The Association of Drinking Water Source and Chlorination By-Products with Cancer Incidence among Postmenopausal Women in Iowa: A Prospective Cohort Study

ABSTRACT

Objectives. This study assessed the association of drinking water source and chlorination by-product exposure with cancer incidence.

Methods. A cohort of 28 237 Iowa women reported their drinking water source. Exposure to chlorination by-products was determined from statewide water quality data.

Results. In comparison with women who used municipal groundwater sources, women with municipal surface water sources were at an increased risk of colon cancer and all cancers combined. A clear dose–response relation was observed between four categories of increasing chloroform levels in finished drinking water and the risk of colon cancer and all cancers combined. The relative risks were 1.00, 1.06, 1.39, and 1.68 for colon cancer and 1.00, 1.04, 1.24, and 1.25 for total cancers. No consistent association with either water source or chloroform concentration was observed for other cancer sites.

Conclusions. These results suggest that exposure to chlorination by-products in drinking water is associated with increased risk of colon cancer. (*Am J Public Health.* 1997;87:1168–1176)

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Introduction

Chlorine disinfection of drinking water has been one of the most successful interventions this century in the prevention of waterborne illness. In the United States, chlorine remains the most common disinfectant and is added to approximately 75% of the nation's drinking water.[1]

Concern arose during the 1970s regarding the potential health hazard of chlorination by-products present in many finished municipal water supplies.[2] These by-products include volatile organic compounds, such as the trihalomethanes formed by the reaction of chlorine with organic acid precursors present in raw water.[3–5]

Rodent feeding studies have shown liver, kidney, and intestinal tumorigenesis with chronic ingestion of trihalomethanes.[6,7] Studies in humans have also suggested that chlorination by-products may be associated with elevated risk of cancer, particularly cancers of the bladder and colorectum.[8–21] As summarized in a recent meta-analysis by Morris et al.,[22] higher exposure to chlorination by-products in drinking water may be related to an approximately 10% to 40% excess risk of cancers of the bladder and colorectum. Virtually all previous epidemiologic studies, however, have involved ecological or retrospective case–control designs. Several of these studies used single measures of exposure. Only 3 of the studies evaluated in the 10-study meta-analysis included exposure information on both historical drinking water sources and trihalomethane concentrations in drinking water for their study participants. Five of the studies grouped study participants into exposure categories by the address on the person's death certificate. Therefore, more epidemiologic studies with better assessment of exposure are needed to clarify the association between chlorination by-products in drinking water and cancer incidence. The Iowa Women's Health Study, a prospective cohort investigation of postmenopausal women, provides a unique opportunity to further assess this association.

Methods

Iowa Women's Health Study Cohort

Details on the methods used in this cohort study have been published elsewhere.[23,24] Briefly, in 1986, 41 836 women 55 to 69 years of age whose names appeared on the 1985 Iowa state drivers' license list completed and returned a mail survey including information on medical history, anthropometric data, and information concerning diet and risk factors for cancer. Cohort members were followed for cancer incidence through computer linkage of participant identifiers with the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

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Follow-up for total mortality was achieved through linkage to the National Death Index and through mailed questionnaires in 1987, 1989, and 1992. On the basis of our follow-up surveys, it is estimated that the out-migration rate among cohort members is less than 1% annually. The site and morphology of cancer were coded according to the first edition of the *International Classification of Diseases for Oncology.* Through December 31, 1993, after 8 years of follow-up, 3567 cohort members had developed at least one new primary cancer.

Exposure Assessment

The source of drinking water for each cohort member was determined in the second follow-up mail survey conducted in 1989. All cohort members were asked to respond to two questions relating to drinking water: (1) "What is your main source of drinking water at home?" and (2) "How long have you been drinking the type of water you indicated above?" The types of drinking water included in the questionnaire were municipal water, private well water, bottled water purchased from a store or dealer, and other. Length categories were 0 through 10 years, 11 through 20 years, and greater than 20 years. A total of 36 127 cohort members completed the second survey. Of the 5710 (13.6%) nonrespondents, 908 had died before initiation of the survey. Among respondents, 27 339 women reported drinking municipal water, 6618 reported drinking private well water at home, and 2170 reported drinking water from a bottle or other "unknown" sources. Analyses were limited to those who reported drinking municipal or private well water for more than the past 10 years (n = 28 237). The sample size was too small for a meaningful analysis of bottle water users (n = 764, accounting for 2.1% of total respondents).

