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INVITED REVIEW

Role of urinary tract infection in bladder cancer: a systematic review and meta-analysis

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Abstract

Purpose We sought to examine the literature reporting the effect of urinary tract infection (UTI) on non-schistosomiasis-related UBC (UBC_{NS}) through a systematic review and meta-analysis.

Methods A predefined study protocol was developed according to PRISMA. Medline and Scopus were searched for all studies investigating exposure to UTI with UBCNS as the primary outcome. Potential studies were screened against eligibility criteria. Clinical heterogeneity was assessed and groups with more than two studies were evaluated by random effect meta-analysis. Study-level bias was assessed with the Newcastle–Ottawa Scale (NOS). In cases of substantial between study heterogeneity ($I^2 > 50\%$), predefined sensitivity and subgroup analyses were performed.

Results Of 16 eligible studies, eight case–control studies spanning four decades and five countries were suitable for quantitative analysis. Main analysis favored exposure to UTI increasing risk of subsequent UBC_{NS} (RR 1.33 [95% CI 1.14–1.55]). This effect was no longer statistically significant after excluding studies published prior to year 2000 and at high risk of bias. Between study heterogeneity was considerable for nearly all analyses and not reduced by predefined sensitivity or subgroup analyses.

Conclusion Exposure to UTI favors increased risk for UBC_{NS}, particularly in men, but these effects were statistically insignificant when pooling data from the most recent and highest quality studies. These data do not support findings of previously published studies, that report on heterogenous populations with poor definitions of UTI and minimal control for important confounders. Results from previous studies should be viewed as hypothesis generating. This review highlights the need for higher quality investigation.

Keywords Urinary tract infections · Cystitis · Urinary bladder neoplasms · Urothelial carcinoma · Bladder cancer

Abbreviations

CI	Confidence interval
HR	Hazard ratio
NOS	Newcastle–Ottawa Scale
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RR	Risk ratio
SCC	Squamous cell carcinoma
UBC	Urinary bladder cancer
UBC_{NS}	Non-schistosomiasis-related UBC
UC	Urothelial carcinoma
UTI	Urinary tract infection

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Introduction

A diverse body of literature has shown associations between urinary tract infection (UTI) and the development of urinary bladder cancer (UBC). The most definitive link established between UTI and UBC consists of the association between *Schistosoma haematobium*, a parasitic worm that causes urogenital schistosomiasis and squamous cell carcinoma (SCC) of the bladder [1]. Although exact pathogenesis is not well defined, egg deposition in the bladder wall is thought to be the major contributor to increased cancer risk.

A link between bacterial UTI and non-schistosomiasis-related UBC (UBC_{NS}), particularly urothelial carcinoma (UC), is less clear. Numerous case–control studies constructed over the last several decades have fairly consistently shown exposure to bacterial UTI is associated with an increased risk of bladder cancer. The concept that chronic bacterial UTI can lead to bladder cancer has permeated urology textbooks. However, these studies were observational and designed to show association, not causation. Furthermore, these studies include weak definitions of UTI and poorly control for confounding variables and biases, including diagnostic bias (i.e., a patient with irritative voiding symptoms may be incorrectly diagnosed with a UTI when the symptoms are caused by undiagnosed UBC).

We sought to clarify the potential connection between UTI and UBC_{NS} through a systematic review and meta-analysis. Our primary objective was to define if exposure to UTI affects the risk for future UBC_{NS}. Evaluation of the influence of lifestyle factors and comorbidities on the association between UTI exposure and UBC_{NS} risk was a secondary objective. At the time of this writing, a meta-analysis of this scope has not been published. One recent publication did not follow established criteria for a systematic review and findings were reported in a narrative format [2].

Methods

Protocol and registration

This review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [3]. A full protocol for this systematic review and meta-analysis was developed according to PRISMA for systematic review protocols (PRISMA-P) guidelines [4]. It was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [5]. The protocol was developed after preliminary literature searches and piloting of the study selection process but before formal screening and data extraction.

Study eligibility criteria

A preliminary literature search did not reveal prospective studies relevant to the topic. We considered all observational studies, including cohort and case–control studies, which reported histologically confirmed UBC as the primary outcome and UTI as a primary or separate exposure variable. We excluded studies that did not confirm UBC by histology or reported SCC as the primary UBC variant (i.e., to exclude, as best as possible, cases that may be caused by schistosomiasis). Likewise, we excluded studies with participants and/or comparators with neurological conditions (e.g., spinal cord injury, as bladder catheterization has been linked to SCC of the bladder) or located in areas where schistosomiasis is endemic.

