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Bladder Cancer and Water Disinfection By-product Exposures through Multiple Routes: A Population-Based Case–Control Study (New England, USA)

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Background: Ingestion of disinfection byproducts has been associated with bladder cancer in multiple studies. Although associations with other routes of exposure have been suggested, epidemiologic evidence is limited.

Objectives: We evaluated the relationship between bladder cancer and total, chlorinated, and brominated trihalomethanes (THMs) through various exposure routes.

Methods: In a population-based case–control study in New England ($n = 1{,}213$ cases; $n = 1{,}418$ controls), we estimated lifetime exposure to THMs from ingestion, showering/bathing, and hours of swimming pool use. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression adjusted for confounders.

Results: Adjusted ORs for bladder cancer comparing participants with exposure above the 95th percentile with those in the lowest quartile of exposure (based on the distribution in controls) were statistically significant for average daily intake mg/d of total THMs [OR = 1.53 (95% CI: 1.01, 2.32), p-trend = 0.16] and brominated THMs [OR = 1.98 (95% CI: 1.19, 3.29), p-trend = 0.03]. For cumulative intake mg, the OR at the 95th percentile of total THMs was 1.45 (95% CI: 0.95, 2.2), p-trend = 0.13; the ORs at the 95th percentile for chlorinated and brominated THMs were 1.77 (95% CI: 1.05, 2,.99), p-trend = 0.07 and 1.78 (95% CI: 1.05, 3.00), p-trend = 0.02, respectively. The OR in the highest category of showering/bathing for brominated THMs was 1.43 (95% CI: 0.80, 2.42), p-trend = 0.10. We found no evidence of an association for bladder cancer and hours of swimming pool use.

Conclusions: We observed a modest association between ingestion of water with higher THMs (>95th percentile vs. < 25th percentile) and bladder cancer. Brominated THMs have been a particular concern based on toxicologic evidence, and our suggestive findings for multiple metrics require further study in a population with higher levels of these exposures. Data from this population do not support an association between swimming pool use and bladder cancer. https://doi.org/10.1289/EHP89

Introduction

Disinfection by-products (DBPs) are formed when organic constituents in source water react with chlorine or other disinfecting agents. Trihalomethanes (THMs), the most common of the DBPs, were first discovered in the 1970s (Bellar and Lichtenberg 1974; Rook 1974), and hundreds of DBP species have been identified since. The by-products formed when water is treated depend on many factors, including the specific disinfection processes used (e.g., chlorination, ozonation, chloramination, use of chlorine dioxide), levels of naturally occurring organic material and anthropogenic compounds, and other characteristics of the raw water such as temperature, pH, and bromide concentration (Richardson et al. 2007). In the United States, three chemical classes of DBPs are regulated: total THMs (chloroform, bromoform, bromodichloromethane, and chlorodibromomethane), haloacetic acids (HAA), and oxyhalides (U.S. EPA 1998). Since the identification of THMs, several studies have reported that exposure to chlorinated water is positively associated with bladder cancer (Villanueva et al. 2004). In its 1991 review, the International Agency for Research on Cancer (IARC) determined that there was inadequate evidence to characterize the use of chlorinated drinking water as carcinogenic to humans (IARC 1991) and that some individual compounds are not classifiable with regard to their carcinogenicity (bromoform, chlorodibromomethane). In addition, IARC has not classified any individual DBPs as Group 1 human carcinogens, although several have been classified as possible [Group 2B; specifically, dichloroacetic acid, trichloroacetic acid, dibromoacetic acid, bromochloroacetic acid, and Mutagen X (MX; 3-chloro-4-(dichloromethyl)-5-hydroxy-5*H*-furan-2-one)] or probable (Group 2A; specifically, chloral and chloral hydrate) human carcinogens (IARC 1999, 2004, 2013). Additional epidemiologic studies published in the last decade are supportive of an exposure–response relationship between THM exposure and bladder cancer risk, with

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associations apparently stronger in men than in women (Costet et al. 2011; Villanueva et al. 2004, 2007). In its 2001 toxicological review of chloroform, the most common THM, the U.S. EPA noted that the majority of mutagenicity assays were negative and concluded that positive assays may have been an indirect consequence of cytotoxicity and cell regeneration in response to high exposures rather than a direct genotoxic effect (U.S. EPA 2001). Brominated THMs have been shown to be mutagenic when activated by glutathione *S*-transferase theta 1 (GSTT1), in contrast to chloroform, which is not activated to a mutagen (Richardson et al. 2007). These brominated compounds are formed when the levels of bromide are high in the source water, and recent reports from water utilities have suggested increasing levels of brominated THMs in in the United States (Regli et al. 2015).

DBPs encompass a wide and expanding list of compounds to which humans might be exposed (Richardson et al. 2007). THM levels in water supplies have been regulated longer than other classes of DBPs; thus, data are more readily available to estimate past exposures to total THMs than other classes of DBPs, and total THMs are often used as a surrogate measure of overall DBP exposures in epidemiologic studies. However, total THMs may not represent the most etiologically relevant DBP exposures.

Beyond considering THM level, route of exposure has been of increasing interest in epidemiologic studies of DBPs. Until recently, ingestion was the major focus in most epidemiologic studies (Costet et al. 2011; Villanueva et al. 2004). Other routes of exposure such as inhalation or dermal absorption may be important for the volatile, nonpolar constituents (Richardson et al. 2007). Showering, bathing, and use of chlorinated or brominated swimming pools likely represent important sources of these exposures (Richardson et al. 2010). To our knowledge, only one study has examined the association between bladder cancer and DBP exposures resulting from showering, bathing, or swimming pool use. This study was conducted in Spain and reported that bladder cancer was associated with estimated THM exposures from showering or bathing (based on the average length of time spent showering or bathing and average residential THM concentration) and with use of swimming pools (never/ever or categorized by lifetime hours of use, without regard to water DBP concentrations) (Villanueva et al. 2007). In the present study, we estimated associations between bladder cancer and DBP exposures through multiple routes, including ingestion, showering and bathing, and use of swimming pools.

