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Lower Urinary Tract Symptoms and Risk of Bladder Cancer in Men: Results from the Health Professionals Follow-Up Study

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Abstract

Objectives—To understand the association between Lower urinary tract symptoms (LUTS) and risk of bladder cancer in a large men's cohort.

Methods—Using data from the Health Professionals Follow-up Study, we examined risk of bladder cancer in relation to severity of LUTS among 30,183 men. During the follow-up period from 1996 until 2010, 476 newly diagnosed cases of bladder cancer occurred. Cox proportional hazards regression was used to adjust for potential confounders.

Results—Among men with severe LUTS, risk of bladder cancer was 64% higher (relative risk (RR): 1.64, 95% confidence interval (CI): 0.87, 3.08) compared with men who reported no LUTS. Subjects with both voiding and storage dysfunction had a significantly higher risk of bladder cancer (RR: 1.60, 95% confidence interval: 1.00, 2.56). Among individual urinary symptoms, urinary hesitancy was strongly associated with bladder cancer; those who experienced urinary hesitancy at least 50% of the time had more than twice the risk of bladder cancer (RR: 2.21, 95% CI: 1.29, 3.78).

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Conclusions—Our findings suggest that LUTS, especially urinary hesitancy, are associated with the development of bladder cancer in men.

Keywords

Lower Urinary Tract Symptoms; Bladder cancer; Epidemiology; Hesitancy; Cohort study

Introduction

Bladder cancer is the fourth leading cause of cancer among men in the United States.[1] Approximately 72,570 new cases of bladder cancer were diagnosed in the United States in 2013, among which about 54,610 were men.[1] Because of the lengthy and resource-intensive course, health care expenditure for bladder cancer treatment and management is estimated to be among the highest of all malignancies.[2] Cigarette smoking is the most well-established risk factor for bladder cancer, which has been estimated to account for about 50% of all cases.[3] Occupational exposure to chemical carcinogens increases bladder cancer for workers in industries of aromatic amine manufacture, rubber and cable manufacture, and dyestuff manufacture and use.[4]

Lower urinary tract symptoms (LUTS), a group of common medical conditions among males, can be defined as abnormal voiding sensations that occur with a frequency or severity that affects quality of life.[5,6] About 15–60% of men aged older than 40 years reported having LUTS in different studies, and both the prevalence and severity increase substantially with age.[7-10] When LUTS are present, there is substantial amount of post-void residual urine retained in the bladder after urination, increasing the contact time of potential carcinogens in urine and the bladder urothelium.[11,12] Bladder wall thickening and bladder mass increase have been noticed among men with LUTS in multiple studies.[13-15]

To our knowledge, there has not been any large cohort study that evaluated the association between LUTS and bladder cancer risk among men. We conducted this study to understand whether the development of bladder cancer can be influenced by existence and severity of LUTS among men in the Health Professionals Follow-up Study (HPFS).

Methods

Study population

The HPFS was initiated in 1986, when 51,529 male health professionals residing in all 50 states of United States, aged 40-75 years, were recruited. Participants completed a baseline questionnaire which provided information on age, body size measures, smoking and drinking history, medical history, medication, lifestyle, and physical activity in 1986. Participants' information was updated biennially.[16] Deaths of participants were often reported by family members or by the postal service. The National Death Index was also searched to determine deaths of participants in the cohort. This study was approved by the Institutional Review Board of the Harvard School of Public Health, Boston, MA.

Identification of bladder cancer cases

On each biennial questionnaire, participants were asked to report if they had received a diagnosis of bladder cancer. Medical records for all reported cases were requested from hospitals after receiving permission from the participants. With permission from cases or next-of-kin for the deceased, the medical records and pathology reports were reviewed. 87% of the cases were confirmed by medical record review or cancer registry, and the diagnoses of the remaining cases are confirmed by obtaining additional data from the cohort member or a surviving family member through phone interviews. Cancer registries (listed in acknowledgment section) are mostly used to confirm cancer diagnoses for participants who indicated a cancer diagnosis during follow-up and subsequently died. Name, date of birth, date of death and social security are sent to the cancer registries; all linkages are conducted at the cancer registries.. Bladder cancer cases were included in the analysis only if a medical record or other sources of confirmation were ascertained successfully. Tumors that had invaded subepithelial connective tissue, muscle, perivesical tissues, or pelvic wall or abdominal wall, or metastasis (T1-T4) were categorized as invasive cancer cases. Non-invasive papillary carcinomas (stage Ta) were considered as non-invasive cancer cases, while Carcinoma *in situ* (CIS) tumors were categorized in the invasive group due to high risk of progression.[17]

