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Running title: Water Intake, Disinfection by-Products and Bladder Cancer Risk

Key words: Bladder cancer, case-control study, chlorination by-products, fluid intake, water intake.

List of Abbreviations:

CI	Confidence interval
FFQ	Food frequency questionnaire
MV	Multivariate
OR	Odds ratio
THM	Trihalomethane

Article descriptor: Cancer.

Outline of Section Headers

Abstract

Background: Findings on water and total fluid intake and bladder cancer are inconsistent; this may, in part, be due to different levels of carcinogens in drinking water. High levels of arsenic and chlorinated by-products in drinking water have been associated with elevated bladder cancer risk in most studies. A pooled analysis based on six case-control studies observed a positive association between tap water and bladder cancer but none for nontap fluid intake, suggesting that contaminants in tap water may be responsible for the excess risk.

Objectives: We examined the association between total fluid and water consumption and bladder cancer risk, as well as the interaction between water intake and trihalomethane (THM) exposure, in a large case-control study conducted in Spain.

Methods: 397 bladder cancer cases and 664 matched controls were available for this analysis. Odds ratios (OR) were estimated using unconditional logistic regression controlling for potential confounders.

Results: Total fluid intake was associated with a decrease in bladder cancer risk (OR = 0.62, 95% confidence interval [CI] = 0.40-0.95 for highest vs. lowest quintile comparison). A significant inverse association was observed for water intake (OR = 0.47, 95% CI = 0.33-0.66, >1399 vs. <400 mL/day; p for trend < 0.0001), but not for other individual beverages. The inverse association between water intake and bladder cancer persisted within each level of THM exposure; there was no statistical interaction (p for interaction = 0.13).

Conclusion: Findings from this study suggest that water intake is inversely associated with bladder cancer risk regardless THM exposure level.

Introduction

Established risk factors for bladder cancer, including smoking and high-risk occupational exposures (Silverman et al. 2006), contain known carcinogenic compounds (e.g., aromatic amines) that may form DNA adducts in the bladder when not excreted promptly. Voiding frequency is a main determinant of DNA adduct-formation of known bladder carcinogens in dogs (Kadlubar et al. 1991), and it has been hypothesized that a high fluid intake may reduce bladder cancer risk by increasing urination frequency. In support of this hypothesis, a significantly lower risk of bladder cancer was observed among individuals with high fluid intake in large prospective study of men (Michaud et al. 1999). Alternatively, high water intake may increase bladder cancer risk if contaminants such as arsenic or chlorinated by-products are elevated in the water source (Villanueva et al. 2007), or through other alternative mechanisms.

Overall, studies on water or total fluid intake and bladder cancer have been inconsistent (Bruemmer et al. 1997; Cantor et al. 1987; Geoffroy-Perez and Cordier 2001; King and Marrett 1996; Koivusalo et al. 1998; McGeehin et al. 1993; Mills et al. 1991; Slattery et al. 1988; Vena et al. 1993; Wilkens et al. 1996; Zeegers et al. 2001). The association between water intake and bladder cancer risk has been complicated by the possibility that water contaminants, especially disinfection by-products and arsenic, may increase the risk of bladder cancer (summarized in (Silverman et al. 2006)). In a recent pooled analysis of six case-control studies with data on fluid intake and chlorination by-products, tap water was associated with an elevated risk of bladder cancer at all levels of THM exposure among men but not women (Villanueva et al. 2006b).

We examined the potential role of water and total fluid intake on bladder cancer risk and the effect of exposure to disinfection by-products in water simultaneously in a large multicenter case-control study conducted in Spain.

Methods

Study Population

Between June of 1998 and June of 2001, a hospital-based case-control study of bladder cancer was conducted in multiple centers in Spain. Cases and controls were recruited from 18 participating hospitals in five geographic areas of Spain (3 in Barcelona, 2 in Vallès/Bages, 1 in Alicante, 2 in Tenerife, and 10 in Asturias). Cases, defined as histologically confirmed primary bladder cancer patients (urothelial carcinoma), were identified in the urologic services at diagnosis. Bladder cancer cases were eligible if they were residents of the geographic catchment area of the participating hospitals and were between 20 and 80 years old. Research staff frequently reviewed hospital discharge records and pathology records to ensure that no cases were missed. Controls were selected from the same hospitals at about the time of the case patient diagnosis (median time between the case interview and the interview of the matched control was 150 days), and were individually matched 1:1 on sex, age at diagnosis/interview (within 5-years) and geographic area of residence. Hospital patients admitted for conditions that could be related to exposures under investigation, such as smoking, were not selected as controls for this study. Controls were admitted for the following reasons: hernias (33%), other abdominal surgery (12%), fractures (24%), other orthopedic problems (6%), hydrocele (13%), circulatory disorders (5%), dermatologic

