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Urinary tract infections and risk of squamous cell carcinoma bladder cancer: A Danish nationwide case–control study

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Schistosoma haematobium infection can lead to squamous cell carcinomas (SCC) of the bladder. Whether this also applies to more common urinary tract infections (UTIs) is unclear. We therefore aimed to investigate the association between UTIs, reflected by the use of specific antibiotics and risk of SCC of the bladder. We conducted a Danish nationwide case–control study and identified histologically verified bladder cancer cases (2000–2015; *n* = 12,271) and age- and sex-matched cancer-free controls. We computed odds ratios (ORs) with 95% confidence intervals (CI) associating the use of UTI-specific antibiotics with SCC bladder cancer, using conditional logistic regression. We applied a 2-year lag-time to minimize reverse causation. To aid interpretation, similar analyses were performed for other bladder cancer types and other antibiotics. We identified 333 SCC cases (2.7% of all bladder cancers). Compared to no use (0–1 prescription), high-use (≥10 prescriptions) of UTI-specific antibiotics was associated with SCC with an OR of 11.4 (CI 7.6–17.2) and a clear dose–response pattern (p_{trend} < 0.001). Use of phenoxymethylpenicillin, an antibiotic not used against UTIs, was not associated with SCC after adjustment for use of UTI-specific antibiotics (OR 0.5). Furthermore, UTI-specific antibiotic use was not associated with urothelial carcinomas (*n* = 11,029; OR 1.13; CI 0.97–1.32). Excluding patients with known urogenital disease did not influence the SCC estimates (overall OR 10.8; CI 6.2–18.9). Data on smoking were lacking, however, a quantitative bias analysis suggested this to be of limited importance. In conclusion, common UTIs are strong, dose-dependent and specifically associated with risk of SCC of the bladder.

Introduction

About 75% of bladder cancers occur in men,[1] and the main risk factor for the disease is smoking, estimated to account for approximately half of all urothelial bladder cancers.[2] Urothelial cell carcinoma is the most prevalent subtype in the US and Europe accounting for more than 90% of the cases.[3] In North Africa, however, a predominance of squamous cell carcinoma (SCC) is seen, which is caused by Schistosoma haematobium infections.[4] While the evidence linking infection by Schistosoma infection to SCC of the bladder is convincing,[5,6] the association between common urinary tract infection (UTI) and bladder cancer remains unclear.[7–12] In 1984, Kantor *et al.* found that a history of three or more UTIs was associated with a twofold increased risk of bladder cancer overall and a nearly fivefold increased risk of SCC.[12] The Nijmegen bladder cancer study[7] included 1809 patients with histologically confirmed carcinoma of the urinary bladder and 4,370 controls and found that a history of regular cystitis was associated with increased risk of bladder cancer with an odds ratio (OR) of 6.6 (95% CI, 4.2–11) in men and 2.7 (95% CI, 2.0–3.5) in women. Similarly, a US study[9] including 659 patients with newly diagnosed, histologically confirmed urinary bladder cancer and 689 matched controls also found an increased bladder cancer risk associated with the history of cystitis (OR = 1.52, 95% CI, 1.12, 2.06). However, the risk estimate was attenuated for infections diagnosed >1 year before the time of bladder cancer diagnosis, suggesting reverse causation as the explanation.[9] These studies examined bladder cancer overall but presented no data on SCC specifically. Finally, a recent hypothesis-generating screening study from Denmark examining use of prescription drugs and risk of cancer,[13] found strong associations between use of antibiotic drugs (antibiotics) for UTIs and SCC of the bladder, with ORs of 6.0 for sulfamethizole (95% CI, 2.9, 12.4) and 13.0 for pivmecillinam (95% CI, 6.0, 28.4), the two most commonly used antibiotics for UTI in Denmark. Altogether, this prompted us to further investigate the association between UTIs as measured by use of specific antibiotics and the risk of bladder cancer by histological subtype using the nationwide Danish health registries.

