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Fluid intake and risk of bladder cancer in the Nurses' Health Studies

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Abstract

Increase in fluid intake may reduce bladder cancer risk by decreasing the contact time between carcinogens in urine and bladder epithelium. However, this association has not been examined in a large cohort of women. We examined the association between total fluid intake and bladder cancer risk in two large prospective women's cohorts with 427 incident bladder cancer cases. Detailed information on total fluid intake was collected by repeated food frequency questionnaires over time. Multivariable relative risks (RRs) and 95% confidence intervals (95% CIs) were estimated by using Cox proportional hazards regression models. Results from the two cohorts were pooled together using the random-effects model. Using the average values from the earliest two dietary assessments and lowest quartile as reference, a suggestive inverse association was observed between total fluid intake and overall bladder cancer risk (RR: 0.83, 95% CI: 0.61-1.12, *p*-value for trend: 0.08), and invasive bladder cancer risk (RR: 0.47, 95% CI: 0.23-0.97, *p*-value for trend: 0.04). Among heavy cigarette smokers, women with the highest quartile of total fluid intake had a 38% decrease in bladder cancer risk (RR: 0.62, 95% CI: 0.41-0.93, *p*-value for trend: 0.02). Our findings suggest that total fluid intake may reduce bladder cancer risk for female smokers, as well as reduce the risk of invasive bladder cancer.

Keywords

Bladder cancer; fluid intake; water; cohort studies; cohort study; smoking; women

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Introduction

Total fluid intake may influence the development of bladder cancer. The “urogenous contact” hypothesis states that an increase in total fluid intake can dilute the urine concentration, increase frequency of urination, and reduce the contact time of potential carcinogens in urine with the bladder urothelium, leading to decreased risk of bladder cancer.[1-3] On the contrary, however, drinking water or other fluids could be contaminated with potential bladder carcinogens, such as chlorination byproducts[4-7] or arsenic[8-11]. A high intake of fluid contaminated with bladder carcinogens exposes the bladder to elevated levels of carcinogens and eventually increases the risk of bladder cancer.[12]

Overall, epidemiologic studies on fluid intake and risk of bladder cancer have yielded inconsistent results.[13] To date, the association of total fluid intake and risk of bladder cancer has been investigated in four prospective studies.[14-18] Among them, the Health Professional Follow Study suggested highest total daily fluid intake quintile was associated with about 24% decreased risk of bladder cancer in men.[15, 18] However, results from the other studies, including the Adventist Health Study[14], the Netherlands Cohort Study[16], and the European Prospective Investigation into Cancer and Nutrition[17], did not find significant associations of total fluid intake and bladder cancer risk.

Results from the previous prospective studies were either predominantly or exclusively based on male bladder cancer cases, mostly because the incidence of bladder cancer is more than three times higher among men than women.[19] Thus, we conducted this study to examine the quantity of total fluid intake, as well as specific beverages, in relation to risk of bladder cancer in two exclusive women's cohorts, the Nurses’ Health Study (NHS) and the Nurses’ Health Study 2 (NHS2).

Material and Methods

Study design and study subjects

Data from two ongoing women's cohort studies were available for this analysis: the NHS was established in 1976 when 121,701 married, female registered nurses aged 30-55 years in the United States responded to mailed baseline questionnaires.[20] The NHS was initially designed as a long-term prospective investigation of the health effects of various contraceptive methods in women.[20, 21] The NHS2 was initiated in 1989, when 116,609 female registered nurses between the ages of 25 and 42 years in the United States completed a mailed questionnaire about their lifestyle factors, health behaviors, and medical histories.[22] Individual and behavioral characteristics, including age, weight, height, medical history, medication use, menopausal information, and physical activity, were assessed using baseline questionnaires and updated questionnaires biennially. For both cohorts, nurses were selected to form the study populations because they were knowledgeable about health and disease and expected to provide more complete and accurate information. In addition, nurses were expected to be relatively easier to follow up over time and more cooperative than the general population.

For both cohorts, deaths of participants were often reported by family members or by the postal service in response to the questionnaire mailings. In addition, the National Death Index was searched by study staff to determine which participants died every two years, which has been shown to have a sensitivity of 98%.[23, 24] All remaining participants were considered alive and thus remained in the studies. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital and the Harvard School of Public Health.

