



## History of Urinary Tract Infection and Risk of Renal Cell Carcinoma

Alexander S. Parker<sup>1</sup>, James R. Cerhan<sup>1</sup>, Charles F. Lynch<sup>2</sup>, Bradley C. Leibovich<sup>3</sup>, and Kenneth P. Cantor<sup>4</sup>

<sup>1</sup> Department of Health Sciences Research, Mayo Clinic, Rochester, MN.

<sup>2</sup> Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA.

<sup>3</sup> Department of Urology, Mayo Clinic, Rochester, MN.

<sup>4</sup> Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

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Limited data exist regarding whether a history of urinary tract infection (UTI) increases risk of developing renal cell carcinoma (RCC). Furthermore, it is unclear whether any association of RCC with a history of UTIs is modified by known risk factors for RCC (i.e., smoking, obesity). The authors report data from a 1986–1989 population-based case-control study in Iowa. RCC cases (233 males, 139 females) were identified through the Iowa Cancer Registry; controls (1,497 males, 751 females) were randomly selected from the general population, frequency matched on age and sex. Subjects provided detailed information on demographic, anthropometric, lifestyle, dietary, and medical history risk factors. In age-adjusted analysis, risk increased for subjects who self-reported a history of physician-diagnosed kidney or bladder infection (odds ratio (OR) = 1.9, 95% confidence interval (CI): 1.5, 2.5) compared with those reporting no such history. Both sex and smoking status modified the risk of RCC associated with a history of UTI, with the strongest risk reported for males (OR = 2.7, 95% CI: 1.9, 3.8) and current smokers (OR = 4.3, 95% CI: 2.7, 6.7). The strongest risk was reported for male current smokers with a history of UTI (OR = 9.7, 95% CI: 5.0, 18.1). Multivariate adjustment for anthropometric, lifestyle, and dietary factors did not alter these findings. Results suggest a positive association of UTI history with RCC development, with elevated risks most notable for males with a history of smoking.

carcinoma, renal cell; case-control studies; smoking; urinary tract infections

Abbreviations: CI, confidence interval; OR, odds ratio; RCC, renal cell carcinoma; UTI, urinary tract infection.

The etiology of renal cell carcinoma (RCC) remains largely unexplained. Although smoking, obesity, and hypertension are widely considered the primary risk factors for RCC, it has been estimated that these three factors account for less than one half of the RCCs diagnosed in the United States (1, 2). Thus, there is a need to identify additional independent risk factors associated with the development of RCC.

A history of urinary tract infection (UTI) is currently accepted as an independent risk factor for developing bladder cancer (3), and such a history could also play a role in the development of RCC. To date, however, only a limited number of epidemiologic studies have reported data regarding whether a history of UTI increases the risk of developing RCC. To complicate matters further, the data are

inconsistent, with some investigators suggesting a positive association (4, 5) and others suggesting no association (6, 7). To our knowledge, no attempt has been made to address the question of whether other known risk factors for RCC (i.e., smoking, obesity, and hypertension) could modify an association that may exist between a history of UTI and RCC.

In the current study, we estimated the association of a history of UTI with RCC development after adjustment for accepted and other possible risk factors for RCC. In addition, we addressed the issue of whether the effect of a history of UTI on RCC development is modified by other well-known risk factors for RCC including sex, smoking, obesity, and a history of hypertension. To do so, we used data from a population-based case-control investigation conducted in Iowa from 1986 to 1989.

Correspondence to Dr. Alexander S. Parker, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (e-mail: parker.alexander@mayo.edu).