Ascertainment of Lower Urinary Tract Symptoms

LUTS condition was assessed from all participants in 1992, 1994, 1998, and 2000.[18] The American Urological Association Symptom Score Index (AUA-7) was slightly modified to fit the constraints of the mailed questionnaires to assess LUTS information in the HPFS.[19] The AUA-7 consisted of seven questions assessing two broad categories of male LUTS: storage and voiding dysfunction. The AUA-7 was extensively validated and found to have good construct and criterion validity, and high test-retest reliability.[20,21] Each participant was asked to report the frequency of experiencing the six symptoms over the past month, including sensation of incomplete bladder emptying, frequent urination, stopping and urinary intermittence, urinary urgency, weak urinary stream, and urinary hesitancy. For each of the symptoms, a score of 0 to 5 was assigned corresponding to 0, 10, 25, 50, 75, and almost 100 percent of the time that the symptom was experienced. Further, they were also asked about frequency of night urination. A score of 0 to 4 was assigned corresponding to 0 to 4 times of urination per night, and a score of 5 was assigned for 5 or more times per night. If part of the seven questions were responded, values of other items were replaced with a score of 0. The scores for each of the seven questions were summed up. To evaluate the impacts of voiding dysfunction and storage dysfunction, the scores for the four voiding symptoms (sensation, intermittence, weak stream, and hesitancy) and the scores for the two storage symptoms (urgency and frequent urination) and frequency of night urination were summed up separately.

Assessment of smoking history and dietary factors

Information on cigarette smoking was collected on the baseline questionnaire and updated biennially. A validated, 131-item semiquantitative food-frequency questionnaire was used to assess the baseline dietary intake and every 4 years thereafter.[22,23]

Statistical analysis

We investigated the risk of bladder cancer in relation to total LUTS condition, voiding dysfunction and storage dysfunction, individual urinary symptoms, and frequency of night urination. The average total LUTS scores from 1992 and 1994 assessments, as well as the average total LUTS scores from 1998 and 2000 assessments, were obtained separately. Participants who did not provide valid LUTS information on either 1992 or 1994 questionnaire were excluded (n=249). If LUTS information was missing on both 1998 and 2000 questionnaires, the average of 1992 and 1994 score was carried forward. All participants with valid LUTS information were classified into four overall LUTS severity groups as having: 1) no LUTS (AUA-7≤ 1 of 35 points), 2) mild LUTS (AUA-7>1 but ≤7 of 35 points), 3) moderate LUTS (AUA-7>7 but ≤19 of 35 points), 4) severe LUTS (AUA-7>19 of 35 points). Participants were also grouped into voiding dysfunction group (≥8 of 20 points for sensation, intermittence, weak stream, and hesitancy), or storage dysfunction group (≥6 of 15 points for frequent urination, urgency, night urination).

As some bladder cancer cases may present urinary symptoms that were similar to LUTS which can bias the underlying association away from the null, the 1994 and 1995 follow-up were excluded to minimize the possibility of reverse causation. We calculated the person-time of follow-up for each participant from the return data of the questionnaire in 1996 to the date of diagnosis of bladder cancer, the date of death from any cause, or January 31, 2010, whichever came first. With the 2-year lag, person-time occurred during 1996-2002 was related to the average of 1992 and 1994 LUTS assessments, and person-time occurred after 2002 was related to the average of 1998 and 2000 LUTS assessments. Additional analyses excluded the first 4 years of follow-up to further rule out the possibility of reverse causation.

