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Case-control study of bladder cancer and chlorination by-products in treated water (Ontario, Canada)

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Chlorine is by far the most commonly used chemical for the disiiection of water supplies in North America. However, chlorine reacts with organic material in the raw water producing a number of halogenated hydrocarbon by-products. This population-based case-control study in Ontario, Canada examined the relationship between bladder cancer and exposure to chlorination by-products in public water supplies. Residence and water source histories and data from municipal water supplies were used to estimate individual exposure according to water source, chlorination status, and by-product levels (represented by trihalomethane [THM] concentration). Exposures were estimated for the 40-year period prior to the interview, using 696 cases diagnosed with bladder cancer between 1 September 1992 and 1 May 1994 and 1,545 controls with at least 30 years of exposure information. Odds ratios (OR) adjusted for potential confounders were used to estimate relative risk. Those exposed to chlorinated surface water for 35 or more years had an increased risk of bladder cancer compared with those exposed for less than 10 years (OR= 1.41, 95 percent confidence interval [CI] = 1.10-1.81). Those exposed to an estimated THM level ≥ 50 μg/liter for 35 or more years had 1.63 times the risk of those exposed for less than 10 years (CI = 1.08-2.46). These results indicate that the risk of bladder cancer increases with both duration and concentration of exposure to chlorination by-products, with population attributable risks of about 14 to 16 percent. Chlorination by-products represent a potentially important risk factor for bladder cancer. *Cancer Causes and Control* 1996, 7, 596-604

Key words: Bladder neoplasms, Canada, chlorine, environmental exposures.

Introduction

Chlorine is by far the most commonly used chemical for the disinfection of water supplies in North America.[1] Chlorinated water sources serve over 75 percent of the population of Canada? During the chlorination process, chlorine reacts with organic material in the water producing hundreds of halogenated hydrocarbon compounds as by-products.[1] Organic materials include both naturally occurring substances and those resulting from industrial and municipal waste water or run-off. Of the identified by-products, trihalomethanes (THM) occur most frequently and have been the most thoroughly investigated.[1-6] Comprised primarily of a group of four volatile organics (chloroform, bromodichloromethane; dichlorobromomethane, and bromoform), THMs are mutagenic and are possible human carcinogens: Because the concentration of THMs in treated water is measured routinely and it is reasonable to assume that it correlates highly with the formation of other chlorination by-

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products,' it is a useful indicator of the level of chlorination by-products in treated water.

Recent case-control studies consistently have reported an association between exposure to chlorination by-products and risk of bladder cancer.[7-9] A meta-analysis of seven studies,[8-14] which were conducted between 1978 and 1988, yielded a statistically significant overall relative risk estimate of 1.21 (95% confidence interval [CI] = 1.09-1.34).[15] The methods used, populations studied, and exposure indices varied among these studies. The magnitude of the association tended to increase with improved exposure assessment. In general, studies which collected more detailed information about participants' lifetime residences and sources of drinking water and those which accurately represented level of chlorination by-products produced higher risk estimates.[15,16]

Assessment of individual exposure to chlorination by-products in water supplies is difficult because of the lack of specific historical exposure data. Epidemiologic studies have employed a variety of indicators of exposure to chlorination by-products, including use of surface water, use of chlorinated surface water, and current level of THMs in the water supply. However, the composition of chlorinated water differs from location to location as a result of variations in the characteristics of the raw water and in the treatment procedures employed. Therefore, none of these indicators necessarily represent the same exposure to chlorination by-products in different locations. Because of the misclassification inherent in these exposure assessment methods, it has been difficult to detect risks of relatively small magnitude. In addition, the methods of assessing exposure to chlorination by-products described above have not permitted examination of risk associated with exposure to varying concentrations of chlorination by-products, particularly cumulative lifetime exposure.