We used historical water treatment data from the state of Iowa[25] to ascertain exposure to chlorination by-products in drinking water in a qualitative fashion by characterizing municipalities as providing 100% groundwater, a mixture of groundwater and surface water, or 100% surface water to their residents during the period 1969 to 1989. Surface water supplies have consistently been shown to have higher concentrations of chlorination by-products as a result of the greater abundance of organic acid precursors required for the formation of trihalomethanes.[1,10,13] Cohort members were then linked to these qualitative exposure categories by community name.

Exposure levels to specific chlorination by-products for cohort members were assessed by means of two statewide water surveys conducted in 1979 and in 1986/87. The 1979 survey was carried out as part of the National Bladder Cancer Study.[26] Measurements of four trihalomethanes (bromodichloromethane, bromoform, chloroform, and dibromochloromethane) were performed on 252 municipal water supplies in Iowa. With the exception of one sample, water samples were collected between March and May of 1979. The second water survey was conducted by the Iowa Department of Natural Resources.[27] Water samples were collected from 856 municipal water systems between November 1986 and October 1987, and measurements were taken for the same four trihalomethanes.

These two databases on trihalomethane levels were linked to Iowa Women's Health Study participants by community name in order to quantify exposure levels to chlorination by-products. All women who lived in the same community and reported drinking municipal water were assigned the same exposure level of trihalomethanes. The data from the 1986/87 water survey were used for the primary analyses presented here, since this survey covered more communities than did the 1979 survey.

Cohort members who failed to link by city with either the historical data or the water survey data were excluded from that particular analysis. Women who reported a change in city residence between 1986 and 1989 (n = 502) were excluded from all analyses, along with premenopausal women (n = 403) and women who reported a prior diagnosis of cancer (other than skin cancer) at baseline (n = 2516).

Data Analysis

The exposure variables of primary interest were drinking water source and trihalomethane concentration detected in the 1986/87 water survey. Information on potential confounding variables was derived from the Iowa Women's Health Study baseline questionnaire. Diet was assessed with a 127-item food frequency questionnaire. A paper tape measure was enclosed, along with written instructions for having a friend measure circumferences of the waist and hips from which waist-to-hip ratio was computed. Relative risks (RRs) were used to measure the strength of associations of exposure variables with incidence of cancer by anatomic sites and all sites combined. With the exception of kidney cancer, site-specific analyses were restricted to sites with at least 40 cancer cases diagnosed during the follow-up period. Kidney cancer (n = 37) was included in the analyses because it has been reported previously to be associated with chlorination by-products in drinking water.[22] Cox proportional hazards regression[28] was used to control for potential confounders and to derive adjusted relative risks and 95% confidence intervals (CIs). The proportional hazards assumption for risk of any cancer was tested and found to be valid. For cancer cases, person-years were accumulated up to the date of cancer diagnosis; for noncases, person-years were accumulated up to the date of loss to follow-up, death, or December 31, 1993.

All relative risks were adjusted for the following common risk or protective factors shared by most major cancers: age, education, smoking status, cigarette pack-years, physical activity, total fruit and vegetable intake, total calorie intake, body mass index, and waist-to-hip ratio.[23,24,29–33] With the exception of age (continuous), smoking (never, former, current), and pack-years (continuous), the categories for all adjusting variables included in the Cox regression model are specified in Table 1.

Additional adjustments were made in the analyses of kidney cancer (for history of blood transfusion [yes/no]) and cancers of the breast, ovary, and corpus uteri (for age at menarche, age at menopause, and age at first pregnancy [quartiles]). These additional adjusting variables had previously been found to be risk factors for the corresponding cancer sites in this study population.[32,34]

A trend test for a dose–response relation was performed in some analyses by treating an ordinal score variable (1, 2, 3, or 4) as a continuous variable in proportional hazards regression after adjustment for potential confounders.

Results

The distribution of cohort members by drinking water source and common risk or protective factors for cancer is presented in Table 1. Approximately 18% of cohort members analyzed reported using private wells as their main source of drinking water. This was much more common among farm and rural residents. The percentage of women served by

TABLE 1—Relationships between Drinking Water Source and Selected Demographic and Risk Factors among Postmenopausal Women: Iowa Women's Health Study, 1986 through 1993