Relative risks (RRs) for each of the exposed categories were computed by dividing the incidence rates in these categories by the rate in the reference category. Cox proportional hazard models were used to obtain RRs and 95% confidence intervals (CI) adjusting for potential confounders, which were included in the models if they were found to be risk factors of bladder cancer in previous HPFS studies.[24-27] All final models were adjusted for age (continuous in years), pack-years of smoking (6 categories), updated smoking status (current, past, never), geographic region (4 regions), cumulative intake of total fluid (in quartiles), cumulative consumption of bacon (3 categories), cumulative intake of fruit and vegetables (4 categories), and diagnosis of diabetes (updated status with 2 year lag). A new data record was created for every questionnaire cycle at which a subject was at risk by use of covariate values at the time that the questionnaire was returned (i.e., time-varying covariates were used for variables that could potentially change during follow-up, including smoking status, pack-years of smoking, and diagnosis of diabetes). For intake of total fluid, bacon, and fruit and vegetables, the cumulative average values were computed using preceding measurements from all available questionnaires for each participant. Statistical analyses in this study were conducted using SAS 9.3 statistical package (SAS Institute Inc.) and all reported *p*-values are two-sided.

Results

Valid LUTS information was obtained from 37,591, 37,587, 35,633, and 33,186 participants in the cohort in 1992, 1994, 1998, and 2000, respectively. Percentage of men with self-reported total LUTS score (AUA-7) equal to or higher than 8 were noticed to increase over time (17.31% in 1992, 21.36% in 1994, 26.19% in 1998, and 28.64% in 2000). The percentages of men reporting having voiding dysfunction, storage dysfunction, and mixed dysfunction increased by 59.6%, 54.3%, and 51.4% from 1992 to 2000, respectively.

After excluding participants who reported implausibly high or low values for total energy intake (<800 or >4200 kcal/day) or left more than 70 items blank on the baseline dietary questionnaire, who died between 1986 and 1996, and who reported a diagnosis of cancer (not including nonmelanoma skin cancer) before 1996, the remaining 30,183 men were eligible for the analysis. A total of 476 bladder cancer cases and 373,442 person-years occurred in the cohort during 1996 - 2010. Age-standardized characteristics of the remaining cohort in 1996 by categories of LUTS severity status according to the average AUA-7 from 1992 and 1994 assessments are shown in Table 1.

Results of the age-adjusted analysis excluding person-years of the first 2 years' follow-up after exposure assessments are shown in Table 2. Among men with severe LUTS status (AUA-7 > 19), bladder cancer risk was 1.64 times as likely (95% CI: 0.87, 3.08) as among men who reported no LUTS. The multivariable RR of bladder cancer for men reporting mixed voiding and storage symptoms were 1.60 (95% CI: 1.00, 2.56), comparing to men reporting no LUTS symptoms. Voiding dysfunction was more strongly related to bladder cancer risk than storage dysfunction ($RR_{voiding:}$ 1.41, 95% CI: 0.95, 2.11; $RR_{storage:}$ 1.28, 95% CI: 0.92, 1.80). RRs showed minimal changes before and after controlling for multiple potential risk factors. Every one-unit increase in total LUTS score, voiding subgroup score, or storage subgroup score was all associated with about 2%-4% increase in risk of bladder cancer (Table 3). When further excluding the first 4 years' follow-up after exposure assessments to further minimize the possibility of reverse causation (Table 2), the RR for mixed voiding and storage symptoms were 1.87 (95% CI: 1.16, 3.00), comparing to men reporting no LUTS symptoms.

We evaluated the associations of each of the six urinary symptoms and frequency of night urination with risk of bladder cancer individually in the 2-year-lag multivariable models (Table 3). Results showed that urinary hesitancy was most strongly associated with bladder cancer risk. Men experiencing urinary hesitancy at least 50% of the time had more than twice the risk of bladder cancer compared to men who never experienced this symptom (RR: 2.21, 95% CI: 1.29, 3.78). Having to urinate equal to or more than 3 times per night showed a nonsignificant decreased risk of bladder cancer comparing to those who did not have night urination among the study population (RR: 0.82, 95% CI: 0.53, 1.29). In a separate multivariable model, all categorical variables of the seven urinary items were added in simultaneously, the RR was 2.69 (95% CI: 1.41, 5.12) for experiencing urinary hesitancy at least 50% of the time as compared with never experiencing urinary hesitancy. When the seven urinary items were added in the multivariable model simultaneously as continuous

variables, every one-unit increase in the score of urinary hesitancy elevated the risk of bladder cancer by 21% (RR: 1.21, 95% CI: 1.03, 1.42).