The objective of this study was to examine the relationship between bladder cancer and exposure to chlorination by-products in household water supplies. An attempt was made to build on previous methodologies by considering individual's residences and water sources over many years and estimating historical concentrations of chlorination by-products in water supplies. Bladder cancer risks are examined according to duration and level of exposure to chlorination by-products in household water supplies.

Materials and methods

Selection of cases and controls

A population-based case-control study was conducted, where cases were residents of Ontario (excluding the North), Canada, identified with a histologically confirmed diagnosis of primary cancer or carcinoma *in situ* of the bladder (site code 188, ICD-9);[17] diagnosed between 1 September 1992 and 1 May 1994, at ages between 25 and 74 years. Cases were identified from pathology reports routinely submitted to the Ontario Cancer Registry (OCR) at the Ontario Cancer Treatment and Research Foundation. Pathology reports typically are received at the OCR within six months of diagnosis and an estimated 95 percent of cancer incidence in Ontario is registered.'*

Of 1,694 eligible cases identified in the OCR, an appropriate physician could not be identified for 18 patients. The physician consent process indicated that 232 patients were recently deceased or too ill to be contacted. Of the remaining 1,444 patients, consent was received to contact 1,262 (87 percent). A few physicians in the study area refused to participate in the study, thus eliminating 76 patients (five percent). The physician refused to provide consent for 51 patients (four percent) and no response was received from the physician by the end of data collection for 55 patients (four percent).

Controls were an age-gender frequency-matched sample of the general population in the same area. Since the control subjects were used also to study cancers of the colon and rectum with respect to the same exposures, they were selected to have the expected age-gender distribution of the three cancer sites combined. Controls were accrued through a multistage procedure where households were selected randomly from a computerized database of residential telephone listings, a census of each household led to the identification of the appropriate study subject according to age and gender, and this subject was asked whether he/she would participate. The database of telephone numbers was a random sample of all listed residential telephone numbers in the study area. Interviewers contacted 10,219 households during control accrual, and 91 percent provided a census of residents. Because of the age-gender frequency-matching criteria employed, many households did not have a resident who was eligible and needed for the study at a particular point in time. In over 90 percent of the households with an eligible resident ($n = 2,768$), the person selected for the study agreed to receive a questionnaire ($n = 2,494$).

Exposure assessment

Relevant exposure and confounding variables were collected using a mailed questionnaire in combination with a computer-assisted telephone interview. Structured interviews following computer prompts and validity checks were conducted after subjects had received the mailed questionnaire. Interviewers were blinded as to case-control status of the subject. Questions were included on demographics (*e.g.*, gender, date of birth, and education), other potentially important confounding variables (*e.g.*, smoking history and usual diet prior to

diagnosis) and information pertaining to the primary exposures of interest (*e.g.*, residence and water source history and usual water consumption prior to diagnosis). Subjects reported their drinking-water source and other household water sources at each residence as municipal, household well, bottled water, or other. Volume of tap water consumed was calculated from the reported daily frequency of consuming beverages containing water, two years prior to the interview, and usual source of water (tap or bottled) used to make hot and cold beverages.

Individual information was supplemented by water treatment data collected through a mailed survey of historical treatment practices at plants serving the study area, The survey ascertained, for each plant currently operating in the study region, area served, water source and characteristics, and treatment practices for years of operation between 1950 and 1990. Water treatment information was reported for an average day in August in five-year intervals and that observation was used to represent water characteristics for the years surrounding that date. Each water supply in the study area used by each participant was characterized by three parameters: source (surface cf ground), chlorination status (chlorinated *cf* unchlorinated), and level of chlorination by-products (estimated summer THM level). Water source and chlorination status were provided directly by treatment plant surveys. Past levels of chlorination by-products were represented by historical THM levels. These were estimated from the treatment plant survey data using a model which was developed to predict the THM level in treated water, from characteristics of the treatment process.