Additional Supporting Information may be found in the online version of this article.

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What's new?

Squamous cell carcinoma (SCC) of the bladder cancer frequently arises as a result of *Schistosoma haematobium* infection, particularly in North Africa. Outside this region, SCC of the bladder is suspected of being linked to recurrent urinary tract infection (UTI). In this nationwide study in Denmark, increased risk of SCC of the bladder was strongly associated with high UTI-specific antibiotic use, indicative of recurrent UTI. The association displayed a clear dose–response relationship. By contrast, no association was detected between non-UTI-specific antibiotics and SCC or other bladder cancer histologies. The findings suggest that UTIs are an important cause of SCC bladder cancer.

Methods

In a nationwide case–control study, we compared the use of antibiotics against UTIs among patients diagnosed with bladder cancer (cases) to that of cancer-free individuals (controls) to obtain the odds ratio (OR) for bladder cancers, stratified by histological subtype, associated with the use of these antibiotics.

Data sources

We used five Danish nationwide registries: the Danish Cancer Registry,[14,15] the National Prescription Registry,[16] the Danish National Patient Register,[17] Danish Education Registers at Statistics Denmark[18] and the Civil Registration System.[19] The data sources are described in detail in Supporting Information S1, and codes for cancer diagnoses, drug exposures and covariates are provided in Supporting Information S2.

Virtually all medical care in Denmark is furnished by the national health authorities, allowing true population-based register linkage studies covering all Danish inhabitants. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.[20]

Selection of bladder cancer cases and population controls

From the Danish Cancer Registry, we identified cases as all patients in Denmark recorded with a first-time diagnosis of bladder cancer, between 2000 and 2015, using the date of cancer diagnosis as the index date. Bladder cancer diagnoses in the Cancer Registry comprise both invasive and, for urothelial carcinoma, noninvasive tumors. To ensure the validity of our case material, we only included histologically verified bladder cancer cases with either invasive or carcinoma-*in situ* histology. Cases with benign or unverified histology were thus excluded. We stratified bladder cancer cases into SCCs, urothelial carcinomas, adenocarcinomas, small cell carcinoma and 'other histologies' (including unspecified histologies). Further inclusion criteria were age 40–95 years at index date and continuous Danish residency within 10 years before index date, thus ensuring at least 10 years of follow-up for all study subjects and a minimum of 5 years of prescription data (the Prescription registry opened in 1995). We further required patients to have no previous history of cancer (except nonmelanoma skin cancer).

For each case, we selected 50 controls using risk set sampling, matched for sex and birth year, while applying the same selection criteria as for cases. Controls were assigned an index date identical to that of the corresponding case. Subjects were eligible for sampling as controls before they became cases. Thereby, the calculated odds ratios (ORs) are unbiased estimates of the incidence rate ratios (IRRs) that would have emerged from a cohort study in the source population.[21]

Analytical variables

In accordance with Danish therapeutic traditions, we defined exposure to antibiotics used to treat urinary tract infection (UTI-specific antibiotics) as sulfamethizole, trimethoprim, pivmecillinam or nitrofurantoin. As treatment with these drugs served as proxies for urinary tract infection, the main analysis considered a composite exposure to any of these four drugs. Fluoroquinolones have never been recommended for treatment of UTIs in primary care in Denmark. Throughout all analyses, having filled 0–1 antibiotics for UTIs comprised the reference category, while risk estimates were analyzed for intermediate use (2–9 prescriptions) and for high-use (≥10 prescriptions). For dose–response analyses, we used the following prespecified strata: 2–4, 5–9, 10–19 and ≥20 prescriptions. To avoid counting change in antibiotic treatment or refills as two separate episodes, we disregarded prescriptions filled <30 days after a previous prescription. Similarly, combination products or prescription for multiple UTI-specific antibiotics only counted as one treatment episode. Further, we disregarded prescriptions redeemed within 2 years prior to the index date. This was done to reduce the possibility of reverse causation,[22] also judging that such recent exposure is unlikely to be associated with cancer development. This 2-year lag-period was subject to sensitivity analyses.