## MATERIALS AND METHODS

### Study population

Details of this case-control study have been reported previously (8). Briefly, we conducted a population-based case-control investigation of cancer occurrence at six anatomic sites (pancreas, bladder, kidney, brain, colon, and rectum). The state of Iowa was chosen as the location for this study in part because of the availability of cancer incidence data from the Iowa Cancer Registry, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (9). Eligible cases were residents of the state of Iowa, aged 40–85 years, and newly diagnosed with histologically confirmed RCC. Cases with a prior diagnosis of a malignant neoplasm, except basal and squamous cell carcinomas of the skin, were excluded. Eligible cases were identified from 1985 to 1987 by the Iowa Cancer Registry, with supplementation by a rapid reporting system in 1987. Of 463 eligible RCC cases, 406 (88 percent) cases or proxies completed mailed questionnaires ( $n = 379$ ) or abbreviated telephone interviews ( $n = 27$ ). Of the 406 subjects, 218 RCC cases were direct respondents, 112 were proxies, and 76 were not determined. It is likely that most of these 76 subjects were self-respondents, since 1) they requested a questionnaire whose wording was designed for direct respondents (prior to inclusion of the relevant question about proxy completion), and 2) among those who were sent a later version of this questionnaire with the proxy question, only 11 percent indicated that it was completed by someone other than the subject.

Controls for this investigation were frequency matched to cases by sex and 5-year age group. Controls younger than age 65 years were randomly selected from computerized state driver's license records, whereas controls aged 65 years or older were selected randomly from listings provided by the US Health Care Financing Administration (HCFA). Each of these selection rosters has been shown to achieve greater than 95 percent coverage of the intended underlying population (10, 11). Similar to the cases enrolled in this study, controls with a history of cancer, except nonmelanoma skin cancer, were excluded. Of the controls younger than age 65 years, we selected 999 eligible subjects from state driver's license listings; 817 (81.8 percent) participated, 66 (8 percent) with an abbreviated telephone interview. Of 2,034 eligible controls aged 65 years or older selected from Health Care Financing Administration listings, 1,615 (79.5 percent) participated, 128 (8 percent) with an abbreviated telephone interview. Of the 2,432 controls sent direct respondent questionnaires, 2,064 questionnaires were completed by the subject, 241 were completed by another person (proxy), and 127 controls were not asked who had completed the form. As for the cases, most of these 127 questionnaires were likely completed by the study subject.

### Data collection

Data for this study were collected by using a mailed questionnaire supplemented by a telephone interview. The questionnaire assessed major and proposed RCC risk factors including demographics, anthropometric measures at

various times in life, smoking history and status, medical history (including self-report of a physician-diagnosed history of hypertension), reproductive factors, occupational history, usual physical activity (nonoccupational), and family history of cancer. Also included in the questionnaire was a 55-item food frequency section.

Information regarding a history of UTI was ascertained in the health history section of the questionnaire. Subjects were asked to report whether a physician had ever told them that they had a bladder or kidney infection. Subjects were asked not to include diagnoses of UTI that had occurred in the past year. No data were collected on the frequency, severity, or timing of UTI diagnoses.

### Statistical analysis

In our analysis, a history of UTI was treated as a dichotomized exposure variable (yes, no). Odds ratios and 95 percent confidence intervals were used to estimate the association of a history of UTI with RCC. We used unconditional logistic regression to estimate both age-adjusted as well as multivariate-adjusted odds ratios. Decisions regarding confounding factors in multivariate analysis were based on 1) whether the covariate is an accepted risk factor for RCC, 2) whether the covariate was associated with a history of UTI (among controls only) and RCC development in our data set, and 3) what effect inclusion of the particular covariate had on the risk estimate for a history of UTI. Covariates considered in the final multivariate model included age (continuous), sex, pack-years of smoking (none, 1–19, 20–39,  $\geq 40$ ), body mass index ( $< 24$  kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>,  $> 30$  kg/m<sup>2</sup>), alcohol consumption (none,  $< 35$  g/week,  $\geq 35$  g/week; 35 g/week = median split among users), and history of physician-diagnosed hypertension (yes, no) before the prior year. Tests for interaction with other known risk factors for RCC (sex, body mass index, smoking, and hypertension) were conducted by including interaction terms, along with the appropriate main effects, in logistic regression models and then reporting the Wald chi-square  $p$  value for the interaction term. We also assessed the potential for interaction by conducting stratified analysis on each covariate and comparing the resulting risk estimates for UTI.