	Drinking Water Source				
		Municipal Source, %			
	Private Well, %	100% Ground	Mixed	100% Surface	Total No.
Cohort members	18.2	57.6	16.9	7.4	23 202
Residence					
Farm	85.2	12.6	1.3	0.9	3 576
Rural, nonfarm	69.5	18.9	8.0	3.6	1 236
Town, < 1000 residents	4.4	89.7	3.0	2.9	1 768
1000–2499 residents	1.7	86.6	4.5	7.2	2 615
2500–10 000 residents	1.3	79.1	12.1	7.4	4 399
> 10 000 residents	1.3	55.5	32.1	11.1	9 443
Baseline age, y					
55–59	19.7	56.2	17.0	7.1	8 273
60–64	18.4	56.9	17.1	7.6	8 189
65–69	16.1	60.1	16.5	7.3	6 740
Education					
< high school	19.9	59.9	12.3	7.9	3 973
High school	18.7	57.3	16.4	7.6	9 818
> high school	17.0	56.8	19.3	6.9	9 411
Cigarette smoking					
Never smoked	22.0	56.5	15.2	6.4	15 107
Ex-smoker	11.0	59.3	20.7	9.0	4 639
Current smoker					
1–19 pack-years	12.4	59.7	18.8	9.2	3 299
20–39 pack-years	11.1	59.6	20.2	9.2	2 764
≥40 pack-years	9.3	59.7	21.9	9.1	2 032
Leisure time physical activity					
Low	18.2	57.0	17.2	7.6	10 718
Moderate	18.8	58.8	15.6	6.9	6 303
Vigorous	17.4	57.4	17.7	7.5	5 796
Total calorie intake					
<1351.4	13.8	60.0	18.7	7.4	5 801
1351.4–1695.2	16.5	58.2	17.7	7.6	5 799
1695.3–2103.3	18.7	57.3	16.1	7.9	5 802
>2103.3	23.8	54.7	15.0	6.5	5 800
Fruit & vegetable servings/mo					
<102.49	14.8	60.2	17.5	7.5	5 797
102.49–145.55	18.0	57.8	16.8	7.4	5 794
145.56–197.07	19.1	57.2	16.4	7.3	5 797
>197.07	20.9	55.0	16.9	7.2	5 796
Body mass index, kg/m^2					
<23.40	15.0	58.9	18.6	7.5	5 810
23.40–25.92	17.2	58.8	16.9	7.1	5 822
25.94–29.32	19.2	56.9	16.6	7.3	5 766
>29.32	21.4	55.8	15.4	7.5	5 804
Waist-to-hip ratio					
<.7751	17.5	58.2	17.4	6.9	5 818
.7751–.8285	18.2	58.0	17.1	6.7	5 734
.8286–.8898	18.9	56.6	16.5	8.0	5 791
>.8898	18.3	57.5	16.4	7.8	5 783
History of blood transfusion					
No	18.5	57.7	16.5	7.3	17 364
Yes	17.3	57.1	18.2	7.4	5 838

Note. Percentages were calculated without inclusion of subjects for whom data were missing in the denominator, and values may not sum to 100% in each row as a result of rounding.

municipal surface water increased with urbanicity. Women who reported drinking private well water were more likely to be never smokers, while women with 100% surface water sources were more likely to be former or current smokers. Women with private wells also tended to have higher fruit and vegetable intakes, higher total calorie intakes, and higher body mass indexes. No other obvious differences among women by water source were noted.

Table 2 presents the multivariate-adjusted relative risks for major cancers in relation to drinking water source. The relative risks were estimated for women with private well, municipal mixed, or municipal surface water sources relative to women with municipal groundwater sources. Women served by municipal groundwater sources were chosen as the reference category because of the large proportion of cohort members in this group and because of the relatively lower levels of chlorination by-products typically detected in groundwater sources in comparison with mixed or surface water sources.[1,10,13] The most notable associations were elevated risks of colon cancer and all cancers combined with increasing proportion of water supplied by surface sources. Among women served by 100% surface water sources, the risks were 1.67 (95% CI = 1.07, 2.63) for colon cancer, 1.25 (95% CI = 1.02, 1.52) for total combined cancer, and 1.15 (95% CI = 0.92, 1.43) for all cancers excluding colon cancer. For bladder cancer, the relative risks were 2.27 (95% CI = 1.20, 4.31) and 0.62 (95% CI = 0.15, 2.63) for mixed ground/surface and 100% surface water sources, respectively, but the number of bladder cancer cases was small (n = 43). An excess risk of breast cancer (RR = 1.33, 95% CI = 1.02, 1.74) was also observed in relation to surface water use. No statistically significant associations were observed for other cancer sites. With the exception of breast cancer, these patterns persisted after exclusion of women who reported having used their current water source for 11 to 20 years (n = 3206) and women who lived in three communities (n = 1128) classified as receiving 100% groundwater between 1969 and 1989 that were served by surface water sources for significant periods prior to 1969. The association previously observed for breast cancer disappeared after exclusion of women who reported having used their current source for 11 to 20 years.

