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CHAPTER 12

Drinking Water Source and Risk of Bladder Cancer: A Case-Control Study

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Chlorine reacts with naturally occurring organic compounds in water treatment plants to produce halogenated by-products, including chloroform and other trihalomethanes. Among these compounds, chloroform is a carcinogen,[1] others are mutagenic in bacterial tester strains,[2] and some concentrated mixtures of higher-molecular-weight organic fractions transform mammalian cells in tissue culture[3] and induce skin-painted tumors in rodents.[4] This raises the possibility that the time-tested benefits of chlorine to control infectious disease may be, in part, offset by increased cancer risk in continuously exposed populations.

Some drinking water supplies are also contaminated by other potentially toxic agents from industrial or municipal outfalls, agricultural and municipal runoff, or toxic waste dumps. While organic chemicals such as trichloroethylene, benzene, or perchloroethylene, and cations such as cadmium or arsenic, pose important public health threats to some exposed populations, affected water supplies are usually limited geographically and temporally. This does not minimize the threat posed by such contaminants in some local water supplies nor the threat of future problems in many others. In contrast, chlorination by-products have been widespread, and their historical distribution patterns can be deduced from knowledge of water sources and disinfection practices used in the past.

Several epidemiologic studies have evaluated the possibility of a link between drinking water contaminants and cancer in human populations. The first studies were ecologic in design. More recent work used a case-control approach based on death certificates. Many of these studies linked bladder cancer mortality with exposure indicators—water source type and treatment—that were used as surrogates of contaminant levels.[5-7] Among these surrogate measures are surface (as contrasted with ground) source, chlorinated (as compared with nonchlorinated) source, and recent measures of chloroform concentration. To further pursue these observations, we incorporated a water source component in a large population-based case-control interview study of bladder cancer designed at the National Cancer Institute (NCI) in 1977.

Eligible cases included all persons between the ages of 21 and 84 diagnosed with cancer of the urinary bladder in 1978 and residing in ten areas of the United States, including Connecticut, Iowa, New Jersey, New Mexico, and Utah, and the metropolitan areas of Atlanta, Detroit, New Orleans, San Francisco, and Seattle. Slightly less than a third of the cases were from New Jersey. Connecticut, Iowa, Detroit, and San Francisco each accounted for more than 10%. Bladder cancer is primarily a disease of older men. There were three times as many men as women cases, and the median age was 67. A total of 2982 cases, 73% of the eligible pool, were interviewed. Controls were randomly selected from the population of each area, frequency matching on sex, 5-year age group, and study area. Controls between 21 and 64 years of age were selected by a random-digit dialing method, and controls between 65 and 84 years of age were randomly selected from a roster provided by the Health Care Financing Agency; 5782 population-based controls were interviewed. Details of the study design and methods have been published.[8]

Cases and controls were interviewed at home by trained interviewers. Items on the questionnaire included demographic background; a smoking, occupational, and medical history; artificial sweetener use; and other factors possibly linked to bladder cancer, including hair dyes, coffee and tea consumption, and fluid ingestion. Each respondent was also asked to name each city or town in which he or she had lived for a year or more, the years moved into and out of that place, and whether the primary source of drinking water at each place was a private well, the community water supply, bottled water, or another source. We coded geographic areas by a standard coding scheme.[9]

In collaboration with the Cincinnati Health Effects Research Laboratory of the Environmental Protection Agency, we independently surveyed all community water supplies that served more than 1000 persons in the ten study areas. We collected historical information on water source, treatment, and geographic distribution since 1900. Water sources were classified as surface or ground, and further details on source characteristics and potential contamination were recorded. Treatment information, especially chlorination, was also gathered. Although details on amounts of added chlorine were often lacking, we were able to ascertain the years in which chlorination disinfection had been used. The towns and cities historically served by each water source were listed and coded with the same geocoding scheme used for residential histories.

A year-by-year record of water source and treatment was created for each study respondent. For each year that a respondent lived in one of the ten study areas and used a community supply, we looked up water source and treatment information in the water supply data file. We were not able to describe water source for years when respondents used community sources outside of the study areas or when they lived in very small communities with supplies not covered by our survey.

Of the 587,565 person-years lived by all respondents since 1900, 444,735 (76%) were at a known water source. This ranged from 63% in New Mexico to 83% in Iowa. The year-by-year profile of water source and treatment informa-

tion for each person provided us with a flexible tool to look at patterns of water use in the study population as well as to define individual exposures.

We have estimated relative risk according to several different measures derived from drinking water histories. Here we report on risk as related to the number of years that a respondent lived at a residence served by a chlorinated surface source. Most chlorinated surface sources have much higher levels of chlorination by-products than most chlorinated or nonchlorinated groundwater sources;[10] therefore, duration of exposure is a crude index of dose.