To address the issue of whether proxy reporting could affect our results, we also conducted a separate analysis in which we removed data provided by any next-of-kin respondents. The results did not differ between the two methods; therefore, in this paper, we report findings including all respondents only. All statistical analyses were performed by using the PROC LOGISTIC procedure in SAS software, version 8.0 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

After we excluded subjects for whom information on history of UTI was lacking (34 cases, 184 controls), 372 RCC cases and 2,248 controls were available for this analysis. Table 1 includes mean values (standard deviation) or percentages of potential confounding factors for the controls with or without a history of UTI. Those with a history of UTI were slightly older, more likely to be female, and more likely

**TABLE 1. Mean value (standard deviation) or percentage of potential confounding factors by history of UTI\* among controls, Iowa, 1986–1989**

| Factor                               | No history of UTI<br>(n = 1,708) | History of UTI<br>(n = 540) | p value† |
|--------------------------------------|----------------------------------|-----------------------------|----------|
| Age (years)                          | 68 (9.9)                         | 69 (9.6)                    | 0.06     |
| Red meat (servings/week)‡            | 10.0 (7.5)                       | 8.9 (6.4)                   | 0.01     |
| Fruit (servings/week)‡               | 16.8 (11.8)                      | 18.7 (15.4)                 | 0.02     |
| Vegetables (servings/week)‡          | 26.6 (14.9)                      | 28.1 (15.9)                 | 0.09     |
| Sex                                  |                                  |                             |          |
| Male                                 | 73                               | 44                          |          |
| Female                               | 27                               | 56                          | <0.0001  |
| Body mass index (kg/m <sup>2</sup> ) |                                  |                             |          |
| <24                                  | 36.3                             | 41.0                        |          |
| 24–30                                | 30.9                             | 29.5                        |          |
| >30                                  | 32.8                             | 29.5                        | 0.15     |
| Cigarette smoking status             |                                  |                             |          |
| Never                                | 39.8                             | 51.4                        |          |
| Former                               | 39.0                             | 33.0                        |          |
| Current                              | 21.2                             | 15.6                        | 0.0013   |
| History of hypertension              |                                  |                             |          |
| No                                   | 66.0                             | 55.1                        |          |
| Yes                                  | 34.0                             | 44.9                        | <0.0001  |
| Alcohol consumption (g/week)         |                                  |                             |          |
| None                                 | 48.9                             | 52.5                        |          |
| <35                                  | 23.6                             | 28.0                        |          |
| ≥35                                  | 27.5                             | 19.5                        | 0.001    |
| Family history of kidney cancer      |                                  |                             |          |
| No                                   | 98.6                             | 98.7                        |          |
| Yes                                  | 1.4                              | 1.2                         | 0.8      |

\* UTI, urinary tract infection.

† Either global test for differences among means or chi-square test for differences in proportions, as appropriate.

‡ Adjusted for total energy intake.

to report never smoking than those without a history of UTI. In addition, subjects with a history of UTI were more likely to report a history of hypertension. Conversely, those with a history of UTI were less likely to report drinking more than 35 g of alcohol a week (35 g/week = median level among controls who reported consuming alcohol). Small differences were noted between those controls with and those without a history of UTI for levels of red meat, fruit, and vegetable consumption. Finally, no differences were noted between the two exposure groups for usual adult body mass index or family history of kidney cancer.

After adjusting for age, we found evidence of a positive association between a history of UTI and development of RCC (odds ratio (OR) = 1.9, 95 percent confidence interval (CI): 1.5, 2.5) (table 2). This association remained apparent after multivariate adjustment for age, sex, usual adult body mass index, pack-years of smoking, alcohol consumption, and hypertension (OR = 1.8, 95 percent CI: 1.4, 2.3). Further adjustment for family history of kidney cancer, physical activity, and dietary consumption of red meat, fruits, and vegetables did not modify the results (data not shown).