To study whether LUTS had different effects on different stages of bladder cancer, we restricted bladder cancer cases to stage of bladder cancer at diagnosis (non-invasive bladder cancer *vs* invasive bladder cancer) (Table 4). Results excluding the first 2 years of follow-up after exposure assessments showed that there is a stronger association between LUTS severity and non-invasive bladder cancer. The multivariable RRs for the moderate group (7<AUA-7≤19) and severe group (AUA-7>19) compared with no symptoms were 1.87 (95% CI: 1.05, 3.34) and 2.62 (95% CI: 0.84, 8.19) respectively for non-invasive cancer. Participants with mixed storage and voiding dysfunction had 3.36 times of bladder cancer risk compared with no LUTS group (95% CI: 1.52, 7.44). The magnitudes of the above associations increased in analyses further excluding the first 4 or 6 years of follow-up after exposure assessments.

Discussion

In this prospective study with updated LUTS measurements, we observed a consistent, positive association between voiding dysfunction or mixed dysfunction with risk of bladder cancer. There was a stronger association between bladder cancer risk with voiding dysfunction symptoms comparing with storage dysfunction ones. Total AUA-7 score, storage dysfunction score, or specific storage symptoms, were not found to be significantly related to bladder cancer risk in our study.

Voiding dysfunction is classically attributed to the direct effect of mechanical obstruction of the lower urinary tract, inducing extended contact time of any potential carcinogens present in the urine and the bladder urothelium. Among all specific urinary voiding symptoms, the frequency of urinary hesitancy was found to be strongly associated with elevated bladder cancer risk in our study. Urinary hesitancy, indicating a delay between trying to urinate and the urine flow actually beginning, causes high intravesical pressure. We investigated the relation between hesitancy and other urinary symptoms in this study population. At baseline, 1,892 men reported experiencing urinary hesitancy for at least 50% of the time, among which 1,069 (56.5%) had mixed storage and voiding dysfunctions and 642 (33.93%) had isolated voiding dysfunction. Participants reporting experiencing hesitancy for at least 50% of the time had the highest overall total AUA-7 score (18.84) comparing to experiencing the other urinary symptoms for at least 50% of the time. These results suggest that the presence of severe urinary hesitancy might indicate higher volume of post-void residual urine, which can increase the contact time of potential carcinogens in urine and the bladder urothelium and the risk of bladder cancer.

We found that men who urinated equal to or more than 3 times per night might have a decreased risk of bladder cancer. A recent case-control study found that both men and women who urinated at least twice per night had 40-50% reduction in bladder cancer risk comparing to those who did not urinate at night.[28] In a separate analysis which was restricted to men with no or mild LUTS, increased frequency of night urination was not related to reduced bladder cancer risk controlling for total fluid intake and other covariates.

In our study, because the night urination question was designed as part of the LUTS severity assessment, it was placed under the six urinary symptom questions. Participants who had the habit of night urination but also believed they did not suffer from urinary problems might unintentionally underreport on the night urination frequency question, which may bias the result toward the null. Future studies directly measuring the volume of post-void residual urine are warranted.

Major strengths of this study include its large sample size, long follow-up period, and repeated measurements of LUTS scores, with participants from all geographic regions of the United States. Because all the participants in this study were health professionals, the self-reported urinary symptoms, as well as other medical conditions, were considered to be relatively accurate. Among participants who responded to at least part of the seven LUTS questions, the missing rates of each of the seven symptoms were very small, ranging from 0.38% to 6.17% in 1992 and 0.23% to 2.09% in 1994. When the missing items were replaced with a score of 0, the results would only be attenuated slightly if the corresponding symptoms were present. The prospective design and application of lag analysis allowed us to minimize the possibility of bias due to reverse causation, meaning the cancer should not occur before the urinary symptoms. In addition, urinary symptoms related to undiagnosed bladder cancer occur mostly on patients with later stages of bladder cancer or carcinoma in situ. However, we found a stronger association between the presence of LUTS and early stages of bladder cancer instead of later stages, which further excludes the possibility that the observed positive associations in this study were all due to reverse causation.