The model was built using measurements recorded by the Ontario Drinking Water Surveillance Program (ODWSP) between 1988 and 1992 for 114 treatment plants. In the database maintained by this Program, plants have variable numbers of observations recorded at different points in time for a total of 2,494 observations. Potential predictors of THM level in treated water were identified on the basis of the literature, availability in the ODWSP database, and availability historically in treatment plant records (1950-90). The latter was determined through consultation with a number of plant operators and representatives of ODWSP. At this stage, it was indicated that two potentially important predictors of THM level, turbidity and pH, were not consistently available on an historical basis. Those predictors selected for inclusion in the model-building process were: characteristics of the raw water (source-surface lake, surface river, or ground; depth of the intake pipe; water temperature); pre-treatment procedures (chlorination dose; chloramination); treatments employed (coagulation; polyelectrolytes; activated carbon); and post-treatment procedures (chlorination dose; de-chlorination). Separate models were created for three subgroups: surface water source with pre-treatment chlorination; surface water source without pre-treatment chlorination; and ground water source.

To evaluate how well these models predicted historical THM levels, they were applied to data for the independent variables available in the ODWSP database for 1986 and 1987 ($n = 354$). Values of total THMs predicted by the models were compared with those observed and present in the database. The correlation between observed and predicted values was 0.76. When observed and predicted THM concentrations were dichotomized at 50 μg/L, the model predicted values with a sensitivity of 84 percent and a specificity of 76 percent.

These models were applied to survey data from the water treatment plants to estimate historical THM levels by time for each plant. Since the treatment plant survey requested information for August, when chlorination by-product levels are usually the highest, the THM estimate represents a summer level and generally will be close to the annual peak value for that plant. Private wells were assigned a THM concentration of zero.

Study participants' water exposures were estimated by linking a subject's residence and water source history to the relevant treatment-plant data by time and geographic area. For each residence, only the subject's drinking-water source was employed, as another household source was seldom reponed. Thus, each subject would have, for each year of residence in the study area, indicators of the exposures of interest (source, chlorination status, and THM level). Duration of exposure estimates were calculated for each subject by summing the number of years in each exposure category. Results are presented for total years of exposure to chlorinated surface water and to water with estimated summer THM level at or above 25, 50, and 75 μg/L, in addition to quartiles of THM-years, the product of the continuous estimate of summer THM level and years at that level (analogous to pack-years of cigarette smoking).

The analysis considers exposures occurring over the 40-year period preceding two years prior to the subject's interview. To reduce the level of misclassification in exposures, these analyses are restricted to subjects with 30 or more years of known water history.

Analysis

Odds ratios (OR) are used throughout as estimates of relative risk. For categorical variables, ORs are presented for each level of exposure in comparison with the lowest category of exposure. For the exposures of primary interest, unconditional logistic regression was used to obtain ORs and CIs adjusted for potential confounders.[19]

Age and gender were included in all analyses. Other potentially important confounders were determined on

the basis of the bladder cancer literature and a backward stepwise logistic regression was used to identify a parsimonious model predicting bladder cancer risk. Factors considered to be potential confounders were: smoking; education; consumption of alcoholic beverages; coffee consumption; total fluid consumption; and dietary intake of energy (total calories), protein, fat, cholesterol, fiber, and vitamin A. Potential confounders which demonstrated a log linear relationship with risk in categorical form were analyzed as continuous variables. Exclusion of factors from the model was based on a score-test P-value of greater than 0.10; this conservative P-value ensured that all factors which might confound the relationship of interest were included in the model.

The test for trend for categorical variables was based on the likelihood ratio test conducted by including the factor as a continuous term in a logistic regression model.

Results

Response rates

Questionnaires were mailed to **1,262** cases and **2,494** control subjects. One hundred and fifty-six cases and **62** controls were unable to complete questionnaire because of illness, death, or communication barriers. Of those remaining, questionnaires were completed, by **84** percent of cases (n= **927**) and **87** percent of controls (n= **2,118**). The overall response rate in cases is 73 percent, calculated as the product of physician consent and case participation, and in controls is **72** percent, the product of the response to initial contact (*i.e.*, agreed to give a household census, and where an eligible subject was present, agreed to receive a questionnaire) and the response to the telephone interview.