Statistical evidence of an interaction with history of UTI was noted for sex ( $p = 0.006$ ) and smoking status ( $p = 0.001$ ) but not for usual adult body mass index ( $p = 0.9$ ) or a history of hypertension ( $p = 0.5$ ). Stratified analysis confirmed the lack of interaction with usual adult body mass index and hypertension (data not shown). The risk associated with UTI was stronger for males (OR = 2.7, 95 percent CI: 1.9, 3.8) than females (OR = 1.3, 95 percent CI: 0.9, 1.9) (table 2). Multivariate adjustment did not significantly alter the risk estimates associated with history of UTI for either sex. Table 3 presents estimates of the joint effect of smoking status (never, former, current) and history of UTI on RCC development. When we compared nonsmokers with no history of UTI with smokers, the strongest evidence of a positive association with RCC development was limited to those former and current smokers with a history of UTI (OR = 2.3, 95 percent CI: 1.5, 3.4 and OR = 4.3, 95 percent CI: 2.7, 6.7, respectively). Multivariate adjustment did not significantly alter the risk estimates. Of interest, we also constructed a joint-effects table for history of UTI and pack-years of smoking (table 4) and noted results similar to those shown in

**TABLE 2. Risk of renal cell carcinoma associated with a self-reported history of physician-diagnosed UTI,\* Iowa, 1986–1989**

| History of UTI | Cases (no.) | Controls (no.) | OR*,† | 95% CI*  | OR‡ | 95% CI   |
|----------------|-------------|----------------|-------|----------|-----|----------|
| Overall        |             |                |       |          |     |          |
| No             | 246         | 1,755          | 1.0   |          | 1.0 |          |
| Yes            | 126         | 493            | 1.9   | 1.5, 2.5 | 1.8 | 1.4, 2.3 |
|                |             |                |       |          | OR§ | 95% CI   |
| Males          |             |                |       |          |     |          |
| No             | 167         | 1,278          | 1.0   |          | 1.0 |          |
| Yes            | 66          | 219            | 2.7   | 1.9, 3.8 | 2.5 | 1.8, 3.5 |
| Females        |             |                |       |          |     |          |
| No             | 79          | 477            | 1.0   |          | 1.0 |          |
| Yes            | 60          | 274            | 1.3   | 0.9, 1.9 | 1.2 | 0.8, 1.8 |

\* UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.

† Adjusted for age.

‡ Adjusted for age, sex, body mass index (<24 kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>, >30 kg/m<sup>2</sup>), pack-years of smoking (none, 1–19, 20–39, ≥40), history of hypertension (yes, no), and alcohol consumption (none, <35 g/week, ≥35 g/week).

§ Adjusted for age, body mass index (<24 kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>, >30 kg/m<sup>2</sup>), pack-years of smoking (none, 1–19, 20–39, ≥40), history of hypertension (yes, no), and alcohol consumption (none, <35 g/week, ≥35 g/week).

table 3, namely that the positive association with RCC development appeared to be limited to smokers with a history of UTI.

Finally, given our reporting of an interaction of history of UTI with both sex and smoking status, we generated a single summary table to display the effect of all three of these variables on RCC development. Table 5 reports the joint effect of history of UTI and smoking status on RCC development stratified by sex. For females, the only evidence of an increase in risk of RCC was for current smokers with a history of UTI (OR = 2.2, 95 percent CI: 1.2, 4.1). Conversely, for males, there was evidence of a positive association for smokers (former and current) both with and without a history of UTI. However, the association was

noticeably more pronounced for male current smokers with a history of UTI (OR = 9.7, 95 percent CI: 5.0, 18.1).

## DISCUSSION

Data from this population-based case-control investigation support a positive association of a history of UTI with RCC development even after adjustment for other known and suspected risk factors for RCC. In our study, a history of UTI was defined as having one or more physician-diagnosed kidney or bladder infections. Furthermore, our data suggest evidence of an interaction of history of UTI with both sex and cigarette smoking. The largest risk estimates were reported for male smokers with a history of UTI. Given that

