

FLUID INTAKE AND THE RISK OF BLADDER CANCER IN MEN

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ABSTRACT

Background Studies in animals have shown that the frequency of urination is inversely associated with the level of potential carcinogens in the urothelium. In humans, an increase in total fluid intake may reduce contact time between carcinogens and urothelium by diluting urinary metabolites and increasing the frequency of voiding. The data on fluid intake in relation to the risk of bladder cancer are inconclusive.

Methods We examined the relation between total fluid intake and the risk of bladder cancer over a period of 10 years among 47,909 participants in the prospective Health Professionals Follow-up Study. There were 252 newly diagnosed cases of bladder cancer during the follow-up period. **Information** on total fluid intake was derived from the reported frequency of consumption of the 22 types of beverages on the food-frequency questionnaire, which was completed by each of the 47,909 participants who were free of cancer in 1986. Logistic-regression analyses were performed to adjust for known and suspected risk factors for bladder cancer.

Results Total daily fluid intake was inversely associated with the risk of bladder cancer; the multivariate relative risk was 0.51 (95 percent confidence interval, 0.32 to 0.80) for the highest quintile of total daily fluid intake (>2531 ml per day) as compared with the lowest quintile (<1290 ml per day). The consumption of water contributed to a lower risk (relative risk, 0.49 [95 percent confidence interval, 0.28 to 0.86] for ≥ 1440 ml [6 cups] per day vs. <240 ml [1 cup] per day), as did the consumption of other fluids (relative risk, 0.63 [95 percent confidence interval, 0.39 to 0.99] for >1831 ml per day vs. <735 ml per day).

Conclusions A high fluid intake is associated with a decreased risk of bladder cancer in men. (N Engl J Med 1999;340:1390-7.)

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AN estimated 310,000 new cases of bladder cancer were diagnosed worldwide in 1996.¹ In the United States, bladder cancer is the fourth leading type of cancer among men, excluding nonmelanoma skin cancer, and women have approximately one fourth the incidence of men.² The cause of bladder cancer is not well understood, but it may relate in part to direct contact of the bladder urothelium with carcinogens excreted in the urine.³ High consumption of fluids may reduce this exposure by diluting the urine and reducing contact time through increased frequency of urination.⁴

Specific types of beverages may have other influ-

ences on bladder cancer. Some of the numerous metabolites of coffee modulate the activity of metabolizing enzymes,⁵ and alcohol increases the risk of cancer at several sites outside the bladder.^{6,7} Both alcohol and coffee also have a diuretic effect mediated by alterations in the hormonal control of renal function.⁸ Fruit and vegetable juices may contain bioactive compounds that can modulate the response to carcinogens,⁹ and chlorinated byproducts formed during the purification of water for public consumption may be potential carcinogens.¹⁰

Most investigations, primarily case-control studies, have not indicated a relation between coffee or alcohol consumption and the risk of bladder cancer.¹¹⁻¹⁹ Findings with respect to an association between total fluid intake and the risk of bladder cancer have been inconsistent.¹⁸⁻²⁷ Several case-control studies have tended to support an association between an increased risk of bladder cancer and consumption of water from public sources.²⁸⁻³¹ Such unsettled questions, and sparse prospective data, led us to examine the relation of the total intake of fluids and the types of beverages to the risk of bladder cancer.

METHODS

Study Population

The Health Professionals Follow-up Study was initiated in 1986, when 51,529 male health professionals 40 through 75 years of age from all 50 states answered a detailed mailed questionnaire on diet and medical history. The men were predominantly white, although no exclusions were made on the basis of race. Every two years, follow-up questionnaires were mailed to all surviving members of the cohort (up to six times per follow-up cycle for nonrespondents) to update the data on medical conditions and exposures.

To form the cohort for the current analysis, we excluded 1596 men with implausibly high or low scores for total food intake (outside the range of 800 to 4200 kcal per day) or with 70 items left blank on the base-line dietary questionnaire and 18 men whose questionnaires were missing the date of birth. In addition, 2006 men with cancer (other than nonmelanoma skin cancer) diagnosed before 1986 were excluded, in part because these men may have changed their diets as a result of their disease. The remaining 47,909 men were eligible for follow-up. The follow-up rate for this cohort averaged 94 percent per follow-up cycle during the five biennial cycles between 1986 and 1996. Participants who

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failed to respond to a questionnaire during one follow-up cycle were not removed from the study and were included in the next mailing of the questionnaire (they could skip one questionnaire but answer the next). The National Death Index was used to determine the vital status of nonrespondents, and the remaining nonrespondents were assumed to be alive and at risk for bladder cancer.