We used the odds ratio to estimate the relative risk. Logistic regression for unmatched data was used to obtain a maximum likelihood point and 95% confidence interval estimates of the odds ratio, and also to control for the potential confounding effects of selected variables.[11,12] Among the potential confounders in most calculations were geographic area (ten levels), six levels of cigarette smoking intensity, three age groups, a 1/0 variable for usual employment as a farmer, and race and sex when the analyses were not race- or sex-specific.

Table I shows the overall relative risk among whites by the number of years at a chlorinated surface water source. All risks are relative to those who lived at places never served by such sources. Compared to this base-line measure are respondents with less than 20, 20 to 39, 40 to 59, and 60 or more years at places with chlorinated surface sources. Relative risks are not elevated in the exposed groups, and there is no suggestion of a duration-response relationship.

Eligibility for inclusion in the analyses reported here was restricted in two major ways: (1) Preliminary analyses suggested a potential for confounding of drinking water associations by employment in a high-risk occupation for bladder cancer (as identified by D. Silverman, L. Levin, and R. Hoover at NCI). As a control, we included only persons who never held a high-risk job. (2) Among some persons in low-exposure categories (i.e., those with few years known to be served by a chlorinated surface source), there was uncertainty as to exposures during years they were not known to be served by a chlorinated surface source. Some of these years were classified as "municipal, not otherwise specified," or "unknown," and, in such cases, assignment to a more precise exposure category was not possible. We wished to remove from the analysis those persons whose exposures were least certain. In addition, we desired to maximize the number of nonexposed years spent at nonchlorinated ground sources (low exposure) while still including enough subjects to maintain adequate statistical power. To these ends, we further reduced the analysis population to those whose years at a chlorinated surface source plus years at a nonchlorinated ground source summed up to at least half of their lifetimes.

Interesting differences in relative risk for duration of exposure to chlorinated surface waters are observed within geographic regions (Table II). Elevated relative risks are seen in New Mexico, Utah, and Iowa, with the number of years resident at a place served by a chlorinated surface source. The number of respondents in New Mexico and Utah is small, but the result is statistically significant. The pattern in Iowa is also interesting and is apparent among

Table I. Relative Risks (RR) and 95% Confidence Intervals (CI) for Bladder Cancer According to Number of Years at a Residence Served by a Chlorinated Surface Drinking Water Source[a]

Years	RR	95% CI	Number	
			Cases	Controls
0	1.0		231	570
1 – 19	1.1	0.8 – 1.4	141	285
20 – 39	1.0	0.8 – 1.3	324	650
40 – 59	1.0	0.8 – 1.3	437	849
60 +	1.1	0.8 – 1.5	111	196

[a]Whites, from logistic regression adjusted for study area (10 strata), sex, age (3 strata), smoking level (6 strata), and usual employment as a farmer (2 strata).

Table II. Relative Risks (RR) and 95% Confidence Intervals (CI) for Bladder Cancer According to Number of Years at a Residence Served by a Chlorinated Surface Drinking Water Source[a]

Study area	Years	RR	95% CI	Number	
				Cases	Control
San Francisco, Seattle	0	1.0		20	26
	1 – 19	0.7	0.3 – 2.0	16	37
	20 +	1.05	0.4 – 2.7	163	332
New Mexico, Utah	0	1.0		15	75
	1 – 19	4.5	1.03 – 19.5	6	8
	20 +	11.8	2.5 – 55.1	8	5
New Orleans, Atlanta	0	1.0		5	8
	1 – 19	0.2	0.03 – 1.1	5	23
	20 +	0.4	0.1 – 1.9	70	156
Iowa	0	1.0		111	323
	1 – 19	1.04	0.6 – 1.8	26	64
	20 +	1.6	0.94 – 2.7	35	55
Detroit	0	1.0		6	9
	1 – 19	1.4	0.4 – 5.4	12	15
	20 +	1.2	0.4 – 3.6	197	278
Connecticut	0	1.0		17	53
	1 – 19	1.7	0.8 – 3.4	36	64
	20 +	1.17	0.7 – 2.1	158	378
New Jersey	0	1.0		57	76
	1 – 19	0.7	0.4 – 1.3	40	76
	20 +	0.7	0.5 – 1.1	241	491

[a]Whites, from logistic regression adjusted for sex, age (3 strata), smoking level (6 strata), and usual employment as a farmer (2 strata).