TABLE 2—Relative Risks (RRs) for Major Cancers in Relation to Drinking Water Source among Postmenopausal Women: Iowa Women's Health Study, 1986 through 1993

Cancer Site	Private Well	Municipal Water Source		
		100% Ground (Ref)	Mixed	100% Surface
Digestive organs				
Upper digestive organs (excluding lip and major salivary glands)				
Age-adjusted RR (95% CI)	0.95 (0.41, 2.30)	1.00	0.73 (0.28, 1.91)	1.32 (0.46, 3.81)
Multivariate RR (95% CI)	1.16 (0.49, 2.74)	1.00	0.66 (0.25, 1.74)	1.24 (0.43, 3.59)
Events (n = 40)	7	24	5	4
Colon				
Age-adjusted RR (95% CI)	1.11 (0.77, 1.62)	1.00	1.54 (1.09, 2.17)	1.72 (1.10, 2.70)
Multivariate RR (95% CI)	1.14 (0.78, 1.67)	1.00	1.52 (1.08, 2.14)	1.67 (1.07, 2.63)
Events (n = 213)	37	106	47	23
Rectum and anus				
Age-adjusted RR (95% CI)	0.92 (0.52, 1.63)	1.00	1.32 (0.79, 2.20)	0.90 (0.38, 2.08)
Multivariate RR (95% CI)	0.97 (0.54, 1.73)	1.00	1.28 (0.76, 2.14)	0.88 (0.38, 2.06)
Events (n = 94)	15	53	20	6
Urinary organs				
Kidney (renal cell)				
Age-adjusted RR (95% CI)	1.26 (0.56, 2.84)	1.00	0.83 (0.32, 2.21)	1.13 (0.34, 3.80)
Multivariate RR (95% CI)[a]	1.35 (0.59, 3.08)	1.00	0.78 (0.29, 2.07)	1.09 (0.33, 3.67)
Events (n = 37)	8	21	5	3
Bladder				
Age-adjusted RR (95% CI)	0.28 (0.07, 1.20)	1.00	2.43 (1.29, 4.61)	0.69 (0.16, 2.92)
Multivariate RR (95% CI)	0.34 (0.08, 1.44)	1.00	2.27 (1.20, 4.31)	0.62 (0.15, 2.63)
Events (n = 43)	2	23	16	2
Lung				
Age-adjusted RR (95% CI)	0.53 (0.31, 0.91)	1.00	1.10 (0.73, 1.65)	1.42 (0.85, 2.38)
Multivariate RR (95% CI)	0.83 (0.49, 1.42)	1.00	0.99 (0.65, 1.49)	1.17 (0.70, 1.96)
Events (n = 158)	16	95	30	17
Melanoma				
Age-adjusted RR (95% CI)	0.88 (0.40, 1.93)	1.00	1.43 (0.73, 2.81)	1.09 (0.38, 3.10)
Multivariate RR (95% CI)	0.87 (0.39, 1.91)	1.00	1.41 (0.72, 2.78)	1.13 (0.40, 3.22)
Events (n = 53)	8	29	12	4
Non-Hodgkin's lymphoma				
Age-adjusted RR (95% CI)	1.38 (0.78, 2.43)	1.00	0.78 (0.38, 1.61)	0.79 (0.28, 2.22)
Multivariate RR (95% CI)	1.28 (0.72, 2.28)	1.00	0.77 (0.38, 1.60)	0.80 (0.29, 2.23)
Events (n = 70)	17	40	9	4
Reproductive organs[b]				
Ovary				
Age-adjusted RR (95% CI)	0.60 (0.25, 1.45)	1.00	1.45 (0.76, 2.78)	0.75 (0.23, 2.45)
Multivariate RR (95% CI)[c]	0.61 (0.25, 1.49)	1.00	1.38 (0.72, 2.66)	0.76 (0.23, 2.48)
Events (n = 53)	6	31	13	3
Endometrium				
Age-adjusted RR (95% CI)	1.07 (0.70, 1.64)	1.00	1.22 (0.80, 1.87)	1.48 (0.88, 2.50)
Multivariate RR (95% CI)[c]	0.97 (0.63, 1.48)	1.00	1.22 (0.80, 1.87)	1.39 (0.82, 2.34)
Events (n = 159)	29	84	29	17
Breast[b]				
Age-adjusted RR (95% CI)	1.17 (0.96, 1.41)	1.00	0.96 (0.78, 1.19)	1.35 (1.03, 1.76)
Multivariate RR (95% CI)[c]	1.16 (0.95, 1.41)	1.00	0.95 (0.76, 1.18)	1.33 (1.02, 1.74)
Events (n = 692)	140	381	106	65
All cancers excluding colon cancer[b]				
Age-adjusted RR (95% CI)	0.95 (0.80, 1.13)	1.00	1.21 (1.03, 1.42)	1.20 (0.96, 1.49)
Multivariate RR (95% CI)[a,c]	0.99 (0.84, 1.18)	1.00	1.17 (0.99, 1.38)	1.15 (0.92, 1.43)
Events (n = 1031)	178	566	194	93
All cancers combined[b]				
Age-adjusted RR (95% CI)	0.96 (0.82, 1.13)	1.00	1.25 (1.07, 1.45)	1.30 (1.06, 1.59)
Multivariate RR (95% CI)[a,c]	1.01 (0.86, 1.18)	1.00	1.21 (1.04, 1.41)	1.25 (1.02, 1.52)
Events (n = 1167)	201	631	223	112
Person-years	20 607	61 385	17 581	8 439