Assessment of Diet and Beverage Intake

To assess dietary intake, we used a 131-item semiquantitative food-frequency questionnaire^{32,33} in 1986 and again in 1990 and 1994. The baseline dietary questionnaire was completed in 1986, and dietary information was updated in 1990 and 1994. The questionnaire assessed the average intake over the previous year and included questions on the consumption of 22 different beverages. For each man, we calculated nutrient intake by multiplying the frequency reported for the consumption of each food item by the nutrient content of the specified portion size. The data on food composition were primarily from the U.S. Department of Agriculture.³⁴ We calculated the total fluid intake using the 22 beverage items on the food-frequency questionnaire. The information on frequency and serving size was combined to give each member a score in milliliters.

In a study of the reproducibility and validity of the questionnaire among 127 men from this cohort, the Pearson correlation coefficient for nutrient intake measured by two one-week dietary records and by a food-frequency questionnaire was 0.50 for total fluid intake (Feskanich D: personal communication) and ranged from 0.52 for the intake of water to 0.93 for the intake of coffee.³⁵ These values are within the range of correlations typically found in dietary-validation studies.³⁶ In addition, we previously reported a correlation of 0.59 between total fluid intake as reported in a food-frequency questionnaire and 24-hour urine volume for men in the same validation study.³⁷ In this cohort, the alcohol intake reported on the food-frequency questionnaire correlated highly with the alcohol intake as measured by two one-week dietary records ($r = 0.86$).³⁸

Assessment of Nondietary Factors

At base line, and every two years thereafter, the participants provided information on their state of residence, current smoking status, exercise habits, weight, height, and use of medication. The base-line questionnaire provided detailed information on past smoking habits, the amount of time since quitting, the average number of cigarettes smoked per day before 15 years of age and at the ages of 15 through 19, 20 through 29, 30 through 39, 40 through 49, 50 through 59, and 60 or more years. To control for smoking, we derived total pack-years of smoking, incorporating all past smoking experience. One pack-year is equivalent to having smoked one pack, or 20 cigarettes, per day over an entire year.

Ascertainment of Cases

On each questionnaire, participants indicated whether they had received a diagnosis of cancer, heart disease, or other medical conditions. We confirmed the self-reported diagnosis of bladder cancer by a review of medical records (in 84 percent of the cases) or by obtaining additional data from the cohort member or a surviving family member (16 percent). The end points in this study were cases of bladder cancer that were first diagnosed between February 1986 and January 31, 1996; there were 252 such cases. According to a review of pathology reports, more than 90 percent of the cases of bladder cancer were transitional-cell carcinomas.

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of diagnosis of bladder cancer, death from any cause, or January 31, 1996, whichever came first. In the main analysis, categories of exposure were determined on the basis of the responses to the 1986 questionnaire, except for age and current smoking status, which

were updated every two years in all analyses. Current smoking status was based on the questionnaires returned in 1986, 1988, 1990, 1992, and 1994. The incidence of bladder cancer for each category of fluid intake was calculated as the number of participants with bladder cancer divided by the person-time of follow-up. The relative risk was computed as the incidence among the participants in a category of fluid intake divided by the incidence in a specific reference category. Participants whose questionnaires were missing information for any specific beverages (less than 10 percent for any beverage) were assigned to the lowest category of intake for that beverage, because our cohort validation study indicated that, in most instances, the missing item was not consumed.

We used pooled logistic regression³⁹ with two-year increments to adjust for age (in five-year categories), pack-years of smoking (six categories, including no history of smoking), current smoking status, geographic region, and total intake of fruits and vegetables (a potential risk factor⁴⁰). Data on participants who died or received a diagnosis of bladder cancer during a two-year cycle were censored at the end of that two-year period and were not entered in any subsequent two-year cycles. With short intervals between questionnaires and low rates of events, this approach tends to give results very similar to those from a Cox regression model with time-dependent covariates.³⁹ In addition, we included total energy intake in all multivariate models to reduce extraneous variation introduced by underreporting or overreporting on the food-frequency questionnaire.³⁶