Identification and selection of studies

In January 2017, Medline and Scopus were searched for potentially eligible studies using a predefined strategy with medical subject headings and keywords. The full search strategy for both databases is available through our PROSPERO registration [5]. All identified studies were screened by title and abstract (e.g., "first-level" assessment) for further review. Eligibility criteria were applied to full-text articles (e.g., "second-level" assessment) using a predefined worksheet. In cases of duplicate studies or studies on duplicate populations, the study presenting the most recent data was assessed (unless there was a contraindication to doing so). References of all full-text articles evaluated as part of the second-level assessment were screened to ensure literature saturation. All literature searches and reviews were independently performed by two unblinded reviewers (CB, DF) before developing consensus lists. Disagreements were resolved by a third reviewer (MH).

Data collection and assessing risk

For studies meeting eligibility criteria, data were extracted using a predefined worksheet. For our primary outcome of UBC and exposure history of UTI, we extracted total raw numerator and denominator data for controls and comparators and, when possible, excluded data ≤ 2 years preceding UBC diagnosis for cases and interview for comparators to control for diagnostic bias. Studies were excluded for quantitative analysis if raw data were not presented in the published article. When possible, we extracted secondary outcome data related to UTI exposure subgroups, such as gender, smoking status, and recurrent UTI exposure. We

did not collect adjusted outcome statistics given that the methods and variables were inconsistent across studies.

We developed a grading system (1–5) to categorize study definitions of UTI exposure in which higher grades indicate higher quality definitions of UTI (Supplementary Table 1). When defined by individual studies, only data related to exposure to lower tract UTI (e.g., cystitis) were extracted.

We used the Newcastle–Ottawa Scale (NOS), a validated tool for assessing risk of bias in nonrandomized clinical studies, to assess study-level bias [6]. NOS uses a "star system" to grade studies on selection of study groups (up to 4 stars), comparability of the groups (up to 2 stars), and ascertainment of exposure or outcome (up to 3 stars). Higher total star ratings equate to higher study quality and less risk of bias. Two reviewers (CB, DF) independently assessed all eligible studies according to NOS scales. If consensus was not reached, a third reviewer (MH) served as arbiter.

Data synthesis

Clinical heterogeneity was assessed by grouping studies according to design, UTI definition, and UTI subgroups. For groups with two or more studies, data were pooled using Mantel–Haenszel random effect meta-analysis. Risk ratios (RR) with 95% confidence intervals (CI) were calculated as they are more intuitive to understand than odds ratio (OR). CIs that did not cross RR 1.0 were considered statistically significant.

Between study heterogeneity was assessed visually using forest plots and statistically using the I^2 statistic. No threshold of heterogeneity excluded pooled analysis, but substantial heterogeneity (considered $I^2 > 50\%$) was further investigated through predefined, logical sensitivity analyses excluding those studies investigating hospital-based sample populations (under the assumption hospitalized patients are more likely to have cancer and/or UTI than the general population), published prior to year 2000 (to exclude less sophisticated and/or rigorous methods of investigation), and with highest risk of bias (NOS total ≤ 6). We also performed sensitivity analyses excluding either European or U.S. studies (as these populations may be different in racial makeup as well as social, cultural, and environmental factors). Additional subgroup analyses separated data by gender, smoking status, and multiple UTI status. As all pooled analyses included < 10 studies, we assessed the potential for small study effects only visually using a funnel plot [7, 8].

All data were maintained in and meta-analyses were performed with Review Manager (RevMan) 5 [9].

Results

Study selection

The study selection process is shown in Supplementary Figure 1. Full text for all 21 studies passing the first-level assessment was available for review. Of these, five were excluded based on eligibility criteria. A total of 16 studies met eligibility criteria and were considered for quantitative synthesis [10–25]. All studies were retrospective in nature, and all but one was of case–control design. Of the 16, only 8 studies were suitable for pooled analysis [10–17]. Table 1 identifies details for all 16 full-text articles meeting eligibility criteria.

Eligible studies

The eight studies considered suitable for pooled analysis were published over a 30-year period from a range of countries. All were designed as case–control studies with the majority selecting community-based case and control populations. The studies included a range of sample sizes for case ($n = 170$–2932) and control populations ($n = 282$–5698). All studies utilized the lowest grade of our predefined UTI definitions. Vermeulen et al. were the only investigators to collect data for UTI definitions 1 and 2, thus only data pertaining to definition 1 were synthesized in the overall pooled analysis. According to the NOS, only four (50%) studies, all published in the last 11 years, were judged to be at low risk of bias (NOS total > 6).