Methods

Study Population

We conducted a population-based case–control study in Maine, New Hampshire, and Vermont, as described previously (Baris et al. 2009). Cases included individuals 30–79 y old who were diagnosed with histologically confirmed carcinoma of the urinary bladder (including *in situ*) (WHO 2000) between 2001 and 2004 in Maine and Vermont or between 2002 and 2004 in New Hampshire, and who were ascertained through hospital pathology departments and hospital and state cancer registries. Controls, frequency matched to cases on state of residence (at diagnosis for cases or identification for controls), sex, and age (in 5-y groups, using the age at diagnosis for cases and the age at the time of identification for controls) were selected randomly from Department of Motor Vehicles (DMV) records in each state for those 30–64 y old and from beneficiary records of the Center for Medicare and Medicaid Services (CMS) for those 65–79 y old. Of the 1,878 eligible cases identified, 1,213 were interviewed (65%). A total of 1,418 controls participated in the study (65% of those identified from DMV and 65% from CMS). The study protocol was reviewed and approved by the relevant Institutional Review Boards, and all participants provided signed, informed consent.

Exposure Assessment

A trained study interviewer visited participants' homes and administered a computer-assisted personal interview that elicited information on a variety of factors, including global positioning system (GPS) coordinates, and a lifetime residential history that was used to reconstruct lifetime water-source information, which has been described (Nuckols et al. 2011). The median time from diagnosis to interview was 5.9 mo. When exact address information was not known, we obtained the most detailed information available (e.g., the nearest cross-street or landmark). For each home, the participant provided information on water sources, including whether a private source (well, spring, or other source) or a public utility (including the utility name for current homes) was used. In addition, if multiple sources were reported, the participant identified which source was the primary one used for drinking. We also batch-geocoded the home address using ArcGIS 9.2 (ESRI) and Matchmaker SDK Professional v4.3 (TeleAtlas) software. If the GPS and geocoded locations were within 500 m and were in the same township, we used the GPS location. If not (97 residences), we resolved the location using MapQuest (MapQuest, Inc.) and Google Maps (Google, Inc.). For past residences, we batch-geocoded home addresses and followed with manual interactive geocoding of addresses that were not batch-matched to a street address. We ascertained all jobs held for at least six months since the age of 16 and the town where each workplace was located. We assigned employment locations to the centroid of the appropriate census place, which includes census-designated places, consolidated cities, and incorporated places (U.S. Census Bureau. 2000). We mapped home and workplace locations in a geographic information system (GIS), including the attribute data on the water supply source (public, private well, other) as reported by study participants.

For former residences and workplaces served by a public water system (PWS), we assigned the most likely utility as described in Nuckols et al. (Nuckols et al. 2011). We were able to link 90% of residences reported or assumed to be served by a PWS to a specific utility and contacted individual utilities to verify our assignments in the study states and in Massachusetts, where many of the study participants had previously lived, and which therefore contributed the largest number of exposure-years on public water supplies. We verified service for 76.9% of total exposure-years on public water supplies.

For all utilities in the three study states and Massachusetts, we obtained historical measurement data and current water supply source (ground, surface, or mixed) from state files. We also abstracted historical water supply source, water treatment information, and additional THM measurement data from individual utilities, where available. Most reported THM values were above the limit of detection (96.5% of the reported total THM measurements within these states). However, if a measurement for total THM or for one of the constituent THMs was reported as below the detection limit, we imputed a value based on the measured values from other sources with measurements at low levels. Outside the four-state region, we abstracted current water supply source type (ground/surface) from U.S. EPA and state databases, and we abstracted historical measurement data for the 22 states with the highest percentage of person-years in the residential histories. A review of these records indicated that chlorination was the primary treatment used for disinfection of water. Using this information, we assigned yearly THM concentrations to each residence and workplace. For each residence within Maine, New

Hamphsire, Vermont, or Massachusetts, we were also able to assign concentration of chlorinated and brominated compounds based on the reported levels of constituent THMs. For residences or workplaces with a private water supply, we assumed zero exposure to THMs in primary analyses.

We had limited information on seasonal or spatial variability in THM concentrations within water supply distribution systems. Therefore, all residences and workplaces within a given distribution system in a given year were assigned the same THM concentration. We used direct measurements reported by the utility for a given year within a utility for 13.5% of the years to which we assigned a value to a public water supply. When monitoring data were not available from a utility for a given year, we used a weighted average of data reported by the utility for other years in which they used the same water source type (e.g., ground, surface); this accounted for 64.6% of the public water supply assignments. If the source type changed, we used a population weighted average from all utilities within the state with the same water source type (21.9% of public water supply assignments). If there was no information on historical water source, we assumed that the current reported primary source was also the historical water source (19.4% of public water supply assignments).