**TABLE 3. Joint effect of smoking status and self-reported history of physician-diagnosed UTI\* on risk of renal cell carcinoma, Iowa, 1986–1989**

| History of UTI | Smoking status | Cases (no.)† | Controls (no.)† | OR*,‡ | 95% CI*   | OR§ | 95% CI    |
|----------------|----------------|--------------|-----------------|-------|-----------|-----|-----------|
| No             |                |              |                 |       |           |     |           |
|                | Never          | 82           | 669             | 1.0   | Reference | 1.0 | Reference |
|                | Former         | 82           | 656             | 1.1   | 0.8, 1.5  | 1.2 | 0.8, 1.6  |
|                | Current        | 68           | 356             | 1.3   | 0.9, 1.9  | 1.5 | 1.1, 2.2  |
| Yes            |                |              |                 |       |           |     |           |
|                | Never          | 41           | 246             | 1.4   | 0.9, 2.1  | 1.3 | 0.8, 1.9  |
|                | Former         | 40           | 158             | 2.3   | 1.5, 3.4  | 2.2 | 1.4, 3.4  |
|                | Current        | 43           | 75              | 4.3   | 2.7, 6.7  | 4.3 | 2.9, 7.3  |

\* UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.

† Lower numbers are due to missing data on smoking status (cases:  $n = 16$ , controls:  $n = 88$ ).

‡ Adjusted for age.

§ Adjusted for age, sex, body mass index (<24 kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>, >30 kg/m<sup>2</sup>), pack-years of smoking (none, 1–19, 20–39, ≥40), history of hypertension (yes, no), and alcohol consumption (none, <35 g/week, ≥35 g/week).

**TABLE 4. Joint effect of pack-years of smoking and self-reported history of physician-diagnosed UTI\* on risk of renal cell carcinoma, Iowa, 1986–1989**

| History of UTI | Pack-years of smoking (no.) | Cases (no.)† | Controls (no.)† | OR*,‡ | 95% CI*   | OR§ | 95% CI    |
|----------------|-----------------------------|--------------|-----------------|-------|-----------|-----|-----------|
| No             |                             |              |                 |       |           |     |           |
|                | Never                       | 82           | 669             | 1.0   | Reference | 1.0 | Reference |
|                | 1–19                        | 32           | 266             | 0.9   | 0.6, 1.5  | 1.0 | 0.7, 1.6  |
|                | 20–39                       | 41           | 267             | 1.2   | 0.8, 1.8  | 1.4 | 0.9, 2.2  |
|                | ≥40                         | 76           | 475             | 1.3   | 0.9, 1.8  | 1.5 | 1.0, 2.1  |
| Yes            |                             |              |                 |       |           |     |           |
|                | Never                       | 41           | 246             | 1.4   | 0.9, 2.1  | 1.2 | 0.8, 1.9  |
|                | 1–19                        | 16           | 64              | 2.1   | 1.1, 3.8  | 2.2 | 1.2, 4.1  |
|                | 20–39                       | 19           | 69              | 2.2   | 1.3, 3.9  | 2.2 | 1.3, 4.0  |
|                | ≥40                         | 45           | 99              | 3.9   | 2.5, 5.9  | 4.1 | 2.6, 6.4  |

\* UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.

† Lower numbers are due to missing data on pack-years of smoking (cases:  $n = 20$ , controls:  $n = 93$ ).

‡ Adjusted for age.

§ Adjusted for age, sex, body mass index (<24 kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>, >30 kg/m<sup>2</sup>), history of hypertension (yes, no), and alcohol consumption (none, <35 g/week, ≥35 g/week).

this is the first known investigation of RCC etiology to report an interaction of UTI history with smoking status, caution is necessary in interpreting this result until it has been replicated, because we cannot completely rule out the role of chance.

Data regarding the association of a history of UTI with RCC have been reported by investigators from four case-control studies. Comparisons of our data with those from these existing studies should be made with caution since most existing studies report risks associated with infections of the kidney specifically. Using data from a population-based case-control study in Minnesota, McLaughlin et al. (4) reported an increased risk of RCC associated with a history of kidney infection for both males (OR = 2.8, 95 percent CI: 1.3, 5.7) and females (OR = 2.2, 95 percent CI: 1.1, 4.4) after

adjustment for age, cigarette smoking, and weight (females only). Similar results of a positive association were reported from a case-control study conducted by using members of a large medical care program in Northern California (5). Both males (OR = 5.5, 95 percent CI: 1.2, 25.7) and females (OR = 2.2, 95 percent CI: 0.3, 15.8) who had a history of kidney infection were at increased risk of RCC. However, because of missing data on approximately 30 percent of the subjects and a low overall prevalence of kidney infections, risk estimates were unstable for both sexes. Studies suggesting no association of kidney infection with RCC also exist. Investigators from a large, international case-control study of RCC reported only limited evidence of an increased risk of RCC for those with a history of kidney infections (OR = 1.2, 95 percent CI: 0.8, 1.5) (6). Similarly, authors of a population-