In a separate analysis, we examined the relation between total daily fluid intake and the incidence of bladder cancer by updating the base-line information on fluid intake with data on fluid intake from subsequent questionnaires (1990 and 1994). In these analyses, data on fluid intake from the 1986 questionnaire were used to allocate person-time to each of the quintiles of exposure between 1986 and 1990; the average of the fluid intakes from 1986 up to 1990 was used from 1990 up to 1994, and the average of 1986, 1990, and 1994 was used for subsequent years (1994 through 1996). Cumulative updating may reduce the effects of variations in the intake of individual participants and better represents long-term intake. We performed tests for trend by assigning the median value for each category and modeling this variable as a continuous variable, using pooled logistic regression for multivariate analyses. All reported *P* values are two-sided. Tests for interaction were performed with use of likelihood-ratio tests. In addition to the tests for trend described above, pooled logistic-regression models of the log relative risk of bladder cancer on the restricted cubic spline⁴¹ of beverage and total fluid intake were fitted to the data. When likelihood-ratio tests were used to test the hypothesis of a linear relation through a comparison of the spline models to linear models, none of the associations between specific beverages or total fluid intake and the risk of bladder cancer showed evidence of departure from linearity.

RESULTS

A total of 252 cases of bladder cancer and 435,458 person-years were available for the main analyses. Age and smoking were both strongly associated with the risk of bladder cancer. Among men with a history of 65 or more pack-years of cigarette smoking, bladder cancer was 3.7 times as likely (95 percent confidence interval, 2.2 to 4.5) as among men who had never smoked. The relative risks of bladder cancer were 5.6, 6.2, and 11.6 for men 70 through 74, 75 through 79, and 80 or more years old, respectively, as compared with those younger than 50. The risk of bladder cancer was also higher (relative risk, 1.8; 95 percent confidence interval, 1.2 to 2.7) in the northeastern United States than in the West.

The distribution of established or potential risk

factors, standardized for age, was examined according to total daily fluid intake (Table 1). Both the number of pack-years of smoking and the proportion of participants who were current smokers increased with higher levels of total fluid intake. The level of physical activity and the total number of servings of fruits and vegetables per day increased with higher quintiles of total fluid intake. Macronutrient intakes did not differ substantially among the levels of total fluid intake.

In an age-adjusted analysis, total fluid intake in 1986 was inversely associated with the risk of bladder cancer (Table 2). This relation became more evident after adjustment for potential risk factors; the difference between the age-adjusted and multivariate models was explained almost entirely by the smoking var-

iables. Although the level of physical activity was not included in our main model because it is not a risk factor for bladder cancer, adding this variable to our multivariate model did not change the results substantially; the relative risk for the highest quintile of fluid intake as compared with the lowest was 0.51 (95 percent confidence interval, 0.32 to 0.80). The association between total fluid intake and the risk of bladder cancer did not change appreciably when cumulative average updating with data from 1986, 1990, and 1994 was used for total fluid intake (relative risk, 0.58; 95 percent confidence interval, 0.36 to 0.94). The multivariate relative risk of bladder cancer associated with an increase of 240 ml in total daily fluid intake (approximately one 8-oz glass) was 0.93 (95 percent confidence interval, 0.89 to 0.98) (Table 3).

TABLE 1. BASE-LINE CHARACTERISTICS OF 47,909 MEN WHO WERE FREE OF CANCER IN 1986, ACCORDING TO QUINTILE OF TOTAL DAILY FLUID INTAKE.*

CHARACTERISTIC	QUINTILE OF TOTAL FLUID INTAKE				
	1	2	3	4	5
Fluid intake (ml/day)					
Median	1026	1489	1857	2267	2952
Range	<1290	1290-1674	1675-2050	2051-2531	>2531
Age (yr)	54.3	54.2	54.1	54.1	52.8
Body-mass index†	25.0	25.2	25.5	25.7	26.1
Current smoker (% of participants)	6.4	7.5	8.9	10.9	14.4
Pack-years of smoking	10.3	11.8	13.3	15.2	19.4
Physical activity (MET-hr/wk)‡	21.6	23.6	24.2	24.2	25.1
Underwent routine physical examination between 1986 and 1988 (% of participants)§	17	18	18	18	18
Dietary intake					
Total fat (%)¶	31.8	32.1	32.2	32.4	32.1
Carbohydrate (%)¶	47.9	47.6	47.4	46.9	46.3
Protein (%)¶	19.2	18.8	18.6	18.6	18.5
Fruit and vegetable (servings/day)¶	5.4	5.7	5.9	6.1	6.6
Dietary fiber (g/day)**	21.9	21.4	21.2	20.8	20.0
Vitamin E (IU/day)**	101.9	101.8	94.0	94.6	92.0
Vitamin C (mg/day)**	440.3	434.2	423.8	421.7	420.7
Beverage intake					
Milk (ml/day)††	126	171	204	252	335
Fruit juice (ml/day)‡‡	109	126	132	143	166
Coffee and tea (ml/day)	248	408	518	675	954
Soda (ml/day)§§	169	222	269	325	524
Water (ml/day)	288	500	652	765	902
Alcoholic beverage (ml/day)¶¶	74	101	124	152	271

*All factors (except age) have been standardized according to the age distribution of the entire cohort. Except for fluid intake, values are means.