We created multiple THM exposure metrics based on these data and on other information derived from the study questionnaires. For analyses focused on ingestion, we considered both residential and workplace exposures as described. First, we created a time-weighted average THM concentration, which was calculated by summing the weighted THM concentrations for each year and dividing by the total number of years with an assigned THM value. The result represented the THM concentration in the water supplies to the home and, where applicable, the workplace combined. We estimated the proportion of water consumed from the home and workplace taps by using information that the participant provided on the percentage they typically consumed from the home tap during their usual adult lifetime, with the remainder assigned to the workplace where applicable. Second, we calculated an average daily THM ingestion by multiplying each participant's average THM concentration by the amount of water that they reported consuming per day during their adult lifetime. Finally, we calculated cumulative THM ingestion by multiplying each participant's average THM concentration by the amount of water intake and the total number of years with an assigned THM exposure. Analyses based on average concentration, cumulative intake, and average daily intake were restricted to individuals for whom we were able to make an assignment of annual average THM concentration for $\geq$ 70% of their lifetime, including residential and workplace exposures [974 cases (80.2%) and 1,184 controls (83.5%)]. To evaluate the showering and bathing route of exposure, we used information that the participants provided on the average number of showers and/or baths that they took during their usual adult life. We then multiplied this number by the average THM concentration for water sources that served the home. Because showering and bathing exposures were estimated based on residence alone, we were able to assign exposures to 1,061 cases (87.5%) and 1,290 controls (90.9%). The proportion of various compounds contained within the class of total THMs can vary substantially, and there is evidence that the carcinogenicity of these compounds also varies. Therefore, we also calculated exposure metrics separately for chlorinated and brominated THMs, for both ingestion and showering/bathing, using data for residences and workplaces within the three study states (Maine, New Hampshire, and Vermont) and Massachusetts to define these exposures. These analyses were limited to participants whose exposures could be classified for $\geq$70% of their lifetime since the age of 15, including 909 (74.9%) cases and 1,095 (77.2%) controls for showering and bathing (based on residence exposures only) and 910 (75.1%) cases and 1,101 controls (77.5%) for ingestion metrics (based on residence and workplace exposures). All metrics included information starting from the age of 10 for residential exposures, when the residential history was collected, and from the age of 16, when work histories began.

Participants reported the number of hours of use of swimming pools separately during both summer and nonsummer months at ages <20 y, during their 20s and 30s, during their 40s and 50s, and at ages $\geq$60 y. Responses to these questions were used to calculate both age-specific and lifetime hours of use during summer and nonsummer months.

Statistical Methods

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for exposure to total THMs and for the concentrations of chlorinated and brominated compounds. Categories were based on quartiles, with the top quartile further split at the 90th and 95th percentiles based on the distribution among controls. We used the 95th percentile to define the highest exposure category. For average THM concentration, this cut point of 45.73 μg/L was similar to the concentration used to define the highest exposure category in a previous analysis of pooled data from three European studies (>50 μg/L) (Costet et al. 2011). ORs were calculated using the lowest quartile as the referent group except for analyses based on the use of swimming pools, which used nonusers as the referent. We adjusted for age (<55 y, 55–64 y, 65–74 y, and 75–79 y), sex, ethnicity (Hispanic/non-Hispanic), race (white only, mixed race, other race), smoking status [never, former, occasional, current as defined in (Baris et al. 2009)], state of residence (Maine, New Hampshire, Vermont), and ever employment in a high-risk occupation for more than 6 mo since the age of 16 as identified in this study, including metal workers, textile machine operators, mechanics/repairers, automobile mechanics, plumbers, computer systems analysts, landscape industry workers, health services, cleaning and building services, electronic components manufacturing, and transportation equipment manufacturing (Colt et al. 2011). We explored whether the results were confounded by arsenic concentration in the water assessed using similar methods to those used for the disinfection byproducts (Nuckols et al. 2011). We also evaluated the interaction between all total THM exposure metrics and smoking status (never, former, current) using a common referent group consisting of nonsmokers in the lowest category of THM exposure, and we conducted lagged analyses with lags from 10–50 y. Tests for trend were performed using the Wald test and used the midpoint value of each exposure category treated as a continuous variable in regression models. All tests were two-sided, and results were considered significant at $\alpha = 0.05$ all statistical analyses were conducted using SAS (v9.2; SAS Institute Inc.).

Because people with private wells are instructed to disinfect them with bleach, our assignment of zero THMs for private wells may be misclassified. Therefore, we conducted sensitivity analyses restricting private well exposure-years to those where the participant reported that the well was never disinfected with bleach. Using the same requirement of assigning THM levels for $\geq$70% of the participant's lifetime, this analysis included 815 cases (67.2%) and 963 controls (67.9%) for ingestion analyses of THMs.

Results

Cases and controls were similar with respect to the matching factors (age at diagnosis or interview, sex, and state of residence) (Table 1). Approximately 75% of both cases and controls were

male, which is typical for bladder cancer in Western populations (Silverman et al. 2006). Cases were more likely to be current smokers than were the controls and were more likely to have worked in a high-risk occupation for bladder cancer. Accounting for ingestion of water at sources other than the home, the mean percentage of water consumed from the home tap was 79% for males [standard deviation (SD) = 25%] and 86% for females (SD = 24%).

We evaluated several metrics of total THM exposure, including average concentration in the water, cumulative and average daily intake, and exposures associated with showering and bathing (Table 2). The adjusted OR for bladder cancer in association with average water THMs >95th percentile (>45.73 μg/L) vs. the lowest quartile (≤6.83 μg/L) was 1.27 (95% CI: 0.83, 1.96). ORs for all lower categories of exposure were negative but close to the null (p-trend = 0.41). The corresponding OR for cumulative intake (>1864.16 mg vs. ≤ 138.05 mg) was 1.45 (95% CI: 0.95, 2.20), with a similar OR for the 90–95th percentile category. For all other exposure categories, the ORs were close to the null (p-trend = 0.13). For average daily intake, the OR for the highest exposure group (>103.89 vs. < 8.69 μg/d) was 1.53 (95% CI: 1.01, 2.32), whereas ORs for lower levels of exposure were close to the null (p-trend = 0.16). There was no association with frequency of showering or bathing overall. Compared with those who reported showering or bathing 3 or fewer times per week, the OR for 4–6 showers/baths per week was 1.09 (95% CI: 0.84, 1.41), and the OR for ≥7 showers/baths per week was 1.04 (95% CI: 0.82, 1.33) (data not shown). Similarly, as shown in Table 2, associations were close to the null in every exposure category for showering or bathing combined with the level of total THMs in the water (p-trend = 0.85). We also examined potential confounding for arsenic concentration in the water and use of private wells, but the results were unchanged (data not shown).