Main analysis: UTI exposure and risk of UBC_{NS}

The pooled overall effect favored a statistically significant increased risk of UBC_{NS} following exposure to UTI (RR 1.33 [95% CI 1.14–1.55, eight studies]; Fig. 1). Only one study (Jiang et al.) reported exposure to UTI reduced the risk of UBC_{NS}. Between study heterogeneity was considerable ($I^2 = 87\%$). A funnel plot (Supplementary Figure 2) did not reveal an asymmetric distribution, making it unlikely the overall pooled effect was strongly impacted by small study biases. The absence of studies along the lower left-side of the graph prevents us from excluding publication bias.

To investigate the substantial between study heterogeneity, predefined sensitivity analyses were performed (Fig. 2a–e). Between study heterogeneity remained considerable in all analyses ($I^2 \geq 79\%$). After excluding studies published prior to year 2000 and those with the highest risk of bias (NOS total ≤ 6), pooled effects no longer met

Table 1 List of 16 studies meeting eligibility criteria presented in chronological order of publication

Study details[a]			Sample populations (case–control studies only)				Newcastle–Ottawa Scale			
First author (year)	Country	Study design	Case population		Control population		Selection (max 4)	Comparability (max 2)	Exposure (max 3)	Total
Included in quantitative synthesis										
Kantor (1984) [10]	U.S.	Case–control	SEER, NJCR (community)		Random-digit dialing, HCFR (community)		2	0	2	4
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	2213	719	4217	1481	Confounders stratified or accounted for in selection of cases and controls: age, sex, geographic area			
		Mean age (years)	Unreported		Unreported					
		% ever smokers	Unreported		Unreported		Years excluded prior to UBC diagnosis or data acquisition: none			
Kjaer (1989) [11]	Denmark	Case–control	Community		Community		2	2	2	6
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	290	98	595	195	Confounders stratified or accounted for in selection of cases and controls: age, sex, municipality			
		Mean age (years)	Reported as subgroups		Reported as subgroups					
		% ever smokers	Unreported		Unreported		Years excluded prior to UBC diagnosis or data acquisition: none			
Hartge (1990) [12]	U.S.	Case–control	NBCR (community)		Random-digit dialing, HCFR (community)		3	0	2	5
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	2117	689	3892	1366	Confounders stratified or accounted for in selection of cases and controls: unclear, if any			
		Mean age (years)	Unreported		Unreported					
		% ever smokers	82.9	53.9	68.9	35	Years excluded prior to UBC diagnosis or data acquisition: none			
La Vecchia (1991) [13]	Italy	Case–control	Hospital (admitted)		Hospital (admitted)		2	0	1	3
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	303	61	336	111	Confounders stratified or accounted for in selection of cases and controls: hospital			
		Mean age (years)	Median 63		Median 62					
		% ever smokers	86.1	36.1	71.4	22.5	Years excluded prior to UBC diagnosis or data acquisition: none			
Jhamb (2006) [14]	U.S.	Case–control	MD Anderson (unclear community vs. hospital)		Houston, Texas clinics (community)		4	1	2	7
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	512	147	540	149	Confounders stratified or accounted for in selection of cases and controls: age, sex, ethnicity			
		Mean age (years)	63.2 (combined)		62.4 (combined)					
		% ever smokers	73.1 (combined)		53.7 (combined)		Years excluded prior to UBC diagnosis or data acquisition: ≤ 1			

Table 1 (continued)