Note. All relative risks were adjusted for age, education, smoking status, pack-years of smoking, physical activity, fruit and vegetable intake, total energy intake, body mass index, and waist-to-hip ratio. CI = confidence interval. Women whose municipality did not appear in the historical water database (n = 1674 [6.7%]) were excluded from the analyses.

[a]Additionally adjusted for history of blood transfusion.

[b]Excluding, as well, women with baseline oophorectomy for ovarian cancer analyses, women with baseline hysterectomy for endometrial cancer analysis, women with baseline mastectomy for breast cancer analysis, and any of these conditions for analysis of all cancers combined.

[c]Additionally adjusted for age at menarche, age at menopause, and age at first birth.

TABLE 3—Characteristics of Trihalomethanes Detected in 1986/87 Test, by Water Source

Analyte	Positive Samples, %	r[a]	100% Groundwater Sources (n = 474) Geometric Mean[b]	Interquartile Range[b]	Maximum Value[b]	100% Surface Water Sources (n = 44) Geometric Mean[b]	Interquartile Range[b]	Maximum Value[b]
Chloroform	57	.93	0.231	3	71	46.117	79.5	287
Bromodichloromethane	46	.86	0.121	2	51	8.658	14	37
Dibromochloromethane	39	.74	0.082	2	33	0.376	2	6
Bromoform	15	.37	0.029	0	31	0	0	0
Total trihalomethanes			0.520	10	125	56.164	97.5	315

Note. Analyses excluded communities with a mixture of groundwater and surface water sources.
[a]Correlation coefficient of each analyte with total trihalomethane concentration using log-transformed values for all samples.
[b]Measured in μg/L.

We next analyzed the relationship between drinking water source and specific concentrations of trihalomethanes detected in the 1986/87 water survey. Table 3 presents characteristics of trihalomethanes measured in the 1986/87 survey by water source. On the basis of this and other analyses,[1,2,6,7,13,35] chloroform was selected as the trihalomethane exposure variable of primary interest in subsequent analyses since it is the most commonly occurring trihalomethane, it has the broadest range of concentration, and it correlates well with the concentration of other chlorination by-products in drinking water, including total trihalomethane concentration.

Table 4 presents associations of chloroform levels in drinking water with major cancers derived through water test data obtained in the 1986/87 survey. The analyses reported in Table 4 involved 19 199 cohort members who met the inclusion criteria but did not include women who reported private well sources, since specific chemical concentrations in drinking water were not available for these women. Subjects living in communities with detectable levels of chloroform were classified into three groups according to the tertile distribution of total at-risk cohort members. The cancer rates in these groups were compared with rates among women living in communities with no detectable chloroform in their drinking water. We found a clear dose–response relation between chloroform concentration and cancer of the colon and total combined cancer. The risks were 1.00, 1.06, 1.39, and 1.68 (trend test, $P < .01$) for colon cancer and 1.00, 1.04, 1.24, and 1.25 (trend test, $P < .01$) for total cancer across increasing levels of chloroform. The excess risk for total cancer was largely due to the positive association of chloroform with colon cancer cases (accounting for 18% of total cancer cases). Across increasing levels of chloroform, the multivariate-adjusted relative risks were 1.00, 1.02, 1.19, and 1.14 (trend test, $P = .08$) for all cancers other than colon cancer. Melanoma and lung cancer were also positively associated with increased chloroform concentration, but the dose–response relations were less evident. These observed associations persisted after exclusion of women who reported having used their current water source for 11 to 20 years (n = 2590).

