



## ORIGINAL CONTRIBUTIONS

### Drinking Water Source and Chlorination Byproducts in Iowa. III. Risk of Brain Cancer

Kenneth P. Cantor,<sup>1</sup> Charles F. Lynch,<sup>2</sup> Mariana E. Hildesheim,<sup>1</sup> Mustafa Dosemeci,<sup>1</sup> Jay Lubin,<sup>1</sup> Michael Alavanja,<sup>1</sup> and Gunther Craun<sup>3</sup>

The authors conducted a population-based case-control study in Iowa of 375 brain cancer patients and 2,434 controls. A postal questionnaire was used to gather information on lifetime residential history, sources of drinking water, beverage intake, and other potential risk factors. Exposure to chlorination byproducts in drinking water was estimated by combining questionnaire data with historical information from water utilities and trihalomethane levels in recent samples. The analysis included 291 cases (77.6%) and 1,983 controls (81.5%), for whom water quality information was available for at least 70% of lifetime years. Proxies represented 74.4% of cases. The mean number and mean duration of places of residence were comparable between direct and proxy respondents, suggesting little contribution to bias. After multivariate adjustment, odds ratios for brain cancer were 1.0, 1.1, 1.6, and 1.3 for exposure to chlorinated surface water of 0, 1–19, 20–39, and  $\geq 40$  years ( $p$  trend = 0.1). Among men, odds ratios were 1.0, 1.3, 1.7, and 2.5 ( $p$  trend = 0.04), and among women, 1.0, 1.6, and 0.7 ( $p$  trend = 0.7). Similar findings were found with estimates of average lifetime level of trihalomethanes. The association was stronger among men with above-median tap water consumption. These observations deserve further attention, especially in view of increasing glioma rates. *Am J Epidemiol* 1999;150:552–60.

brain neoplasms; case-control studies; smoking; trihalomethanes; water supply

Chlorination byproducts in treated drinking water were discovered in 1974 as inadvertent chemical interaction products of chlorine and organic compounds in raw water (1, 2). Exposure to the byproduct mixture has been associated with elevated risk of bladder and colorectal cancers (3–8). The evidence for a link with brain cancer is limited, and comes from an ecologic study of mortality (9) and two case-control studies based on death certificates (10, 11). Brain cancer etiology is poorly understood (12). Incidence and mortality have increased in recent years (13, 14), due in part to diagnostic improvements. However, changes in exposure to etiologic agents, such as drinking water

contaminants, also may have influenced these increases (15).

To evaluate associations for brain and other cancers with water quality measures, we conducted a population-based case-control study in Iowa of incident cancer at six anatomic sites. Findings for bladder, colon, and rectal cancers are presented elsewhere and results for kidney and pancreas cancers are in preparation (5, 6). Brain cancer (glioma) is the focus of this report.

#### MATERIALS AND METHODS

##### Study population

Eligible cases were residents of Iowa, aged 40–85 years, newly diagnosed with histologically confirmed glioma in the period January 1984 to December 1987, and without previous diagnosis of a malignant neoplasm. Cases were identified by the State Health Registry of Iowa, supplemented by a rapid reporting system during 1987. Controls aged under 65 years were selected randomly from computerized state driver's license records. Controls aged 65 years and older were selected from US Health Care Financing Administration listings. Persons with a previous can-

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Abbreviations: CI, confidence interval; OR, odds ratio; THM, trihalomethane.

<sup>1</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

<sup>2</sup>Department of Preventive Medicine and Environmental Health, University of Iowa College of Medicine, Iowa City, IA.

<sup>3</sup>Formerly with the US Environmental Protection Agency, Cincinnati, OH. (Current address: 101 W. Frederick St., Staunton, VA 24401.)