disorders (2%), ophthalmologic disorders (2%), and other diseases (3%). The study was approved by the human subjects review board of each participating institution and all participants provided signed informed consent prior to being enrolled in the study.

Interview Data

Cases and controls were interviewed during hospitalization by trained interviewers. The interviewers used computer-assisted software to record the information directly during the interview. The information collected during the interview included sociodemographic characteristics, family history of cancer, smoking history, occupational history, residential history (all residences of at least 1 year starting from birth), drinking water source at each residence (municipal/bottled/private well/other) and medical history. Of the 1,457 eligible cases, 84% were interviewed (n=1,219), and of the 1,465 eligible controls, 87% were interviewed (n=1,271). For the in-person interview, cases and controls were instructed to report usual adult lifetime consumption of beverages.

In addition, cases and controls were instructed on how to complete a food-frequency questionnaire (FFQ), which was then self-administered. For the FFQ, cases and controls were asked to report diet intake during the past 5 years. Specific beverage consumption, including water, was added to the interview after the study had been in the field for almost one year due to concerns that the FFQ may not provide sufficiently detailed data. For each beverage, a serving size was specified, and categories of intake frequency were provided. Intake of total fluid was estimated by multiplying volume and frequency of intake and summing over all individual beverages, for both the personal

interview and the FFQ. Questions on beverages included coffee, beer, wine, liquor, champagne, soda, juices, tea, milk, and water.

Historical Trihalomethanes (THMs)

Details on how the levels of THMs were calculated for this study are described elsewhere (Villanueva et al. 2006a). Briefly, annual average THM levels, water source history since 1920, and year that chlorination began were obtained from local authorities and water companies and available for 78.5% of the total study person-years. Individual and municipal databases were merged by year and municipality, to obtain individual year-by-year average THM levels. Residential THM exposure (ug/liter) was based on the time-weighted annual average municipal THM level at all residences since age 15 years (years prior to age 15 were excluded to minimize missing or poorly recalled residential data in those early years). We used the same cutpoints that were used in the main study on THM levels (Villanueva et al. 2007) and these were based on the distribution of the controls. Other THM variables were derived for this study, but the association with risk of bladder cancer was strongest for the residential THM variable (as reported in (Villanueva et al. 2007)) and thus selected for this analysis. The residential THM exposure was assumed to be zero if water came from private well, bottled water or other nonmunicipal source, and before municipal chlorination started.

Statistical Analysis

We excluded from our analyses individuals with missing interview data on fluids (n=1,412; as questions on fluid intake were added to in-person interviews after study

initiation), missing smoking data (n=12), non-White (n=1), unsatisfactory overall quality of interview (n=1) and non-urothelial carcinoma (n=3). The final dataset for this analysis consists of 1,061 individuals (397 cases and 664 controls).

To estimate the relation between our exposures of interest and bladder cancer risk, we calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression models adjusting for matching factors (age at diagnosis/interview, geographic region, sex) and other potential confounding variables (smoking status/duration, nighttime urination frequency, and exposure to THMs). Unconditional models were used to increase statistical power by inclusion of unmatched pairs. In most models, and unless otherwise specified, only smoking status was included in the models because including categories for smoking duration did not change the estimate of interest. In addition, high-risk occupations (painters, paperhangers, and plasterers; truck drivers, tractor-trailer drivers; railroad brake, signal and switch operators; sailors and deckhands; precision laundering, cleaning, and dyeing occupations; textile machine setup operators; welders and solderers; general building contractors; heavy construction contractors; heavy construction; yarn & thread mills; textile goods) were also included in the final models. Quintiles for total fluid intake were created based on the distribution among controls. For most individual beverages, nondrinkers formed one category that was used as the reference and the remaining individuals were grouped into categories based on the distribution among controls and range of available data for each item. Tests for trend were conducted using the median value for each level of the categorical variable among controls and entering this variable as a continuous variable in the models.

