with chronic bladder catheterisation, we further required all patients had a second catheterisation code occurring at least 28 days after the index date[7] (date of first catheterisation) (online supplemental appendix 1). The study population represented a broad cohort of patients with chronic bladder instrumentation and could include an indwelling suprapubic or urethral catheter or patients preforming clean intermittent catheterisation. In the absence of individual patient-level data, it was not possible to distinguish clean intermittent from indwelling catheterisation or to identify patients who transitioned from intermittent to indwelling catheterisation or vise versa.

We excluded patients who had a catheterisation code prior to the study period and those with a pre-existing invasive cancer diagnosis. To mitigate the potential effect of reverse causation, we excluded patients who developed bladder cancer within 1 year[8] of receiving a catheter as patients could have presented with urinary retention or hematuria requiring a catheter due to bladder cancer. To include only patients actively receiving medical care in Ontario during the study interval, we excluded individuals who died or emigrated prior to the index date.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Matching

We matched each patient in the catheter group to three patients from the general population without prior catheterisation and who did not undergo catheterisation during the study period. Index dates were randomly assigned to the comparison group based on the distribution of index dates among the exposed group. We hard matched based on age (within 1 year of the index date), gender, region

(Local Health Integration Network), socioeconomic status (income quintile), index year, resource utilisation band (RUB) and Adjusted Disease Groups comorbidity score from the validated Johns Hopkins ACG® System Version 10.0 operationalised into categories. A look-back window of 2 years was used to ascertain comorbidity score.

Study outcomes

To identify incident bladder cancers, we used the Ontario Cancer Registry (OCR), which captures more than 95% of all malignancies within the Province of Ontario.[9] Secondary outcomes included bladder cancer-specific mortality and a comparison of bladder cancer histologies between groups. We used the Registered Persons Database and Ontario Registrar General-Death to capture all-cause mortality and bladder cancer-specific mortality (online supplemental appendix 1).

Covariates

UTIs have been described as another potentially important risk factor for the development of bladder cancer.[10–12] We captured all UTI-related emergency department visits, hospital admissions and interventions that occurred prior to the index date and during the observation period using a combination of diagnostic and billing codes described in previous series (online supplemental appendix 1).[13–15]

We captured various conditions known to be associated with chronic urinary retention using validated algorithms, including traumatic spinal cord injury (TSCI),[16] multiple sclerosis (MS),[17] cerebrovascular accident (CVA),[18] dementia[19] and Parkinson's disease.[20] We also captured benign prostatic enlargement, urethral stricture disease, spina bifida,[21 22] transverse myelitis and cauda equina using diagnostic codes. Although not validated specifically, identification of conditions using diagnostic codes has been shown to have high agreement with chart abstraction (kappa: 0.81).[13]

Exploratory outcomes

As an exploratory analysis, we wanted to determine the association between duration of catheter exposure and bladder cancer risk. Using all billing and procedures codes during the study period, we calculated a catheter duration for each patient defined as the number of days between the index date (date of first catheterisation) and the date of the last catheter code. Catheter duration was then operationalised into quintiles.

Statistical analysis

All datasets were linked using unique encoded identifiers and analysed at ICES. Continuous variables were reported as median with IQR. Categorical variables were reported as numbers with percentages. Baseline characteristics were compared between groups using standardised differences (SD). Categorical outcomes were compared using the χ^2 test and Fisher's exact test for cell counts less than five.

Univariable and multivariable Fine and Gray subdistribution proportional hazards models[23] were used to compare time from index date to bladder cancer diagnosis and bladder cancer mortality between our exposure groups, adjusting for the number of UTIs as a continuous time-varying covariate. Multicollinearity was assessed within the model. Assumptions were verified, including proportional hazards, influential observations and overspecification. Subdistribution HRs (sdHRs) with 95% CIs were reported. Cumulative incidence function (CIF) curves were derived to graphically compare time to bladder cancer and time to bladder cancer death between groups.

To determine the association between catheter duration and bladder cancer risk, we separated the exposure group based on catheter duration quintile. Crude bladder cancer rates over time were presented graphically. A $p < 0.05$ was used to indicate statistical significance for a two-tailed comparison. All analyses were performed using SAS V.9.4 (SAS Institute).