Of **431** water treatment-plant surveys mailed, 385 (**89** percent) were returned with all or partial information. Response rates were similar across regions, and data were received from all major population centers. The Ontario Drinking Water Surveillance Program (**1986-95**) and the National Survey of Water Facilities (conducted in **1986**) provided information on water source and treatments used for **1985** and 1990 for **44** of the **46** facilities with no returned survey.

The presented analyses includes the **696** cases (**75** percent) and **1,545** controls (**73** percent) for whom water source characteristics were available for at least 30 of the 40 years prior to interview, as described earlier.

Potential confounders

As seen in Table 1, cases are more often male (76 percent) in comparison with the control group (**63** percent) and are slightly older. This occurred because controls were selected to match the total case group of bladder, colon, and rectum cancers. Potential confounders included in the parsimonious model predicting cancer risk are age, gender, pack-years of smoking (log [pack years + 1]), current smoking status, highest level of education, and total energy intake (Table 1). The strongest predictor of risk is pack-years of smoking and we found that the best fit with the data for this factor is obtained with the form log(pack-years + 1). Using the parameter estimate from this representation, along with that for current smoking

Table 1. Distribution and odds ratios (OR) and 95% confidence intervals (CI) for cancer of the bladder associated with potential confounders, Ontario

Confounder	Cases (n= 696)	Controls (n= 1,545)	OR[a]	(CI)
Age (yrs)[b]	64.2'	61.0[c]	—	—
Gender				
Female	24%	37%	—	—
Male	76%	63%	—	—
Smoking (log [pack-years + 1])	47.8'	40.4'	1.27	(1.18-1.36)
Current smoker				
No	60%	76%	1.0	—
Yes	40%	24%	1.59	(1.25-2.03)
Level of education				
c Complete high school	51%	39%	1.0	—
Complete high school	18%	22%	0.76	(0.59-0.99)
Community college, some or complete university	31%	40%	0.75	(0.60-0.94)
Energy (1,000 kcal/wk)	410[c]	396'	1.03	(1.00-1.07)

[a] Odds ratio (95 percent confidence interval [CI]) adjusted for all other factors in the table.
Age and gender distribution of controls was restricted by the sampling procedure, therefore odds ratios for these factors are not presented.
Mean values; for smoking mean number of pack-years among ever smokers.

status, a current smoker with a total of 40 pack-years (the mean level among control ever-smokers) has four times the risk of bladder cancer than a life-long nonsmoker. A pattern of decreasing risk with higher educational attainment is observed. Bladder cancer risk increases with higher levels of energy intake. Other potential confounders (consumption of alcoholic beverages, coffee, and total fluid consumption; and dietary intake of protein, fat, cholesterol, fiber and vitamin A) are not associated with bladder cancer risk after controlling for the factors listed in Table 1.

Water *source*

Chlorinated surface water was used for 35 or more years by 35 percent of controls, and for 20 to 34 years by 28 percent (Table 2). Among controls, exposure for 35 or more years to estimated THM levels ≥ 25, 50 and 75 µg/L is observed for 14, five, and four percent of subjects, respectively.

There is a pattern of increasing risk with years exposed to chlorinated surface-water, where exposure to chlorinated surface-watersource for 35 years or more is associated with a relative risk estimate of 1.41 (CI = 1.09-1.81) in comparison with those exposed for less than 10 years.