Interaction between water intake volume and THM levels were examined by creating cross-product terms of continuous variables and including them in the logistic regression models. For these analyses, we only included individuals who had complete fluid data from the interview and for whom information on residential THM history was 70% or more complete (292 cases; 487 controls).

Results

In this subpopulation, cases and controls were similar with respect to age, sex, geographic area, and education levels, but cases were more likely to be current smokers than controls (Table 1). Mean and median water intake was similar by admission diagnosis of control patients (mean ranged between 844-896 ml/day and the median was exactly 700 ml/day in each of the diagnostic categories which contributed to more than 2% of total controls). Among men (controls), water made up the majority of fluids (42%), followed by milk (14%), wine (14%), coffee (8%), beer (6%), juice (4%), soda (4%), and other beverages (8%). Women (controls) consumed substantially less alcohol than men; their fluid consumption was as follows: water (50%), milk (23%), coffee (12%), juice (5%), wine (3%), and other beverages (7%).

A statistically significant 39% decrease in risk of bladder cancer was observed for men and women in the highest vs. lowest levels of total fluid intake (Table 2), but the test for trend did not reach statistical significance (p trend = 0.07). Unadjusted ORs were slightly attenuated compared to the fully adjusted model (Table 2). Exclusion of THM level from the models had little of no impact on estimates of risk (data not shown). The associations were similar in men (OR = 0.61, 95% CI = 0.38-0.97) and women (OR =

0.58, 95% CI = 0.18-1.87) for the same comparisons of highest vs. lowest intake of total fluid. For water intake, a 53% decrease in risk was observed for men and women consuming 1,400 ml or more per day, compared with <400 ml per day. The associations were similar when stratified on sex (comparing >1,399 vs. <400 ml/day, men: OR = 0.47, 95% CI = 0.33-0.68, women OR = 0.61, 95% CI = 0.23-1.65). Risk decreased with increasing water intake among never smokers, past smokers and current smokers, although only the trend among past smokers was statistically significant (Table 3). We did not observe a statistically significant interaction between smoking status and water intake (*p* for interaction = 0.32); never, past, and current smokers had a 51%, 67% and 44% lower risk of bladder cancer for >1399 vs. <400 ml/day, respectively.

The joint effect of water intake and THM exposure was examined by creating four categories of residential THM exposure as reported in a previous publication from this study (Villanueva et al. 2007). The estimates for THM levels by quartiles in this dataset were similar to those previously published (Table 4). We observed a greater than 2-fold increase in risk of bladder cancer among individuals with elevated residential THM levels who consumed 400 or less ml per day of water, compared to those consuming the same amount of water but with low THM levels (Table 4). In the low THM strata, high vs. low water intake was associated with a significantly lower risk of bladder cancer (OR = 0.36, 95% CI = 0.15-0.83). In the highest THM strata, high vs. low water intake was also associated with a lowering of risk. There was no interaction between THM exposure and water intake (*p*-interaction = 0.13), however.

Consumption of individual beverages (other than water), including coffee, beer and wine intake, was not related to risk of bladder cancer in multivariate models (OR for

highest vs. lowest category of beverage intake ranged between 0.97 and 1.17). Similarly, total fluid intake not including water was not associated with risk (OR = 0.84, 95% CI = 0.53-1.33, for highest vs. lowest quintile comparison, controlling for water in the model).

Discussion

In this case-control study conducted in Spain, we observed an inverse association for total fluid intake that was mostly driven by water intake. A 53% lower risk of bladder cancer was observed in individuals who consumed 1,400 ml of water per day or more compared with less than 400 ml per day after adjusting for known and potential confounders. The inverse association for water intake was seen across all strata of smoking status. Similarly, higher water intake was associated with lowering of bladder cancer risk within each THM exposure strata.

The inverse association for water intake and bladder cancer risk in this study is consistent with findings from a prospective cohort (Michaud et al. 1999). In contrast to that study, however, we did not observe inverse associations for other beverage items combined. Given that the main biological hypothesis is that fluids “flushes” out carcinogens, or reduces their contact time with the urothelium (Kadlubar et al. 1991), it is unclear why other beverages that also contribute fluid volume are not inversely associated with risk in this study. One reason for this observation may be that water consumption in this population better reflects long term intake, if consumption is consistent over time; in contrast, consumption of other beverages, such as soda, may be more prone to change over time.