Additional analyses were performed for colon cancer to assess whether the observed positive associations could be explained by other factors. The relative risks were 1.00, 1.09, 1.44, and 1.72 after adjustment for additional risk or protective factors previously identified in this cohort, such as history of polyps or ulcerative colitis, height, dietary calcium, sucrose, and vitamins D and E.[36–38] These relative risks were 1.00, 1.46, 1.96, and 2.44 (P for trend <.0001) after exclusion of 1238 women who reported a history of colorectal polyps at baseline.

Analyses similar to those shown in Table 4 were performed with the 1979 water survey data. The correlation between chloroform concentrations measured in the 1979 and 1986/87 water surveys was .66 ($P < .0001$) for the 241 community water supplies included in both surveys. Since the 1979 water survey involved fewer communities, only 16 461 cohort members were included in the analyses. Colon cancer was again shown to be associated with chloroform concentration. The relative risks were 1.00, 1.55, 2.25, and 3.08 (P for trend <.01) from the lowest to highest exposure groups (data not shown in table). A dose–response relationship was also suggested for total combined cancer (relative risks were 1.00, 1.14, 1.13, and 1.32 from the lowest to the highest exposure category), although the trend test was only borderline significant ($P = .08$). Elevated risks of melanoma (RR = 2.40, 95% CI = 0.56, 10.34) and lung cancer (RR = 1.24, 95% CI = 0.58, 2.64) were also seen in the highest exposure category but were not statistically significant.

In an effort to take into account the temporal fluctuations in chloroform concentration, we further defined the exposure status of study participants according to the median levels of chloroform in both the 1979 and 1986/87 water surveys. Melanoma and cancers of the colon, lung, breast, and all sites combined were selected in this analysis since they had been found, in previous analyses, to be associated with either surface water sources or chloroform concentration. The analysis included 16 447 cohort members for whom chloroform data were available in both the 1979 and 1986/87 water surveys. As shown in Table 5, no consistent associations were observed for melanoma and cancers of the lung and breast. However, women who were consistently in the high exposure categories in the two water surveys had the highest risk of developing colon cancer (RR = 1.86, 95% CI = 1.29, 2.69). The risk was 1.28 (95% CI = 1.10, 1.48) for total combined cancer. The risks were further elevated when the quartile distribution was used to define exposure status. The relative risks were 2.86 (95% CI = 1.52, 5.39) for colon cancer and 1.36 (95% CI = 1.07, 1.73) for all cancers combined for women in the uppermost quartile level of exposure (vs women in the lowermost quartiles) in both the 1979 and 1986/87 water surveys.

TABLE 4—Relative Risks (RRs) for Major Cancers in Relation to Chloroform Levels in Drinking Water among Postmenopausal Women: Iowa Women's Health Study, 1986 through 1993

