

## URINARY TRACT INFECTION AND RISK OF BLADDER CANCER

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In an epidemiologic study of 2982 bladder carcinoma patients and 5782 population controls from 10 geographic areas of the United States, the role of urinary tract infection and inflammation in the etiology of this neoplasm was evaluated. A history of urinary tract infection significantly elevated the risk of bladder cancer, particularly in individuals who reported three or more infections (relative risk (RR) = 2.0). Significantly increased bladder cancer risk was also found for bladder stones (RR = 1.8), while kidney stones showed no relation. A history of three or more urinary tract infections was strongly related to squamous cell carcinoma in particular (RR = 4.8).

**bladder calculi; bladder neoplasms; diabetes mellitus; kidney calculi; urinary tract infections**

Several epidemiologic studies have suggested that infection or inflammation of the urinary tract may be a risk factor for cancer of the bladder. Two hospital-based case-control studies (1, 2) indicated that histories of cystitis and bladder stones were more frequent in bladder cancer patients than in controls. A recent population-based study of bladder cancer (3) has also reported an association with history of urinary tract infection, although the

risk of bladder cancer was lower when analysis was restricted to infections that occurred more than five years before interview.

Bladder cancer has been reported in excess among individuals who are prone to chronic cystitis, such as spinal cord injury patients (4-6). The proportion of tumors that are squamous cell carcinoma, or mixed with elements of both squamous and transitional cell carcinoma, appears to be especially high in these patients (7). A marked tendency toward squamous metaplasia in chronically infected bladders suggests a precursor stage in squamous cell carcinoma (8, 9). Bladder tumors associated with schistosomiasis in endemic areas of the world also tend to be squamous cell in origin (10).

Several mechanisms have been proposed to explain the association between infection and bladder cancer. For instance, urinary retention and stasis may increase exposure of the bladder to carcinogens in the urine (11). Chronic inflammation of the bladder may increase

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absorption of these carcinogens. Also, bacterial flora in the urine may contribute to the production of nitrites that are converted to carcinogenic nitrosamines (12–14). Alternatively, urinary tract infection may represent a complication of cancer during its early growth before clinical diagnosis.

To examine the role of urinary tract infection and inflammation as risk factors for bladder cancer, we analyzed data from a large population-based case-control interview study of bladder cancer, which was designed to assess the role of artificial sweeteners and other suspected factors in the risk of bladder cancer (15).

#### METHODS

Through the Surveillance, Epidemiology and End Results (SEER) Program and the New Jersey Cancer Registry, we identified residents of metropolitan Atlanta, Detroit, New Orleans, San Francisco, Seattle and the states of Connecticut, Iowa, New Jersey, New Mexico and Utah, aged 21–84, who were newly diagnosed with histologically proven carcinoma of the urinary bladder during a one-year period beginning in December 1977. Details of the study and methods are presented elsewhere (15). During the study period, 4045 eligible cases were identified and approached for interview, usually within 90 days of diagnosis; 3763 cases were alive at that time and 2982 agreed to be interviewed. The vast majority of tumors were histologically transitional cell carcinomas (97 per cent). Information on stage of bladder cancer at initial diagnosis was available from SEER records for 1777 interviewed cases.

Controls comprised an age- and sex-stratified random sample of the general populations in the 10 geographic areas, using a 2:1 frequency-matching ratio of controls to cases. Controls aged 21–64 were chosen from a census of individuals obtained through a random-digit dialing procedure, in which telephone numbers

were randomly selected from all residential telephones in each geographic area (98 per cent of cases also had telephones). Controls aged 65–84 were randomly selected from the enumeration of US citizens over age 65 obtained by the Health Care Financing Administration. Eighty-three per cent of the controls thus selected agreed to participate (5782 controls).

Structured questionnaires were administered through personal interviews conducted by trained interviewers in respondents' homes. Information obtained on urinary tract infections or stones that occurred more than one year before interview, and detailed lifetime histories of tobacco use and diabetes, were used in analyses presented here. Respondents were asked whether a bladder or kidney infection was ever diagnosed by a physician and, if so, whether this kind of infection occurred on at least three separate occasions.

The measure of association used was the maximum likelihood estimate of the relative risk. Potentially confounding variables were controlled through multiple contingency table analysis (16), and through multiple logistic regression analysis with bladder cancer as the outcome variable (17). Logistic regressions with exposure as the outcome variable (18) gave similar results to those presented here. Confidence intervals for individual risk estimates obtained through multiple contingency table analysis were calculated according to Gart (16).