The fluid results based on the FFQ were similar to those obtained using the in-person interviews among individuals who completed both an in-person interview and a FFQ (data not shown). For women, results were also identical when comparing data for all subjects who responded to the FFQ to the subset with fluid data obtained during the in-person interview. For men, the water results were slightly attenuated using all subjects who answered the FFQ compared to results from FFQ on those with in-person interviews only (OR = 0.77, 95% CI = 0.56-1.07, comparing >1399 ml/day with <400 ml/day). This difference could be due to measurement error in the overall FFQ responders, as those who completed the FFQ and did not have in-person water data were more like to have FFQ errors (defined as double entries or blank items; 58% any error vs. none) than those who completed both a FFQ and an in-person interview (48% error vs. none). These data suggest that the FFQ data in this population may have been more prone to error than the in-person interview data.

The inconsistencies in findings on fluid/water intake and bladder cancer risk are apparent in both cohort and case-control studies. The Netherlands Cohort Study (Zeegers et al. 2001) did not replicate the inverse association for total fluid intake and bladder cancer that was observed in the Health Professionals Follow-up Study (Michaud et al. 1999). One meta-analysis on fluid intake and bladder cancer concluded that "there is possible evidence that total fluid intake is not associated with bladder cancer"(Zeegers et al. 2004). In contrast, a pooled analysis of six case-control studies (2,729 bladder cancer cases) reported that total fluid intake was associated with an increased risk of bladder cancer in men, but not women (Villanueva et al. 2006b) (note: our present study was not part of this pooled analysis). Inconsistencies may be due to differences in exposures to

disinfection by-products and other water contaminants that can vary substantially by study population. In the pooled study by Villanueva et al. (2006b), tap water intake was associated with increased risk of bladder cancer at the lowest THM exposure level, and further increased within each category of THM exposure level. In contrast, in our analysis, higher water intake reduced the risk of bladder cancer even among those exposed to the highest levels of THM. It is possible that water contaminants other than disinfection by-products were present in one or more of the pooled studies, thereby leading to different results.

Other methodological issues may also have contributed to positive findings for total or water intake in previous studies. Past studies have varied substantially in how fluid intake was assessed. Such differences as number of fluid questions and what reference period was used for beverage intake (e.g., lifetime average intake, 2 years prior to interview/diagnosis, adulthood exposure) could have contributed to inconsistencies in findings. For example, fluid intake in years close to diagnosis may not be the relevant exposure, given the long latency for bladder cancer. Changes in fluid intake occurring in patients prior to diagnosis may also have introduced bias.

The strengths of this study included detailed interview data on individual beverage consumption on usual adult intake, detailed assessment of THM exposure, detailed smoking data to adjust for confounding, and high response rates.

As with any case-control study, recall bias is a concern in drawing inferences as it is possible that there was some differential reporting of water intake between cases and controls. However, recall bias tends to occur when cancer patients attempt to find an explanation for their condition and consequently over-report consumption of a “bad”

exposure, rather than *vice versa*, as in this situation where water appears to be beneficial. Furthermore, in Spanish population there is no general perception of a beneficial effect of high water intake (whereas it is likely to be the case in the US). Even though selection bias could also have occurred in this study as the controls were selected from hospitals, we saw no differences in water intake by control diagnostic category. Similarly, we observed very similar associations for smoking (Samanic et al. 2006) and THM levels (Villanueva et al. 2007) as those previous published on this population, suggesting that this study is representative of the overall study.

In sum, results from this study suggest that water intake is inversely associated with risk of bladder cancer. The decrease in bladder cancer risk observed with higher water intake was perceivable among current, past and never smokers, and for low and high THM exposures alike.