Study details[a]			Sample populations (case–control studies only)				Newcastle–Ottawa Scale			
First author (year)	Country	Study design	Case population		Control population		Selection (max 4)	Comparability (max 2)	Exposure (max 3)	Total
Jiang (2009) [15]	U.S.	Case–control	SEER Los Angeles		Community		3	2	2	7
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	1237	349	1237	349	Confounders stratified or accounted for in selection of cases and controls: age, sex, race, neighborhood			
		Mean age (years)	Unreported		Unreported					
		% ever smokers	Unreported	76.3[b]	Unreported	54.4[b]	Years excluded prior to UBC diagnosis or data acquisition: ≤ 2			
Erdurak (2013) [16]	Turkey	Case–control	Hospital (admitted)		Hospital (admitted)		1	2	2	5
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	156	17	232	50	Confounders stratified or accounted for in selection of cases and controls: age, sex, location (city, district)			
		Mean age (years)	Reported as grouping		Reported as grouping					
		% ever smokers	82.1 (combined)		58.9 (combined)		Years excluded prior to UBC diagnosis or data acquisition: none			
Vermeulen (2015) [17]	Netherlands	Case–control	Netherlands Cancer Registry (community)		Nijmegen Biomedical Study (community)		4	2	2	8
			Male	**Female**	**Male**	**Female**	**Case–control population details**			
		Total *n*	1463	346	1974	2396	Confounders stratified or accounted for in selection of cases and controls: age, sex			
		Mean age (years)	62.9	61.3	61.8	56.5				
		% ever smokers	91.8	74.6	75.5	56.7	Years excluded prior to UBC diagnosis or data acquisition: ≤ 2			

Not included in quantitative synthesis					Reason excluded from quantitative synthesis
Howe (1980) [18]	Canada	Case–control	Interviewed in home; unclear how selected		Raw data on UTI exposure not presented
Sullivan (1982) [19]	U.S.	Case–control	–	–	No data on UTI exposure
Claude (1986) [20]	Germany	Case–control	Hospital (admitted)		Raw data on UTI exposure not presented
Piper (1986) [21]	U.S.	Case–control	NYHD (unclear community vs. hospital distribution)	Random-digit dialing (community)	Data presented as matched analysis only
González (1991) [22]	Spain	Case–control	Hospital (registry)	Community	Data presented as matched analysis only
Kunze (1992) [23]	Germany	Case–control	Hospital (admitted)		Raw data on UTI exposure not presented. Similar population to Claude et al.
D'Avanzo (1995) [24]	Italy	Case–control	Hospital (admitted)		No group without UTI exposure. Similar population to La Vecchia et al.

Table 1 (continued)

Not included in quantitative synthesis				Reason excluded from quantitative synthesis
Sun (2013) [25]	Taiwan	Cohort study	UTI-exposed and non-UTI exposure group selected from cohort of Taiwan National Health Insurance database (based on diagnosis codes)	Only cohort study identified

HCFR Health Care Financing Administration; *NBCR* National Bladder Cancer Registry; *NJCR* New Jersey Cancer Registry; *NYHD* Cancer Registry of the New York Health Department; *SCC* squamous cell carcinoma; *SEER* Surveillance, Epidemiology, and End Results (SEER) Program; *UBC* urinary bladder cancer

[a] All studies utilized the lowest grade (1) of our predefined UTI definitions (see Supplementary Table 1)

[b] Based on data excluding women reporting bladder infection occurring within 5 years of cancer diagnosis

criteria for statistical significance as the CIs crossed 1.0 (RR 1.21 [CI 0.88, 1.68, four studies] and RR 1.15 [95% CI 0.83, 1.59, four studies], respectively; Fig. 2d, e) and with considerable between study heterogeneity ($I^2 = 91\%$).

Subanalyses: UTI exposure subgroups and risk of UBC_{NS}

Pooled analysis was performed for raw data available for five subgroups of UTI exposure: males, females, exposure to UTI with smoking history, exposure to UTI without smoking history, and exposure to multiple UTIs.

Five (62.5%) studies reported raw data on UTI exposure by gender (Supplementary Figures 2A–B). Overall effect of UTI exposure on UBC_{NS} risk increased when considering only males (RR 1.67 [95% 1.14, 2.45, five studies]; Supplementary Figure 3A) but was statistically insignificant when pooling only female data (RR 1.27 [95% CI 0.96, 1.69, five studies]; Supplementary Figure 3B). Both analyses demonstrated considerable between study heterogeneity ($I^2 = 95$ and 94%). The effect for only males was no longer significant after excluding studies published prior to year 2000 and at highest risk of bias (RR 2.59 [95% 0.3, 22.3, two studies]; data not shown). Predefined sensitivity analyses did not sizably reduce between study heterogeneity for either subgroup comparison (data not shown).

Two (25%) studies provided data permitting subgrouping by smoking status, though Jiang et al. only provided data regarding female subjects (Supplementary Figure 4A–B). Pooling data from subjects with (RR 1.03 [95% CI 0.34, 3.06, two studies]; Supplementary Figure 4A) and without smoking history (RR 1.05 [95% CI 0.35, 3.11, two studies]; Supplementary Figure 4B) revealed no effect given the broad CIs of both analyses. Between study heterogeneity was considerable ($I^2 = 98$ and 92%) for both analyses.