Reprint requests to Dr. Kenneth P. Cantor, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 8106, Bethesda, MD 20892-7240.

cer diagnosis were excluded from consideration as controls. Controls were frequency-matched by sex and 5-year age group to all cases (five anatomic sites in addition to brain), resulting in a matching ratio for the brain cancer cases of approximately 6.5:1. Additional controls were selected in 1988–1989 in conjunction with an extension of the overall study to evaluate additional bladder cancer cases (5). Sixty-two percent of the controls were selected in 1986–1987, and the remainder in 1988–1989.

### Data collection and study subjects

After obtaining physician consent for cases, we contacted study subjects or next of kin, first by mail and then by telephone, to invite participation through completion of a postal questionnaire. Estimates of exposure were derived from questionnaire data on lifetime residential history and detailed fluid consumption information, including intake of beverages containing tapwater and other beverages. The questionnaire also included demographic information, a food frequency table, smoking history, occupational history, and other factors. For residential histories, we requested information on all cities and towns of residence for at least one year, with the time period and the primary source of drinking water at each residence (private well, community supply, bottled, or other). We retrieved missing information by telephone. We offered hesitant subjects a 15-minute telephone interview that included items only of direct relevance to the analysis of water quality and risk.

### Response rates

Of 412 eligible brain cancer cases, 375 cases or proxies (91 percent) completed mail questionnaires ( $n = 343$ ) or abbreviated telephone interviews ( $n = 32$ , 8.5 percent of all respondents). Of the 375 respondents, 279 (74.4 percent) were proxies, comprised of 184 spouses, 21 siblings, 55 offspring, and 19 others, mostly blood relatives or in-laws. Thirty-six proxy respondents reported assistance by one or more other persons, mostly spouses or first-degree family members. Among controls younger than age 65 years, we selected 999 eligible subjects from state driver's license listings, and 817 (81.8 percent) participated. Among 2,034 eligible controls age 65 years and older selected from Health Care Financing Administration listings, 1,617 (79.5 percent) participated.

### Survey of water purveyors

In spring and summer 1987, we conducted a survey of all Iowa water utilities that served at least 1,000 per-

sons (16). We collected historical information from 280 utilities that served 345 Iowa communities with a total 1980 population of 1.94 million (of a total state population in 1980 of 2.91 million). The information came from visits and personal interviews with water plant operators at each water utility, as well as from the Iowa State Departments of Health and Natural Resources, and a 1979 historical survey of Iowa communities conducted as part of the National Bladder Cancer Study (3). The database that we developed included information about all water sources and treatments of drinking water used by these utilities since their inception.

### Trihalomethane measurements

One or two samples, quenched with sodium thiosulfate to arrest byproduct formation, were taken from the clear well of each utility (where water enters the distribution system) or from a nearby location in the distribution system. Samples were collected in duplicate 40 ml vials with teflon lids and analyzed at Iowa's University Hygienic Laboratory, using US Environmental Protection Agency method 524.2 (including all required quality control measures) for the presence and concentration of chloroform, bromodichloromethane, dibromochloromethane, and bromoform (17).

### Exposure measures

We combined information from the water utility survey, the recent trihalomethane (THM) measurements of water samples, and personal questionnaire data to create several related indices of past exposure for each subject. Using historical information from utilities about water sources and chlorination treatment, we estimated the yearly mean THM level for each water utility service area (usually a town or city), by applying geometric mean levels of recent (1987) THM levels to types of water sources and chlorination treatments used in the past (5). We merged individual residential history of each respondent with this statewide file, by year and by geographic location, to provide a year-by-year profile of water source, chlorination treatment, and estimated THM level for each person.

We also combined these duration and THM estimates with questionnaire responses regarding tap water and total fluid consumption. Total daily tap water consumption was calculated by summing the daily fluid volume of glasses of water (8 oz (237 ml)), cups of coffee and tea (6 oz (178 ml)), bowls of soup (8 oz (237 ml)), and glasses of reconstituted fruit juice (5 oz (148 ml)).