Subgroup and sensitivity analyses

Our primary analysis was repeated among patients with a diagnosis suggestive of neurogenic bladder (specifically, TSCI, MS, spina bifida, CVA, dementia, Parkinson's disease, transverse myelitis and cauda equina syndrome). Second, our primary analysis was repeated on a subgroup of patients who had either endoscopic or open treatment for bladder calculi during the study period, identified using CCI and OHIP procedure codes (online supplemental appendix 1).

Finally, to address the potential for verification bias, whereby patients with a chronic catheter and routine access to urological care may be more likely to be diagnosed with bladder cancer compared with patients from the general population, we generated a second comparison group of patients who received care for renal or ureteric calculi for at least two non-consecutive years during the study period (online supplemental appendix 2). Urolithiasis was chosen because it is present in both genders, has no direct relationship between the risk of chronic retention nor bladder cancer. It is also often associated with regular urological follow-up whereby cystoscopy is not a standard requirement for diagnosis or treatment but would be offered if there was any underlying clinical suspicion for bladder cancer (eg, haematuria or bothersome lower urinary tract symptoms). We hard matched patients from our original exposure group 1:1 to patients with urolithiasis based on age (within 1 year of the index date), gender and index year. Time to bladder cancer diagnosis was compared, adjusting for number of UTIs, income quintile, geographical region and comorbidity score. Due to few events in the urolithiasis group, we were unable to compare bladder cancer specific mortality between groups.

RESULTS

Our final study cohort consisted of 36 903 patients with chronic bladder catheterisation matched to 110 709

patients from the general population (online supplemental appendix 3). The median age was 62 years (IQR: 50–71) and 52% of patients were female. The median catheterisation duration was 2.0 years (IQR: 0.6–5.0 years). Median follow-up was similar between groups: 8.5 years (IQR: 4.9–11.7 years) in the catheter group compared with 8.9 years (IQR 5.2–11.9 years) in the comparison group (table 1).

Overall comorbidity and RUB score were well matched between groups. Patients in the catheter group were more likely to have a history of benign prostatic enlargement (25.4% vs 13.1%, SD=0.32), urethral stricture disease (8.1% vs 2.1%, SD=0.28), MS (2.2% vs 0.3%, SD=0.17) and cauda equina syndrome (1.1% vs 0.1%, SD=0.13) (table 1).

A significantly higher proportion of patients in the catheter group developed bladder cancer during the study period (393/36,903, 1.1% after a median 8.4 years) compared with patients from the general population (304/110,709, 0.3% after a median 8.9 years, p<0.001). More patients in the catheter group developed a symptomatic UTI (40.0% vs 12.6%, p<0.001) during the study period. There was a total of 26 546 all-cause deaths and 165 bladder cancer deaths during the observation period, both of which were more common among patients with chronic catheterisation (22.6% vs 16.4% and 0.3% vs 0.1%, respectively) (table 2).

On univariable regression analysis, chronic indwelling or intermittent catheterisation (sdHR=5.04, 95% CI: 4.47 to 5.68, p<0.001) and the number of symptomatic UTIs (sdHR=1.05 per UTI, 95% CI: 1.05 to 1.06, p<0.001) were associated with an increased relative rate of bladder cancer. On multivariable analysis, chronic indwelling or intermittent catheterisation (sdHR=4.80, 95% CI: 4.26 to 5.42, p<0.001) and the number of symptomatic UTIs (sdHR=1.04 per UTI, 95% CI: 1.04 to 1.05, p<0.001) remained significant predictors of bladder cancer (table 3 and figure 1).

Similarly, chronic catheterisation and the number of symptomatic UTIs were predictors of cancer-specific mortality on both univariable and multivariable analysis. The relative rate of bladder cancer-specific death was more than eightfold higher among patients with chronic indwelling or intermittent catheterisation compared with the comparison group (adjusted sdHR=8.68, 95% CI: 6.97 to 10.81, p<0.001) (table 3) (figure 1).

Urothelial carcinoma was the most commonly diagnosed cancer in both groups (84.5% in the catheter group and 87.2% in the comparison group). Squamous cell carcinoma (SCC) was more common in the catheter group compared with the comparison group (3.8% vs <=2.0%, p<0.001).