†The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

‡One MET-hour is the metabolic equivalent of sitting at rest for one hour.

§The data are from the 1988 questionnaire; this question did not appear on the 1986 questionnaire.

¶The percentage is that of total daily energy intake.

||This category included fruit juices.

**The amount has been adjusted for total energy intake.

††This category included whole milk, low-fat milk, and skim milk.

‡‡Orange, apple, grapefruit, tomato, and other juices were included.

§§Low-calorie, regular, and caffeine-free sodas and lemonade (or punch) were included.

¶¶Beer, liquor, white wine, and red wine were included.

TABLE 2. RELATIVE RISK OF BLADDER CANCER ASSOCIATED WITH TOTAL DAILY FLUID INTAKE.

VARIABLE	QUINTILE OF TOTAL FLUID INTAKE					P VALUE FOR TREND
	1	2	3	4	5	
Total fluid intake (ml/day)	<1290	1290-1674	1675-2050	2051-2531	>2531	
Cases of bladder cancer	61	54	57	47	33	
Person-years of follow-up	89,415	93,961	93,458	93,469	91,675	
Age-adjusted relative risk	1.0	0.85	0.95	0.78	0.62	0.03
Multivariate relative risk (95%CI)*	1.0	0.84 (0.58-1.21)	0.89 (0.62-1.29)	0.70 (0.47-1.04)	0.51 (0.32-0.80)	0.004

*The multivariate relative risk was adjusted for geographic region (five regions), age (in five-year categories), pack-years of smoking (six categories), current smoking status (smoker or nonsmoker), energy intake (in quintiles), and intake of fruits and vegetables (five categories). CI denotes confidence interval.

TABLE 3. RELATIVE RISK OF BLADDER CANCER ASSOCIATED WITH AN INCREASE OF 240 ml IN TOTAL DAILY INTAKE OF FLUIDS AND SPECIFIC BEVERAGES, WITH ADJUSTMENT FOR AGE AND OTHER VARIABLES.*

BEVERAGE	AGE-ADJUSTED RELATIVE RISK (95% CI)	MULTIVARIATE RELATIVE RISK (95% CI)†	P VALUE FOR TREND‡
Water	0.87 (0.81-0.93)	0.89 (0.83-0.96)	0.002
Milk§	0.90 (0.80-1.03)	0.92 (0.80-1.05)	0.22
Juice¶	1.08 (0.90-1.31)	1.14 (0.93-1.40)	0.21
Soda and lemonade	1.03 (0.95-1.12)	0.99 (0.90-1.08)	0.82
Coffee and tea	1.01 (0.95-1.08)	0.94 (0.88-1.01)	0.12
Coffee**	1.00 (0.92-1.09)	0.93 (0.85-1.02)	0.10
Tea	0.94 (0.80-1.11)	0.91 (0.77-1.07)	0.25
Alcoholic beverages††	1.00 (0.88-1.14)	0.92 (0.80-1.06)	0.24
Total fluids	0.96 (0.92-1.00)	0.93 (0.89-0.98)	0.002

*CI denotes confidence interval.

†Adjustment was made for geographic region (five regions), age (in five-year categories), pack-years of smoking (six categories), current smoking status (smoker or nonsmoker), energy intake (in quintiles), intake of fruits and vegetables (five categories), and intake of all other beverages listed (except in the total-fluid model).

‡The P values are for the multivariate models.

§This category included low-fat milk, skim milk, and whole milk.

¶Grapefruit, apple, orange, tomato, and other juices were included.

||This category comprised cola and noncola sodas (regular, low-calorie, caffeinated, and noncaffeinated sodas), punch, and lemonade.

**This category included decaffeinated and regular coffee.

††Alcoholic beverages included red wine, white wine, beer, and liquor.

To ensure that the findings were not influenced by changes in fluid intake by participants with preclinical disease, we excluded all cases of bladder cancer diagnosed during the first three years of the analyses (before 1989). The results of the analysis including only the 195 remaining cases were similar to those observed with all cases (multivariate relative risk for

the highest quintile of fluid intake as compared with lowest quintile, 0.46; 95 percent confidence interval, 0.27 to 0.76).