Assessment of diet and beverage intake

A 131-item semiquantitative food frequency questionnaire (FFQ) was sent to each NHS and NHS2 participant in 1986 and 1991 respectively, and updated every 4 years thereafter. These FFQs were used to collect the information of the intake of dietary items, including water and specific beverages. All participants were asked about the average frequency of consuming a specified amount of different dietary items over the previous year. We then calculated nutrient intake by multiplying the reported frequency for the consumption of each dietary item by the nutrient content of the specified portion size. Food consumption values for nutrients were obtained from the US Department of Agriculture, supplemented with other data. Total fluid intake was estimated by multiplying the frequency of using each beverage item by serving size and then summing up all of the beverages. Each participant was given a score of daily total fluid intake in milliliters.

A study was conducted among a random sample of 173 women in the NHS to assess the validity of the FFQ used in 1980 by comparing two FFQs administered approximately 12 months apart to four one-week diet records; the mean of Pearson correlation coefficients for intake of beverage items between the dietary records and first FFQ was 0.68 (range: 0.34 for fruit punch to 0.89 for beer), and between the dietary records and second FFQ was 0.77 (range: 0.36 for noncola carbonated beverages to 0.94 for beer).[25, 26] Water was not included in the FFQ used in 1980 NHS study. In another study which assessed the validity and reproducibility of the same FFQ used in the Health Professionals Follow-up Study, the Pearson correlation coefficient for beverage intake measured by a FFQ and two one-week dietary records ranged from 0.52 for water intake to 0.93 for coffee intake.[27] Results from these validation studies indicated that the FFQ used in NHS could provide useful information about individual nutrient intakes.

Assessment of smoking history and other nondietary factors

For both cohorts, information on age, weight, height, cigarette smoking, physical activity, medical conditions, and use of medication was collected on the baseline questionnaires and updated biennially. Detailed information on cigarette smoking history, the amount of time since quitting, and the average number of cigarettes smoked per day at different age periods was obtained on the baseline questionnaires. To control for history of cigarette smoking in regression models, we calculated total pack-years of smoking for each participant. One pack-year was defined as 20 cigarettes (or one pack) smoked per day for one year.

Identification of bladder cancer cases

On each biennial follow-up questionnaire, participants were asked whether they had received diagnosis of bladder cancer during the past 2 years. When permission was received from the self-reported cases or next of kin for deceased participants, medical records and pathology reports were obtained from the hospitals and reviewed by study investigators, blinded to questionnaire exposure information. Bladder cancer cases were confirmed by review of medical records in 85% and 68% of the self-reported cases in the NHS and NHS2 respectively. When medical records were unavailable or inaccessible, we attempted to corroborate diagnoses of bladder cancer from another source, including death certificate, physician, or telephone interview of a family member. Cases were included in the analysis only when a medical record or other confirmation was ascertained.

Statistical analysis

Participants who reported implausibly high or low daily calorie intake (<600 or >3,500 kcal/day), who had 2 or more broad food sections entirely blank, or who had more than 70 dietary items with missing values, were excluded from the analysis. We also excluded participants who were diagnosed with cancer (other than nonmelanoma skin cancer) before 1986 for NHS and before 1991 for NHS2.

We calculated person-time of follow-up for each participant from the return date of the first FFQ questionnaire (1986 for NHS and 1991 for NHS2) until the date of diagnosis of bladder cancer, the date of death from any cause, or the end of follow-up (June 30, 2010 for NHS, and June 30, 2009 for NHS2), whichever occurred first. Cox proportional hazard regression was used to obtain relative risks (RRs) and 95% confidence intervals (CIs). All models were adjusted for age in years, pack-years of smoking (5 categories), current smoking status (yes *vs* no), consumption of bacon (3 categories), energy intake (in quartiles), and intake of fruit and vegetables (in quartiles). The models for NHS was adjusted additionally for diabetic status two years before (yes *vs* no). All eligible participants were divided into quartiles based on the distributions of total fluid intake observed in each cohort, with the lowest quartile as the reference group. Tests for linear trend were performed by assigning the median values of each quartile and modeling them as single continuous variables.