To determine the association between catheter duration and bladder cancer risk, we separated the exposure group based on catheter duration quintile and examined the crude 15-year cumulative incidence of bladder cancer compared with the general population comparison group. For patients with a catheter duration in the lowest two quintiles (up to 1.3 years), the absolute risk for bladder cancer was similar to the general population (figure 2). Among patients in the comparison group, there were 42 cases of bladder cancer per 10 000 persons after 15 years compared with 69 and 53 cases per 10 000 persons in the first (0.1–0.4 years) and second (0.4–1.3 years) quintiles, respectively. For patients in the third quintile of catheter duration (1.3–2.9 years), the risk was higher (103 cases per 10 000 persons), but the annual rates were similar to the comparison group. However, for patients in the fourth (2.9–5.9 years) and fifth (5.9–15.5 years) quintiles, the risk for bladder cancer appeared to be the highest, both in risk at 15 years (198 and 281 cases per 10,000, respectively) and by annual rates (figure 2).

Subgroup and sensitivity analyses

Among 3921 patients with chronic catheterisation who likely had underlying neurogenic bladder, the relative rate of bladder cancer and bladder cancer death was significantly increased compared with the general population (adjusted sdHR=4.43, 95% CI: 3.07 to 6.38, p<0.001 and 5.16, 95% CI: 2.77 to 9.61, p<0.001, respectively) (online supplemental appendix 4).

Among 2553 patients in the catheter group who underwent endoscopic or open treatment for bladder calculi during the study period, the relative rate of bladder cancer (adjusted sdHR=4.96, 95% CI 3.57 to 6.87, p<0.001) and bladder cancer mortality (adjusted sdHR=10.34, 95% CI: 5.38 to 19.88, p<0.001) was significantly higher than the general population comparison group (online supplemental appendix 4).

To determine whether comparing patients with chronic catheterisation to patients from the general population would overestimate the risk for bladder cancer due to detection bias, we examined a comparison group of patients with urolithiasis. We hard matched 31 684 patients from our original exposure group 1:1 to patients from the general population with at least two non-consecutive annual visits for urolithiasis (online supplemental appendix 5). There were 317 (1.0%) bladder cancers and 91 (0.3%) bladder cancer specific deaths in the catheter group compared with 134 (0.4%) and 26 (0.1%) in the urolithiasis group, respectively. On multivariable analysis, both chronic catheterisation (adjusted sdHR=3.07, 95% CI: 2.61 to 3.62, p<0.001) and the number of UTIs (adjusted sdHR=1.04 per UTI, 95% CI: 1.04 to 1.05, p<0.001) remained independent predictors of bladder cancer (online supplemental appendix 6).

DISCUSSION

In this large population-based cohort study of 147 612 patients, 1.1% of patients with chronic indwelling or intermittent bladder catheterisation developed bladder cancer over the study period. These patients were more than four times as likely to develop bladder cancer and eight times as likely to die from bladder cancer compared with matched patients from the general population. UTI