We estimated associations for men (737 cases, 867 controls) and women (237 cases, 317 controls) separately (Table 3). The general patterns were similar to the overall results in both groups, with positive associations for the highest categories of exposure to average concentration, cumulative intake, and average daily intake (>95th percentile vs. the lowest quartile), but with stronger associations in women [e.g., for cumulative exposure, OR = 1.82 (95% CI: 0.81, 4.10) in women and OR = 1.37 (95% CI: 0.83, 2.26) in men]. However, estimates were imprecise owing to small numbers of observations, particularly in the high-exposure groups. The highest category of exposure via showering and bathing was positively associated with bladder cancer in women [OR = 1.40 (95% CI: 0.61, 3.23)] but not men [OR = 0.83 (95% CI: 0.49, 1.40)]. We also estimated associations between chlorinated and

Table 1. Selected characteristics of cases and controls in the New England Bladder Cancer Study with total THM assignments for ≥70% of lifetime residential history, 2001–2004.

Condition	Cases (n = 1,061)	Controls (n = 1,290)
Age, y		
<55	175 (16.5)	228 (17.7)
55–64	271 (25.5)	299 (23.2)
65–74	390 (36.8)	498 (38.6)
≥75	225 (21.2)	265 (20.5)
Sex		
Male	805 (75.9)	945 (73.3)
Female	256 (24.1)	345 (26.7)
State		
Maine	521 (49.1)	667 (51.7)
New Hampshire	353 (33.3)	395 (30.6)
Vermont	187 (17.7)	228 (17.7)
Race		
White	996 (93.9)	1,218 (94.4)
Mixed race	54 (5.1)	56 (4.4)
Other	11 (1.0)	16 (1.2)
Hispanic ethnicity		
No	22 (2.1)	22 (1.0)
Yes	1,039 (97.9)	1,266 (98.1)
Don't know	0	2 (0.9)
Smoking status[a]		
Nonsmoker	19 (1.8)	36 (2.8)
Occasional smoker	157 (14.8)	438 (34.0)
Former smoker	543 (51.2)	626 (48.6)
Current Smoker	341 (32.2)	189 (14.7)
Employment in a high-risk occupation[b]		
Never worked in paying job	11	9
Never worked in high-risk occupation	465 (44.3)	871 (68.0)
Ever worked in high-risk occupation	585 (55.7)	410 (32.0)

Note: Controls were frequency-matched on age, sex, and state of residence. THM, trihalomethane.
[a]Occasional smokers were defined as subjects who had smoked >100 cigarettes overall but never smoked cigarettes regularly. Former smokers were regular smokers who had quit smoking ≥1 y before diagnosis (cases) or selection date (controls). Current smokers were regular smokers who were still smoking or who had quit within 1 y of diagnosis or selection.
[b]High-risk occupations included metal workers, textile machine operators, mechanics/repairers, automobile mechanics, plumbers, computer systems analysts, landscape industry workers, health services, cleaning and building services, electronic components manufacturing, and transportation equipment manufacturing.

Table 2. Association between total THMs and bladder cancer, New England Bladder Cancer Study, 2001–2004.

Exposure metric	Cases	Controls	OR	95% CI
Average concentration (μg/L)[a,b]				
0–6.83	250	296	1.00	
>6.83–15.73	228	296	0.86	0.66, 1.11
>15.73–26.75	241	296	0.96	0.74, 1.25
>26.75–37.14	150	178	0.97	0.72, 1.30
>37.14–45.73	47	59	0.92	0.59, 1.44
>45.73	58	59	1.27	0.83, 1.96
			p-trend = 0.41	
Cumulative intake (mg)[b,c]				
0–138.05	215	296	1.00	
>138.05–398.33	246	296	1.12	0.86, 1.45
>398.33–801.93	243	296	1.09	0.84, 1.42
>801.03–1362.01	144	178	0.98	0.72, 1.33
>1362.01–1864.16	58	59	1.32	0.86, 2.04
>1864.16	68	59	1.45	0.95, 2.20
			p-trend = 0.13	
Average daily intake (μg/d)[b,c]				
0–8.69	214	296	1.00	
>8.69–23.16	244	296	1.12	0.86, 1.46
>23.16–47.00	257	296	1.17	0.90, 1.52
>47.00–76.30	132	178	0.94	0.69, 1.28
>76.30–103.89	56	59	1.18	0.76, 1.81
>103.89	71	59	1.53	1.01, 2.32
			p-trend = 0.16	
Showering and bathing by total THM level (μg/L-wk)[a,d]				
0–21.42	268	323	1.00	
>21.42–66.29	280	322	1.02	0.79, 1.30
>66.29–136.82	227	323	0.83	0.64, 1.07
>136.82–221.32	188	193	1.21	0.92, 1.60
>221.32–287.48	50	65	0.94	0.61, 1.45
>287.48	48	64	0.94	0.60, 1.46
			p-trend = 0.85	

Note: The p-trend was derived by using the midpoint of the category as a continuous variable. CI, confidence interval; OR, odds ratio; THMs, trihalomethanes.
[a]Adjusted for age (<55, 55–64, 65–74 and 75–79 y), sex, ethnicity (Hispanic/non-Hispanic), race (white only, mixed race, other race), smoking status (never, occasional, former, current, state of residence (Maine, New Hampshire, Vermont), ever employment in a high-risk occupation and water intake (≤1.09 L/d, >1.09–1.53 L/d, >1.53–2.24 L/d, >2.24–3.79 L/d, >3.79 L/d).
[b]THM assignments based on residential and workplace sources; 974 cases and 1,184 controls have ≥70% of lifetime assignments.
[c]Adjusted for age, sex, ethnicity, race, smoking status, state, and employment in high-risk occupation.
[d]THM assignments based on residential sources; 1,061 cases and 1,290 controls have ≥70% of lifetime assignments.