As dietary information was assessed multiple times during the follow-up in both cohorts, we compared the following four different approaches for handling these repeated dietary measurements in the regression models.1) Fluid intake was ascertained on the basis of the baseline FFQs (1986 for the NHS and 1991 for the NHS2). 2) Bladder cancer incidence between each biennial questionnaire cycle was related to the cumulative average of fluid intake calculated from all available preceding dietary measures. Using the cumulative average values could reduce within-subject variation and best represent long-term dietary intake during the follow-up.[28] 3) Only the most recently measured dietary values were used. Using the simple updated approach could best relate bladder cancer incidence to the most recent dietary intake information.[28] 4) We calculated the average dietary values from the first two FFQs in each cohort. Bladder cancer incidence occurred during the first follow-up period was still related to the first FFQ but the subsequent bladder cancer incidence was related to the average dietary values calculated from the first two FFQs. For example,

bladder cancer incidence in NHS during 1986-1990 was related to 1986 FFQ, and bladder cancer incidence after 1990 was all related to the average fluid intake from the 1986 and 1990 FFQs. In NHS2, bladder cancer incidence occurred between 1991 and 1995 was related to 1991 FFQ, and bladder cancer incidence after 1995 was all related to the average fluid intake from the 1991 and 1995 FFQs. Using multiple measurements at the beginning of the follow-up could reduce within-subject variation and capture baseline dietary intake information, assuming relatively long latency between exposure and the detection of cancer.[29] In both cohorts, if dietary data from the second FFQ was missing, only data from the first FFQ was used.

We examined whether cigarette smoking status (ever smoker *vs* never smoker) could modify the association of interest. The test for interaction was performed with the Wald test by using the cross-product term of the median trend variable with the stratification variable. In addition, all bladder cancer cases were examined separately according to pathological stages at diagnosis. Medical records were obtained and reviewed by specific investigators to determine the tumor, node, metastasis (TNM) classification at diagnosis. Tumors that had invaded subepithlial 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.[30, 31]

All above analysis was conducted separately for each cohort, and then we pooled the data from the two cohorts using a random-effects model to obtain the summary RR and 95% CI[32], unless statistically significant heterogeneity was observed. Tests of heterogeneity by using Q statistic were conducted before pooling.[32]

We also investigated whether there were possibly non-linear relations between the reported total fluid intake and bladder cancer risk non-parametrically using restricted cubic splines.[33] Tests for non-linearity used the likelihood ratio test, comparing the models with only the linear term to the models with both the linear and the cubic spline terms. All statistical procedures were performed with the use of SAS version 9.2 (SAS Institute Inc, Cary, NC). All reported *p* values are based on two-sided statistical tests.

RESULTS

A total of 68,767 and 91,274 eligible female participants were included at baseline in the analysis from NHS and NHS2 respectively. Characteristics of participants from both cohorts at baseline according to quartiles of total daily fluid intake, standardized for age, are shown in Table 1. In both cohorts, women who reported higher levels of total fluid intake also reported higher values of body mass index, higher intake of total energy and specific beverages, higher pack-years of cigarette smoking, and were more likely to be current smokers. Comparing to women in NHS2, women in NHS on average reported higher intake of bacon, wine, liquor, coffee and decaffeinated coffee, but less intake of beer and soda. 372 and 55 bladder cancer cases were identified during the follow-up from the eligible populations of NHS and NHS2 respectively. Table 2 shows relative risks of bladder cancer

and 95% CIs estimated from the three groups of models with different approaches to calculate quantity of fluid intake based on multiple longitudinal measurements. No statistically significant heterogeneity was found between the results from the two cohorts. When pooling results from the two cohorts together, we noticed that associations were stronger when quantity of total fluid intake was calculated from the average of first two FFQs; total fluid intake showed a possible inverse association with risk of bladder cancer (RR: 0.83, 95% CI: 0.61-1.12), comparing the highest total daily fluid intake quartile with the lowest quartile. A possible inverse trend in bladder cancer risk was observed with increasing level of total fluid intake, although it was not statistically significant (*p*-value for trend: 0.08). Using baseline total fluid intake only, a weaker association was found (RR: 0.91, 95% CI: 0.68-1.23, *p*-value for trend: 0.38), comparing the highest total daily fluid intake quartile with the lowest quartile. When using the cumulative fluid intake or simple updated fluid intake, we did not find an association between total fluid intake and risk of bladder cancer. To ensure that the findings were not affected by possible changes in habit of fluid intake by women with preclinical bladder cancer, we further excluded all person-years during the first two years of the follow-up. The RRs of the analysis were slightly lower than those observed with all person-years. The tests for non-linearity did not find any non-linear associations between total intake of daily fluid with risk of bladder cancer.