The following potential confounders were identified and incorporated in the analyses: (*i*) Use of drugs potentially associated with risk of bladder cancer, including nonsteroidal anti-inflammatory drugs (NSAIDs; 0–1, 2–4, 5–9, ≥10 prescriptions) and thiazolidinediones (ever use); (*ii*) Use of drugs associated with bleeding risk within 1 year before index date, as such drugs could alter the threshold for diagnosis of a bladder cancer, including low dose aspirin, other platelet inhibitors, and oral anticoagulants; (*iii*) Ever use of drugs serving as markers for cardiovascular disease, as these relate to both smoking and to general frailty, including statins, antihypertensives and loop diuretics; (*iv*) A diagnosis of urogenital disease; (*v*) Diagnoses potentially associated with bladder cancer risk, including diabetes, chronic obstructive pulmonary disease (COPD), ischemic heart disease and alcohol-related disease;

(*vi*) Charlson comorbidity index[23,24] (0, 1, 2, ≥3); (*vii*) Highest achieved education (as a crude measure of socioeconomic status). As in the assessment of drug exposure, we disregarded the period 2 years prior to the index date in the identification of confounder status, except for drugs associated with bleeding risk.

Analysis

Using conditional logistic regression and adjusting for the above potential confounders, we estimated ORs for SCC of the bladder, as well as other bladder cancer subtypes, associated with the use of UTI-specific antibiotics. In the dose–response analysis, we restricted to ever users (≥2 prescriptions) and estimated the *p*-value (p_{trend}) for the incremental OR for each prescription filled, using ordinary logistic regression (i.e., breaking the matched risk-sets) while also adjusting for sex, age and calendar year. We performed several preplanned supplementary and sensitivity analyses, as described in detail in Supporting Information S3. First, we examined whether sex, age and clinical stage modified the association by including these as interaction terms in the regression model. Second, we repeated the analyses looking at the individual UTI specific antibiotics and, as a negative control exposure, with phenoxymethylpenicillin. Third, we conducted a probabilistic bias analysis to quantify the degree of bias that was introduced from not being able to adjust for smoking.[25] Based on the literature, we defined probability distributions for three bias parameters: The prevalence of smoking in unexposed, the relative risk of SCC associated with smoking and the relative risk of UTI associated with smoking. We sampled random values of these bias parameters 10,000 times to provide a bias-adjusted OR with 95% simulation intervals.[26] Fourth, assuming causality, we estimated the number of cases attributable to UTIs by multiplying the number of exposed cases with the attributable proportion calculated as [(OR − 1)/OR].[27] Additionally, we estimated the number of person-years spent with high-use of UTI-specific antibiotics required for one

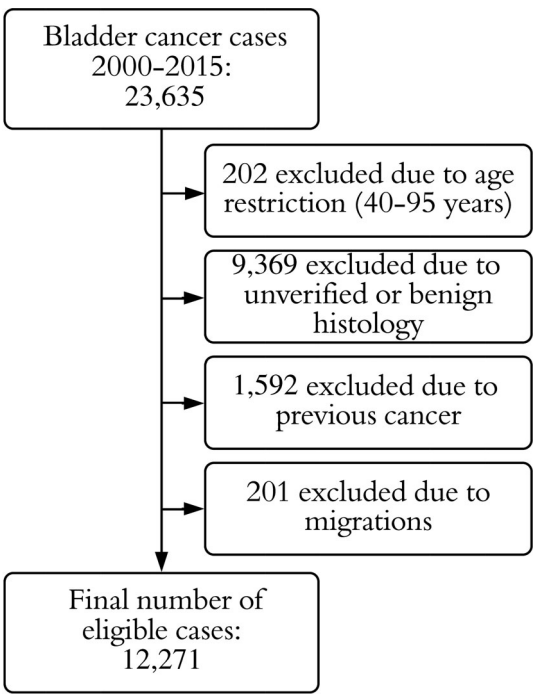

Figure 1. Flow-chart of the selection of cases.