Table 1 Baseline demographic characteristics of our study cohort

Variable	Chronic catheter n=36 903	General population n=110 709	Total N=147 612	Standardised difference
Age (years) median (IQR)	62 (50–71)	62 (50–71)	62 (50–71)	0
Gender				
Female	19 290 (52.3%)	57 870 (52.3%)	77 160 (52.3%)	0
Male	17 613 (47.7%)	52 839 (47.7%)	70 452 (47.7%)	0
Income quintile				
1	7165 (19.4%)	21 495 (19.4%)	28 660 (19.4%)	0
2	7591 (20.6%)	22 773 (20.6%)	30 364 (20.6%)	0
3	7026 (19.0%)	21 078 (19.0%)	28 104 (19.0%)	0
4	7475 (20.3%)	22 425 (20.3%)	29 900 (20.3%)	0
5	7646 (20.7%)	22 938 (20.7%)	30 584 (20.7%)	0
LHIN				
1	1435 (3.9%)	4305 (3.9%)	5740 (3.9%)	0
2	3397 (9.2%)	10 191 (9.2%)	13 588 (9.2%)	0
3	1188 (3.2%)	3564 (3.2%)	4752 (3.2%)	0
4	6151 (16.7%)	18 453 (16.7%)	24 604 (16.7%)	0
5	1595 (4.3%)	4785 (4.3%)	6380 (4.3%)	0
6	2190 (5.9%)	6570 (5.9%)	8760 (5.9%)	0
7	3319 (9.0%)	9957 (9.0%)	13 276 (9.0%)	0
8	4497 (12.2%)	13 491 (12.2%)	17 988 (12.2%)	0
9	3204 (8.7%)	9612 (8.7%)	12 816 (8.7%)	0
10	1503 (4.1%)	4509 (4.1%)	6012 (4.1%)	0
11	5941 (16.1%)	17 823 (16.1%)	23 764 (16.1%)	0
12	733 (2.0%)	2199 (2.0%)	2932 (2.0%)	0
13	1492 (4.0%)	4476 (4.0%)	5968 (4.0%)	0
14	258 (0.7%)	774 (0.7%)	1032 (0.7%)	0
RUB				
0	320 (0.9%)	960 (0.9%)	1280 (0.9%)	0
1	132 (0.4%)	396 (0.4%)	528 (0.4%)	0
2	1270 (3.4%)	3810 (3.4%)	5080 (3.4%)	0
3	21 258 (57.6%)	63 774 (57.6%)	85 032 (57.6%)	0
4	10 452 (28.3%)	31 356 (28.3%)	41 808 (28.3%)	0
5	3471 (9.4%)	10 413 (9.4%)	13 884 (9.4%)	0
ADG score				
0–4	6841 (18.5%)	20 523 (18.5%)	27 364 (18.5%)	0
5–9	21 499 (58.3%)	64 497 (58.3%)	85 996 (58.3%)	0
10–14	8308 (22.5%)	24 924 (22.5%)	33 232 (22.5%)	0
15+	255 (0.7%)	765 (0.7%)	1020 (0.7%)	0
Traumatic spinal cord injury	235 (0.6%)	43 (0.0%)	278 (0.2%)	0.1
Multiple sclerosis	822 (2.2%)	364 (0.3%)	1186 (0.8%)	0.17
Spina bifida	174 (0.5%)	125 (0.1%)	299 (0.2%)	0.07
Benign prostatic enlargement	9365 (25.4%)	14 463 (13.1%)	23 828 (16.1%)	0.32
Cerebrovascular accident	1454 (3.9%)	3491 (3.2%)	4945 (3.3%)	0.04
Dementia	969 (2.6%)	2984 (2.7%)	3953 (2.7%)	0
Transverse myelitis	40 (0.1%)	19 (0.0%)	59 (0.0%)	0.04

Continued

Table 1 Continued

Variable	Chronic catheter n=36 903	General population n=110 709	Total N=147 612	Standardised difference
Cauda equina syndrome/injury	420 (1.1%)	132 (0.1%)	552 (0.4%)	0.13
Urethral stricture disease	3006 (8.1%)	2312 (2.1%)	5318 (3.6%)	0.28
Parkinson disease	432 (1.2%)	772 (0.7%)	1204 (0.8%)	0.05
COPD, chronic emphysema or chronic bronchitis	1535 (4.2%)	4456 (4.0%)	5991 (4.1%)	0.01
Follow-up time (years) median (IQR)	8.5 (4.9–11.7)	8.9 (5.2–11.9)	8.8 (5.2–11.9)	0.06

ADG, Adjusted Disease Groups; COPD, chronic obstructive pulmonary disease; LHIN, local health integration network; RUB, resource utilisation band.

was also an independent predictor of bladder cancer and bladder cancer death. We found a dose response relationship between duration of catheterisation and bladder cancer risk with the highest risk seen when the catheter duration exceeded 2.9 years.

To our knowledge, this is the first study to quantify the increase in risk of bladder cancer among a large, diverse group of patients and to explore the impact on bladder cancer mortality, accounting for the competing risk of death. We were also able to account for the effect of UTI in a time-varying manner. Our study findings remained robust on sensitivity analysis accounting for potential verification bias using a second comparison group of patients with renal or ureteric calculi who would have had access to regular urological care during the study period.