We investigated whether the association between total fluid intake and the risk of bladder cancer could be modified by cigarette smoking history (Table 3). The average of the first two FFQs was used to determine total fluid intake in both cohorts. When pooling the results from the two cohorts together, we found that there was a stronger inverse association among ever cigarette smokers than never smokers; the relative risk of bladder cancer for the highest quartile as compared with the lowest quartile of total fluid intake was 0.73 (95% CI: 0.51-1.04, *p*-value for trend: 0.03) among ever smokers, and 1.02 (95% CI: 0.58-1.81, *p*-value for trend: 0.86) among never smokers. The analysis did not show significant interaction between smoking history and total fluid intake in bladder cancer risk in either cohort (*p-for interaction*: 0.86 in NHS, *p-for interaction*: 0.30 in NHS2). We further restricted the analysis to women who had smoked 10 pack-years or more in the NHS. Comparing to women with the lowest quartile of total fluid intake, women in the highest quartile had about 38% decrease in bladder cancer risk (RR: 0.62, 95% CI: 0.41, 0.93, *p*-value for trend: 0.02). The analysis was not conducted in NHS2 because there were not sufficient smokers who had smoked 10 or more pack-years at the time of analysis.

The analysis by cancer stages (noninvasive *vs* invasive) was only conducted with the NHS cohort, due to insufficient cases with confirmed specific stage of bladder cancer at diagnosis in the NHS2 at the time of analysis. 167 non-invasive and 94 invasive bladder cancer cases were included in this analysis (Table 4). The relative risk of noninvasive bladder cancer for the highest quartile as compared with the lowest quartile of total daily fluid intake was 0.81 (95% CI: 0.50, 1.30, *p*-value for trend: 0.23), while the relative risk for invasive bladder cancer was 0.47 (95% CI: 0.23, 0.97, *p*-value for trend: 0.04).

In order to explore the possibility that a substance contained in particular beverages may be associated with risk of bladder cancer, rather than the total quantity of fluid intake, we evaluated each specific type of beverage, adjusting for the intake of all other beverages.

Using the average of the first two FFQs, intake of individual beverage categories was categorized into quartiles in the multivariable model simultaneously to examine their associations with the risk of bladder cancer in both cohorts. Pooling results from the two cohorts, women in the highest quartile of water intake showed decreased risk of bladder cancer (RR: 0.75, 95% CI: 0.56, 1.01, *p*-value for trend: 0.02),. Apart from water, consumption of other beverages was not observed to be significantly associated with bladder cancer risk.

DISCUSSION

Using data from two large cohorts of US women, we observed a possible inverse association of intake of total fluid and bladder cancer risk, which was more apparent among cigarette smokers. We also found an approximately 50% reduction in invasive bladder cancer risk for the highest quartile as compared with the lowest quartile of total daily fluid intake.

To our knowledge, this is the first study to prospectively examine the association of fluid intake on bladder cancer risk with large female cohorts. Previously, in the Health Professional Health Study, a large cohort of US men, baseline total fluid intake was inversely associated with risk of bladder cancer (RR: 0.76, 95% CI: 0.60, 0.97), comparing the highest total daily fluid intake quintile with the lowest quintile.[18] Results from three other cohort studies did not suggest a link between total fluid intake and bladder cancer risk.[14, 16, 17] Inconsistencies across the results from the previous studies could arise from different study populations and different qualities of drinking water.