Table III. Relative Risks (RR) and 95% Confidence Intervals (CI) for Bladder Cancer According to Number of Years at a Residence Served by a Chlorinated Surface Drinking Water Source (by cigarette smoking status)[a]

Cigarette smoking status	Years	RR	95% CI	Number	
				Cases	Controls
Never smoked	0	1.0		61	268
	1 – 19	1.3	0.7 – 2.2	29	110
	20 – 39	1.5	0.9 – 2.4	73	236
	40 – 59	1.4	0.9 – 2.3	108	348
	60 +	2.3	1.3 – 4.2	46	77
Past smokers	0	1.0		83	193
	1 – 19	1.0	0.7 – 1.7	49	104
	20 – 39	1.1	0.7 – 1.8	115	228
	40 – 59	1.2	0.8 – 1.8	163	290
	60 +	0.8	0.5 – 1.5	38	82
Current smokers	0	1.0		87	109
	1 – 19	0.9	0.6 – 1.5	63	71
	20 – 39	0.7	0.4 – 1.1	136	186
	40 – 59	0.7	0.5 – 1.2	166	211
	60 +	0.6	0.3 – 1.2	27	37

[a]Whites, from logistic regression adjusted for study area (10 strata); sex; age (3 strata); usual employment as a farmer (2 strata); 2 smoking levels for past smokers, and 3 smoking levels for current smokers.

smokers and nonsmokers. It may be important that these three areas are the most intensely agricultural of the study areas. In New Jersey, the overall relative risk was less than 1.0, and risk decreased with the number of years that a chlorinated surface source was used. We cannot explain this observation by confounding with other risk factors for bladder cancer that we have evaluated. Associations of bladder cancer with contaminated groundwater in New Jersey is one issue that deserves exploration.

Table III shows results of analysis by major smoking category, that is, nonsmokers, former smokers, and current smokers. Among nonsmokers, the relative risk generally increases with the number of years at a residence with a chlorinated surface source. The relative risk among those with the longest exposure, 60 or more years, is 2.3, and the increase is statistically significant. Former smokers show an uneven risk pattern, and the risk among current smokers appears to vary inversely with the number of years exposed. The unusual and unexpected inverse risk pattern among current smokers could not be explained by confounding by smoking level within broad smoking category or by several other factors that we investigated, including age. Among nonsmokers, there are similar risk patterns for each sex, with the relative risk

increasing with the number of years at a surface source, rising to 2.2 in men and 2.5 in women in the longest exposure category. Former smokers show divergent patterns for the sexes. Current smokers of both sexes show inverse risk patterns with the number of years exposed.

When evaluating these results, some limitations must be considered. The study had its origins in the issue of saccharin as a human bladder carcinogen, and, therefore, study areas were not selected with the water source hypothesis in mind.[13] Some of the places, notably the five metropolitan areas, are predominantly served by one water source. This limits intraregional variability of exposure in some areas and dampens the statistical power of our large numbers. The exposure measure used here simplifies a complex world by dichotomizing water sources into chlorinated surface and nonchlorinated ground. While based on extensive environmental information, this classification ignores other differences among sources and may completely misclassify exposure in places with contaminated groundwater.

The detection of relatively small risk differences expected in environmental epidemiologic studies is a challenging task, and great care must be taken to minimize bias and account for risk factors that may confound the result.[14] Given the stringent study design and its careful execution, it is unlikely that bias from case or control selection, or from differentially conducted interviews of cases and controls, has influenced our findings.[8] Information on factors that remain unknown or that are now thought to possibly influence bladder cancer risk were not available and could have confounded the results. Although unlikely, confounding could occur if drinking water source is correlated with ingestion of beta-carotene, retinol, or other micronutrients that may behave as tumor promotors or anticarcinogens.

Our finding is that there is no overall elevation in bladder cancer risk among persons who have lived at places with chlorinated surface water as compared with those who have lived at places with nonchlorinated groundwater; and no dose response is observed. Among the 10 study areas, respondents from three places with agricultural land use show elevated risk for bladder cancer with the number of years at a surface source. This is in contrast with decreased risk in the largest study area, New Jersey. Cigarette smoking is a well-known bladder cancer risk factor.[15] Among smokers, there is an unexplained negative association with the number of years at a chlorinated surface source that is also consistent in the sexes. The pattern among former smokers is variable. Among nonsmokers who never were employed in a high-risk occupation, a group otherwise at low risk for bladder cancer, the risk is elevated among those served by chlorinated surface sources; there is a duration-response relationship, and the pattern is similar in men and women.

Although the overall result is reassuring, these findings raise questions warrant further elaboration. Although smokers within each water exposure category are at higher risk for bladder cancer than nonsmokers, the risk of bladder cancer among smokers with lifetime exposure to nonchlorinated groundwater appears to be higher than that among smokers with chlorinated

surface drinking water. Whether this is due to confounding by unmeasured risk factors, such as chance or biological interaction, is not currently understood. Geographical differences in bladder cancer risk patterns suggest the possibility of water contaminants in agricultural areas or groundwater contaminants in New Jersey. An increasing risk of bladder cancer with duration of exposure to chlorinated surface water is observed among persons otherwise at lowest risk and is consistent across the sexes. An analytical study with limited statistical power has also noted positive associations of bladder cancer risk with the use of chlorinated surface water sources.[16] A causal interpretation of these findings would be strengthened by similar observations in another setting.

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