Large-scale observational studies have compared the risk of bladder cancer among patients with a chronic catheter and TSCI. In a retrospective cohort study of 3670 patients with TSCI, the adjusted relative risk of bladder cancer was 4.9-fold higher (95% CI: 1.3 to 13.8) compared with population controls.[4] This group also had an increased risk of bladder cancer mortality compared with controls. In a smaller series, patients with a chronic urinary catheter with TSCI (adjusted HR 6.51, 95% CI: 2.56 to 16.52) and without TSCI (adjusted HR 9.11, 95% CI: 3.90 to 21.29) had an increased relative rate of bladder cancer compared with general population controls.[24] We believe our estimates were lower than the above studies given that we studied a heterogeneous patient population and accounted for the independent effects of UTI.

In the current study, UTI was an independent predictor of bladder cancer diagnosis and mortality. In a large European case–control study of over 6000 patients, regular cystitis was associated with a threefold to sixfold increase in the likelihood of bladder cancer diagnosis. In a recent large population-based study of 38 084 patients from Taiwan who presented with any UTI, after a median follow-up of only 25 months, cases were more likely to be diagnosed with colorectal or genitourinary cancer, including bladder cancer (adjusted HR in men: 12.10, 95% CI: 2.70 to 54.19 and women: 30.02, 95% CI: 3.97 to 227.28) compared with propensity score matched

Table 2 Study outcomes among patients with a chronic catheter compared with the general population-matched comparison group

Outcome	Chronic catheter n=36 903	General population n=110 709	Total N=147 612	P value
Urinary tract infection				
N	22 142 (60.0%)	96 802 (87.4%)	118 944 (80.6%)	<0.001
Y	14 761 (40.0%)	13 907 (12.6%)	28 668 (19.4%)	
Death (all cause)				
N	28 555 (77.4%)	92 511 (83.6%)	121 066 (82.0%)	<0.001
Y	8348 (22.6%)	18 198 (16.4%)	26 546 (18.0%)	
Bladder cancer				
N	36 510 (98.9%)	110 405 (99.7%)	146 915 (99.5%)	<0.001
Y	393 (1.1%)	304 (0.3%)	697 (0.5%)	
Bladder cancer death				
N	36 797 (99.7%)	110 650 (99.9%)	147 447 (99.9%)	<0.001
Y	106 (0.3%)	59 (0.1%)	165 (0.1%)	
Time to bladder cancer (years) median (IQR)	8.4 (4.9–11.7)	8.9 (5.2–11.9)	8.8 (5.1–11.8)	<0.001

Table 3 Univariable and multivariable subdistribution hazard regression analysis, time to bladder cancer diagnosis and time to bladder cancer-specific mortality

	Univariable analysis			Multivariable analysis		
Parameter	**sdHR**	**95% CI**	**P value**	**sdHR**	**95% CI**	**P value**
Bladder cancer diagnosis						
Chronic catheter (reference: general population)	5.04	4.47 to 5.68	<0.001	4.80	4.26 to 5.42	<0.001
No of urinary tract infections*	1.05	1.05 to 1.06	<0.001	1.04	1.04 to 1.05	<0.001
Bladder cancer-specific mortality						
Chronic catheter (reference: general population)	9.23	7.42 to 11.48	<0.001	8.68	6.97 to 10.81	<0.001
No of urinary tract infections*	1.06	1.06 to 1.06	<0.001	1.05	1.05 to 1.05	<0.001

*Incorporated into the model as a time-varying covariate.
sdHR, subdistribution HR.

population controls.[12] However, given the limited follow-up duration and failure to exclude patients with a diagnosis of bladder cancer within a designated lag time, this study is limited by selection bias and reverse causation.