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Table 1. Characteristics of the participants with complete beverage data in a case-control study in Spain, 1998-2001

	Cases (N = 397)		Control (N = 664)	
	No.	%	No.	%
Sex				
Men	338	85.1	582	87.7
Women	59	14.9	82	12.3
Age				
<40	10	2.5	8	1.2
40-44	13	3.3	20	3
45-49	14	3.5	25	3.8
50-54	36	9.1	55	8.3
55-59	32	8.1	76	11.4
60-64	58	14.6	99	14.9
65-69	89	22.4	167	25.1
70-74	73	18.4	120	18.1
75+	72	18.1	94	14.2
Geographic area				
Barcelona	75	18.9	136	20.5
Valles	54	13.6	93	14
Alicante	37	9.3	41	6.2
Tenerife	84	21.2	138	20.8
Asturias	147	37	256	38.5
Smoking status				
Never	79	19.9	240	36.1
Former	144	36.3	247	37.2
Current	167	42.1	153	23
Occasional	7	1.8	24	3.6
Education				
<Primary school	174	43.8	320	48.2
<High school	163	41.1	243	36.6
≥High school	57	14.4	97	14.6
Other	3	0.7	4	0.6
High-risk occupation[a]				
No	310	78.1	574	86.5
Yes	74	18.6	67	10.1
Missing	13	3.3	23	3.5

[a]Defined in Methods.

Table 2.	Total fluid and water intake and bladder cancer risk				
	Ca / Co	OR[a]	OR[b]	95% CI[b]	P-trend
Total fluid quintiles[c]					
1	98 /134	1.0	1.0	ref	
2	76 /132	0.80	0.67	0.44-1.02	
3	81 /134	0.82	0.72	0.48-1.09	
4	73 /132	0.76	0.68	0.45-1.04	
5	69 /132	0.72	0.62	0.40-0.95	0.05
Water intake (ml/day)					
<400	155 /190	1.0	1.0	ref	
400-1399	144 /237	0.75	0.71	0.51-0.98	
>1399	98 /237	0.51	0.47	0.33-0.66	<.0001

[a]Adjusting for age and sex only.
[b]Adjusting for age, sex, region, cigarette smoking, high-risk occupation, nighttime urination frequency, and THM levels (and nontap fluid for water intake).
[c]Quintiles are sex-specific as follows, males: <1375, 1375-1800, 1800.1-2249, 2249.1-2825.5, >2825.5 ml/day
females: <1129, 1129-1400, 1400.1-1682.5, 1682.6-2259.5, >2259.5 ml/day

Table 3. Water intake and bladder cancer risk stratified by smoking status

Water intake	Never smoker			Past smoker			Current smoker		
(ml/day)	Ca / Co	OR[a]	95% CI	Ca / Co	OR[a]	95% CI	Ca / Co	OR[a]	95% CI
<400	29 / 75	1.0	ref	63 / 54	1.0	ref	61 / 54	1.0	ref
400-1399	32 / 88	0.95	(0.49-1.85)	47 / 92	0.42	(0.24-0.76)	62 / 48	0.99	(0.56-1.75)
>1399	18 / 77	0.49	(0.23-1.05)	34 / 101	0.33	(0.18-0.59)	44 / 51	0.56	(0.30-1.05)
p for trend		0.05			<0.001			0.06	

[a]Adjusting for age, sex, region, high-risk occupation, THM level, nighttime urination frequency, nontap fluid and smoking duration for past and current smokers.

Table 4. Joint effect of water and THM levels on bladder cancer risk

Water intake (ml/day)	THM level ≤8 ug/L Ca / Co	OR[a]	95% CI	8-26 ug/L Ca / Co	OR[a]	95% CI	26-49 ug/L Ca / Co	OR[a]	95% CI	>49 ug/L Ca / Co	OR[a]	95% CI
<400	25 / 34	1.0	ref	21 / 37	0.92	(0.37-2.28)	43 / 36	2.63	(1.05-6.55)	29 / 28	2.07	(0.68-6.28)
400-1399	30 / 50	0.66	(0.31-1.41)	22 / 51	0.69	(0.29-1.63)	25 / 34	1.08	(0.41-2.83)	27 / 44	1.16	(0.38-3.54)
>1399	16 / 46	0.36	(0.15-0.83)	8/29	0.40	(0.14-1.17)	22 / 39	1.07	(0.40-2.88)	24 / 59	0.80	(0.26-2.51)
Overall	71 / 130	1.0	ref.	51 / 117	1.02	(0.54-1.90)	90 / 109	2.34	(1.16-4.71)	80 / 131	2.06	(0.83-5.08)

[a]Adjusting for age, sex, region, cigarette smoking, high-risk occupation, nighttime urination frequency, nontap fluid.