To examine the possibility that an anticarcinogenic substance in a particular beverage, rather than fluid intake itself, accounted for our findings, we evaluated each specific type of beverage (Table 3). Apart from water, no beverage had a statistically significant association with the risk of bladder cancer, although all (except fruit juice) had inverse relations. We also created categories for the intake of individual beverages to examine extreme consumption levels in relation to the risk of bladder cancer (Table 4). The daily consumption of 1440 ml (6 or more cups) of water was associated with a substantial reduction (51 percent) in the risk of bladder cancer as compared with the risk among participants who consumed less than 240 ml (1 cup) per day (P for trend, = 0.001). Although none of the other individual beverages had a statistically significant association with the risk of bladder cancer, when we added water and all other fluids to a multivariate model simultaneously, the relative risk was 0.49 (95 percent confidence interval, 0.28 to 0.86) for water intake of 1440 ml or more per day as compared with less than 240 ml per day and 0.63 (95 percent confidence interval, 0.39 to 0.99) for the consumption of more than 1831 ml of other fluids per day as compared with less than 735 ml per day (data not shown).

We also examined the total intake of caffeine (in milligrams) from all beverages and foods containing caffeine. No association with bladder cancer was found for caffeine intake (the multivariate relative risks for quintiles 2, 3, 4, and 5, as compared with quintile 1, were 1.24, 1.32, 1.04, and 0.84, respectively; 95 percent confidence interval for highest quintile vs. the lowest, 0.53 to 1.31).

We investigated whether the relation between total fluid intake and the risk of bladder cancer was mod-

TABLE 4. RELATIVE RISK OF BLADDER CANCER ASSOCIATED WITH INTAKE OF BEVERAGES PREVIOUSLY IMPLICATED AS CAUSING BLADDER CANCER.*

BEVERAGE†	FREQUENCY OF INTAKE‡				P VALUE OF TEST FOR TREND
	<1/MO	1/MO-6/WK	1-3/DAY	≥4/DAY	
Coffee (1 cup)					
No. of cases	75	56	98	23	
No. of person-yr	145,351	101,672	165,995	48,961	
Multivariate relative risk (95%CI)	1.0	0.97 (0.68-1.37)	1.00 (0.73-1.37)	0.79 (0.48-.30)	0.56
Decaffeinated coffee (1 cup)					
No. of cases	106	65	72	9	
No. of person-yr	222,336	129,718	93,897	16,027	
Multivariate relative risk (95%CI)	1.0	0.94 (0.69-1.29)	1.20 (0.87-1.65)	0.83 (0.41-.66)	0.47
Tea (1 cup)					
No. of cases	122	86	29	15	
No. of person-yr	201,963	160,693	63,107	36,215	
Multivariate relative risk (95%CI)	1.0	0.98 (0.74-1.29)	0.74 (0.49-1.11)	0.69 (0.40-1.19)	0.08
Beer (1 glass, bottle, or can)					
No. of cases	130	44	52	19	
No. of person-yr	204,565	82,603	118,169	38,694	
Multivariate relative risk (95%CI)	1.0	0.91 (0.64-1.29)	0.89 (0.64-1.24)	1.00 (0.61-1.63)	0.34
Wine (14-oz glass)					
No. of cases	120	37	52	24	
No. of person-yr	200,020	52,358	111,437	62,602	
Multivariate relative risk (95%CI)	1.0	1.35 (0.93-1.96)	0.92 (0.61-1.27)	0.80 (0.51-1.25)	0.96
Liquor (1 drink or shot)					
No. of cases	105	33	44	45	
No. of person-yr	219,127	73,332	95,806	44,449	
Multivariate relative risk (95%CI)	1.0	0.98 (0.66-1.45)	0.87 (0.61-1.25)	1.33 (0.93-1.90)	0.96
Water (1 cup)					
No. of cases	50	53	89	44	
No. of person-yr	84,681	81,649	155,573	91,807	
Multivariate relative risk (95%CI)	1.0	1.18 (0.80-1.75)	0.96 (0.67-1.36)	0.71 (0.47-1.07)	0.001

*The multivariate relative risk was adjusted for geographic region (five regions), age (in five-year categories), pack-years of smoking (six categories), current smoking status (smoker or nonsmoker), energy intake (in quintiles), and intake of fruits and vegetables (five categories). Because of rounding, the total number of person-years varies for different beverages.

†The metric equivalents of the amounts of various beverages are as follows: coffee, 240 ml; decaffeinated coffee, 240 ml; tea, 240 ml; beer, 360 ml; wine, 120 ml; liquor, 45 ml; and water, 240 ml. CI denotes confidence interval.