We used the number of years spent at a residence with a defined water source/treatment type as a direct index of exposure. The most useful of these was duration of water use from chlorinated surface water sources where chlorination byproduct levels are usually much above chlorinated or non-chlorinated ground waters (5). The geometric mean values of total THM from our survey were 38.1  $\mu\text{g/liter}$  for postchlorinated surface water sources ( $n = 10$ ); 73.9  $\mu\text{g/liter}$  for surface waters with both pre- and postchlorination ( $n = 20$ ); 1.7  $\mu\text{g/liter}$  for chlorinated ground water; and  $<1.0$   $\mu\text{g/liter}$  for non-chlorinated ground water. A default level of 0.5  $\mu\text{g/liter}$  was used in calculating geometric means for samples below the detection limit of 1.0  $\mu\text{g/liter}$ . We also constructed an index of average lifetime THM concentration using our estimates of yearly trihalomethane concentrations. Details on this index are provided elsewhere (5).

The high proportion of proxy respondents among cases raises the issue of bias arising from differential reporting from proxies (74.4 percent of cases) and direct respondents, who constituted almost all of the control series. Bias in the reporting of historical residential information was of particular importance because it was central to our estimates of exposure to disinfection byproducts in drinking water. We did not have information from independent sources that could be used to directly verify the historical residential location and duration information provided by surrogate respondents. In the absence of these data, we indirectly assessed validity by comparing mean values of the number and duration of residences (all residences, most recent residence, and previous residences) reported by direct case subjects, proxy case subjects, and controls. Standard  $t$  tests were used in the comparisons.

### Statistical analysis

We used the maximum likelihood estimate of the odds ratio to estimate the relative risk for brain cancer associated with various estimates of exposure (18, 19). Odds ratios were adjusted for several known or suspected risk factors using unconditional logistic regression analysis with case-control status as the response variable. Where appropriate, we included the following potential confounding variables in regression models (in addition to the drinking water exposure of interest): sex; age (four strata: 40–54, 55–64, 65–74, 75–85 years); ever employed as a farmer, and population size of places of residence (based on 1980 census), averaged over a lifetime. Tests of linear trend and of homogeneity of trend were based on standard score statistics (20). The trend tests used the exposure metric of interest as a continuous variable. We evaluated several other factors in logistic models and ruled them out as poten-

tial confounders: brain cancer in a first-degree relative; employment (ever) in a high risk (non-agricultural) occupation for brain cancer in this study; dietary variables describing the consumption frequency of several individual foods and food groups; and intake level of tap water and total beverages.

### RESULTS

Of the 375 histologically confirmed malignant brain cancer cases in this study, 193 were diagnosed with glioblastoma, not otherwise specified (*International Classification of Diseases for Oncology* (ICDO) code 9440); 114 with astrocytoma, not otherwise specified (ICDO code 9400); 27 with fibrillary astrocytoma (ICDO code 9420); 12 with mixed glioma (ICDO code 9382); 6 with gemistocytic astrocytoma (ICDO code 9411); 5 with malignant glioma, not otherwise specified (ICDO code 9380); and 18 with other, defined histologies.

The mean number of lifetime residences was 5.0 among direct ( $n = 96$ ) case respondents, 4.9 among case proxies ( $n = 279$ ), and 5.1 among controls ( $n = 2,434$ ). The mean residence duration, considering all residences, was 11.8 years among direct case respondents ( $n = 476$  residences), 13.3 years among proxies ( $n = 1,353$  residences), and 13.4 years among controls ( $n = 12,428$  residences). Study subjects, both cases and controls, generally lived for longer time periods in their most recent place of residence than prior residences. Direct case respondents averaged 25.8 years; proxies, 29.1 years; and controls, 30.4 years in the place of most recent residence. In previous residences, the respective mean durations were 8.3, 9.2, and 9.3 years. Using standard  $t$ -tests, most pairwise comparisons (between direct and proxy cases or between proxy cases and controls) of mean number of residences, or mean duration of residences (total, most recent, and previous) between the three respondent groups were not significant.