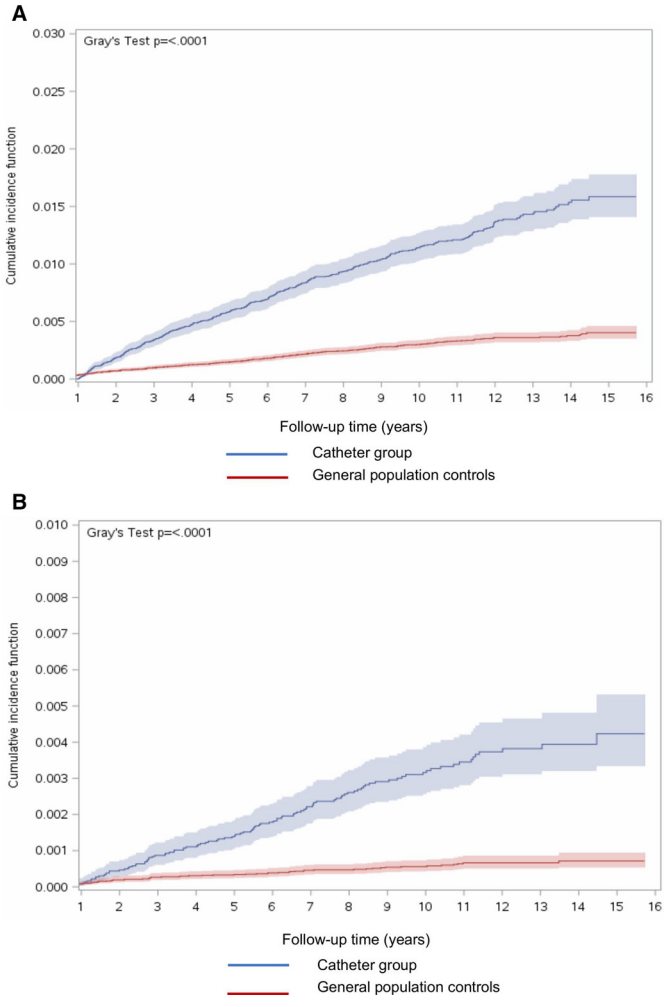

Figure 1 Cumulative incidence function curves with 95% CIs. (A) cumulative incidence of bladder cancer and (B) cumulative incidence of bladder cancer mortality among patients with a chronic catheter compared with the general population-matched comparison group.

One hypothesised mechanism for the observed increase in bladder cancer risk with chronic catheterisation and UTI is secondary to chronic inflammation. Studies have shown pathological changes including keratinising squamous metaplasia and cystitis glandularis in as many as one quarter of patients with TSCI and chronic bladder catheters.[25] Due to the overlapping effect of UTI and bladder calculi, we completed a subgroup analysis of patients who underwent surgical management of bladder calculi during the study period. We found this group of patients had a higher relative rate of bladder cancer and bladder cancer death. Indeed, all studied markers of chronic inflammation appeared to have a gradational increase in the risk of bladder cancer diagnosis and cancer-specific death. It remains uncertain whether this association represents a direct relationship between inflammation and bladder cancer incidence or other cellular-level alterations that occur as a result of neurogenic bladder dysfunction.

It is possible that chronic inflammation leads to the development of histologically more aggressive bladder cancer subtypes, specifically SCC. Although only a small proportion of patients in our study developed SCC of the bladder -compared with other series of patients with TSCI[26] and neurogenic bladder,[27] the low rate may be due

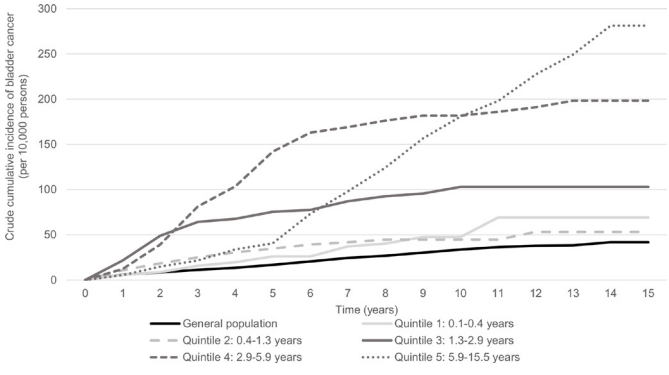

Figure 2 Crude cumulative incidence of bladder cancer among patients with a chronic catheter (stratified by catheter duration quintile) compared with the general population-matched comparison group after 1-year lag period, per 10 000 persons.

to limitations of capturing complete histological subtype data within the OCR.

