Does increased urination frequency protect against bladder cancer?

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Our purpose was to evaluate the effect of urination frequency on risk of urothelial (transitional cell) carcinoma of the bladder in a large, multicenter case–control study of bladder cancer.

Material and methods

We conducted a hospital-based case–control study in 5 areas of Spain. The case series included all patients with histologically confirmed carcinoma of the urinary bladder or carcinoma in situ (International Classification of Diseases 9 = 1880–1889; 2,337) newly diagnosed in 1998–2001 who were 21–80 years of age at the time of diagnosis/interview and resided in the catchment areas of 18 hospitals in 5 areas of Spain (i.e., Barcelona, Valles/Bages, Asturias, Alicante and Tenerife). Patients with a previous diagnosis of cancer of the lower urinary tract (i.e., bladder, renal pelvis, ureters or urethra) were not eligible for study. Diagnostic slides for each patient were reviewed by a panel of expert pathologists to confirm the diagnosis of bladder cancer and ensure uniformity of classification criteria based on the 1998 World Health Organization/International Society of Urological Pathology system as well as the histologic subtype. Of the 1,453 patients found to be eligible for study, we interviewed 1,219 (84%).

For each eligible case, we selected 1 control matched to the case on age at diagnosis/interview (within 5 years), gender, race/ethnicity and hospital. Controls were identified from patients admitted to the same hospital as the case for diseases/conditions unrelated to the exposures under investigation including urination frequency. Reasons for hospital admission were: 36% hernias, 12% other abdominal surgery, 24% fractures, 11% hydrocele, 6% orthopedic conditions, 4% circulatory diseases, 2% dermatological diseases, 1% ophthalmological diseases and 4% other diagnoses). Of the 1,442 controls found to be eligible for study, we interviewed 1,271 (88%).

Experimental evidence suggests that if carcinogens are present in the urine, increased urination frequency may reduce bladder cancer risk if carcinogens are present in the urine. Only 2 small studies of the effect of increased urination frequency on bladder cancer risk in humans have been conducted with conflicting results. Our purpose was to evaluate the effect of increased urination frequency on risk of bladder cancer in a large, multicenter case–control study. We analyzed data based on interviews conducted with 884 patients with newly diagnosed, bladder cancer and 996 controls from 1998 to 2001 in Spain. We observed a consistent, inverse trend in risk with increasing nighttime voiding frequency in both men ($p = 0.0003$) and women ($p = 0.07$); voiding at least 2 times per night was associated with a significant, 40–50% risk reduction. The protective effect of nocturia was apparent among smokers who did not urinate at night, current smokers who did not urinate at night had an OR of 7.0 (95% CI = 4.7–10.2), whereas those who voided at least twice per night had an OR of 3.3 (95% CI = 1.9–5.8) ($p$ value for trend = 0.0005). Our findings suggest a strong protective effect of nocturia on bladder cancer risk, providing evidence in humans that the time of contact with carcinogens in urine is increased urination frequency, coupled with possible dilution of the urine from increased water intake, may diminish the effect of urinary carcinogens on bladder cancer risk.

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Experimental studies suggest that if carcinogens are present in the urine, frequent urination may reduce bladder cancer risk. Three lines of limited evidence support this hypothesis. First, dogs exposed to the bladder carcinogen 2-naphthylamine who have undergone surgical diversion of the urine do not develop tumors in the part of the bladder with no urine contact. Second, dogs administered the bladder carcinogen 4-aminobiphenyl and catheterized to regulate urination frequency have decreased levels of urothelial DNA adducts with increased urination frequency. Third, urine appears to be a promoter of bladder carcinogenesis in rat. A protective effect of increased urinary frequency is further supported by the results of 2 observational studies. In high-risk areas for bladder cancer in Israel, infrequent micturition and high urine concentration were more prevalent than in low-risk areas. In Serbia, a significant protective effect was associated with increased urination frequency based on 130 cases and 130 controls in a hospital-based case–control study. This study had a number of limitations, however, including small sample size and minimal information on methods used to determine urination frequency was provided.

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Subjects were interviewed in the hospital by trained interviewers using computer-assisted personal interviews (CAPIs). Before the interview, written informed consent to participate in the study was obtained from each subject. The CAPI was designed to elicit detailed information on past usual adult urination frequency during 5-time periods in a typical day: before breakfast, between breakfast and lunch, between lunch and dinner, between dinner and bedtime, and the number of times per night that the subject woke to urinate. Based on this information, we computed 3 exposure metrics: 24-hr urination frequency, daytime urination frequency and nighttime urination frequency. Among controls, the median 24 hr and nighttime frequencies were 6 and 0, respectively, for both men and women, which is comparable to urination frequencies observed in the general population.1,3

The CAPI also obtained information on average adult fluid consumption (instituted after the first year of data collection), smoking habits, dietary factors, medical conditions (e.g., benign prostatic hyper trophy (BPH) and urinary tract infections), occupational and residential histories, family history of cancer and history of medication use (i.e., analgesics and nonsteroidal anti-inflammatory drugs). The effects of smoking have been described in detail elsewhere.10,11 This study was approved by the Institutional Review Board of the National Cancer Institute as well as the Ethics Committees of all participating hospitals.