‡The frequency of intake varied according to beverage type because of differences in the levels of consumption among beverages.

ified by cigarette smoking (Table 5). Because the numbers of cases for some of the strata were small, we collapsed total daily fluid intake into quartiles. The relative risk of bladder cancer for the **highest** as compared with the lowest quartile of total daily fluid intake was 0.31 among current smokers, 0.59 among former smokers, and **0.58** among those who had never smoked. There was no statistically significant interaction between smoking and total fluid intake ($P=0.61$ for current smokers vs. those who had nev-

er smoked; $P=0.99$ for former smokers vs. those who had never smoked).

DISCUSSION

In **this** prospective study of **47,909** men, a high intake of fluids was associated with a reduced risk of bladder cancer after control for potential risk factors. When fluid intake was modeled as a continuous variable, the risk of bladder cancer decreased by 7 percent for every increment of **240 ml** in daily fluid intake

TABLE 5. RELATIVE RISK OF BLADDER CANCER ASSOCIATED WITH TOTAL DAILY FLUID INTAKE, ACCORDING TO SMOKING STATUS IN 1986.*

VARIABLE	QUARTILE OF TOTAL FLUID INTAKE				P VALUE FOR TREND
	1	2	3	4	
Total fluid intake (ml/day)	<1398	1398-1859	1860-2390	>2391	
Nonsmokers (incidence, 3/10,000)					
No. of cases	22	18	9	8	
No. of person-yr	61,493	56,057	49,398	41,419	
Relative risk (95%CI)	1.0	0.90 (0.48-1.69)	0.51 (0.23-1.14)	0.58 (0.24-1.37)	0.11
Former smokers (incidence, 7/10,000)					
No. of cases	35	45	34	22	
No. of person-yr	41,446	46,007	50,581	53,908	
Relative risk (95%CI)	1.0	1.33 (0.87-2.01)	0.65 (0.39-1.09)	0.59 (0.31-1.07)	0.02
Current smokers (incidence, 1/1000)					
No. of cases	13	14	14	7	
No. of person-yr	7,183	9,135	11,508	15,769	
Relative risk (95%CI)	1.0	0.74 (0.34-1.59)	0.70 (0.32-1.54)	0.31 (0.11-0.84)	0.02

*Eleven cases in patients for whom information on smoking was missing were excluded. For nonsmokers, the multivariate relative risk was adjusted for geographic region (five regions), age (in five-year categories), energy intake (in quintiles), and intake of fruits and vegetables (five categories). For current and former smokers, adjustment was also made for pack-years of smoking (six categories). CI denotes confidence interval.

we measured. Study participants in the highest quintile of fluid intake had a 49 percent lower incidence of bladder cancer than those in the lowest quintile. The consumption of both water and all other types of fluid combined contributed to the lower risk.

In the only other cohort study of fluid intake, which involved 52 cases of bladder cancer, the total intake of fluid was not significantly associated with the risk of bladder cancer,¹⁸ although the statistical power of the study was low. A case-control study did report a significant inverse association between total fluid intake and bladder cancer in women, particularly among smokers.²⁷ A number of case-control studies,^{20-24,31} but not all,^{19,25-27,42} have reported positive associations between the total intake of fluids and the risk of bladder cancer, explained largely by the intake of coffee or alcohol.²¹⁻²³ In part, the positive findings for coffee and alcohol intake in some studies may be due to residual confounding resulting from incomplete control for the effect of cigarette smoking. The results of most studies, including ours, do not provide evidence that the intake of alcohol^{13-15,17,18} or coffee¹¹ increases the risk of bladder cancer.

Because our base-line questionnaire did not assess the source of water consumed (tap water vs. bottled water), we were unable to determine the influence of the source of water on our results. However, according to a questionnaire filled out by 34 percent of the cohort in 1993 and 1994, 78 percent of the men usually drank municipal water, and of the bladder cancers in that subgroup, 75 percent of the cases developed in participants who drank municipal water. Moreover, an inverse association between water in-

take and the risk of bladder cancer was consistent among all regions of the United States and was apparent among the participants who were known to drink municipal water (48 cases; relative risk, 0.57; 95 percent confidence interval, 0.21 to 1.53 for highest vs. lowest quintile of total fluid intake). Previous investigators have hypothesized that chlorination byproducts may account for the increased risk of bladder cancer in some regions.^{10,28-31} However, establishing a person's exposure to chlorination byproducts is difficult. In studies that have examined persons with long-term exposure to chlorinated water (exposure lasting 40 or more years), the relative risk of bladder cancer, as compared with that among persons with no such exposure, has not exceeded 2.0.^{28,31,42} Although we cannot exclude the possibility that long-term exposure to chlorination byproducts in public water may increase the risk of bladder cancer, our data suggest that in the United States, a high intake of water may reduce the risk of bladder cancer by about 50 percent on average.