Table 3. Association between total trihalomethanes (THMs) and bladder cancer by sex, New England Bladder Cancer Study, 2001–2004.

	Males				Females			
Exposure metric	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Average concentration (μg/L)[a,b]								
0–6.83	194	220	1.00		56	76	1.00	
>6.83–15.73	173	213	0.83	0.61, 1.11	55	83	0.92	0.54, 1.57
>15.73–26.75	183	223	0.94	0.69, 1.26	58	73	1.08	0.63, 1.87
>26.75–37.14	111	123	0.92	0.65, 1.30	39	55	1.01	0.56, 1.82
>37.14–45.73	37	49	0.80	0.49, 1.32	10	10	1.70	0.59, 4.88
>45.73	39	39	1.20	0.73, 2.06	19	20	1.66	0.74, 3.70
			p-trend = 0.80				*p*-trend = 0.18	
Cumulative intake (mg)[b,c]								
0–138.05	171	223	1.00		44	73	1.00	
>138.05–398.33	189	219	1.06	0.78, 1.43	57	77	1.30	0.75, 2.28
>398.33–801.93	181	215	1.00	0.74, 1.36	62	81	1.36	0.78, 2.38
>801.03–1362.01	108	129	0.98	0.69, 1.39	36	49	1.04	0.55, 1.96
>1362.01–1864.16	39	40	1.27	0.75, 2.13	19	19	1.39	0.61, 3.15
>1864.16	49	41	1.37	0.83, 2.26	19	18	1.82	0.81, 4.10
			p-trend = 0.24				*p*-trend = 0.29	
Average daily intake (μg/day)[b,c]								
0–8.69	168	225	1.00		46	71	1.00	
>8.69–23.16	188	219	1.10	0.82, 1.49	56	77	1.07	0.62, 1.87
>23.16–47.00	191	216	1.08	0.80, 1.46	66	80	1.44	0.84, 2.49
>47.00–76.30	98	119	1.01	0.71, 1.45	34	59	0.79	0.42, 1.46
>76.30–103.89	43	47	1.02	0.62, 1.65	13	12	1.74	0.68, 4.47
>103.89	49	41	1.48	0.90, 2.45	12	18	1.79	0.80, 3.96
			p-trend = 0.30				*p*-trend = 0.23	
Showering and bathing by total THM level (μg/L-week)[a,d]								
0–21.42	217	246	1.00		51	77	1.00	
>21.42–66.29	210	238	1.00	0.75, 1.32	70	84	1.07	0.64, 1.80
>66.29–136.82	170	234	0.81	0.60, 1.08	57	89	0.92	0.54, 1.57
>136.82–221.32	136	135	1.20	0.87, 1.66	52	58	1.30	0.74, 2.30
>221.32–287.48	40	48	0.90	0.56, 1.46	10	17	1.12	0.44, 2.89
>287.48	32	44	0.83	0.49, 1.40	16	20	1.40	0.61, 3.23
			p-trend = 0.79				*p*-trend = 0.34	

Note: The *p*-trend was derived by using the midpoint of the category as a continuous variable. CI, confidence interval; OR, odds ratio.
[a]Adjusted for age (<55, 55–64, 65–74 and 75–79 y), ethnicity (Hispanic/non-Hispanic), race (white only, mixed race, other race), smoking status (never, occasional, former, current, state of residence (Maine, New Hampshire, Vermont), ever employment in a high-risk occupation, and water intake (≤1.09 L/d, >1.09–1.53 L/d, >1.53–2.24 L/d, >2.24–3.79 L/d, >3.79 L/d).
[b]THM assignments based on residential and workplace sources; 974 cases and 1,184 controls have ≥70% of lifetime assignments.
[c]Adjusted for age, state, ethnicity, race, smoking status, employment in high-risk occupation.
[d]THM assignments based on residential sources; 1,061 cases and 1,290 controls have ≥70% of lifetime assignments.

brominated compounds separately for both ingestion and showering/bathing routes (Table 4). There was no apparent association for chlorinated or brominated compounds associated with average concentration in the water. However, ORs increased in magnitude with increasing cumulative intake and average daily intake for both chlorinated and brominated compounds. For cumulative intake, there were positive trends for both chlorinated (*p*-trend = 0.07) and brominated (*p*-trend = 0.02) compounds, with statistically significant associations in the highest categories of exposure compared with the lowest quartile [95th percentile OR = 1.77 (95% CI: 1.05, 2.99) for chlorinated compounds and 95th percentile OR = 1.78 (95% CI: 1.05, 3.00) for brominated compounds]. Average daily intake was positively associated with the highest level of exposure to brominated compounds [OR = 1.98 (95% CI: 1.19, 3.29), *p*-trend = 0.03] and chlorinated compounds [OR = 1.67 (95% CI: 0.98, 2.85), *p*-trend = 0.10]. For showering and bathing and chlorinated compounds, the OR in the highest 10% compared with the lowest quartile was 1.05 (95% CI: 0.60, 1.85), *p*-trend = 0.68. For the brominated compounds, the OR in the highest category was 1.43 (95% CI: 0.84, 2.42), *p*-trend = 0.10). However, the associations at lower exposure categories were more similar.