The effects of urination frequency on bladder cancer risk were quantified by the odds ratio (OR). ORs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression. Final statistical models included terms for exposure (i.e., 24-hr urination frequency, daytime urination frequency or nighttime urination frequency), the matching factors (i.e., age at diagnosis/interview, gender, race/ethnicity and hospital/region), as well as terms for potential confounding factors (i.e., cigarette smoking, tap water intake and history of BPH). We selected “tap water intake,” rather than “total fluid intake,” for inclusion in the final models because only “tap water intake” was associated with a significant reduction in risk in our study; intake of other beverages appeared unrelated to risk.12 Other potential confounders, such as employment in high-risk occupations for bladder cancer, use of nonsteroidal anti-inflammatory drugs, consumption of water containing elevated levels of disinfection by-products and consumption of fruits and vegetables, were not included in the final models because they had little or no impact on estimates of risk. To test for trend, the median value for each level of the categorical variable among the controls was entered into the model. To test for interaction between 2 risk factors, we added a cross-product term to the logistic model and conducted a likelihood ratio test.

Interviewed subjects were excluded from analysis for the following reasons: nonurothelial carcinoma (16 cases) and nonwhite (5 cases and 1 control). Three hundred fourteen cases and 274 controls received an abridged version of the questionnaire that did not include detailed information regarding urination frequency (i.e., only categorical data on 24-hr urination frequency are available), water intake and BPH in men. Although these data were not included in Tables I–III, risks based on subjects with abridged data were compared to those based on the unabridged questionnaire in the Results section pertaining to Table I. The primary analysis of urination frequency presented in this work was based on unabridged interviews with 884 cases (764 men and 120 women) with newly diagnosed, urothelial carcinoma of the bladder and 996 controls (850 men and 146 women) with detailed information on urination frequency.

### Results

Table I shows the risk of bladder cancer for 3 urination frequency metrics: nighttime urination frequency, daytime urination frequency and 24-hr urination frequency. For nighttime urination frequency, a consistent, inverse trend in risk was apparent with increasing voiding among both men and women (p-value for trend: 0.0003 in men; 0.07 in women) (Table I). Men who voided at least twice per night experienced a significant, 40% reduction in risk and women experienced a marginally significant, 50% reduction in risk.

Among both men and women, no significant trend in risk was apparent with either increasing daytime urination frequency or with increasing 24-hr urination frequency, although a nonsignificant, decreased risk was found among subjects who voided at least 9 times per day during the daytime (men: OR = 0.6, 95% CI = 0.3–1.1; women: OR = 0.8, 95% CI = 0.2–4.3). For 24-hr urination frequency, the inverse trend in risk with increasing urination frequency based on the 200 cases and 197 controls with abridged questionnaires was not significantly different from that based on participants with unabridged questionnaires shown in Table I (p = 0.26).

All risk estimates in Table I were adjusted for potential confounding from cigarette smoking, age at diagnosis/interview,
TABLE II – ODDS RATIOS AND 95% CONFIDENCE INTERVALS BY WATER INTAKE AND NIGHTTIME VoidING (379 CASES AND 647 CONTROLS)  

<table>
<thead>
<tr>
<th>No. of voids/night</th>
<th>Water intake (ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (&lt;400 ml)</td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>95/112</td>
<td>85/128</td>
</tr>
<tr>
<td>1</td>
<td>0.9 (0.5–1.7)</td>
</tr>
<tr>
<td>32/37</td>
<td>37/57</td>
</tr>
<tr>
<td>≥2</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td>21/37</td>
<td>14/47</td>
</tr>
</tbody>
</table>

1 Adjusted for age, gender, geographic region, cigarette smoking and BPH (men).—Five hundred and five cases and 345 controls were excluded because they did not report information on water intake.—Cases/controls.

Table III shows the effect of nighttime voiding cross classified by smoking status. The reduced risk associated with increased nighttime voiding frequency was apparent among nonsmokers, former smokers and current smokers. Moreover, nocturia had a powerful effect on the bladder cancer risk associated with smoking. Current smokers who did not urinate at night had an OR of 7.0 (95% CI = 4.7–10.2), whereas current smokers who voided once per night had an OR of 4.0 (95% CI = 2.5–6.5) and those who voided at least twice per night had an OR of 3.3 (95% CI = 1.9–5.8) (p-value for trend = 0.0005). Former smokers who voided at least twice per night also experienced a reduced risk (OR = 2.3, 95% CI = 1.4–3.7) compared to risk among those who did not void at night (OR = 3.4, 95% CI = 2.3–4.9). Among current smokers, risk decreased with 1 void per night, whereas the risk reduction in former smokers and nonsmokers occurred with at least 2 voids per night. However, no statistical interaction between nighttime voiding frequency and smoking status was apparent (p = 0.30).