**TABLE 5. Joint effect of smoking status and self-reported history of physician-diagnosed UTI\* on risk of renal cell carcinoma stratified by sex, Iowa, 1986–1989**

| History of UTI | Smoking status | Males       |                |       |           |      |           | Females     |                |     |           |     |           |
|----------------|----------------|-------------|----------------|-------|-----------|------|-----------|-------------|----------------|-----|-----------|-----|-----------|
|                |                | Cases (no.) | Controls (no.) | OR*,† | 95% CI*   | OR‡  | 95% CI    | Cases (no.) | Controls (no.) | OR† | 95% CI    | OR‡ | 95% CI    |
| No             |                |             |                |       |           |      |           |             |                |     |           |     |           |
|                | Never          | 29          | 348            | 1.0   | Reference | 1.0  | Reference | 53          | 321            | 1.0 | Reference | 1.0 | Reference |
|                | Former         | 72          | 584            | 1.7   | 1.1, 2.6  | 1.6  | 1.0, 2.6  | 10          | 72             | 0.8 | 0.4, 1.7  | 1.0 | 0.5, 2.2  |
|                | Current        | 52          | 272            | 2.0   | 1.2, 3.3  | 2.1  | 1.3, 3.5  | 16          | 84             | 1.0 | 0.5, 1.8  | 1.1 | 0.6, 2.2  |
| Yes            |                |             |                |       |           |      |           |             |                |     |           |     |           |
|                | Never          | 6           | 56             | 1.6   | 0.6, 4.1  | 1.4  | 0.5, 3.7  | 35          | 190            | 1.1 | 0.7, 1.7  | 1.1 | 0.7, 1.7  |
|                | Former         | 33          | 117            | 4.1   | 2.3, 7.0  | 3.7  | 2.1, 6.5  | 7           | 41             | 1.1 | 0.4, 2.5  | 1.0 | 0.4, 2.5  |
|                | Current        | 25          | 32             | 9.7   | 5.0, 18.1 | 10.1 | 5.1, 19.8 | 18          | 43             | 2.2 | 1.2, 4.1  | 2.5 | 1.2, 4.8  |

\* UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.

† Adjusted for age.

‡ Adjusted for age, body mass index (<24 kg/m<sup>2</sup>, 24–30 kg/m<sup>2</sup>, >30 kg/m<sup>2</sup>), pack-years of smoking (none, 1–19, 20–39, ≥40), history of hypertension (yes, no), and alcohol consumption (none, <35 g/week, ≥35 g/week).

based case-control study in Australia reported no association of a history of kidney infection with RCC but did report evidence of a positive association with cancer of the renal pelvis (7).

Cohort studies of an association of UTI history with RCC are extremely limited. Chow et al. (12) reported on the risk of RCC in a population-based cohort of patients hospitalized for kidney or ureteral stones in Sweden from 1965 to 1983 ( $n = 61,144$ ). After 25 years of follow-up, standardized incidence ratios did not suggest an increase in risk of RCC for this cohort of patients. Of more interest to our findings, Chow et al. (12) also reported no increase in risk of RCC for the subset of cohort patients who had a UTI at their index visit. Interestingly, the risk of both bladder and renal pelvis cancer was increased for these same patients who were diagnosed with a UTI at their index visit. To our knowledge, no additional data from cohort investigations exist regarding an association of a history of UTI with RCC.