Five (62.5%) studies reported data on multiple UTI exposures (Supplementary Figures 5A–B). Each study categorized frequency of UTI differently. For purposes of comparison, data from Kantor et al. and Vermeulen et al. were extracted as ≥ 3 episodes of UTI compared to no exposure. Data from the remaining three studies were extracted as ≥ 4 episodes of UTI compared to no exposure. Notably, in collecting data regarding the number of UTI episodes, Vermeulen et al. changed their definition of UTI, eliciting the number to times subjects were treated with an antibiotic (corresponding to UTI definition 2). Jhamb et al. excluded data within 3 years of cancer diagnosis. Jiang et al. reported episodic UTI data for females only and excluded data within 5 years of cancer diagnosis. Pooled analysis showed no association between recurrent UTI exposure and risk of UBC_{NS} (RR 1.03 [95% CI 0.47, 2.28, five studies]; Supplementary Figure 5A) with considerable between study heterogeneity ($I^2 = 98\%$). Predefined sensitivity analyses did not sizably

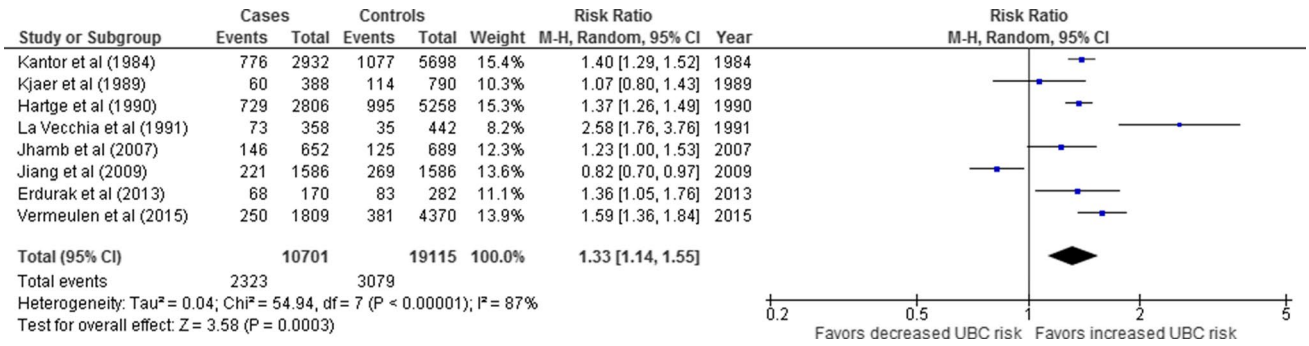


Fig. 1 Meta-analysis of studies reporting effect of exposure to UTI on risk of UBC

alter these results until studies with published prior to year 2000 and highest risk of bias were eliminated (for this analysis, Kantor et al. and La Vecchia et al. met both criteria). Under these criteria, exposure to multiple UTIs favored a statistically significant reduction in risk of UBC_{NS} (RR 0.56 [95% CI 0.38, 0.81, three studies]; Supplementary Figure 5B) but between study heterogeneity remained substantial ($I^2 = 63\%$).

Discussion

We performed a systematic review and meta-analysis to evaluate the effect of UTI on the risk of developing UBC_{NS}. Eight case–control studies suitable for pooled analysis, according to predefined criteria, revealed an overall effect favoring exposure to UTI increasing the risk of UBC_{NS} (RR 1.33 [95% CI 1.14–1.55, eight studies]). The statistical significance of this effect was lost after excluding European studies, studies published prior to year 2000, and studies at the highest risk of bias. There may be a gender-specific increased risk for males (RR 1.67 [95% 1.14, 2.45, five studies]), yet this effect was statistically insignificant after excluding studies published prior to year 2000 and at highest risk for bias. Female-only data showed no statistically significant effect. Pooling data from subjects with and without smoking history showed no effect. Exposure to multiple UTIs was not associated with UBC_{NS} risk until studies published prior to year 2000 and those with a high risk of bias were excluded. Under these conditions, analysis favored a decreased risk of UBC_{NS} (RR 0.56 [95% CI 0.38, 0.81, three studies]) with substantial between study heterogeneity ($I^2 = 63\%$). For all analyses, between study heterogeneity was considerable and was not explained by logical exclusion of studies with different sample populations (e.g., hospital versus community, European versus American), early publication dates, or high risk of bias.