Many carcinogenic xenobiotics are ultimately metabolized to methylated or conjugated products, which increases their water-solubility and facilitates excretion. Although most conjugated substances are not highly reactive, certain urinary conditions can facilitate the conversion of inactive substances to their carcinogenic forms.⁴³ Concentrated urine, or less-frequent micturition, will increase the exposure of the bladder urothelium to urinary carcinogens. This theory, named the urogenous-contact hypothesis, has been offered as an explanation for the inverse association found between the risk of bladder cancer and fluid intake.^{4,27} This hypothesis is supported by a

study in which dogs that had been administered a known human urinary bladder carcinogen (4-aminobiphenyl) had significantly increased urothelial levels of DNA adducts when the average frequency of voiding was reduced.⁴⁴ The relation of fluid intake to risk that we found in our study was at least as strong among smokers, who have a high concentration of tobacco-related carcinogens in the urine, as among nonsmokers. Because the underlying rate of cancer is three to five times as high among smokers as among nonsmokers, smokers stand to benefit most by increased fluid intake.

The removal of cases diagnosed during the first three or five years of this study did not alter the overall results; therefore, it is unlikely that the associations between total fluid intake and the risk of bladder cancer arose because of dietary changes made before diagnosis by men with latent tumors. Because dietary factors and known confounders were measured before bladder cancer was detected, it is unlikely that the findings were influenced substantially by recall or selection bias.

We cannot rule out the possibility that some unmeasured confounder accounted for the associations found in this study, but residual confounding by the covariates that we included is unlikely. In this cohort, the only strong risk factor for bladder cancer (with the exception of age) was smoking. The control for smoking accounted for virtually all the differences found between the age-adjusted and multivariate relative risks, including the stronger inverse relation of the multivariate risk to total fluid consumption. Additional controls for the amount of current cigarette smoking, and for time since quitting among former smokers, did not alter the results, and we found an inverse association between total fluid intake and the risk of bladder cancer among those who had never smoked. Therefore, residual confounding by smoking is unlikely to be responsible for our findings. Furthermore, we observed similar results when we fitted a Cox regression model with time-dependent covariates and age as the time scale to our data. For these reasons, residual confounding by either smoking or age is unlikely to explain the findings. We found almost no differences in the relative risk of bladder cancer calculated before and after we controlled for fruit and vegetable intake.

Additional studies are needed to evaluate the temporal relation between increased fluid consumption and changes in the risk of bladder cancer and to determine the generalizability of our results to other populations. In the meantime, a generous intake of fluids is sensible, because it can reduce the risk of kidney stones^{37,45} and possibly bladder cancer as well.