We selected cases and controls with at least 70 percent of their lifetime years with a known source of drinking water in order to define a population that would minimize misclassification of exposure yet maximize the number of subjects with useful information (5, 6). This restricted database included 291 cases (77.6 percent of all study case respondents, 155 males (77.1 percent) and 136 females (78.2 percent)) and 1,983 controls (81.4 percent of all control respondents, 1,308 males (81.7 percent) and 675 females (81.0 percent)). The excluded population was somewhat better educated and more urban than the included population, but there was no differential in these characteristics between cases and controls (5).

In table 1, we show characteristics of the 291 cases and 1,983 control subjects. More than half the cases

**TABLE 1. Characteristics of cases and controls included in a case-control study of brain cancer and drinking water conducted in Iowa in the 1980s (source of drinking water ascertained for at least 70% of lifetime)\***

Characteristic	Cases (n = 291)		Controls (n = 1,983)		Odds ratio	95% CI†
	No.	%	No.	%		
Age (years)						
40-54	72	24.7	189	9.5		
55-64	81	27.8	441	22.2		
65-74	99	34.0	738	37.2		
75-84	39	13.4	615	31.0		
Sex						
Male	155	53.3	1,308	66.0		
Female	136	46.7	675	34.0		
Proxy respondent						
No	81	27.8	1,982	99.9		
Yes	210	72.2	1	0.1		
Average population (thousands)						
≤2.50	112	38.5	780	39.3	1.0	
2.51-10.00	81	27.8	528	26.6	0.9	0.7, 1.3
10.01-50.00	66	22.7	429	21.6	0.9	0.7, 1.3
≥50.01	32	11.0	246	12.4	0.7	0.5, 1.1
Farm occupation						
No	206	70.8	1,355	68.3	1.0	
Yes	85	29.2	628	31.7	1.5	1.1, 2.1

\* Odds ratios were calculated using logistic regression, with adjustment for age (four groups) and sex.

† CI, confidence interval.

were less than 65 years of age at diagnosis, in contrast with the older age distribution of controls. The median age of cases was 64 years, and that of controls, 69 years. Among cases, the median age of males was 62 years, and that of females, 66 years. Proxies provided information for 72 percent of cases. Among control subjects, all but one completed their own questionnaires. Relative risk estimates for two potential risk factors, adjusted for age (four groups) and sex, are also shown in table 1. Odds ratios decreased with increasing population size of place of residence, averaged over a lifetime (geometric mean). Farming (ever) was associated with brain cancer risk (odds ratio (OR) = 1.5, 95 percent confidence interval (CI) 1.1, 2.1). The odds ratios shown in table 1 were not adjusted beyond age and sex.

Table 2 shows person-years of experience at residences served with different types of drinking water among cases and among controls. The overall proportions of person-years with different types of drinking water were comparable between the cases and controls, with 56.3 percent of case person-years and 56.4 percent of control person-years at places served by non-chlorinated ground water, 24.1 percent of case person-years and 26.2 percent of control person-years by chlorinated ground water, and 13.0 percent of case person-years and 11.1 percent of control person-years by chlorinated surface water. We were not able to

**TABLE 2. Person-years at residences with different types of drinking water supplies among cases and controls included in a case-control study of brain cancer and drinking water conducted in Iowa in the 1980s\***

Characteristic	Cases (n = 291)		Controls (n = 1,983)	
	Person-years	% of total person-years	Person-years	% of total person-years
Total	18,723	100.0	136,448	100.0
Missing information	1,146	6.1	7,532	5.5
Ground, non-chlorinated (total)	10,548	56.3	76,912	56.4
Private well or spring	9,118	48.7	64,747	47.5
Public well or spring	1,430	7.6	12,165	8.9
Ground, chlorinated (public)	4,506	24.1	35,735	26.2
Surface, nonchlorinated (public)	78	0.4	575	0.4
Surface, chlorinated (public)	2,441	13.0	15,111	11.1
Other, non-chlorinated	4	0.02	583	0.4

\* Includes respondents (291 cases and 1,983 controls) who resided for 70-100% of their lifetime at a place with a water supply where water source and chlorination practices were known and trihalomethanes could be estimated.

determine type of water source and chlorination treatment for 6.1 percent of case person-years and 5.5 percent of control person-years.