Table 1. Characteristics of bladder cancer cases and their matched controls

	Cases (*n* = 12,271)	Controls (*n* = 609,974)
Sex		
Male	9,168 (75%)	454,903 (75%)
Female	3,103 (25%)	155,071 (25%)
Age		
Median (IQR)	72 (65–79)	72 (65–79)
40–60 years	1,623 (13%)	81,150 (13%)
60–69 years	3,477 (28%)	173,850 (29%)
70–85 years	6,271 (51%)	313,550 (51%)
Histology		
Urothelial carcinoma	11,029 (90%)	–
Planocellular carcinoma	333 (2.7%)	–
Adenocarcinoma	505 (4.1%)	–
Small-cell carcinoma	155 (1.3%)	–
Other histologies	249 (2.0%)	–
Drug use		
Nonaspirin NSAIDs	6,644 (54%)	317,241 (52%)
Thiazolidinediones	55 (0.4%)	1,995 (0.3%)
Aspirin	3,569 (29%)	152,324 (25%)
Nonaspirin antiplatelets	940 (7.7%)	39,908 (6.5%)
Anticoagulants	971 (7.9%)	41,690 (6.8%)
Statins	3,615 (29%)	162,099 (27%)
Antihypertensives	1,294 (11%)	58,287 (9.6%)
Loop diuretics	1,223 (10.0%)	40,179 (6.6%)
Medical history		
Urogenital disease	1,986 (16%)	90,096 (15%)
Diabetes	1,294 (11%)	58,287 (9.6%)
COPD	1,223 (10%)	40,179 (6.6%)
Ischemic heart disease	2,192 (18%)	92,604 (15%)
Alcohol related disorders	718 (5.9%)	29,155 (4.8%)
Charlson Comorbidity Index		
0	7,218 (59%)	396,365 (65%)
1	2,587 (21%)	116,822 (19%)
2	1,315 (11%)	51,370 (8.4%)
3+	1,151 (9.4%)	45,417 (7.4%)
Highest achieved education		
Short (≤10 years)	4,656 (38%)	225,414 (37%)
Intermediate (11–13 years)	4,813 (39%)	223,169 (37%)
Long (>13 years)	1,896 (15%)	113,372 (19%)
Unknown	906 (7.4%)	48,019 (7.9%)

additional SCC to occur.[28] Finally, we varied the lag time of 2 years in the main analyses from 0 to 5 years.

Other

All analyses were performed using Stata Release 15.2 (StataCorp, College Station, TX). The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board.[29]

Data availability

Due to Danish legislation, the individual-level data used in our study cannot be made available to other researchers. However, all data applications and specifications, as well as all analytical code, will be made available on request to the corresponding author.

Results

We identified 23,635 bladder cancer cases during 2000–2015. Following exclusions, we included 12,271 cases (Fig. 1), comprising 90% urothelial carcinomas, 4.1% adenocarcinomas and 2.7% SCCs. The median age of cases was 72 years and 75% were male. As expected, cases generally had higher prevalences of comorbidity compared to population controls, both in terms of cardiovascular disease and markers of cardiovascular disease as well as alcohol-related disorders, and slightly lower levels of education (Table 1).

Among 333 SCC cases (Table 2), 66 (20%) had received 2–9 treatments for UTIs (intermediate use) and 48 (14%) had received 10+ treatments (high-use). The corresponding proportions among healthy controls were 9 and 2%, respectively. This yielded a crude OR of 3.3 (95% CI 2.5–4.5) for intermediate use and 13.5 (95% CI 9.3–19.6) for high use. Adjustment for covariates attenuated the associations slightly, with adjusted ORs of 3.1 (95% CI 2.3–4.3) and 11.4 (95% CI 7.6–17.2), respectively. A clear dose–response pattern emerged across categories of number of prescriptions (test for trend $p < 0.001$).