Our study detected a possible inverse association between total fluid intake and bladder cancer risk among cigarette smokers which supports the hypothesis that fluid intake reduces risk of bladder cancer induced by extraneous carcinogens, possibly by dilution and an increased clearing effect. Further, a 38% reduction in bladder cancer risk was associated with increased total fluid intake among heavy smokers, which indicates that high fluid intake may be most beneficial to those who had been exposed to a high load of bladder carcinogens. We also observed a strong inverse association between total fluid intake and risk of invasive bladder cancer in this study for the first time; invasive bladder cancer and non-invasive bladder cancer have distinct molecular profiles[34] such that fluid intake may only be associated with the more aggressive molecular changes. Consistent with our observations, more aggressive bladder cancer has been associated with exposure to cigarette smoking[35, 36] and occupational history.[37] Our results suggest that a high fluid intake may reduce the development of invasive subtype of bladder cancer in women. In other recent studies, acid urine, which can result in cleavage of acid-labile glucuronides of carcinogenic aromatic amines[38], was linked with elevated risk of bladder cancer, with stronger association among heavy smokers.[39] Also, the risk of bladder cancer associated with cigarette smoking was found to be associated with increased nighttime voiding.[40] These studies, together with our findings, support the urogenous contact hypothesis as a possible mechanism for bladder cancer development.

In our study, we were able to compare four different approaches to analyze repeated measurements of dietary intake. The model that used the average value from the first two

dietary assessments yielded stronger associations than other models. Major advantages of this approach, which uses multiple baseline exposure measurements to predict subsequent disease risk, are that it could reduce measurement error due to intra-individual variation and best capture dietary intake information at the beginning of the follow-up.[41] Null findings in cumulative or most recent fluid intake and bladder cancer risk was also noticed previously in the Health Professional Follow-up Study, but fluid intake recorded at baseline (up to 20 years prior to cancer) was inversely associated with bladder cancer risk.[18] The long time lag between exposure to fluid intake and its effect on risk of bladder cancer is similar to the association with cigarette smoking; bladder cancer risk remains elevated among former smokers who quit smoking 10 or more years prior to cancer diagnosis.[42] Consequently, the baseline values in our study, reflecting fluid drinking approximately 20 years before the end of the follow-up, may be more relevant etiologically to the development of bladder cancer given the possible long induction and latency periods of bladder cancer.[43]

Thus far, this study is the largest prospective study to investigate the association of fluid intake and bladder cancer in women. The prospective study design precluded potential recall bias. In addition, we were able to control for exposure to cigarette smoking with updated detailed smoking information reported by participants. Some potential limitations exist in this study. Both of the cohorts consisted of female registered nurses living in the United States who were predominantly Caucasians. Consequently, the generalization of our findings to other racial or socioeconomic groups is not guaranteed. Further, although our findings suggest that overall, higher water consumption is likely to be more beneficial than harmful for bladder cancer risk, we cannot rule out that this finding would apply to geographic sub-groups with highly contaminated water. Although we were able to pool results from two studies, the low incidence of bladder cancer in women still may preclude us from detecting weak associations, especially among subgroups.

In summary, results from this study suggest a possible decline in bladder cancer risk associated with increased total fluid intake among female cigarette smokers, especially heavy smokers. While high fluid intake may reduce risk of bladder cancer among those exposed to high levels of carcinogens, our data along with previous work[18] suggest that the relevant time period for fluid intake may be decades prior to cancer diagnosis.

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Abbreviations

NHS	Nurses' Health Study
NHS2	Nurses' Health Study 2

FFQ	food frequency questionnaire
RR	relative risk
CI	confidence interval
CIS	Carcinoma *in situ.*

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Novelty and Impact

It is the first prospective study to examine the association of fluid intake and risk of bladder cancer with large female populations. The findings suggest a generous amount of intake of total fluid reduces risk of bladder cancer for female cigarette smokers, as well as risk of developing invasive bladder cancer.

Table 1

Baseline characteristics of participants by quartile (Q) of total fluid intake in Nurses' Health Study (NHS) and Nurses' Health Study 2 (NHS2).[1]