The main effect from pooled case–control studies corroborates data from the only cohort study we identified in our systematic search [25]. Sun et al. reviewed 9 years of reimbursement data in Taiwan and reported those diagnosed with UTI experienced a significantly increased risk of urinary tract cancer during follow-up compared to a non-UTI exposed group (hazard ratio [HR] 4.66 [95% CI 3.55–6.1]). Results grouped by UTI and cancer location reinforce an association between lower UTIs and future bladder cancer (HR 5.68 [95% CI 3.91, 8.25]). A notable limitation of this study is the Taiwanese database did not identify cancer histology.

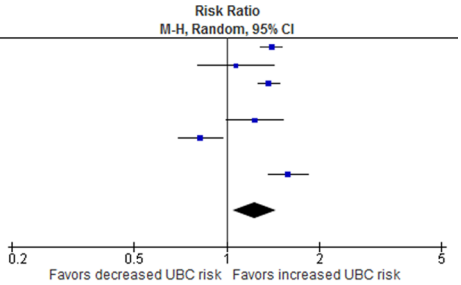
The finding that increased frequency of UTI exposure may decrease the risk of UBC_{NS} is interesting and warrants discussion. First, it argues against the common criticism of diagnostic bias in research on UTI exposure and UBC risk. Second, it does not necessarily follow the intuitive extrapolation of our main pooled analysis. If any exposure to UTI is associated with an increased risk for UBC_{NS}, why would repeated exposure decrease oncogenic potential? Some [15, 17] have theorized that repeated antibiotic exposure may exhibit a dose-dependent anti-cancer effect as fluoroquinolones, trimethoprim/sulfamethoxazole, and nitrofurantoin have been found to inhibit cell proliferation of bladder cancer cell lines [26, 27]. However, closer inspection of the Nijmegen data suggests a threshold above which the "protective" effect of multiple UTIs is lost: for men and women, the adjusted OR of UBC rose above 1.0 after 6 UTIs and increased sharply for men reporting ≥ 11 UTIs [17].

Finally, in our analysis, the decreased cancer risk associated with multiple UTIs was strengthened and between study heterogeneity slightly decreased following sensitivity analyses selecting for the most recently published and highest quality data. Regarding this result, it is important to consider that while Vermeulen et al. present the highest quality and overall most recent study on this topic, in eliciting information on UTI frequency, the authors changed their definition of UTI from self-reported symptoms (definition 1) to a definition based on the prescription of antibiotics (definition 2). As these definitions do not necessarily extract the same information, their data may be incomplete when trying

A

Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kantor et al (1984)	776	2932	1077	5698	19.3%	1.40 [1.29, 1.52]	1984
Kjaer et al (1989)	60	388	114	790	12.4%	1.07 [0.80, 1.43]	1989
Hartge et al (1990)	729	2806	995	5258	19.2%	1.37 [1.26, 1.49]	1990
La Vecchia et al (1991)	73	358	35	442	0.0%	2.58 [1.76, 3.76]	1991
Jhamb et al (2007)	146	652	125	689	15.0%	1.23 [1.00, 1.53]	2007
Jiang et al (2009)	221	1586	269	1586	16.8%	0.82 [0.70, 0.97]	2009
Erdurak et al (2013)	68	170	83	282	0.0%	1.36 [1.05, 1.76]	2013
Vermeulen et al (2015)	250	1809	381	4370	17.3%	1.59 [1.36, 1.84]	2015
Total (95% CI)		**10173**		**18391**	**100.0%**	**1.24 [1.05, 1.45]**	
Total events	2182		2961				

Heterogeneity: Tau² = 0.03; Chi² = 43.27, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.57 (P = 0.01)



B

Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kantor et al (1984)	776	2932	1077	5698	27.2%	1.40 [1.29, 1.52]	1984
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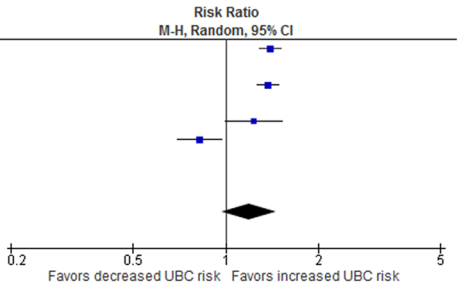
Vermeulen et al (2015)	250	1809	381	4370	0.0%	1.59 [1.36, 1.84]	2015
Total (95% CI)		**7976**		**13231**	**100.0%**	**1.19 [0.97, 1.46]**	
Total events	1872		2466				