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REFERENCES

1. The world health report 1997 conquering suffering enriching humanity: report of the Director-General. Geneva: World Health Organization, 1997.
2. Ries LAG, Kosary CL, Hankey BF, Miller BA, Hargis A, Edwards BK, eds. SEER cancer statistics review, 1973-1994. Bethesda, Md.: National Cancer Institute, 1997. (NIH publication no. 97-2789.)
3. Siverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. *Hematol Oncol Clin North Am* 1992;6:1-30.
4. Braver DJ, Modan M, Chetrit A, Lusky A, Braf Z. Drinking, micturition habits, and urine concentration as potential risk factors in urinary bladder cancer. *J Natl Cancer Inst* 1987;78:437-40.
5. Schilter B, Perrin I, Cavin C, Huggett AC. Placental glutathione S-transferase (GST-P) induction as a potential mechanism for the anti-carcinogenic effect of the coffee-specific components cafestol and kahweol. *Carcinogenesis* 1996;17:2377-84.
6. Tuyns AJ. Epidemiology of alcohol and cancer. *Cancer Res* 1979;39:2840-3.
7. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta analysis and review. *Cancer Causes Control* 1994;5:73-82.
8. Robertson GL. Regulation of vasopressin secretion. In: Seldin DW, Giebisch G, eds. The kidney: physiology and pathophysiology. 2nd ed. Vol. 2. New York: Raven Press, 1992:1595-613.
9. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. *Cancer Res* 1993;53:536-43.
10. Cantor KP, Lynch CF, Hildesheim ME, et al. Drinking water source and chlorination by-products. I. Risk of bladder cancer. *Epidemiology* 1998;9:21-8.
11. Viscoli CM, Lachs MS, Horwitz RI. Bladder cancer and coffee drinking: a summary of case-control research. *Lancet* 1993;341:1432-7.
12. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. *Cancer Causes Control* 1994;5:401-8.
13. Howe GR, Burch JD, Miller AB, et al. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst* 1980;64:701-13.
14. Thomas DB, Uhl CN, Hartge P. Bladder cancer and alcoholic beverage consumption. *Am J Epidemiol* 1983;118:720-7.
15. Brownson RC, Chang JC, Davis JR. Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health* 1987;77:1298-300.
16. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Liberati C, Franceschi S. Dietary factors in the risk of bladder cancer. *Nutr Cancer* 1989;12:93-101.
17. Chyou PH, Nomura A, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol* 1993;3:211-6.
18. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol* 1991;133:230-9.
19. Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR. Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol* 1988;127:1179-91.
20. Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL. The Copenhagen case-control study of bladder cancer. 11. Effect of coffee and other beverages. *Int J Cancer* 1986;37:651-7.
21. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany: a case-control study. *Cancer* 1992;69:1776-90.
22. Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. *Am J Epidemiol* 1986;124:578-89.
23. Slattery ML, West DW, Robison LM. Fluid intake and bladder cancer in Utah. *Int J Cancer* 1988;42:17-22.
24. Vena JE, Graham S, Freudenheim J, et al. Drinking water, fluid intake, and bladder cancer in western New York. *Arch Environ Health* 1993;48:191-8.
25. Dunham LJ, Rabson AS, Stewart HL, Frank AS, Young JL. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. *J Natl Cancer Inst* 1968;41:683-709.
26. Wynder EL, Onderdonk J, Mantel N. An epidemiological investigation of cancer of the bladder. *Cancer* 1963;16:1388-407.
27. Wilkins JR III, Comstock GW. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. *Am J Epidemiol* 1981;114:178-90.
28. McGeehin MA, Reif JS, Becher JC, Mangione EJ. Case-control study of bladder cancer and water disinfection methods in Colorado. *Am J Epidemiol* 1993;138:492-501.
29. King WD, Marrett LD. Case-control study of bladder cancer and chlorination by-products in treated water (Ontario, Canada). *Cancer Causes Control* 1996;7:596-604.
30. Freedman DM, Cantor KP, Lee NL, et al. Bladder cancer and drinking

Water: a population-based case-control study in Washington County, Maryland (United States). *Cancer Causes Control* 1997;8:738-44.

31. Cantor KP, Hoover R, Hartge P, et al. Bladder cancer, drinking water source, and tap water consumption: a case-control study. *J Natl Cancer Inst* 1987;79:1269-79.

32. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114-26.

33. Willett WC, Sampson LS, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51-65.

34. Department of Agriculture. USDA nutrient database for standard reference, release 10. Washington, D.C.: Agricultural Research Service, 1995 (software).

35. Feskanech D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993;93:790-6.

36. Willett W. Nutritional epidemiology. Vol. 15 of Monographs in epidemiology and biostatistics. New York: Oxford University Press, 1990.

37. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. *Am J Epidemiol* 1996;143:240-7.

38. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* 1991;133:810-7.

39. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* 1990;9:1501-15.

40. Bladder. In: World Cancer-Research Fund. Food, nutrition and the prevention of cancer: a global perspective. Washington, D.C.: American Institute for Cancer Research, 1997:338-61.

41. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med* 1989;8:551-61.

42. Morrison AS, Buring JE, Verhock WG, et al. Coffee drinking and cancer of the lower urinary tract. *J Natl Cancer Inst* 1982;68:91-4.

43. Rothman N, Tdaska G, Hayes RB, et al. Acidic urine pH is associated with elevated levels of free urinary benzidine and N-acetylbenzidine and urothelial cell DNA adducts in exposed workers. *Cancer Epidemiol Biomarkers Prev* 1997;6:1039-42.

44. Kadlubar FF, Dooley KL, Teitel CH, et al. Frequency of urination and its effects on metabolism, pharmacokinetics, blood hemoglobin adduct formation, and liver and urinary bladder DNA adduct levels in beagle dogs given the carcinogen 4-aminobiphenyl. *Cancer Res* 1991;51:4371-7.

45. Pak CYC. Kidney stones. *Lancet* 1998;351:1797-801.



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