No associations with swimming in swimming pools overall [OR in highest category = 0.94 (95% CI: 0.55, 1.59), *p*-trend = 0.09], during the summer [OR in highest category = 0.82 (95% CI: 0.46, 1.47), *p*-trend = 0.33], or not during the summer [OR in highest category = 0.85 (95% CI: 0.49, 1,48), *p*-trend = 0.16] were observed (Table 5). Although none was statistically significant, several ORs were <1.0. We also evaluated the use of pools at different ages and found no association with bladder cancer with swimming pool use at any age (data not shown).

We observed no interaction between total THMs and smoking, with interaction *p*-values >0.05 for all THM metrics. We conducted lagged analyses for 10, 20, 30, 40, and 50 y for cumulative THM exposure. The results were generally similar to those obtained for the unlagged analyses (see Table S1).

Finally, we conducted sensitivity analyses to evaluate the effect of potential exposure misclassification. First, to address our assumption that private wells have no THM exposure, we conducted sensitivity analyses excluding wells where the participant reported using bleach to disinfect the water. The results were generally similar to those in the primary analysis; risks at the highest level of average concentration were 1.11 (95% CI: 0.67, 1.81), *p*-trend = 0.37); for cumulative exposure, OR = 1.60 (95% CI: 1.01, 2.53), *p*-trend = 0.10; and for average daily intake, OR = 1.82 (95% CI: 1.16, 2.88), *p*-trend = 0.04) (see Table S2).

Discussion

Bladder cancer was positively associated with estimated total THM ingestion via drinking water in the top 5% of the distribution for our study population, although the associations were

Table 4. Associations between chlorinated and brominated trihalomethanes (THMs) and bladder cancer risk by exposure route in the New England Bladder Cancer Study, 2001–2004.

	Chlorinated Compounds[a]					Brominated Compounds[a]			
Exposure metric	Cases	Controls	OR	95% CI		Cases	Controls	OR	95% CI
Average Concentration in Drinking Water (μg/L)[b,c]									
0–1.90	226	276	1.00		0–0.36	229	276	1.00	
>1.90–8.00	217	275	1.02	0.74, 141	>0.36–0.97	213	275	0.90	0.65, 1.24
>8.00–17.11	212	275	0.93	0.64, 1.36	>0.97–1.76	221	275	0.92	0.62, 1.35
>17.11–27.71	154	165	1.10	0.72, 1.69	>1.76–2.60	133	165	0.99	0.63, 1.55
>27.71–34.32	47	55	1.14	0.65, 2.01	>2.60–3.27	58	55	1.04	0.59, 1.80
>34.32	54	55	1.34	0.77, 2.34	>3.27	56	55	1.05	0.61, 1.82
			p-trend = 0.21					*p*-trend = 0.58	
Cumulative intake (mg)[c,d]									
0–40.29	196	269	1.00		0–7.52	190	269	1.00	
>40.29–205.52	219	269	1.28	0.94, 1.75	>7.52–24.92	230	269	1.38	0.99, 1.92
>205.52–509.95	217	269	1.21	0.84, 1.74	>24.92–51.05	184	269	1.03	0.71, 1.49
>509.95–955.25	152	161	1.45	0.97, 2.17	>51.05–86.39	155	141	1.54	1.02, 2.31
>955.25–1359.69	46	54	1.37	0.79, 2.36	>86.39–124.92	65	54	1.76	1.05, 2.95
>1359.69	62	53	1.77	1.05, 2.99	>124.92	68	53	1.78	1.05, 3.00
			p-trend = 0.07					*p*-trend = 0.02	
Average daily intake (μg/d)[c,d]									
0–2.69	197	269	1.00		0–0.5	194	269	1.00	
>2.69–12.04	213	269	1.29	0.94, 1.77	>0.5–1.45	200	269	1.20	0.86, 1.66
>12.04–30.01	223	269	1.26	0.88, 1.82	>1.45–3.06	230	269	1.34	0.94, 1.92
>30.01–54.10	149	161	1.51	1.00, 2.26	>3.06–5.16	148	161	1.42	0.94, 21.3
>54.10–77.28	53	54	1.46	0.85, 2.90	>5.16–7.04	47	54	1.20	0.70, 2.05
>77.28	57	53	1.67	0.98, 2.85	>7.04	73	53	1.98	1.19, 3.29
			p-trend = 0.10					*p*-trend = 0.03	
Showering or bathing (μg/L-wk)[b,e]									
0–8.38	217	274	1.00		0–1.51	212	274	1.00	
>8.38–35.34	210	274	1.10	0.80, 1.52	>1.51–4.50	226	274	1.11	0.81, 1.53
>35.34–95.06	243	274	1.25	0.87, 1.78	>4.50–9.29	209	274	1.07	0.75, 1.51
>95.06–164.35	149	164	1.24	0.83, 1.85	>9.29–15.37	147	164	1.22	0.82, 1.82
>164.35–224.68	51	55	1.36	0.80, 2.30	>15.37–20.43	56	55	1.46	0.87, 2.46
>224.68	39	54	1.05	0.60, 1.85	>20.43	59	54	1.43	0.84, 2.42
			p-trend = 0.68					*p*-trend = 0.10	

Note: The *p*-trend was derived by using the midpoint of the category as a continuous variable. Analyses restricted to water sources in Maine, Massachusetts, New Hampshire, and Vermont. CI, confidence interval; OR, odds ratio.

[a]All analyses of chlorinated compounds adjusted from brominated compound concentrations; all analyses of brominated compounds adjusted for chlorinated compound concentrations.

[b]Adjusted for age (<55, 55–64, 65–74 and 75–79 y), ethnicity (Hispanic/non-Hispanic), race (white only, mixed race, other race), smoking status (never, occasional, former, current) state of residence (Maine, New Hampshire, Vermont), ever employment in a high-risk occupation, and water intake (≤1.09 L/d, >1.09–1.53 L/d, >1.53–2.24 L/d, >2.24–3.79 L/d, >3.79 L/d).