Heterogeneity: Tau² = 0.04; Chi² = 35.34, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.71 (P = 0.09)



C

Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
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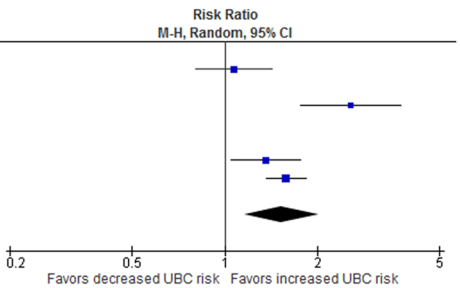
Vermeulen et al (2015)	250	1809	381	4370	29.9%	1.59 [1.36, 1.84]	2015
Total (95% CI)		**2725**		**5884**	**100.0%**	**1.53 [1.16, 2.02]**	
Total events	451		613				

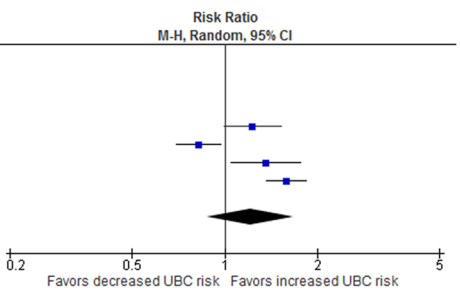
Heterogeneity: Tau² = 0.06; Chi² = 14.18, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 3.02 (P = 0.003)



D

Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kantor et al (1984)	776	2932	1077	5698	0.0%	1.40 [1.29, 1.52]	1984
Kjaer et al (1989)	60	388	114	790	0.0%	1.07 [0.80, 1.43]	1989
Hartge et al (1990)	729	2806	995	5258	0.0%	1.37 [1.26, 1.49]	1990
La Vecchia et al (1991)	73	358	35	442	0.0%	2.58 [1.76, 3.76]	1991
Jhamb et al (2007)	146	652	125	689	24.6%	1.23 [1.00, 1.53]	2007
Jiang et al (2009)	221	1586	269	1586	25.8%	0.82 [0.70, 0.97]	2009
Erdurak et al (2013)	68	170	83	282	23.5%	1.36 [1.05, 1.76]	2013
Vermeulen et al (2015)	250	1809	381	4370	26.1%	1.59 [1.36, 1.84]	2015
Total (95% CI)		**4217**		**6927**	**100.0%**	**1.21 [0.88, 1.68]**	
Total events	685		858				

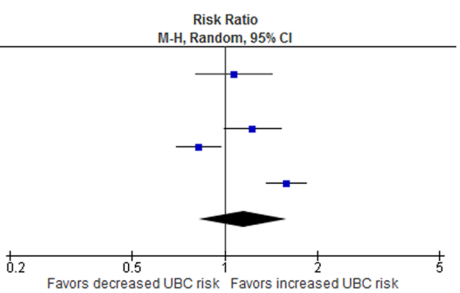
Heterogeneity: Tau² = 0.10; Chi² = 34.79, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.17 (P = 0.24)



E

Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kantor et al (1984)	776	2932	1077	5698	0.0%	1.40 [1.29, 1.52]	1984
Kjaer et al (1989)	60	388	114	790	22.9%	1.07 [0.80, 1.43]	1989
Hartge et al (1990)	729	2806	995	5258	0.0%	1.37 [1.26, 1.49]	1990
La Vecchia et al (1991)	73	358	35	442	0.0%	2.58 [1.76, 3.76]	1991
Jhamb et al (2007)	146	652	125	689	24.9%	1.23 [1.00, 1.53]	2007
Jiang et al (2009)	221	1586	269	1586	26.0%	0.82 [0.70, 0.97]	2009
Erdurak et al (2013)	68	170	83	282	0.0%	1.36 [1.05, 1.76]	2013
Vermeulen et al (2015)	250	1809	381	4370	26.3%	1.59 [1.36, 1.84]	2015
Total (95% CI)		**4435**		**7435**	**100.0%**	**1.15 [0.83, 1.59]**	
Total events	677		889				

Heterogeneity: Tau² = 0.10; Chi² = 34.29, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.83 (P = 0.41)



◂**Fig. 2** Sensitivity analyses of overall pooled analysis of UTI exposure on risk of UBC after. **a** Eliminating studies reporting hospital samples. **b** Eliminating European studies. **c** Eliminating U.S. studies. **d** Eliminating studies published prior to year 2000. **e** Eliminating studies with high risk of bias

to decipher whether multiple exposures to UTI affect cancer risk. The authors even highlighted small overlap between patients who answered "no" to the lesser UTI definition but later reported having been prescribed antibiotics for a UTI.