The observed associations between UTI-specific antibiotics and SCC were consistent across sex, patient subgroups and upon exclusion of those with cardiovascular comorbidity and those with known urogenital disease (Supporting Information S1). As one notable exception, we found a particularly strong association among those aged 40–59 years (OR 48.8; 95% CI 17.0–140.4). Findings

Table 2. Association between exposure to antibiotics used to treat urinary tract infections and risk of squamous cell carcinoma bladder cancer, specified by the number of prescriptions within the entire follow-up-period, excluding the last 2 years prior to the index date

Exposure group	Cases	Controls	Adjusted OR[1]	Adjusted OR[2]
Nonuse (0–1 prescriptions)	219	14,691	1.0 (ref.)	1.0 (ref.)
Intermediate use (2–9 prescriptions)	66	1,529	3.3 (2.5–4.5)	3.1 (2.3–4.3)
High-use use (10+ prescriptions)	48	327	13.5 (9.3–19.6)	11.4 (7.6–17.2)
Dose–response				
2–4 prescriptions	37	1,015	2.7 (1.8–3.9)	2.5 (1.7–3.7)
5–9 prescriptions	29	514	4.4 (2.9–6.8)	4.1 (2.7–6.4)
10–19 prescriptions	32	230	11.9 (7.7–18.3)	10.5 (6.6–16.6)
≥20 prescriptions	16	97	14.4 (7.9–26.4)	11.7 (6.2–22.2)
Test for trend	114	1,856	$p < 0.001$	$p < 0.001$

[1]Adjusted for age, sex and calendar-time (by design; risk-set matching).
[2]Fully adjusted model, see section 'Analytical variables'.

Table 3. Association between exposure to antibiotics used to treat urinary tract infections and risk of urothelial carcinoma of the bladder, specified by the number of prescriptions within the entire follow-up period, excluding the last 2 years prior to the index date

Exposure group	Cases	Controls	Adjusted OR[1]	Adjusted OR[2]
Nonuse (0–1 prescriptions)	9,986	505,013	1.00 (ref.)	1.00 (ref.)
Intermediate use (2–9 prescriptions)	861	35,356	1.25 (1.16–1.34)	1.20 (1.11–1.29)
High-use use (10+ prescriptions)	182	7,789	1.20 (1.03–1.40)	1.13 (0.97–1.32)
Dose–response				
2–4 prescriptions	620	24,445	1.29 (1.19–1.41)	1.25 (1.14–1.36)
5–9 prescriptions	241	10,911	1.13 (0.99–1.29)	1.07 (0.94–1.23)
10–19 prescriptions	110	5,370	1.05 (0.87–1.27)	0.99 (0.82–1.20)
≥20 prescriptions	72	2,419	1.51 (1.19–1.93)	1.42 (1.12–1.81)
Test for trend	1,043	43,145	$p = 0.94$	$p = 0.87$

[1]Adjusted for age, sex and calendar-time (by design; risk-set matching).
[2]Fully adjusted model, see section 'Analytical variables'.

Table 4. Association between exposure to phenoxymethylpenicillin (Penicillin V) and risk of squamous cell carcinoma of the bladder, specified by the number of prescriptions within the entire follow-up-period, excluding the last 2 years prior to the index date