Tap water intake level may provide a measure of exposure to contaminants in drinking water. Among men, the odds ratios for tap water consumption were 1.4 (95 percent CI 0.8, 2.6), 1.5 (95 percent CI 0.8,

2.7), and 2.5 (95 percent CI 1.4, 4.3), for successive quartiles relative to the first quartile of intake ( $p$  trend  $< 0.001$ ). The analogous odds ratios among women were 1.0 (95 percent CI 0.6, 1.8), 0.9 (95 percent CI 0.5, 1.6), and 0.8 (95 percent CI 0.4, 1.4) ( $p$  trend = 0.81); and for both sexes, 1.2 (95 percent CI 0.8, 1.8), 1.2 (95 percent CI 0.8, 1.7), and 1.4 (1.0, 2.1) ( $p$  trend = 0.01). To evaluate if this association was an artifact of differential reporting by proxies (72 percent of cases, essentially no controls) and direct respondents, we compared tap water consumption reported by proxies and by directly responding subjects from three other case series in this study that did not show associations with chlorinated surface water use: colon (79 proxies, 546 direct), kidney (81 proxies, 300 direct), and pancreas cancers (274 proxies, 50 direct) (6, 21). Proxy respondents for all males in these three case series reported median tap water intake of 2.37 liters/day, whereas direct male respondents reported 2.07 liters/day. Female case proxies and direct female respondents reported median intakes of 2.13 and 2.06 liters/day, respectively. We subsequently used these other cancer cases as the control population in calculating odds ratios for glioma by tap water consumption level, controlling for age, proxy status, and other fac-

tors. Among men, quartile-specific odds ratios were 1.4 (95 percent CI 0.7, 2.8), 1.2 (95 percent CI 0.6, 2.3), and 1.6 (95 percent CI 0.9, 3.0) ( $p$  trend = 0.3). Among women, odds ratios were 1.2 (95 percent CI 0.6, 2.2), 1.0 (95 percent CI 0.5, 1.9), and 0.7 (95 percent CI 0.3, 1.4) ( $p$  trend = 0.4), and for the combined population, they were 1.3 (95 percent CI 0.8, 2.0), 1.0 (95 percent CI 0.6, 1.6), and 1.0 (95 percent CI 0.7, 1.6) ( $p$  trend = 0.8). We concluded that the association we first found between brain cancer risk and tap water ingestion was likely due to systematic over-reporting of intake by brain cancer proxy respondents (especially male case proxies) or alternatively, under-reporting by direct respondents.

Odds ratios by duration of chlorinated surface water use are shown in table 3. Among men, the odds ratio increased monotonically with duration ( $p$  trend = 0.04). Among women, risk of glioma was not associated with duration of exposure ( $p$  trend = 0.4). A parallel secondary analysis, using as controls other cancer cases (both direct and proxies) not associated in the overall study with chlorinated surface water duration or trihalomethane exposure (colon, kidney, and pancreas), showed results similar to those in table 3 which used population-based controls. We included a dummy

**TABLE 3. Odds ratios (OR) and 95% confidence intervals (CI) for incident brain cancer in a case-control study conducted in Iowa in the 1980s, by duration of residence with a chlorinated surface water source and lifetime average trihalomethane (THM) concentration\***