It is well accepted that bacteria are the primary cause of UTIs, with the vast majority (70–80 percent) attributed specifically to infection with *Escherichia coli* (13, 14). To date, the involvement of bacteria in carcinogenesis remains controversial (15) because, in part, of a lack of agreement on potential molecular mechanisms. One theory linking bacterial infection and cancer development suggests that the increased inflammation associated with bacterial infections can generate reactive oxygen and nitrogen intermediates that could lead to direct DNA damage (16, 17). It has also been argued that bacterial infections could be linked to cancer development because such infections are known to promote cell proliferation, produce toxins that directly modulate intracellular signaling pathways, and even suppress apoptosis in host cells. Of particular interest, many uropathogenic *E. coli* species produce a toxin known as cytotoxic necrotizing factor, which has been shown to induce elevated expression levels of cyclooxygenase-2 in murine fibroblasts (18). The cyclooxygenase-2 enzyme has gained recent interest because it is overexpressed in many human cancers and has been linked to increased tumor invasiveness via overexpression of *bcl-2* and suppression of apoptosis. Data from animal and human studies suggest that a portion of RCCs overexpress cyclooxygenase-2 (19, 20). An interesting question, but one we were unable to address, is whether the association of UTI with RCC that we report here is apparent only for RCCs in which overexpression of the cyclooxygenase-2 enzyme is evident.

To our knowledge, our reporting of an interaction between a history of UTI and smoking is novel and will require corroboration. Interestingly, Kantor et al. (21) reported evidence of a similar interaction regarding risk of bladder cancer in a large, population-based case-control study. The authors suggested that persons with a history of bladder infection could be especially prone to tobacco-derived carcinogens in the urine, perhaps through increased penetration into the bladder epithelium. An analogous situation could also exist for smokers with a history of UTI who develop RCC. It has also been reported that persons who experience UTI excrete higher levels of nitrate, a precursor to carcinogenic nitrosamines, in their urine (22, 23). Cigarette smoke is also known to contain nitrosamines (24), and

these carcinogens have been linked to RCC development in laboratory animals (25, 26). Therefore, it could be argued that the synergistic effect found in our study for UTI history and smoking is a result of an increase in a nitrosamine-specific pathway for RCC development.

There are alternative explanations for our study findings. The possibility exists that, compared with the relatively healthy controls, cases were more likely to correctly recall a history of UTI. Although this differential misclassification by disease status could indeed result in an artificially positive association, the likelihood that such errors in reporting could be solely responsible for generating risk estimates as strong as we report here is questionable. Furthermore, the modifying effects of sex and smoking status in our data reduce the likelihood that this type of reporting error could fully explain our results. Our lack of data on the timing of UTI precluded us from eliminating the possibility that the occurrence of UTI may have been a consequence of early RCC rather than the cause. Finally, detection bias (or medical surveillance bias) could explain our results given that subjects with recurrent UTI might have had greater contact with the medical system and therefore an increased potential for being diagnosed with RCC, especially subclinical disease. To address this issue, we conducted analysis by stratifying our cases into localized and regional/distant disease using information available from the Surveillance, Epidemiology, and End Results program registry. The magnitude of the effect for history of UTI was greater for localized disease (OR = 2.2, 95 percent CI: 1.6, 3.4) compared with regional/distant disease (OR = 1.7, 95 percent CI: 1.2, 2.2). However, given that the risk remained elevated for regional/distant disease, it would appear that detection bias did not completely explain our observed association.

Strengths of this study include the use of a Surveillance, Epidemiology, and End Results tumor registry to ascertain cases, a randomly selected control population representative of the population at large, and high participation rates among both cases and controls. Additional strengths over previous investigations are our ability to adequately adjust for a wide variety of potential confounding factors and the relatively high prevalence of UTI among study subjects. Limitations include our reliance on self-reported history of physician-diagnosed UTI with no confirmation from medical records. Furthermore, our lack of data on number, timing, and severity of infection prohibited assessment of dose response or issues regarding relevant temporality of the infection. To adequately address this limitation, future investigations should collect information on infection timing and severity. Finally, given the fact that 99 percent of the participants in our study were White, the current results may have limited generalizability to other racial/ethnic groups.

In this population-based case-control investigation, we found evidence of an association of history of UTI with RCC. Our ability to show that this association remained after multivariate adjustment for several confounding factors (i.e., body mass index, hypertension, diet, physical activity, family history, alcohol consumption) strengthens support for a true association. Our data are consistent with those from earlier investigations suggesting that the risk associated with

UTI history may be more pronounced for men than women. The interaction with smoking is novel and needs confirmation.

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