Although the relative rates of bladder incidence and mortality were high, the absolute rates were low. Thus, routine screening procedures with cystoscopy and imaging tests may not be cost-effective. In an exploratory analysis, patients had an increase in the risk of developing bladder cancer with longer catheter duration. The duration cut-offs were arbitrarily based on the quintile distribution. Patients with chronic catherisation beyond 2.9 years appeared to be at the highest risk. We also found that patients with bladder calculi and more frequent symptomatic UTIs had an incremental increase in the risk of bladder cancer incidence and mortality. Future studies are needed to validate these findings. Targeted screening interventions for high-risk populations may be warranted although this was outside the scope of the current study.

There are limitations to the current study. With all administrative studies, there is potential for misclassification. In this patient population, it can be challenging to differential true UTIs from irritative symptomatology from the underlying neurological disease or even bladder cancer-induced storage symptoms. Also, this patient population often has chronic bacteriuria which may prompt unnecessary antibiotic treatment in the outpatient setting, thus, the use of positive urine cultures or antibiotic prescriptions as a marker of UTI could lead to significant bias. To try to more accurately identify UTIs, we included symptomatic events prompting emergency department assessment, instrumentation or hospitalisation. There may still be an element misclassification bias and residual confounding as a result of the challenges associated with defining this covariate and this should be considered when interpreting our results.

In this study, the definition of chronic catherisation using administrative data is unvalidated and it is impossible to differentiate indwelling catheter versus intermittent catheterisation in the absence of individual patient-level data. Hypothetically, intermittent catheterisation could pose less of a risk for cancer development compared with indwelling urethral or suprapubic catheterisation. Given the limitations of administrative data, we were unable to explore this in the current study. On subgroup analysis among patients with suspected neurological lower urinary tract dysfunction, our study findings were consistent. However, we were unable to explore the association between severity of neurological dysfunction and risk of bladder cancer incidence and mortality in the absence of individual patient data. There is potential for detection bias as these patients would have access to relevant diagnostic investigations; although, our findings remained robust on sensitivity analysis with a control-group with access to urological care.

Due to the limitations of administrative data, we were unable to definitively assign a cause for each patient's urinary retention. Also, while validation studies exist for cancer diagnosis and mortality, to our knowledge, the histology codes associated with bladder cancer have not been validated against individual patient-level data. Therefore, there is potential for misclassification of our histology data and these findings should be confirmed in future studies. We were unable to compare bladder cancer stage at diagnosis as this is not captured in the OCR. Follow-up duration was limited to a median of 9 years.

As with all observational studies, there is potential for bias secondary to unmeasured confounding. Race data are not available using the current administrative data sources. Environmental risk factors are known to play an important role in the pathogenesis of bladder cancer. It is not possible to capture occupational exposures or smoking history using population-level data in Ontario. However, patients were matched on comorbidity score, socioeconomic status and geographical region, which may minimise the potential confounding effect. When we compared the proportion of patients at baseline with a diseases that can be associated with smoking, specifically chronic obstructive pulmonary disease, emphysema and chronic bronchitis, there was no difference in the proportion of patients with these conditions between groups. Nevertheless, a study of this magnitude that assesses global bladder cancer risk and bladder cancer mortality with the identification of high-risk subgroups is likely not feasible with a retrospective chart review nor with prospectively collected data.

CONCLUSIONS

We found a significant increase in the risk of bladder cancer and bladder cancer-specific mortality in a large, diverse group of patients with chronic indwelling or intermittent bladder catheterisation. Patients with a catheter duration of at least 2.9 years as well as patients with bladder calculi were at particularly high risk. UTI was an independent predictor of both bladder cancer diagnosis and mortality. Study limitations, including the potential for misclassification, residual confounding and detection bias, highlight the need for validation of our results in future studies. Acknowledging these limitations, the findings highlight the need for physicians to be aware of this risk when managing patients with chronic catheters.

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Contributors RK and AH conceptualised the idea. RK, AH, YLi and RS contributed to the design and implementation of the research. YL and AH analysed the data. All authors (AH, RS, YLi, YLe, KA, RM, RK, LC, GK, SH, SAN and RN) made substantial contributions to the interpretation of the data, were involved in drafting or revising

the work for intellectual content, and approved the final version of the manuscript. All authors (AH, RS, YLi, YLe, KA, RM, RK, LC, GK, SH, SAN and RN) agreed to be accountable for all aspects of the work, including accuracy and integrity. The guarantor (RN) accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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