Detection bias refers to a potential artifact caused by the use of a particular diagnostic technique or type of equipment, meaning LUTS can lead to a higher chance of bladder cancer diagnosis instead of bladder cancer cases. In order to minimize the possibility of detection bias, sensitivity analyses were conducted. First, we examined the association of the six specific urinary symptoms and night urination frequency with bladder cancer risk limited to invasive or noninvasive stages at diagnosis (with 2-year lag and updated LUTS information). If the observed positive association of LUTS and early stage bladder cancer risk was all due to detection bias, we would expect to see relatively constant RRs across different symptoms and night urination frequency, because all urinary symptoms could lead to higher chance of visiting urologists or getting urinalysis. In the multivariable model where all six urinary symptoms and night urination frequency variables were added simultaneously, we observed that urinary hesitancy was strongly related to diagnosis of bladder cancer while the other symptoms and night urination frequency were not.

In conclusion, our findings suggest that urinary voiding symptoms may increase the risk of bladder cancer. If this association is confirmed, LUTS might be used as simple test to identify men who are at higher risk of bladder cancer; however, despite statistically significant associations with a 4-year lag period, we cannot rule out the possibility that bladder cancer in these men was diagnosed as a result of urinary symptoms.

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Table 1

Age-standardized characteristics of the study population who were free of cancer in 1996 according to total LUTS score categories.[1]

	LUTS status[2]			
	AUA-7≤1	**1<AUA-7≤7**	**7<AUA-7≤19**	**19<AUA-7≤35**
n	7,597	17,075	5,161	350
Age, years	58.8 ± 8.1[3]	61.7 ± 8.9	65.5 ± 8.6	66.3 ± 8.5
Caucasian race, percentage	92%	92%	92%	92%
Current smoker, percentage	6%	5%	5%	5%
Weight (kg)	82.9 ± 12.2	83.2 ± 12.8	83.2 ± 13.3	84.4 ± 13.9
Body mass index (kg/m^2)	25.9 ± 3.3	26.0 ± 3.5	26.2 ± 3.8	26.5 ± 3.8
Pack-years of smoking	10.6 ± 16.9	11.6 ± 17.3	12.7 ± 18.1	15.5 ± 21.2
Intake of[4]				
Total fluid (ml/d)	1,871 ± 772	1,987 ± 794	2,007 ± 817	2,102 ± 877
Bacon (servings/week)	0.5 ± 1.1	0.5 ± 1.2	0.5 ± 1.2	0.7 ± 1.7
Diabetes, percentage	3%	4%	5%	6%
Hypertension, percentage	19%	24%	27%	31%

[1] All variables, except for age, were standardized according to the age distribution of the entire cohort.

[2] LUTS status was determined by the average of 1992 and 1994 total AUA-7 scores.

[3] Mean ± SD (all such values).

[4] Dietary information from the 1994 questionnaire.

Table 2

Relative risks of bladder cancer associated with updated LUTS status from latency analysis with 2-year lag and 4-year lag.