Risk estimates are similar for each of the THM measures. While the general tendency is for relative risk to rise with increasing duration of exposure, it is only for 35 or more years of exposure that relative risks are consistently significant and of higher magnitude. Relative risks for 35 or more years of exposure to THM levels ≥ 25 µg/L, ≥ 50 µg/L, and ≥ 75 µg/L, are 1.58, 1.63, and 1.68 compared with those exposed at each level for less than 10 years. A statistically significant increase in bladder cancer risk also is observed for the highest quartiles of cumulative exposure (THM-years) relative to the lowest quartiles of exposure (OR = 1.44, CI = 1.10-1.88). When THM-years is modeled as a continuous factor, bladder

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the bladder according to years of exposure to water factors, Ontario

Water factor and years of exposure[a]	No. of Cases	No. of Controls	Crude		Adjusted[b]	
			OR	(CI)	OR	(CI)
Chlorinated (surface source)						
0-9 yrs	157	413	1.0	—	1.0	—
10-19	55	154	0.94	(0.65-1.37)	1.04	(0.71-1.53)
20-34	169	433	1.03	(0.79-1.34)	1.15	(0.86-1.51)
35+	315	545	1.52	(1.20-1.93)	1.41	(1.09-1.81)
THM ≥ 25 µg/L						
0-9 yrs	154	407	1.0	—	1.0	—
10-19	121	282	1.13	(0.85-1.52)	1.22	(0.90-1.66)
20-34	278	632	1.16	(0.91-1.48)	1.15	(0.88-1.47)
35+	143	224	1.69	(1.26-2.25)	1.58	(1.17-2.14)
THM ≥ 50 µg/L						
0-9 yrs	253	650	1.0	—	1.0	—
10-19	226	519	1.12	(0.90-1.39)	1.10	(0.87-1.38)
20-34	163	297	1.41	(1.10-1.81)	1.36	(1.05-1.76)
35+	54	79	1.76	(1.19-2.60)	1.63	(1.08-2.46)
THM ≥ 75 µg/L						
0-9 yrs	356	876	1.0	—	1.0	—
10-19	233	486	1.18	(0.96-1.45)	1.09	(0.88-1.35)
20-34	67	128	1.29	(0.92-1.80)	1.26	(0.89-1.78)
35+	40	55	1.79	(1.14-2.80)	1.68	(1.06-2.67)
THM-years (quartiles)						
1 (0-583 µg/L-years)	151	387	1.0	—	1.0	—
2 (584-1,505)	160	385	1.07	(0.81-1.40)	1.20	(0.88-1.64)
3 (1506-1956)	165	387	1.09	(0.83-1.43)	1.08	(0.82-1.42)
4 (1957-6425)	220	386	1.46	(1.13-1.89)	1.44	(1.10-1.88)
THM-years (continuous per 1,000 µg/L-years)						
	1.63[c]	1.48[c]	1.12	(1.04-1.21)	1.11	(1.02-1.21)

[a] Years exposed out of the 40 years prior to study.
[b] Odds ratio adjusted for age, gender, log pack-years of smoking, current smoking, education, and calorie intake.
[c] Mean value.

cancer risk increases by 11 percent with each ,000 µg/L-years (OR = 1.11, CI = 1.02-1.21).

Homogeneous water exposures

Assignment of an individual's water exposures is complicated by the fact that people move often, and thereby accumulate exposures from various water supplies during the exposure period. In the previous analyses, exposure was quantified according to the number of years using water with different characteristics. Subjects within a 'years of exposure' level, particularly those shorter than 20 years,, have a heterogeneous mixture of exposures. For example, individuals with 10 to 19 years of exposure to THMs ≥ 25 µg/L could have had 19 years at 100 µg/L and 20 years at 24 µg/L, or 10 years at 25 µg/L and 30 years at zero, *etc*. Table 3 presents the results of an analysis restricted to those who had relatively homogenous water exposures for a period of 30 or more years. Subjects exposed for 30 or more years to chlorinated surface water are compared with those exposed to ground water. Subjects with 30 or more years of exposure to estimated summer THM levels < 25 µg/L are used as the referent group in comparison with those having 30 or more years of exposure to estimated summer THM ≥ 25 and < 75 µg/L, and ≥ 75 µg/L.