	Men		Women		Total	
	OR	95% CI	OR	95% CI	OR	95% CI
Chlorinated surface water (years)						
0	1.0	—	1.0	—	1.0	—
	(92, 875)†		(78, 400)			
1-19	1.3	0.8, 2.1	1.0	0.6, 1.6	1.1	0.8, 1.6
	(36, 268)		(36, 160)			
20-39	1.7	0.9, 3.3	1.6	0.8, 3.0	1.6	1.0, 2.6
	(14, 84)		(15, 55)			
≥40	2.5	1.2, 5.0	0.7	0.3, 1.6	1.3	0.8, 2.3
	(13, 81)		(7, 60)			
$p$ trend	0.04		0.4		0.1	
Lifetime average THM concentration (µg/liter)						
≤0.7	1.0		1.0		1.0	
	(58, 501)		(41, 194)			
0.8-2.2	0.9	0.6, 1.6	0.9	0.5, 1.5	0.9	0.6, 1.3
	(35, 314)		(36, 181)			
2.3-32.5	1.0	0.6, 1.8	0.8	0.5, 1.5	0.9	0.6, 1.4
	(45, 382)		(43, 213)			
≥32.6	1.4	0.7, 2.9	0.9	0.4, 1.8	1.1	0.7, 1.8
	(17, 111)		(16, 87)			
$p$ trend	0.04		0.9		0.3	

\* From logistic regression adjusted for sex (where applicable), age (four strata), farming occupation, and average lifetime population size of residence town or city.

† Numbers of cases and controls in parentheses.

variable for proxy respondent in the logistic regression model, along with the adjustment variables used in the original analysis. The odds ratios among men in this secondary analysis were 1.6 (95 percent CI 0.9, 2.7), 2.2 (95 percent CI 1.0, 4.7), and 2.5 (95 percent CI 1.1, 5.5) for 1–19, 20–39, and  $\geq 40$  years use of chlorinated surface water ( $p$  trend = 0.04) and odds ratios among women were 1.6 (95 percent CI 0.9, 2.8), 1.4 (95 percent CI 0.6, 2.9), and 1.4 (95 percent CI 0.5, 3.8) ( $p$  trend = 0.2).

Results from an analysis of risk by average lifetime trihalomethane level were similar to findings of the analysis by duration of exposure, with weaker associations (table 3). Excess glioma risk was not associated with duration of exposure to chlorinated well water or with duration of exposure to total chlorinated water from well and surface sources combined (data not shown). We did not evaluate risk associated with total lifetime ingestion of trihalomethanes because daily tap water consumption, which appeared to be differentially reported by case proxies and others, is a component of total ingestion.

Table 4 shows odds ratios by duration of chlorinated surface water among high and low consumers of tap water. To account for possible differential misclassifi-

cation of tap-water intake between cases and controls, and between the sexes, we used the group-specific median intake levels among male cases, female cases, male controls, and female controls, respectively, to define high- and low-intake strata. Among men who reported tap water consumption above the median level, we observed an association between glioma and duration of chlorinated drinking water ( $p$  trend = 0.03), whereas we found no association among men with below-median level intake ( $p$  trend = 0.9). Among women, glioma risk was not associated with duration of exposure to chlorinated surface water, either in the high- or low-intake group. Among subjects with tap water intake above median levels, there was no statistically meaningful difference in the findings for men and for women ( $p$  for homogeneity of trend = 0.24). Control for tap water intake level within the above- or below median-intake groups, or in the full study population, did not modify the association with chlorinated surface water duration.