LUTS status	Case No.	Person-Years	Age-adjusted RR (95% CI)	Multivariate RR (95% CI)[3]
			2-year lag[1]	
No LUTS (ref)[5]	73	82,570	1.0	1.0
Mild LUTS[6]	258	207,242	1.14 (0.87, 1.49)[4]	1.14 (0.87, 1.49)
Moderate LUTS[7]	133	78,669	1.18 (0.87, 1.58)	1.18 (0.87, 1.59)
Severe LUTS[8]	12	4,961	1.62 (0.86, 3.03)	1.64 (0.87, 3.08)
p for trend			0.11	0.12
Isolated voiding[9]	15	9,037	1.25 (0.72, 2.18)	1.18 (0.66, 2.08)
Isolated storage[10]	55	30,135	1.20 (0.68, 1.70)	1.17 (0.81, 1.69)
Mixed V+S[11]	26	11,509	1.59 (1.00, 2.52)	1.60 (1.00, 2.56)
All voiding[12]	41	20,546	1.48 (1.01, 2.16)	1.41 (0.95, 2.11)
All storage[13]	81	41,644	1.32 (0.97, 1.80)	1.28 (0.92, 1.80)
			4-year lag[2]	
No LUTS (ref)[5]	66	71,607	1.0	1.0
Mild LUTS [6]	226	174,585	1.12 (0.84, 1.48)	1.13 (0.85, 1.50)
Moderate LUTS [7]	118	63,304	1.24 (0.90, 1.70)	1.24 (0.90, 1.71)
Severe LUTS [8]	10	3,988	1.65 (0.83, 3.26)	1.68 (0.84, 3.33)
p for trend			0.04	0.05
Isolated voiding[9]	13	7,322	1.26 (0.69, 2.31)	1.21 (0.66, 2.23)
Isolated storage[10]	46	24,055	1.15 (0.78, 1.71)	1.17 (0.79, 1.74)
Mixed V+S[11]	26	9,236	1.82 (1.14, 2.92)	1.87 (1.16, 3.00)
All voiding[12]	39	16,558	1.58 (1.05, 2.38)	1.58 (1.04, 2.38)
All storage[13]	72	33,291	1.33 (0.94, 1.89)	1.35 (0.95, 1.93)

[1] Person-time during 1996-2002 was related to the average of 1992 and 1994 LUTS scores; Person-time after 2002 was related to the average of 1998 and 2000 LUTS scores.

[2] Person-time during 1998-2004 was related to the average of 1992 and 1994 LUTS scores; Person-time after 2004 was related to the average of 1998 and 2000 LUTS scores.

[3] Adjusted for age, cumulative total fluid intake (in quartiles), cumulative intake of fruits and vegetables (4 categories), intake of bacon (3 categories), updated smoking status (current smoker *vs* nonsmoker), cumulative pack-years of smoking (6 categories), and diabetes status two years before.

[4] RR; 95% CI in parentheses (all such values).

[5] No LUTS: total AUA-7 score less than or equal to 1.

[6] Mild LUTS: total AUA-7 score greater than 1 but less than or equal to 7.

[7] Moderate LUTS: total AUA-7 score greater than 7 but less than or equal to 19.

[8] Severe LUTS: total AUA-7 score greater than 19.

[9] Isolated voiding: voiding subgroup score equal to or higher than 8 and storage subgroup score less than 6.

[10] Isolated storage: storage subgroup score equal to or higher than 6 and voiding subgroup score less than 8.

[11] Mixed V+S: voiding subgroup score equal to or higher than 8 and storage subgroup score equal to or higher than 6.

[12] All voiding: voiding subgroup score equal to or higher than 8.

[13] All storage: storage subgroup score equal to or higher than 6.

Table 3

Association of frequency of individual lower urination tract symptoms and night urination with risk of bladder cancer.[1]

	Frequency (% of time experienced symptoms)			
	0	**<25**	**≥25 but <50**	**≥50**
Sense of incomplete emptying				
No. of cases	258	166	33	19
Person-years	232,299	111,603	19,034	10,506
Multivariable RR[2]	1.0	1.13 (0.93, 1.38)	1.13 (0.78, 1.64)	1.16 (0.72, 1.87)
Urinary intermittence				
No. of cases	270	142	38	26
Person-years	235,234	102,307	20,794	15,107
Multivariable RR[2]	1.0	1.00 (0.81, 1.23)	1.10 (0.78, 1.56)	1.09 (0.72, 1.65)
Weak stream				
No. of cases	188	170	63	55
Person-years	187,501	117,884	33,888	34,169
Multivariable RR[2]	1.0	1.19 (0.96, 1.48)	1.38 (1.03, 1.85)	1.16 (0.85, 1.58)
Urinary hesitancy				
No. of cases	343	100	18	15
Person-years	284,494	76,132	8,452	4,364
Multivariable RR[2]	1.0	1.01 (0.80, 1.27)	1.42 (0.87, 2.32)	2.21 (1.29, 3.78)
Frequent urination				
No. of cases	129	247	61	39
Person-years	126,028	180,591	42746	24,077
Multivariable RR[2]	1.0	1.25 (1.00, 1.55)	1.17 (0.85, 1.59)	1.29 (0.89, 1.87)
Urinary urgency				
No. of cases	182	195	57	42
Person-years	180,912	138,277	30,814	23,439
Multivariable RR[2]	1.0	1.15 (0.93, 1.41)	1.22 (0.89, 1.66)	1.09 (0.77, 1.55)
Night urination				
Times per night	0	<2	≥2 but <3	≥3
No. of cases	61	277	105	33
Person-years	68,016	226,959	58,572	19,894
Multivariable RR[2]	1.0	1.01 (0.76, 1.34)	1.07 (0.77, 1.49)	0.82 (0.53, 1.29)