[c]THM assignments based on residential and workplaces source; 909 cases and 1,095 controls have ≥70% of lifetime assignments.

[d]Adjusted for age, ethnicity, race, smoking status, and ever employment in high-risk occupation.

[e]THM assignments based on residential sources; 910 cases and 1,101 controls have ≥70% of lifetime assignments.

modest in magnitude. Although estimated THM levels were lower in this study than those reported in some other epidemiologic studies, we observed positive associations at levels >46 μg/L (top 5% of average concentration compared with <6.83 μg/L for the lowest quartile). These results are comparable to those obtained for exposure above this level in other studies (Costet et al. 2011). In the United States, the current maximum contaminant level for total THMs is 80 μg/L as an annual average (U.S. EPA 2006). The associations were stronger for metrics that incorporated the amount of water ingested than for average THM concentration alone. In our population, there was some, although limited, evidence of an association for exposure to total THMs from showering or bathing. Our results also suggest that the associations between THM exposure and bladder cancer are similar in men and women. Other studies have suggested stronger associations in men (Costet et al. 2011; Villanueva et al. 2007). However, previous studies included relatively few women, making evaluation of effects in females problematic. Our results are consistent with those of the National Bladder Cancer Case–Control Study of 2,982 cases and 5,782 controls, including 660 female cases and 1,323 female controls, which observed similar or even higher associations among women who had longer duration at residences served by chlorinated surface water sources compared with men (Cantor et al. 1987).

We evaluated chlorinated and brominated compounds separately. Although toxicologic data suggest that brominated compounds may be more important for bladder carcinogenicity, we did not observe a clear difference in the patterns of association between the brominated and chlorinated compounds. Average concentrations were not associated with bladder cancer for either exposure. However, as with the total THMs, average daily intake and cumulative exposures to both classes of THMs were associated with bladder cancer. There was no association for chlorinated compounds and showering/bathing. However, we did observe a modest increase at the highest levels of brominated compounds through showering and bathing. This finding is important because brominated compounds are more mutagenic than chlorinated compounds and have been implicated as being among the most carcinogenic THMs (Richardson et al. 2007). Two studies have evaluated the role of chlorinated and brominated compounds separately (Bove et al. 2007; Salas et al. 2013). The first study, conducted in New York State, was based on THM measurements from a single utility taken 20–25 y after case diagnosis. This study reported statistically significant associations between bladder cancer and THMs overall as well as with several individual THMs, including chloroform, although the strongest associations were with bromoform (Bove et al. 2007). In the second study, conducted in Spain, associations were strongest with total

Table 5. Associations between hours of swimming pool use and bladder cancer, New England Bladder Cancer Study, 2001–2004.

Exposure metric	Cases ($n = 1,193$)	Controls ($n = 1,414$)	OR	95% CI
Total hours during any time period				
Never used swimming pool	653	743	1.00	
0–1,000	151	168	1.04	0.80, 1.36
>1,000–2,316	149	168	1.11	0.85, 1.45
>2,316–4,824	137	168	0.96	0.73, 1.26
>4,824–8,684	57	100	0.67	0.48, 1.00
>8,684–12,174	15	34	0.55	0.28, 1.05
>12,174	31	33	0.94	0.55, 1.59
				p-trend = 0.09
Total hours during summer				
Never used swimming pool	653	743	1.00	
0–480	123	175	0.86	0.65, 1.13
>480–1,140	145	161	1.10	0.84, 1.44
>1,140–3,000	161	179	1.11	0.85, 1.43
>3,000–4,956	57	89	0.65	0.44, 0.95
>4,956–6,660	31	34	1.06	0.61, 1.81
>6,660	23	33	0.82	0.46, 1.47
				p-trend = 0.33
Total hours not during summer				
Never used swimming pool	653	743	1.00	
0 h not in summer	285	314	1.09	0.88, 1.35
>0–600	25	37	0.65	0.37, 1.14
>600–2,280	134	171	0.92	0.70, 1.21
>2,280–5,320	55	94	0.81	0.55, 1.18
>5,320–7,720	15	25	0.73	0.37, 1.44
>7,720	26	33	0.85	0.49, 1.48
				p-trend = 0.16

Note: Adjusted for age (<55, 55–64, 65–74 and 75–79 y), ethnicity (Hispanic/non-Hispanic), race (white only, mixed race, other race), smoking status (never, occasional, former, current, state of residence (Maine, New Hampshire, Vermont), ever employment in a high-risk occupation, and average trihalomethane concentration (<5.55 mg/L, 5.55 to <14.47 mg/L, 14.47 to <26.39 mg/L, 26.39 to <37.78 μg/L, 37.38 to <47.99 μg/L, >47.99 mg/L). Trend tests based on the midpoint of the category treated as a continuous variable. CI, confidence interval; OR, odds ratio.

THMs, but both the overall level of estimated THMs and the relative concentration of brominated compounds were substantially higher than those in our study, with the median of the average concentration of total THMs being 27.4 μg/L [interquartile range (IQR): 9.4–49.8 μg/L] and the median of the average concentration of brominated compounds being 6.2 μg/L (IQR: 3.8–29.1 μg/L) (Salas et al. 2013). The authors did not evaluate alternative exposure classifications other than total THMs for showering and bathing.