#### RESULTS

*Urinary tract infection.* A history of urinary tract infection was reported by 775 cases (26 per cent) and 1076 controls (19 per cent), and was associated with a significantly elevated risk of bladder cancer (overall relative risk (RR) = 1.6; 95 per cent confidence interval (CI) 1.4–1.8). As seen in table 1, risks were similar for men and women, and rose to twofold in persons with a history of three or more infections.

TABLE 1  
Relative risks (RR) of bladder cancer associated with history of urinary tract infection,\* by number of infections; 10 geographic areas of the United States, 1978

No. of urinary tract infections	Males			Females		
	Cases	Controls	RR (95% confidence interval)	Cases	Controls	RR (95% confidence interval)
0	1758	3642	1.0†	398	979	1.0†
1 or 2	309	423	1.5 (1.3-1.8)	145	296	1.2 (0.9-1.5)
3+	146	152	2.0 (1.6-2.6)	176	206	2.1 (1.6-2.7)

\* Maximum likelihood estimate of relative risk adjusted for race, age, smoking status (never smoked, ex-smoker, current smoker).

† Reference category.

Multivariate analysis allowing for geographic area gave similar estimates to those in table 1. Relative risks were consistent by age.

Relative risk estimates were also examined according to pathologic stage of cancer at diagnosis (table 2). Relative risks were highest among individuals with advanced disease, although significant twofold increases in risk were observed in patients with early localized disease.

To explore the possibility that urinary tract infection enhances the association between bladder cancer and smoking by increasing the absorption or metabolism of tobacco-derived carcinogens in the urine, relative risk estimates were cal-

culated by usual adult pattern of cigarette use (table 3). There was no marked evidence of interaction between urinary tract infection and cigarette smoking; the joint effect of these two exposures was slightly beyond that expected under an additive (but not multiplicative) model, with the exception of persons in the most extreme category of exposures. (Risk estimates for current smokers and ex-smokers, and for men and women, were similar to those in table 3.)

**Bladder stones.** A history of bladder stones was reported by 82 cases (2.8 per cent) and 99 controls (1.7 per cent), and was associated with a significantly elevated risk of bladder cancer (table 4). Among individuals who reported no his-

TABLE 2  
Relative risks of bladder cancer associated with history of urinary tract infection,† by stage of cancer at diagnosis; 10 geographic areas of the United States, 1978

No. of urinary tract infections	Disease limited to bladder				Disease extending beyond bladder**
	Superficial		Invasion into musculature¶	Not otherwise specified	
	Confined to mucosa§	Extension into submucosa¹			
0‡	1.0	1.0	1.0	1.0	1.0
1 or 2	1.3*	1.1	1.1	1.3*	1.6
3+	1.8*	1.5*	1.9*	2.2*	4.8*
(No. of cases)	(471)	(284)	(225)	(658)	(109)

\*  $p < 0.05$ .

† Maximum likelihood estimate of relative risk adjusted for race, sex, age, smoking.

‡ Reference category.

§ Includes Jewett Stages O, A. (For definition of Jewett Stages, see references 24, 25.)

¹ Includes remaining Jewett Stage A.

¶ Jewett Stage B.

\*\* Jewett Stages C, D.

TABLE 3

Multivariate relative risk estimates of bladder cancer associated with history of urinary tract infection, by number of infections and cigarette smoking\*; 10 geographic areas of the United States, 1978

Pattern of cigarette use	No. of urinary tract infections		
	0	1 or 2	3+
Nonsmokers	1.0‡	1.4 (1.1–1.7)	2.0 (1.5–2.7)
Smokers†			
<20 cigarettes/day	1.8 (1.5–2.1)§	2.7 (2.1–3.5)	4.3 (3.0–6.0)
20–39 cigarettes/day	2.6 (2.2–2.9)	3.3 (2.6–4.1)	5.6 (4.1–7.5)
40+ cigarettes/day	2.6 (2.1–3.1)	3.9 (2.6–5.8)	2.8 (1.7–4.6)

\* Multivariate analysis allowing for sex, race, age, geographic area, history of urinary tract stones.

† Smoker refers to current or ex-smoker. Number of cigarettes per day refers to usual adult pattern of use.

‡ Reference category.

§ 95% confidence interval in parentheses.

TABLE 4

Relative risks (RR) of bladder cancer associated with history of bladder stones, by history of urinary tract infection\*; 10 geographic areas of the United States, 1978

History of bladder stones or urinary tract infection	Cases	Controls	RR (95% confidence interval)
No history of urinary tract infection			
No history of bladder stones	2110	4560	1.0
Positive history of bladder stones	40	52	1.8 (1.1–2.8)
Positive history of urinary tract infection			
No history of bladder stones	730	1024	1.6 (1.4–1.8)
Positive history of bladder stones	42	47	2.0 (1.3–3.2)

\* Maximum likelihood estimate of relative risk adjusted for race, sex, age and smoking; relative to persons with no history of either condition.

tory of urinary tract infection, the relative risk of bladder cancer associated with bladder stones was 1.8.