[1] Person-time occurred during 1996-2002 was related to the average of 1992 and 1994 symptom scores; Person-time occurred after 2002 was related to the average of 1998 and 2000 symptom scores. If both 1998 and 2000 LUTS information was missing, the average of 1992 and 1994 symptom scores was brought forward.

[2] Adjusted for age, cumulative total fluid intake (in quartiles), cumulative intake of fruits and vegetables (4 categories), intake of bacon (3 categories), updated current smoking status (current smoker *vs* nonsmoker), cumulative pack-years of cigarette smoking (6 categories), and updated diabetes status two years before.

[3] RR; 95% CI in parentheses (all such values).

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Table 4

Relative risks of bladder cancer associated with LUTS, according to stage at diagnosis.

	2-year lag[1]					
	Noninvasive			**Invasive**		
LUTS status	Case No.	PYs	Multivariate RR[7]	Case No.	PYs	Multivariate RR[7]
No LUTS[2]	19	82,517	1.0	35	82,523	1.0
Mild LUTS[3]	100	239,965	1.60 (0.96, 2.69)[8]	129	240,003	0.97 (0.66, 1.42)
Isolated voiding[4]	3	9,025	1.28 (0.37, 4.46)	9	9,030	1.43 (0.67, 3.04)
Isolated storage[5]	16	30,088	1.82 (0.90, 3.70)	24	30,103	0.96 (0.56, 1.66)
Mixed V+S[6]	11	11,491	3.36 (1.52, 7.44)	10	11,489	1.09 (0.53, 2.26)
	4-year lag[9]					
	Noninvasive			Invasive		
LUTS status	Case No.	PYs	Multivariate RR[7]	Cases No.	PYs	Multivariate RR[7]
No LUTS[2]	10	70,083	1.0	33	70,099	1.0
Mild LUTS[3]	84	196,162	2.69 (1.38, 5.25)	101	196,181	0.82 (0.55, 1.24)
Isolated voiding[4]	2	7,117	1.88 (0.40, 8.80)	8	7,123	1.34 (0.60, 2.99)
Isolated storage[5]	12	23,081	2.99 (1.24, 7.17)	20	23,094	0.94 (0.53, 1.69)
Mixed V+S[6]	9	8,832	6.08 (2.37, 15.64)	12	8,838	1.42 (0.70, 2.86)

[1] Person-time occurred during 1996-2002 was related to the average of 1992 and 1994 LUTS assessments; Person-time occurred after 2002 was related to the average of 1998 and 2000 LUTS assessments.

[2] No LUTS group was defined as the total AUA-7 score less than or equal to 1; it was used as reference group in the regression models.

[3] Mild LUTS group was defined as anyone who did not have high voiding or storage symptoms, or no LUTS.

[4] Isolated voiding group was defined as voiding subgroup score equal to or higher than 8, and storage subgroup score less than 6.

[5] Isolated storage group was defined as storage subgroup score equal to or higher than 6, and voiding subgroup score less than 8.

[6] Mixed V+S group was defined as voiding subgroup score equal to or higher than 8, and storage subgroup score equal to or higher than 6.

[7] Adjusted for age, cumulative intake of fruits and vegetables (4 categories), intake of bacon (3 categories), updated current smoking status (current smoker *vs* nonsmoker), cumulative pack-years of cigarette smoking (6 categories), and updated diabetes status two years before.

[8]RR; 95% CI in parentheses (all such values).

[9]Person-time occurred during 1998-2004 was related to the average of 1992 and 1994 LUTS assessments; Person-time occurred after 2004 was related to the average of 1998 and 2000 LUTS assessments.