## DISCUSSION

We found a dose-response relationship among men between brain cancer risk and duration of consuming

**TABLE 4. Odds ratios (OR) and 95% confidence intervals (CI) for incident brain cancer in a case-control study conducted in Iowa in the 1980s, by duration of residence with a chlorinated surface water source, by tapwater intake level\*,†**

Chlorinated surface water (years)	Men		Women		Total	
	OR	95% CI	OR	95% CI	OR	95% CI
<i>Above median tap water intake level</i>						
0	1.0 (30, 423)‡	–	1.0 (35, 199)	–	1.0	–
1–19	1.3 (16, 139)	0.7, 2.7	1.3 (20, 71)	0.6, 2.5	1.3	0.8, 2.0
20–39	1.8 (5, 43)	0.6, 5.1	1.1 (6, 30)	0.4, 3.1	1.4	0.7, 2.9
$\geq 40$	4.0 (7, 38)	1.5, 10.8	0.6 (3, 28)	0.2, 2.2	1.6	0.7, 3.4
$p$ trend	0.03		1.0		0.09	
<i>Below median tap water intake level</i>						
0	1.0 (45, 437)	–	1.0 (39, 191)	–	1.0	–
1–19	1.0 (15, 124)	0.5, 2.1	0.8 (14, 83)	0.4, 1.6	0.9	0.5, 1.5
20–39	0.8 (5, 41)	0.3, 2.4	2.1 (8, 23)	0.8, 5.5	1.4	0.7, 2.8
$\geq 40$	1.5 (5, 42)	0.5, 4.6	0.8 (4, 31)	0.3, 2.7	1.1	0.5, 2.5
$p$ trend	0.9		0.5		0.6	

\* From logistic regression adjusted for sex (where applicable), age (four strata), farming occupation, and average lifetime population size of residence town or city.

† Median level determined within case-control and sex-specific strata to adjust for apparent report bias (see Results).

‡ Numbers of cases and controls in parentheses.

drinking water from chlorinated surface water sources, especially among high-level consumers of tap water. However, the lack of an association for women was notable and influences our interpretation of the data.

Brain cancer morbidity and mortality have risen in recent decades (13, 14). While some of the increase is due to improved detection and diagnosis, changes in exposures of etiologic agents may also be important (15). Past changes in population exposure to chlorination byproduct levels in drinking water are consistent with this notion. In Iowa, increases in population exposure occurred with increasing use of chlorination, with migration from rural settings to places served by chlorinated supplies, and with the extension of community water distribution systems to surrounding areas. Among controls in this study, average estimated THM levels in water increased from 5.0  $\mu\text{g/liter}$  in 1930 to 7.4  $\mu\text{g/liter}$  in 1940, and to 10.8  $\mu\text{g/liter}$  in 1980.

Inclusion of brain cancer in this multi-site study was motivated by an ecologic study of mortality rates and two death-certificate-based case-control studies (9–11). In 76 US counties, brain cancer mortality rates were weakly associated with measures of trihalomethanes in major water supplies, among both men and women (9). In a case-control study of female cancer mortality in Wisconsin, Young et al. (10) found an association of brain cancer mortality with increasing chlorine dose, with odds ratios rising to 2.48 (confidence interval included 1.0) for exposure in the highest chlorine dose category ( $>1.7$  parts per million). In a study of similar design from Louisiana, Gottlieb et al. (11) found associations between brain cancer mortality and chlorination level that were not consistent among subgroups. In a population cohort from Washington County, Maryland (22), brain cancer mortality was not elevated among persons who consumed chlorinated surface water at cohort entry (OR = 1.10). However, the number of deaths was small (21 exposed and 4 unexposed to chlorinated surface water), and risk estimates were unstable. The genotoxic and carcinogenic potential of chlorination byproduct mixtures, as well as specific chemical constituents, have been demonstrated in toxicologic studies, providing a biologic rationale for elevated cancer risk (23–27).

The gender differences in glioma risk associated with exposure to chlorination byproducts are not readily explained. Hormonal influences are suggested by studies indicating a higher risk of glioma among nulliparous than parous women (28, 29), and other investigations showing associations of childhood brain cancer risk with maternal characteristics such as age at menarche (30) and older maternal age (31). However, the role of hormones remains contro-

versial, and chance may explain the positive association among men or the lack of association among women.