**Kidney stones.** The role of kidney stones in bladder cancer was assessed in individuals who reported no urinary tract infections or bladder stones. Kidney stones were not associated with an increased risk of bladder cancer (RR = 1.0 adjusted for sex, race and age).

**Diabetes.** Diabetes mellitus was evaluated in view of its known predisposition to urinary tract infection (23). A history of diabetes was associated with a small but statistically significant increase in bladder cancer risk (RR = 1.21 adjusted

for sex, race, age, smoking; 95 per cent CI 1.0–1.4). This risk was unrelated to the severity or duration of diabetes. Cigarette smoking was a confounding variable for this association, since a greater proportion of diabetics were ex-smokers or never smoked compared with nondiabetics: the relative risk of bladder cancer uncontrolled for smoking was 1.16 and was not statistically significant. When urinary tract infection was included as a controlling variable, the bladder cancer risk associated with diabetes remained the same.

**Squamous cell carcinoma.** In view of reported excesses of squamous cell carci-

TABLE 5  
*Relative risks (RR) of squamous cell carcinoma of the bladder associated with history and number of urinary tract infections\*; 10 geographic areas of the United States, 1978*

No. of urinary tract infections	No. of cases	RR (95% confidence interval)
0	21	1.0
1 or 2	7	1.9 (0.7-4.8)
3+	10	4.8 (1.9-11.5)

\* Maximum likelihood estimate of relative risk adjusted for sex, age and smoking; relative to 0 urinary tract infections.

noma of the bladder in patients with chronic bladder infection (7), we examined data for the 39 patients with this histologic type in the series (1.3 per cent of all cases). As shown in table 5, the risks of squamous cell carcinoma associated with urinary tract infection were generally higher than those found for the entire series. The relative risk was nearly five-fold among individuals with three or more infections, and was statistically significant. While the tumor was beyond the localized stage in 36 per cent of these patients (compared with 7 per cent for the entire case series), risks associated with infection were not related to stage of disease (overall RR = 3.4 in patients with localized disease versus 3.7 in patients with regional or distant disease). Among individuals who reported no history of urinary tract infection, the relative risk of squamous cell carcinoma associated with bladder stones was 4.4 (adjusted for sex) but was not statistically significant.

#### DISCUSSION

This population-based case-control study confirms the association between bladder cancer and history of urinary tract infection. Risks of bladder cancer increased with number of infections among both men and women. The association between bladder cancer and urinary tract infection was most pronounced in patients with advanced cancer, which suggests that infection may be a premonitory

sign of some bladder tumors or related to more aggressive disease. In addition, information regarding the year in which each infection occurred was not available and thus prevented examination of the temporal aspect of this relationship. Nevertheless, a causal role for infection may be supported by the moderately increased risk that was observed in patients with early-stage cancer and, if confirmed in future studies, might implicate the role of factors such as antibiotic drugs or nitrosamine formation in bladder infections (12, 13). The slight evidence of moderate interaction observed between urinary tract infection and cigarette smoking was not uniformly consistent but may suggest that patients with cystitis may be especially prone to tobacco-derived carcinogens in the urine (19, 20) (perhaps through increased exposure or penetration into bladder epithelium or through metabolism by bacterial flora), although analyses were unable to allow for time relationships between episodes of infection and smoking pattern.

We were also able to confirm an association between bladder cancer and bladder stones. The relationship was not due to urinary tract infection, which may have accompanied an episode of bladder stones, and is unlikely to be explained by recall bias since no increase in risk was observed for kidney stones. The results suggest that factors associated with inflammation of the bladder, or bladder stone formation, are etiologically relevant.

The modest increase in bladder cancer risk among diabetics was not explained by their susceptibility to urinary tract infection. Differences between diabetics and nondiabetics in cigarette use illustrated the relevance of statistical control for its confounding effect when examining other risk factors in this group of patients (21, 22).

Squamous cell carcinoma of the bladder, although accounting for less than 2 per cent of all cases in this series,

was strongly associated with a history of urinary tract infection. This is consistent with the high frequency of squamous cell cancers of the bladder among patients with spinal cord injury and chronic cystitis, or with schistosomal infections of the bladder, and is likely to represent a causal relationship.

In summary, these results show a positive association between urinary tract infection and bladder cancer, particularly squamous cell carcinoma. However, our study was unable to examine temporal relationships and interaction with other exposures in establishing a causal relationship with transitional cell carcinomas. Further epidemiologic and laboratory studies aimed at exploring these findings may help in delineating mechanisms of bladder carcinogenesis.

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