Exposure to chlorinated surface water for 30 or more years is associated with a significant increase in risk (OR = 1.39, CI = 1.09-1.79) in comparison with exposure to a ground water source. There is a trend towards increasing bladder cancer risk with homogeneous exposure to increasing summer THM level (P trend = 0.006). In comparison with those exposed to summer THM levels < 25 µg/L for 30 or more years, those exposed to levels between 25 and 74 µg/L have a 43 percent increase in risk (OR = 1.43, CI = 1.01-2.04), and those exposed to THM levels ≥ 75 µg/L have a 66 percent increase in risk (OR = 1.66, CI = 1.11-2.51).

Risk by volume of water consumed and duration of exposure

Evaluation of the combined effects of quantity of water ingested and duration of exposure to a water source with elevated THM levels (≥ 50 µg/L) is presented in Table 4. Water consumption was categorized into three levels based on thirds of the control distribution of consumption. The referent category for all OR estimates comprised those using water with estimated summer THM level ≥ 50 µg/L for zero to nine years and consuming less than 1.54 liters of water per day.

Overall, the pattern of risk estimates does not provide support for an interaction between volume of water consumed and years of exposure to THM level ≥ 50 µg/L (P-value interaction = 0.775). However, statistically significant risk estimates representing more than a

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the bladder associated with exposure to water source characteristics for 30 or more of the 40 years prior to study, Ontario

Water source	No. of Cases	No. of Controls	Crude		Adjusted[a]	
			OR	(CI)	OR	(CI)
Ground	145	338	1.0	—	1.0	—
Chlorinated surface	402	776	1.39	(1.10-1.75)	1.39	(1.09-1.79)
THM level						
0-24 µg/L	169	447	1.0	—	1.0	—
25-74 µg/L	80	153	1.38	(0.99-1.94)	1.43	(1.00-2.03)
75+ µg/L	63	97	1.72	(1.18-2.51)	1.66	(1.11-2.51)
P-value for trend			0.002		0.006	

[a] Odds ratio adjusted for age, gender, log pack-years of smoking, current smoking, education, and calorie intake.

Table 4. Odds ratios[a] for cancer of the bladder for tap water consumption and duration of exposure to summer THM ≥ 50 µg/L, Ontario

Tap water consumption	Years of exposure to THM ≥ 50 µg/L			
	0-9	10-19	20-34	35+
< 1.54 µg/l per day	1.0 —	1.28 (0.83-1.96)	1.70 (1.08-2.68)	1.26 (0.58-2.71)
1.54-2.08	1.35 (0.91-2.01)	1.32 (0.87-1.98)	1.54 (0.95-2.48)	2.58 (1.28-5.21)
> 2.08	1.29 (0.87-1.90)	1.37 (0.91-2.06)	1.72 (1.10-2.70)	2.28 (1.12-4.67)

[a] Odds ratio (95 percent confidence interval [CI]) adjusted for age, gender, log pack-years of smoking, current smoking, education, and calorie intake.

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the bladder for those with 30 or more years of exposure to Chlorinated surface water according to exposure THM factors, Ontario

Water factor and years of exposure[a]	No. of Cases	No. of Controls	Crude		Adjusted[b]	
			OR	(CI)	OR	(CI)
THM ≥ 50 µg/L						
0-19 yrs	213	470	1.0	—	1.0	—
20-34	138	231	1.32	(1.00-1.73)	1.32	(0.99-1.77)
35+	51	75	1.50	(1.00-2.26)	1.45	(0.95-2.23)
THM ≥ 75 µg/L						
0-19 yrs	314	634	1.0	—		—
20-34	50	88	1.15	(0.78-1.69)	1.21	(0.80-1.82)
35+	38	54	1.42	(0.90-2.25)	1.44	(0.89-2.31)
THM-years (quartiies)						
1 & 2 (0-1,857 µg/L-yrs)	193	420	1.0	—	1.0	—
3 (1,858-2,225)	98	168	1.27	(0.93-1.74)	1.27	(0.91-1.77)
4 (2,226-6,425)	111	188	1.28	(0.95-1.74)	1.32	(0.96-1.81)
THM-years (continuous per 1,000 µg/L-years)						
	2.25[c]	2.18[c]	1.07	(0.94-1.23)	1.08	(0.95-1.22)