	NHS[2]				NHS2[2]			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Total fluid intake (ml/day)								
Range	<1,534	1,534-1,979	1,980-2,482	>2,482	<1,568	1,568-2,072	2,072-2,638	>2,638
Median	1,250	1,763	2,211	2,872	1,254	1,824	2,328	3,082
n	17,124	17,408	17,271	16,964	22,868	23,164	23,023	22,219
Age, years	63.1 ± 9.8[3]	63.3 ± 9.7	63.5 ± 9.7	63.2 ± 9.6	44.6 ± 7.0	44.6 ± 7.0	44.7 ± 7.0	44.8 ± 7.0
Weight (kg)	64.6 ± 16.4	66.2 ± 16.1	67.3 ± 16.5	68.4 ± 17.3	64.0 ± 14.0	66.1 ± 14.8	67.9 ± 15.3	70.5 ± 16.2
Body mass index (kg/m^2)	24.8 ± 4.6	25.1 ± 4.7	25.5 ± 4.7	25.8 ± 4.9	23.7 ± 4.9	24.3 ± 5.2	24.9 ± 5.4	25.7 ± 5.6
Current smoker, percentage	16%	18%	21%	25%	8%	11%	13%	17%
Pack-years of smoking	9.3 ± 15.5	10.6 ± 16.6	12.5 ± 17.6	14.7 ± 19.1	2.8 ± 6.2	3.6 ± 7.2	4.2 ± 7.7	5.5 ± 8.6
Intake of								
Water (ml/day)	324 ± 275	542 ± 368	740 ± 411	957 ± 419	310 ± 301	581 ± 416	759 ± 450	928 ± 454
Whole milk and skim milk (ml/day)	132 ± 151	186 ± 190	236 ± 224	324 ± 285	175 ± 184	235 ± 223	291 ± 253	363 ± 303
Fruit juice (ml/day)	96.2 ± 96.7	118 ± 111	131 ± 122	156 ± 161	84.4 ± 94.2	100 ± 109	112 ± 124	130 ± 157
Soda (ml/day)	166 ± 194	225 ± 264	274 ± 328	434 ± 483	307 ± 268	422 ± 378	545 ± 482	907 ± 751
Coffee and decaf (ml/day)	344 ± 290	514 ± 371	631 ± 403	828 ± 470	184 ± 244	301 ± 337	404 ± 389	596 ± 491
Tea (ml/day)	92.6 ± 172.3	126 ± 225	144 ± 243	201 ± 315	105 ± 178	144 ± 236	174 ± 272	240 ± 348
Alcoholic beverage (ml/day)	36.7 ± 71.8	48.9 ± 93.2	60.7 ± 119.1	97.3 ± 221.7	27.3 ± 58.8	40.0 ± 81.8	52.3 ± 107.2	83.5 ± 187.5
Total energy (kcal/day)	1,548 ± 461	1,713 ± 484	1,821 ± 508	1,997 ± 547	1,538 ± 463	1,724 ± 492	1,858 ± 525	2,047 ± 577
Fruit and vegetable (servings/day)	5.4 ± 2.8	6.1 ± 2.9	6.6 ± 3.0	7.4 ± 3.6	4.2 ± 2.4	4.9 ± 2.7	5.5 ± 2.9	6.2 ± 3.4
Bacon (servings/week)	0.6 ± 0.9	0.6 ± 1.0	0.6 ± 1.0	0.7 ± 1.2	0.3 ± 0.7	0.4 ± 0.7	0.4 ± 0.8	0.4 ± 0.8
Diabetes, percentage	2%	2%	3%	3%	<1%	1%	1%	1%

[1] All variables, except for age and total fluid intake, have been age standardized.

[2] Baseline: 1986 for NHS, 1991 for NHS2.

[3] Mean ± SD (all such values).

Table 2

Daily total fluid intake intake in relation to risk of bladder cancer in Nurses' Health Study (NHS) and Nurses' Health Study 2 (NHS2).