Exposure group	Cases	Controls	Adjusted OR[1]	Adjusted OR[2]	Adjusted OR [3]
Nonuse (0–1 prescriptions)	257	12,276	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Intermediate use (2–9 prescriptions)	64	3,968	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.9 (0.6–1.3)
High use (10+ prescriptions)	12	303	2.8 (1.5–5.2)	2.5 (1.3–4.7)	0.5 (0.1–2.3)
Dose–response					
2–4 prescriptions	46	2,844	1.1 (0.8–1.5)	1.1 (0.8–1.6)	0.9 (0.6–1.4)
5–9 prescriptions	18	1,124	1.2 (0.7–2.0)	1.2 (0.7–2.0)	1.0 (0.5–1.8)
10–19 prescriptions	9	267	2.4 (1.2–4.8)	2.1 (1.0–4.4)	0.6 (0.1–2.7)
≥20 prescriptions	(n < 5)	36	(–)	(–)	(–)
Test for trend	76	4,271	p = 0.03	p = 0.11	p = 0.23

[1]Adjusted for age, sex and calendar-time (by design; risk-set matching).
[2]Fully adjusted model, see section 'Analytical variables'.
[3]Further adjusted for use of antibiotics used against urinary tract infections.

similar to the main analysis were observed when analyzing individual UTI-specific antibiotics (Supporting Information Table S2).

For urothelial carcinoma (n = 11,029), no overall association was found with UTI-specific antibiotics (Table 3). Although intermediate use showed a slight association (OR 1.20; 95% CI 1.11–1.29), the OR for high-use was closer to unity (OR 1.13; 95% CI 0.97–1.32), and there was limited evidence of a dose–response pattern (p = 0.87). Similarly, no apparent associations were found for adenocarcinomas or small cell carcinomas (Supporting Information Table S3), while a slight increase was seen for other/unclassified histology (n = 249; high-use OR 3.6; 95% CI 1.8–7.4; p_{trend} < 0.01).

High use of phenoxymethylpenicillin was associated with SCC with an OR of 2.5 (95% CI 1.3–4.7) (Table 4). However, this association disappeared upon concomitant adjustment for UTI-specific antibiotics, yielding an adjusted OR of 0.5 (95% CI 0.1–2.3). In the fully adjusted model, the risk of SCC did not increase with increasing number of phenoxymethylpenicillin prescriptions (p_{trend} = 0.23).

Considering only antibiotics filled within the last 5 or 10 years only yielded similar results (data not shown). When applying varying lag-times in the analysis (Supporting Information Table S4), risk estimates increased markedly when no lag-time was applied, in particular for intermediate use. Conversely, estimates were generally stable with increasing lag-times beyond 6 months, for example, applying a lag-time of 5 years yielded an OR for high-use of 10.4 (95% CI 6.4–17.0). For urothelial carcinoma, we observed increased risk when no lag-time was applied, whereas this excess risk was not found with lag-times larger than 12 months (Supporting Information Table S5).

In a probabilistic bias analysis to assess the potential for unmeasured confounding by smoking the observed association between high-use of UTI-specific antibiotics and SCC with an OR of 11.4 (95% CI 7.6–17.2) decreased to an OR of 8.8 (95% simulation interval 7.7–13.4).

Assuming causality, an estimated 88 cases of SCC could be explained by UTIs, corresponding to 26% of all SCCs during the study period or 0.7% of all bladder cancer cases. An estimated 19,144 years spent as a high-user of UTI-specific antibiotics were required for one additional SCC case to occur.

Discussion

In this large nationwide study, we found a strong and dose-dependent association between recurring UTIs and an increased risk of SCC of the bladder. This association was highly specific with regards to the outcome as well as the exposure as analyses of other bladder cancer histologies and other antibiotics returned generally neutral associations. Furthermore, the findings were robust across a wide range of supplementary analyses.