[a] Years exposed out of the 40 years prior to study.
[b] Odds ratio adjusted for age, gender, log pack-years of smoking, current smoking, education, and calorie intake.
[c] Mean value.

doubling of risk are observed for those with 35 or more years of exposure who consume between 1.54 and 2.08 liters of tap water per day (OR = 2.58, CI = 1.28-5.21) or more than 2.08 liters per day (OR = 2.28, CI = 1.12-4.67).

Independent effects of chlorination surface water and THM exposure

An important aspect of exposure modeling in this research was the ability to identify different levels of exposure to chlorination by-products within chlorinated surface water supplies. The risk associated with THM exposures among those subjects primarily exposed to chlorinated surface water in the past 40 years is presented in Table 5. For categorical variables, the lowest exposure levels have been collapsed to ensure that a substantial number of subjects are included in the referent category.

Among those with 30 or more years of exposure to chlorinated surface water, results are suggestive of an increase in risk for those with many years of exposure to a THM level ≥ 50 µg/L. For those exposed for 35 or more years, the risk estimate is 1.45, but does not reach statistical significance (CI = 0.95-2.23). A similar suggestive pattern of risk is observed for factors representing years of exposure to a THM level ≥ 75 µg/L, and THM-years.

Discussion

The results indicate an increase in bladder cancer risk with exposure to chlorinated surface water and to estimated THM concentrations ≥ 25, 50, and 75 µg/L for many years. Duration of exposure seems to be an important component of risk, as excess risk is found only after 20 or more years of exposure and the highest risks are observed for those exposed for 35 or more years. Higher estimates of bladder cancer risk are found with more specific indicators of exposure to chlorination by-products (*e.g.*, years with THM ≥ 50 µg/L compared with years exposed to chlorinated surface water). Within subjects primarily exposed to chlorinated surface water, results suggest an effect of exposure to higher concentrations of chlorination by-products. Results also show a trend towards increasing risk with increasing level of chlorination by-products in water.

A primary contribution of this study is the estimation of historical levels of chlorination by-products in water supplies linked to individual residence histories. In addition, the large sample size, relatively high subject-response rates, and systematic data collection strategy add to the validity of study results.

It is difficult to compare results of this study directly with those of other studies of chlorination by-products in water because of differences in the water-source characteristics of the particular populations under study and variations in the methods of exposure assessment. In terms of design (population-based case-control; incident cases) and exposure classification (residence history linked to a survey of water treatment facilities), this study is most similar to the case-control studies of bladder cancer conducted by McGeehin *et al*[7] and Cantor *et al*.[9] The magnitude of risks found in our study are in general consistent with those reported by McGeehin, but are lower than Cantor's. Cantor *et al*[9] observed the largest

increase in bladder cancer risk after 60 or more years of exposure, while in this study, availability of historical information on water treatment plants limited exposure estimation to the past 40 years. Each of these studies identified long-term exposure as an important determinant of bladder cancer risk. Our finding of strongest associations after 35 or more years of exposure to chlorination by-products is consistent with this. In addition, our results did not identify an interaction between volume of water consumed and level of exposure to chlorination by-products. Previous studies[7,9] have not been consistent on this.