Most of the pooled analyses in this review identified considerable between study heterogeneity, evidence of the diverse body of research published on this topic. Obvious sources of heterogeneity include the several decades and countries from which these studies were individually performed. Differences in sample populations regarding age and smoking status cannot be understated given the impact these variables have on overall bladder cancer risk. Individual studies attempted to control these confounders with sophisticated methods of adjusted OR reporting. While it would be convenient to compare these ORs at face value, we made an *a priori* decision to extract and compare raw data given the dissimilar methods authors used to categorize and control for different confounders.

Potential criticism of our work includes meta-analysis in the face of persistent between study heterogeneity despite predefined sensitivity and subgroup analyses. We stress the heterogeneity reflects the quality of the existing literature, which we deem to be overall mediocre, and should not bar pooled synthesis as long as the heterogeneity is cited as a clear limitation. In this analysis, the persistently elevated I^2 values underscore the caution with which readers should view the original studies. In other words, our pooled results should not be perceived to substantiate those studies that previously reported positive associations between bacterial UTI and risk of UBC_{NS}, especially increasingly positive associations after multiple infections. We again highlight that statistical significance of our overall effect was lost following exclusion of European studies, studies published prior to year 2000, and at a high risk of bias.

Readers should consider theories of bacterial UTIs contributing or initiating UBC_{NS} carcinogenesis have developed from the consecutive publication of case–control studies reviewed here as a well as a linkage to other models of UTI and UBC, such as schistosomiasis and patients with spinal cord injury. However, urogenital schistosomiasis is pathophysiologically distinct from bacterial UTI, and many patients with spinal-related neuropathic bladder conditions require intermittent or chronic catheterization, which have been separately implicated as risk factors for UBC [28]. Increased inflammation and cell turnover have been proposed as mechanisms by which schistosomiasis and chronic catheterization increase risk of bladder cancer. The association between UTI and UBC_{NS} is unlikely to be explained by a similar mechanism. Urogenital schistosomiasis and chronic catheterization most commonly cause non-keratinizing forms of SCC. Conversely, UC is the most common form of bladder cancer in the general population of industrialized countries.

There are study-, outcome- and review-level limitations that warrant discussion. At the study level, we decided to exclude (when possible) data at least 1 year prior to the diagnosis of UBC for cases and data acquisition (e.g., subject interview) for controls. The purpose of this decision was to minimize diagnostic bias. Studies in the pooled analysis inconsistently excluded data: some did not categorize and present data this way, and others excluded 2 years of data. Also, as mentioned earlier, all studies were observational in nature and cannot identify causality. At the outcome level, our primary interest, UBC_{NS}, was rarely reported in a subgroup of cases and controls without previous tobacco exposure. Therefore, our pooled results cannot account for the effect of tobacco use. At the review level, access to unpublished data may have clarified or allowed more meaningful analyses. For example, with complete access to raw data, we may have been able to control tobacco exposure or consistently exclude years prior to UBC diagnosis. Additionally, Kantor et al. and Hartge et al. may have used similar control populations. Contacting the authors may have clarified these points. However, given the wide publication timeframe, we decided it was unlikely we would be able to uniformly access all unpublished raw data, so we did not pursue this option. Finally, though the NOS is widely used and has been validated by expert opinion, it has substantial limitations, as noted by Stang [29]. Despite this, we felt the NOS was more appropriate for this investigation than other tools as it was specifically designed for nonrandomized, nonintervention observational studies.

Conclusion

While the results we present are provocative and in some cases statistically significant, we encourage readers to "turn back the dial" and view any association between UTI and UBC_{NS} as hypothesis generating. The heterogeneity and overall mediocre quality of the literature on bacterial UTI and future risk of bladder cancer limit its applicability to clinical medicine. Until future investigation can better control important confounders, such as smoking status, and consistently use a more stringent definition of UTI, the data we present here cannot substantiate earlier reports that bacterial infection of the urinary tract alone modifies risk for bladder cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent For this type of study formal consent is not required.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors.

Protocol registration This study protocol (2016:CRD42016053888) was developed prior to data collection according to PRISMA and PRISMA-P guidelines and registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053888.

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