Cancer Site	Chloroform Concentration in 1986/87 Test				Trend Test *P*
	< Limit of Detection	1–2 µg/L	3–13 µg/L	14–287 µg/L	
Digestive organs					
Upper digestive organs (excluding lip and major salivary glands)					
Age-adjusted RR (95% CI)	1.00	2.02 (0.76, 5.37)	1.06 (0.32, 3.48)	1.71 (0.61, 4.80)	.56
Multivariate RR (95% CI)	1.00	1.93 (0.73, 5.16)	1.01 (0.31, 3.31)	1.59 (0.56, 4.47)	.66
Events (n = 32)	6	12	5	9	
Colon					
Age-adjusted RR (95% CI)	1.00	1.09 (0.70, 1.69)	1.41 (0.91, 2.19)	1.72 (1.14, 2.59)	<.01
Multivariate RR (95% CI)	1.00	1.06 (0.68, 1.66)	1.39 (0.89, 2.15)	1.68 (1.11, 2.53)	<.01
Events (n = 178)	38	41	42	57	
Rectum and anus					
Age-adjusted RR (95% CI)	1.00	0.83 (0.45, 1.53)	0.78 (0.40, 1.51)	1.10 (0.61, 1.97)	.83
Multivariate RR (95% CI)	1.00	0.80 (0.44, 1.48)	0.75 (0.39, 1.46)	1.07 (0.60, 1.93)	.89
Events (n = 78)	23	19	14	22	
Urinary organs					
Kidney (renal cell)					
Age-adjusted RR (95% CI)	1.00	0.56 (0.19, 1.68)	1.28 (0.51, 3.22)	0.89 (0.33, 2.39)	.76
Multivariate RR (95% CI)[a]	1.00	0.54 (0.18, 1.62)	1.22 (0.48, 3.09)	0.86 (0.32, 2.32)	.82
Events (n = 30)	9	5	9	7	
Bladder					
Age-adjusted RR (95% CI)	1.00	0.92 (0.41, 2.10)	1.28 (0.57, 2.84)	0.67 (0.26, 1.69)	.55
Multivariate RR (95% CI)	1.00	0.89 (0.39, 2.01)	1.22 (0.55, 2.72)	0.62 (0.25, 1.59)	.46
Events (n = 42)	12	11	12	7	
Lung					
Age-adjusted RR (95% CI)	1.00	1.36 (0.82, 2.25)	1.96 (1.20, 3.21)	1.85 (1.13, 3.01)	<.01
Multivariate RR (95% CI)	1.00	1.24 (0.75, 2.07)	1.81 (1.11, 2.97)	1.59 (0.97, 2.59)	.025
Events (n = 143)	26	35	40	42	
Melanoma					
Age-adjusted RR (95% CI)	1.00	2.52 (0.98, 6.49)	1.27 (0.41, 3.94)	3.22 (1.27, 8.18)	.06
Multivariate RR (95% CI)	1.00	2.55 (0.99, 6.58)	1.28 (0.41, 3.98)	3.37 (1.33, 8.56)	.049
Events (n = 44)	6	15	6	17	
Non-Hodgkin's lymphoma					
Age-adjusted RR (95% CI)	1.00	0.82 (0.40, 1.71)	0.88 (0.41, 1.89)	1.00 (0.49, 2.06)	.95
Multivariate RR (95% CI)	1.00	0.82 (0.39, 1.70)	0.85 (0.40, 1.84)	0.99 (0.48, 2.02)	.99
Events (n = 54)	16	13	11	14	
Reproductive organs[b]					
Ovary					
Age-adjusted RR (95% CI)	1.00	1.52 (0.68, 3.38)	2.17 (0.99, 4.74)	0.91 (0.36, 2.31)	.96
Multivariate RR (95% CI)[c]	1.00	1.49 (0.67, 3.33)	2.11 (0.97, 4.63)	0.91 (0.36, 2.30)	.97
Events (n = 50)	10	15	17	8	
Endometrium					
Age-adjusted RR (95% CI)	1.00	0.91 (0.57, 1.47)	0.83 (0.49, 1.40)	1.34 (0.85, 2.09)	.30
Multivariate RR (95% CI)[c]	1.00	0.92 (0.57, 1.48)	0.81 (0.48, 1.37)	1.28 (0.82, 2.01)	.40
Events (n = 133)	35	33	23	42	
Breast[b]					
Age-adjusted RR (95% CI)	1.00	1.06 (0.85, 1.34)	1.17 (0.92, 1.48)	1.09 (0.86, 1.37)	.37
Multivariate RR (95% CI)[c]	1.00	1.06 (0.84, 1.33)	1.18 (0.93, 1.49)	1.08 (0.85, 1.37)	.37
Events (n = 561)	143	151	131	136	
Any cancers excluding colon cancer[b]					
Age-adjusted RR (95% CI)	1.00	1.05 (0.87, 1.27)	1.21 (0.99, 1.47)	1.18 (0.98, 1.42)	.04
Multivariate RR (95% CI)	1.00	1.02 (0.85, 1.24)	1.19 (0.98, 1.44)	1.14 (0.94, 1.37)	.08
Events (n = 867)	212	228	202	225	
All cancers combined[b]					
Age-adjusted RR (95% CI)	1.00	1.07 (0.89, 1.28)	1.26 (1.05, 1.51)	1.29 (1.08, 1.54)	<.01
Multivariate RR (95% CI)[a,c]	1.00	1.04 (0.87, 1.25)	1.24 (1.03, 1.49)	1.25 (1.05, 1.49)	<.01
Events (n = 983)	232	253	230	268	
Person-years	23 775	24 326	18 848	21 479	

Note. All relative risks were adjusted for age, education, smoking status, pack-years of smoking, physical activity, all fruit and vegetable intake, total energy intake, body mass index, and waist-to-hip ratio. Three hundred ninety-seven women (2%) who resided in communities not included in the 1986/87 water quality database were excluded from the analyses. CI = confidence interval.

[a]Additionally adjusted for history of blood transfusion.

[b]Excluding women with baseline oophorectomy for ovarian cancer analyses, women with baseline hysterectomy for endometrial cancer analyses, women with baseline mastectomy for breast cancer analyses, and any of these conditions for analysis of all cancers combined.

[c]Additionally adjusted for age at menarche, age at menopause, and age at first birth.