We saw no association between swimming pool use and bladder cancer risk. We evaluated associations separately for use during the summer and nonsummer months because the level and relative concentrations of DBPs are influenced by whether the pool is indoors or outdoors (Simard et al. 2013), but we saw no difference. We also found no association with use of swimming pools at any age (data not shown). Exposure studies have demonstrated increased THM concentrations in the exhaled and alveolar air (Aggazzotti et al. 1993; Caro and Gallego 2007; Kogevinas et al. 2010; Lourencetti et al. 2012), blood (Aggazzotti et al. 1990), and urine (Caro and Gallego 2007, 2008) of swimmers. The lack of association in the present study is not consistent with the only other epidemiologic study to evaluate this question, which showed a statistically significant positive association with bladder cancer with ever use of swimming pools (Villanueva et al. 2007). This Spanish study had no measurements of THMs or other DBPs in pools. Differences in DBPs in swimming pools across different geographic areas and across time are not well understood. The DBPs in swimming pools are affected by the same characteristics as drinking water, including the constituents of the source water. The toxicity of swimming pool water with bromide ions has been estimated to be 27 times that of pool water without bromide ions (Hansen et al. 2011). The specifics of the DBPs formed also vary by the source water and by the disinfection processes used (Lee et al. 2010); they can be additionally affected by factors such as the number of swimmers in the pool and the presence of urine or other body fluids and personal care products (Chowdhury et al. 2014). Exposure through the inhalation route can be further affected by temperature and by the ventilation characteristics of the swimming area. Differences in these characteristics between our study and the Spanish study may partially explain the differences in findings pertaining to swimming pool use, but this matter should be explored further.

The associations observed in this study were stronger for metrics that incorporated water intake (cumulative and average daily intake) than considering the average water concentration alone, particularly for the analyses of chlorinated and brominated compounds separately. A similar pattern was observed in an evaluation of bladder cancer associated with low-to-moderate levels of arsenic in drinking water in the same study population (Baris et al. 2016). Taken together, these results suggest that when contaminants in water are relatively low, it is important to consider not only the concentration but also the amount of exposure through ingestion or through showering and bathing in the case of THMs in estimating individual exposure. Although arsenic and THMs are both water contaminants, they were not strongly correlated ($r = -0.10$ for average concentration) in this study, and controlling for arsenic in these analyses did not have an impact on risk estimates for THMs (data not shown).

Several biologic mechanisms for the carcinogenicity of DBPs have been proposed. Several DBPs are genotoxic or mutagenic, either alone or as part of a mixture, although some, such as the most prevalent THM chloroform, are only considered to be so at very high levels of exposure (Richardson et al. 2007). There has been interest in the effect of genetic susceptibility in modifying risk. In an analysis from the Spanish study, there were significant interactions between genetic variation in key metabolizing pathways and DBP levels on bladder cancer risk (Cantor et al. 2010). Although these findings are consistent with those of experimental

studies, further replication in epidemiologic studies is needed. It has been suggested that epigenetic mechanisms may also be important, particularly related to long-term lower exposures (Salas et al. 2014, 2015).

Strengths of this study include the lifetime water source histories, the validated linkage of the residences and workplaces to specific public water supplies, and the extensive historical monitoring data to generate the exposure estimates that allowed us to evaluate not only total THMs but also brominated and chlorinated species. However, owing to the limited availability of measurements, we were unable to evaluate other classes of DBPs, such as haloacetic acids, although they and other DBPs may be more etiologically relevant. We were also able to evaluate various exposure routes, such as showering and bathing and use of swimming pools, which have been implicated as important routes of exposure. However, despite our efforts, limitations in the exposure assessment may have hindered our ability to detect associations. In our study, the highest 5% of exposure was above approximately 45 μg/L, limiting our ability to perform more detailed analyses above this level. This concentration is near the lowest level of exposure at which statistically significant elevations in bladder cancer risk have been observed in several other populations where exposures were generally much higher (Costet et al. 2011; Villanueva et al. 2004). We were interested in the separate effects of chlorinated and brominated compounds; however, our analyses were limited by the low exposure levels and by the smaller percentage of brominated compounds compared with the only other study that estimated the relative contributions of chlorinated and brominated compounds (Salas et al. 2013). Another limitation of our study is our lack of measured THM levels in private wells. In our primary analyses, consistent with other published studies, we assumed zero exposure, which is valid if the wells were not being disinfected. The results of our sensitivity analyses restricted to those wells with no reported use of bleach were generally similar to those of the primary analyses for average concentration and for cumulative intake; however, there was some evidence that the associations with average daily intake of THMs were increased when these wells were excluded. In the primary analyses, these wells would have contributed exposure-years to the referent category; therefore, the fact that associations appeared to be stronger when they were removed from the analysis could indicate that there is exposure misclassification in our assumption. Another source of potential exposure misclassification is spatial variability within the distribution systems. Because of the long latency of bladder cancer, and therefore the long time period of interest, we were not able to evaluate this potential source of misclassification, although variability within systems is a well-known phenomenon. All of these sources of exposure misclassification should have been nondifferential.

Conclusions

We found modest associations with bladder cancer and average daily intake and cumulative intake of THMs in the highest 5% of exposure compared with the lowest quartile. Although the distribution of THM concentration was lower in this study population than in several others, our suggestive results for this metric are consistent with those of previous studies that observed a modest increase in bladder cancer with THM concentrations above approximately 45 μg/L. The relatively large number of women in the present study allowed us to evaluate associations by sex; our finding of similar results among males and females is notable because some other studies have suggested that the associations are stronger in males. We saw no evidence of an association with total THMs overall through the showering/bathing route. Our suggestive, but not conclusive, finding of an association between showering and bathing with higher brominated compounds requires further study in a population with higher levels of these exposures. Data from this study do not suggest an association between the use of swimming pools and bladder cancer in the U.S. New England population. Overall, the findings from this large population-based study are generally consistent with those of other epidemiologic studies that have reported evidence of an association between disinfection by-products and bladder cancer.

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