	Baseline total fluid intake (quartiles)				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	82	96	101	93	
Person-years	382,161	386,314	382,262	372,328	
Age-adjusted RR	1.0	1.15 (0.85, 1.55)[1]	1.21 (0.90, 1.62)	1.12 (0.83, 1.51)	0.48
Multivariate RR[2]	1.0	1.09 (0.81, 1.47)	1.07 (0.79, 1.45)	0.93 (0.68, 1.28)	0.58
NHS2					
No. of cases	12	19	14	10	
Person-years	406,629	411,841	409,380	394,455	
Age-adjusted RR	1.0	1.52 (0.73, 3.13)	1.15 (0.53, 2.48)	0.84 (0.36, 1.94)	0.49
Multivariate RR[2]	1.0	1.52 (0.73, 3.17)	1.11 (0.50, 2.46)	0.75 (0.30, 1.84)	0.35
NHS & NHS2					
Pooled multivariate RR	1.0	1.14 (0.87, 1.51)	1.08 (0.81, 1.42)	0.91 (0.68, 1.23)	0.38
	Cumulative total fluid intake (quartiles)				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	68	107	103	94	
Person-years	337,293	399,707	403,168	382,897	
Age-adjusted RR	1.0	1.23 (0.91, 1.68)	1.19 (0.87, 1.61)	1.14 (0.83, 1.56)	0.59
Multivariate RR[2]	1.0	1.16 (0.85, 1.58)	1.07 (0.78, 1.46)	0.98 (0.70, 1.36)	0.63
NHS2					
No. of cases	8	21	11	15	
Person-years	358,651	417,782	427,640	418,232	
Age-adjusted RR	1.0	2.29 (1.00, 5.22)	1.14 (0.46, 2.86)	1.59 (0.67, 3.79)	0.81
Multivariate RR[2]	1.0	2.34 (1.02, 5.39)	1.13 (0.44, 2.88)	1.48 (0.60, 3.70)	0.98
NHS & NHS2					
Pooled multivariate RR	1.0	1.48 (0.77, 2.83)	1.07 (0.80, 1.45)	1.03 (0.75, 1.40)	0.67
	Simple updated total fluid intake (quartiles)				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	61	101	106	104	
Person-years	331,187	398,613	398,590	394,674	
Age-adjusted RR	1.0	1.28 (0.93, 1.77)	1.35 (0.98, 1.86)	1.39 (1.01, 1.92)	0.05
Multivariate RR[2]	1.0	1.27 (0.92, 1.76)	1.31 (0.95, 1.80)	1.30 (0.94, 1.80)	0.17

	Simple updated total fluid intake (quartiles)				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS2					
No. of cases	8	16	13	18	
Person-years	347,752	425,083	426,780	422,689	
Age-adjusted RR	1.0	1.67 (0.70, 3.95)	1.35 (0.55, 3.29)	1.90 (0.82, 4.44)	0.21
Multivariate RR[2]	1.0	1.70 (0.71, 4.03)	1.34 (0.54, 3.32)	1.88 (0.79, 4.49)	0.24
NHS & NHS2					
Pooled multivariate RR	1.0	1.32 (0.97, 1.79)	1.31 (0.97, 1.77)	1.36 (1.00, 1.84)	0.09
	Average total fluid intake from first two FFQs (quartiles)				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	85	107	97	83	
Person-years	376,621	393,777	387,680	364,987	
Age-adjusted RR	1.0	1.20 (0.90, 1.59)	1.10 (0.82, 1.47)	0.98 (0.72, 1.33)	0.73
Multivariate RR[2]	1.0	1.11 (0.83, 1.49)	0.96 (0.71, 1.29)	0.80 (0.58, 1.10)	0.09
NHS2					
No. of cases	11	21	10	13	
Person-years	404,553	412,570	411,050	394,131	
Age-adjusted RR	1.0	1.86 (0.89, 3.86)	0.91 (0.38, 2.14)	1.20 (0.54, 2.68)	0.84
Multivariate RR[2]	1.0	1.82 (0.87, 3.84)	0.87 (0.36, 2.11)	1.08 (0.46, 2.53)	0.63
NHS & NHS2					
Pooled multivariate RR	1.0	1.26 (0.83, 1.92)	0.95 (0.71, 1.26)	0.83 (0.61, 1.12)	0.08

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

[2] Adjusted for age in years, pack-years of smoking (5 categories), current smoking status (yes *vs* no), consumption of bacon (3 categories), energy intake (in quartiles), and intake of fruit and vegetables (in quartiles). The models for NHS was adjusted additionally for diagnosis of diabetes two years before (yes *vs* no).