Discussion

In summary, we observed a consistent, inverse trend in bladder cancer risk with increasing number of voids per night among both men and women, which was statistically significant in men but not in women. Men and women who urinated at least twice per night experienced a significant 40–50% reduction in risk compared to those who did not urinate at night. The protective effect of nocturia was apparent among study participants with low, moderate and high water intake, as well as among nonsmokers, former smokers and current smokers. It is noteworthy that the risk associated with cigarette smoking was reduced more than 50% by nocturia.

In the mid-1970s, the urogenous-contact hypothesis was first introduced, suggesting that "contact with urine loaded with carcinogens is the main important factor in the etiology of carcinoma of the bladder."13–15 It is surprising that this observation has been followed up in only two epidemiologic studies. In 1982, Mommens et al.16 conducted a small case-control study in men in Denmark. Based on interviews with 165 bladder cancer patients and 165 population controls, they observed that nocturia (defined as nocturnal urination twice or more at least 2 years before presenting symptoms of bladder cancer) was associated with an increased risk of bladder cancer (relative risk = 2.05; 95% CI = 1.27–3.32). No information on fluid intake was collected, however. In contrast, Radosavljevic et al.7 reported a significant protective effect (OR = 0.27; 95% CI = 0.18–0.41) for increased urination fre-
frequency after adjustment for fluid intake, smoking and other con- founding factors, based on interviews with 130 cases and 130 con- trols in Serbia. Both studies were limited by small numbers and did not provide detailed information on urination frequency.

The protective effect in our study was primarily associated with nighttime voiding. As the longest time period in 24 hr when no voiding typically occurs is nighttime, the protective effect of nocturia may be more pronounced than protection imparted by increased urination during the waking hours. The lack of a consistent protective effect with daytime voiding may be, in part, due to less accurate recall of urination frequency during waking hours compared to that during sleeping hours. In fact, only 40% of cases and 60% of controls who reported nighttime urination frequency were able to provide complete information on daytime urination frequency.

The observed protective effect of nocturia appeared unrelated to the presence of BPH. We observed a reduced risk among those who voided at least twice per night in men without BPH and among women. The protective effect of nocturia was also unre- lated to total daily water intake. We did not, however, obtain in- formation on timing of water intake so we were unable to evaluate the effect of evening water intake on nighttime frequency. We observed a significant, inverse trend in risk with increasing water intake. Heavy consumers of water (at least 1,400 ml per day) experienced about 50% reduced risk of bladder cancer,13 a finding consistent with what is reported by Michaud et al.17 in the Health Profes- sionals Follow-up Study. However, the protective effect of nocturia in our study was independent of water intake, appearing among low, moderate and heavy consumers of water. Although no evidence of interaction between nighttime urination frequency and water intake was observed, the protective effect of both factors acting jointly was profound. Subjects who voided at least twice per night and drank at least 1,400 ml per day experienced a significa- nt 80% reduced risk of bladder cancer compared to those who did not void at night and drank less than 400 ml of water per day.

Increased urination frequency may lessen contact time that any carcinogens present in the urine have with the urothelium of the bladder. Because recent data suggest that urine composition is modified in the lower urinary tract and that the urothelium has a significant transport function, the urothelium may have the ability to reabsorb carcinogens from the urine and decreasing contact time should result in reduced risk. Increased water intake leads to pro- duction of less concentrated urine as well as increased urination fre- quency, which may also result in reduced bladder cancer risk.

Our study had limitations. First, although our study is the largest and most comprehensive investigation of the effect of urination frequency on bladder cancer risk, we did not obtain detailed infor- mation of urination frequency for all study participants. Our analy- sis was based on interviews with the 884 cases and 996 controls with detailed information on urination frequency. We did have limited information (i.e., total number of voids in 24 hr) from partici- pants who were asked the abridged questionnaire. We observed no significant differences in the effect of 24-hr urination frequency when we compared participants with abridged questionnaires to those with unbridged questionnaires. In addition, although sub- jects were queried about their usual adult urination frequency, this information was obtained after diagnosis of bladder cancer, and it is not possible to evaluate the possible effect of differential recall bias. We think it unlikely, however, that bladder cancer patients would underestimate information on urination frequency.

In conclusion, our findings suggest strong protective effects of both nocturia and increased water intake on bladder cancer risk. In particular, the protective effect of nocturia on the risk associated with current smoking among men in our study was noteworthy. Current smokers who did not void at night had a 7.0-fold risk that was more than cut in half to a 3.3-fold risk among current smokers who voided at least twice per night. This observation suggests that nocturia may be a powerful factor in reducing bladder cancer risk. This finding also provides evidence in humans that bladder cancer risk is related to the contact time of the urothelium with carcino- gens in urine. If confirmed, innovative approaches will be needed to translate this finding into meaningful prevention of the occurrence of the nearly 357,000 bladder cancer patients newly diag- nosed worldwide annually and the 145,000 deaths.19,20

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References

Appendix

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