It is unlikely that bias linked to control selection was an important contributor. The population-based control group was randomly selected from the general population of Iowa using driver's license listings (controls aged  $<65$  years old) and rosters of the US Health Care Financing Agency (HCFA) (controls aged  $\geq 65$  years). The population-distribution of individuals aged 40–64 years with drivers' licenses in Iowa parallels census enumeration data with respect to county of residence, 5-year age group, urbanicity, and sex, suggesting an unbiased sampling frame (32). HCFA listings provide an estimated 98 percent coverage of the US population older than age 64 years, and this source has been used successfully in selecting controls elsewhere (33).

Proxy respondents accounted for 72 percent of cases, but essentially none of the controls, and differential responses from proxy and direct respondents could have biased our results. This appeared to occur in reporting of tap water intake, especially among men. On average, case proxies reported higher intake than self-respondent cases, and estimates of risk for this exposure were elevated when the population-based control group was used as the comparison. However, when we used cancer cases from the broader study as controls, and adjusted for proxy/self reporting, the association was much diminished.

In contrast with water intake, it is unlikely that differential response from proxies systematically overestimated the duration measure for chlorinated surface water exposure. The quality of residential history information was comparable between proxies and direct respondents regarding the number of places of residence (lifetime) and the average duration of all residences, the most recent residence, and previous residences. In general, average residence durations were slightly lower among cases than controls, as expected due to a small age differential. Any resulting bias therefore would likely be toward the null for associations between risk and duration of exposure to chlorinated surface water.

Residential histories from cases and controls were linked with historical information from community water supplies using blinded, automated methods. We reduced exposure misclassification by restricting analyses to respondents with at least 70 percent of their lifetime at residences with a known source of water. Applying the 70 percent cutoff resulted in accepting 77.6 percent of all eligible cases, and 81.4 percent of controls. In this restricted analysis group, the median percent of lifetime with a known source of water was 98 percent, with little difference between

cases and controls. Inaccuracies by proxy or direct respondents in reporting the location, dates, or water source for past residences would likely result in random misclassification of exposure, and a lowering of relative risk estimates.

We found little evidence of confounding by non-farm occupation, tap water or total beverage intake, familial brain cancer, previous medical conditions, or dietary patterns. However, farming occupation and rural residence were identified as potential confounders. Most farmers and other rural residents in Iowa obtain drinking water from non-chlorinated private wells. Brain cancer has been linked in other studies with rural residence (34) and with agricultural occupations (35-40), and farmers were at excess risk in our study population. Thus, farming and rural residence were linked both with risk of disease and with a low probability of exposure to chlorination byproducts.

If chlorination byproducts are indeed risk factors for glioma, it is not surprising that there was little overall association of glioma with tap water intake level. The great majority of person-years of experience in this study population was at residences served by water sources with low levels of these contaminants (private wells and chlorinated ground water), and therefore relatively few study subjects were exposed to elevated levels. On the other hand, one would expect to find elevated risk among the relatively few individuals with extended duration of exposure to water sources with high levels of these contaminants, and also an enhanced dose-response relationship with duration among high-level consumers of tap water, as we found among men.

Among the limitations of using current THM measures to estimate past levels are historic changes in chlorination practices and possible secular trends in raw water quality. We attempted to minimize seasonal variation in levels by taking samples within a restricted calendar period. However, we could not control for diurnal variation. We used the geometric mean in calculating THM levels by type/treatment of water supply (5). The geometric mean level was about one-half the value of the arithmetic mean for each group of water supplies having similar characteristics. Using these procedures, we were not able to account for systematic differences in water quality within groups of water sources/treatments, and this likely contributed to misclassification of historic THM level.

Caution is warranted in interpreting our findings. This investigation is the first evaluation of chlorination byproducts as risk factors for incident brain cancer in a carefully conducted population-based study, and further confirmation is required.

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