Table 3

Daily total fluid intake in relation to risk of bladder cancer in Nurses' Health Study (NHS) and Nurses' Health Study 2 (NHS2) by cigarette smoking history.[1]

Ever smokers	**Total fluid intake (quartiles)**				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	60	73	71	64	
Person-years	179,776	207,764	218,766	223,908	
Age-adjusted RR	1.0	1.03 (0.73, 1.46)[2]	0.98 (0.69, 1.39)	0.86 (0.60, 1.22)	0.34
Multivariate RR[3]	1.0	0.96 (0.68, 1.36)	0.87 (0.61, 1.24)	0.73 (0.50, 1.06)	0.07
NHS2					
No. of cases	4	13	6	6	
Person-years	104,306	128,194	146,634	167,384	
Age-adjusted RR	1.0	2.24 (0.73, 6.90)	0.95 (0.27, 3.40)	0.86 (0.24, 3.05)	0.27
Multivariate RR[3]	1.0	2.30 (0.73, 7.23)	0.88 (0.24, 3.24)	0.72 (0.19, 2.77)	0.18
NHS and NHS2					
Pooled multivariate RR	1.0	1.25 (0.57, 2.74)	0.87 (0.62, 1.22)	0.73 (0.51, 1.04)	0.03
Never smokers	**Total fluid intake (quartiles)**				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	25	34	25	19	
Person-years	194,402	183,487	166,375	137,816	
Age-adjusted RR	1.0	1.39 (0.82, 2.34)	1.12 (0.64, 1.95)	0.92 (0.50, 1.72)	0.67
Multivariate RR[4]	1.0	1.40 (0.82, 2.37)	1.13 (0.64, 2.01)	0.94 (0.49, 1.80)	0.72
NHS2					
No. of cases	7	8	4	5	
Person-years	296,334	280,692	259,900	220,695	
Age-adjusted RR	1.0	1.25 (0.45, 3.45)	0.67 (0.19, 2.28)	0.99 (0.31, 3.12)	0.76
Multivariate RR[4]	1.0	1.49 (0.53, 4.24)	0.87 (0.25, 3.06)	1.39 (0.42, 4.64)	0.79
NHS and NHS2					
Pooled multivariate RR	1.0	1.42 (0.88, 2.27)	1.08 (0.64, 1.82)	1.02 (0.58, 1.81)	0.86

[1] Total fluid intake was determined by the average values of total fluid intake from the first two FFQs in each cohort.

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

[3] Adjusted for age in years, pack-years of smoking (4 categories), current smoking status (yes *vs* no), consumption of bacon (3 categories), energy intake (in quartiles), and intake of fruit and vegetables (in quartiles). The model for NHS was adjusted additionally for diagnosis of diabetes two years before (yes *vs* no).

[4] Adjusted for age in years, consumption of bacon (3 categories), energy intake (in quartiles), and intake of fruit and vegetables (in quartiles). The models for NHS was adjusted additionally for diagnosis of diabetes two years before (yes *vs* no).

Table 4

Daily total fluid intake and water intake in relation to risk of bladder cancer in Nurses' Health Study (NHS) by cancer stage at diagnosis.[1]

Non-invasive bladder cancer	**Total fluid intake (quartiles)**				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	37	47	44	39	
Person-years	376,572	393,707	387,620	364,930	
Age-adjusted RR	1.0	1.27 (0.82, 1.96)[2]	1.15 (0.74, 1.78)	1.09 (0.70, 1.72)	0.84
Multivariate RR[3]	1.0	1.16 (0.75, 1.79)	0.94 (0.60, 1.48)	0.81 (0.50, 1.30)	0.23

Invasive bladder cancer	**Total fluid intake (quartiles)**				
	Q1	**Q2**	**Q3**	**Q4**	***p*-trend**
NHS					
No. of cases	23	30	27	14	
Person-years	376,554	393,696	387,601	364,904	
Age-adjusted RR	1.0	1.18 (0.68, 2.04)	1.07 (0.61, 1.87)	0.54 (0.27, 1.07)	0.08
Multivariate RR[3]	1.0	1.15 (0.66, 2.00)	1.01 (0.57, 1.79)	0.47 (0.23, 0.97)	0.04

[1] Total fluid intake was determined by the average values of total fluid intake from the first two FFQs in each cohort.

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

[3] Adjusted for age in years, pack-years of smoking (5 categories), current smoking status (yes *vs* no), consumption of bacon (3 categories), energy intake (in quartiles), and intake of fruit and vegetables (in quartiles), diagnosis of diabetes two years before (yes *vs* no).