In the study by Cantor *et al*,[9] associations of bladder cancer risk with duration of exposure to chlorinated surface water were due mostly to effects among nonsmokers. In analyses not presented here, we found higher risk estimates for nonsmokers associated with many years of exposure to chlorinated surface water; however, the difference in risk compared with smokers was not statistically significant. In addition, this pattern of higher risks in nonsmokers was not observed consistently for factors representing exposure to chlorination by-products.

During the chlorination process, organic material reacts with chlorine to produce a number of halogenated hydrocarbon compounds.' THMs are the most common of these' and have known mutagenic and possibly carcinogenic properties.[6] In this study, THM level in water supplies was estimated on the basis of chlorine dose, water source, and treatment characteristics of each water supply over time and has the strongest association with bladder cancer risk among the water exposure factors. However, THMs may not be the by-product responsible for the observed increase in bladder cancer risk. Other by-products, such as haloacetonitriles, are also potentially carcinogenic" and their presence may be correlated highly with THMs in treated water.

There are several methodologic issues relevant to the interpretation of these results. In any case-control study, an important aspect of the source of controls is its representativeness of the underlying population from which the cases arose. Our controls were restricted to households with listed telephones. However, 95 percent of a random sample of participating cases were located in telephone directories, supporting the validity of telephone listings database.

Previous studies have identified different response patterns in control subjects according to rural or urban residence." Because of the relationship between urban/rural residence and chlorination status of drinking water, and our differing response rates by case-control status, there is a concern about possible response bias. Control response rates were calculated according to designations based on postal codes of rural Ontario, metropolitan Toronto (the most highly urbanized area in Canada), and other; there were no differences among the three groups.

Etiologic studies employing a case-control design typically must be concerned with the potential for differential recall between case and control subjects. In this study, such recall bias is not expected to affect results, since subjects were unaware of the specific research hypothesis under study, and exposure assessment was accomplished through a combination of subject information (primarily a residence history) and information obtained from water treatment facilities.

Despite efforts at detailed individual exposure assessment, complete information on water source was unavailable for some subjects, particularly those residing for significant time periods outside of the study area. The large sample size permitted analyses to be restricted to those for whom a large proportion of their exposure history was known and to those with relatively homogeneous exposures to specific water sources. Since the proportion of cases and controls included in these analyses were similar, a systematic bias is unlikely.

While the analysis controlled for the effects of several factors, the possibility remains that results may be confounded by other factors. Of particular concern are bladder cancer risk factors which may be more common in urban areas associated with chlorinated surface-water supplies. The study ascertained subjects' occupation *two* years prior to interview and employment in a high risk occupation[22] at this time did not confound the relationship of interest.

If the relationships identified in this study are causal, the public health impact can be described in terms of population attributable risk (PAR), which is the proportion of cases of disease in a population that can be attributed to exposure to the risk factor. The risk estimates associated with duration of exposure to chlorinated surface water, and to estimated summer THM levels $\geq$ 25, and $\geq$ 50 μg/L, as well as THM-years, result in PAR estimates which range from 14 to 16 percent?' A lower PAR (eight percent) was obtained for exposure to a summer THM level $\geq$ 75 μg/L. These results suggest that control of chlorination by-products in water supplies could lead to a meaningful reduction in bladder cancer incidence in Ontario. It is important to note, however, that the largest risk factor for bladder cancer is smoking, where a population attributable risk of 56 percent was calculated from this study.

The estimate of chlorination by-products used in this study represents the annual peak THM level for each plant. The relationship between peak and average THM level was examined using observed data from ODWSP between 1986 and 1992, and the average THM value was 76 percent of the peak value. Therefore, if average levels are considered, increases in bladder cancer risk are associated with lower average THM levels and ORs per

unit of average THM exposure are higher than reported in this paper.

Disinfection with chlorine compounds is an effective and cost efficient means of ensuring that drinking-water is safe from bacteriologic contaminants. For this reason, water disinfection with chlorine should not be abandoned. However, the results of this study do suggest that disinfection practices which reduce the formation of chlorination by-products should be investigated.

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