The principal strength of our study is the high-quality nationwide data sources used, which minimized the risk of selection bias and provided a large sample of histologically verified cancer cases. The principal weakness of the study is the lack of data on smoking, which is strongly associated with bladder cancer risk[30] and also likely associated with an increased risk of infection. However, our bias analyses found that confounding from smoking cannot explain our findings, even when assuming a strong association between smoking and UTIs. Furthermore, the fact that we found very clear null associations for our negative control antibiotics as well as limited associations to urothelial carcinomas also indicates that confounding by smoking is minimal. Confounding by indication, for example, prophylactic use among patients with bladder catheters are also a concern, however, the analyses excluding patients with the known urogenital disease (including catheters) yielded virtually unchanged estimates. Another potential weakness is the use of filled prescriptions for UTI-specific antibiotics as a proxy for UTI. First, although used very specifically for UTIs in Denmark, these antibiotics may to some extent have been used for other infections. Further, this proxy did not have full sensitivity, as some milder UTIs

might be treated with analgesics and hydration only. However, both reasons for slight exposure misclassification would be expected to attenuate the observed associations. Second, we do not know whether patients who redeemed antibiotic prescriptions were compliant with their treatment. However, given that its use was a proxy for UTI, adherence is of minor importance.

There was evidence of effect measure modification on the relative scale by age, as we observed higher ORs for individuals aged 40–59 years. However, this likely reflects the fact that SCC of the bladder is rare, especially among younger individuals, and that a given increase in absolute risk would lead to a higher relative risk increase in this group. In line with this point, even though we found a substantially increased odds ratio for SCC associated with urinary tract infections, the absolute risk increase remained low both at the population level and at the individual level.

To the best of our knowledge, no previous studies have focused specifically on SCC when examining the association between UTI and bladder cancer. In contrast, previous smaller case–control studies have focused only on urothelial carcinomas[11] or on bladder cancer overall.[7–9,31] In the Dutch study by Vermeulen *et al.*,[7] only 15 of the included 1,767 bladder cancer cases had SCC. Studies on larger number of SCC patients have either focused on specific schistosomal infection[4] or human papillomavirus.[32] With our findings that common UTIs specifically increases the risk of SCC, but show limited association to urothelial carcinomas, our study thus emphasizes the importance of distinguishing between histological types when examining risk of bladder cancer.[33] In interpreting our finding of a slight association for urothelial carcinoma with UTI-specific antibiotics it should be acknowledged that even a small relative increase in risk of urothelial carcinoma would translate to a higher absolute risk than that observed for SCC, due to the higher incidence of urothelial cancer. While we did observe slightly increased risk estimates for urothelial carcinoma in some exposure strata, there was limited evidence of a dose–response pattern and the slightly increased risk estimates could well be explained by unmeasured confounding from smoking. Our findings for urothelial carcinoma do however contrast those of some of the existing studies[7,9,11,31] which found relative risk estimates ranging between 1.5 and 6.6. All these previous studies obtained information on UTI based on interviews of cases and controls with questions about diagnoses of UTI any time before index date. Such information may be difficult to recall and the accuracy of recalling UTIs likely differ between cases and controls which would lead to recall bias. The Nijmegen bladder cancer study, which found a sixfold increased risk of bladder cancer in men and a nearly threefold increased risk in women following UTI, found a slightly protective effect of UTIs that had been treated with antibiotics (adjusted ORs of 0.74 (95% CI, 0.59–0.93) in men and 0.86 (95% CI, 0.5–1.5) in women).[7] This discrepancy could potentially suggest misclassification of exposure. In addition, none of the previous studies was population-based as controls were identified from hospitals,[11] annual health check-ups[9] or participants in health surveys (with participation rate 43%).[7] These controls may represent selected populations and not appropriately reflect exposure status in the source population. A previous US case–control study[8] used age-gender and race-matched neighborhood controls and found no overall association between history of UTI and bladder cancer (OR 1.0; 95% CI 0.8–1.2) which is corroborated by our findings.

In conclusion, we have shown a very strong correlation between recurring UTIs and risk of SCC of the bladder. As SCC of the bladder is rare, the absolute risk at the individual level is low. However, these findings resolve previous discrepancies in the literature and adds common UTIs to the list of risk factors for SCC of the bladder, thereby expanding our understanding of the pathophysiology of this cancer.

Conflict of interest

The authors declare no potential conflicts of interest.

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