TABLE 5—Multivariate Relative Risks (RRs) for Selected Cancers Associated with Exposure to Chloroform in Drinking Water, Using Data from 1979 and 1986/87 Water Surveys: Iowa Women's Health Study, 1986 through 1993

Chloroform Level in 1979 Survey	Chloroform Level in 1986/87 Survey: Low			High		
	Cases	RR	95% CI	Cases	RR	95% CI
Colon						
Low	44	1.00	Reference	13	1.47	0.79, 2.74
High	17	1.54	0.88, 2.69	80	1.86	1.29, 2.69
Lung						
Low	39	1.00	Reference	17	2.05	1.16, 3.63
High	11	1.31	0.67, 2.57	59	1.56	1.04, 2.33
Melanoma						
Low	15	1.00	Reference	2	0.68	0.16, 2.97
High	3	0.86	0.25, 2.99	21	1.53	0.79, 2.98
Breast						
Low	189	1.00	Reference	44	1.15	0.83, 1.60
High	52	1.13	0.83, 1.54	199	1.11	0.91, 1.35
Any cancer						
Low	308	1.00	Reference	82	1.24	0.97, 1.58
High	87	1.09	0.86, 1.39	380	1.28	1.10, 1.48

Note. Subjects were classified into low or high exposure groups according to the median distribution of total at-risk cohort members according to data from the 1979 and 1986/87 surveys. The median levels of chloroform were 1.1 parts per billion in the 1979 survey and 3 μg/L in the 1986/87 survey. Relative risks were adjusted for the same covariates included in the site-specific analyses found in Tables 2 and 4; women without data available from the 1979 water survey were also excluded.

To assess the association of other trihalomethanes with colon cancer, we performed similar analyses for bromodichloromethane, dibromochloromethane, and bromoform, using data from the 1986/87 water survey. No statistically significant association was observed for any of these trihalomethanes. At increasing concentrations of bromodichloromethane, dibromochloromethane, and bromoform, respectively, the relative risks of colon cancer were 1.00, 1.23, 1.40, and 1.18 (trend test, $P = .35$); 1.00, 1.14, 0.72, and 1.09 (trend test, $P = .78$); and 1.00, 0.60, 0.85, and 1.21 (trend test, $P = .39$). The levels of these three compounds, however, were considerably lower than that of chloroform, and a large proportion of water sources had undetectable levels of these trihalomethanes (see Table 3), resulting in unstable relative risk estimates.

Discussion

To our knowledge, this is only the second prospective cohort study to assess the relation of exposure to chlorination by-products in drinking water with cancer risk.[11] We found that women who resided in areas supplied with municipal surface water or water with higher levels of chloroform were at significantly increased risk for colon cancer and total combined cancer. In particular, the risk of these cancers was increased with levels of chloroform in a dose–response manner after adjustment for potential confounders. Since fewer than 430 cohort members lived in communities with chloroform concentrations exceeding the US Environmental Protection Agency limit of 100 μg/L, we were unable to meaningfully assess the risk associated with exposure to drinking water exceeding this limit.

Our findings are supported by some but not all previous epidemiologic studies.[10,22] Both Alavanja et al.[9] and Young et al.[12] found an association between colon cancer mortality and chlorinated drinking water. Exposure data in these studies were somewhat crude, however, and were determined by the addresses of study participants appearing on their death certificates. Cragle et al. also found an association between colon cancer and chlorinated water using more complete exposure data.[15] Two case–control studies using statistical models to estimate past trihalomethane levels, however, found no significant association between past exposure and colon cancer.[14,17] Some studies have grouped colon cancer with rectal cancer and found an overall increased risk for colorectal cancer associated with exposure to chlorinated water.[22] We found no increased risk of rectal cancer associated with the exposure variables in our study.

We also found excess risks of melanoma and lung cancer associated with higher levels of chloroform in drinking water. Although dermal and inhalation routes of chloroform absorption have been reported,[39–42] the lack of a clear dose–response relation for these malignancies in this study does not support a causal association. An excess risk of breast cancer was observed to be related to surface water sources but not chloroform concentration, indicating that this association is more likely due to contaminants in surface water other than chlorination by-products or risk factors for breast cancer related to increased urbanicity.

Several previous studies have shown that an increased risk of bladder cancer is associated with chlorination by-products.[8–11,13,18,19,21] We found no clear association for this cancer site. The small number of bladder cancer cases in this cohort of women may have limited our ability to detect an association.

The mechanisms of carcinogenesis caused by exposure to chlorination by-products are not fully understood but are likely to be due to a tumor promotion effect on mucosal epithelial tissue via direct contact.[43] Chloroform itself has not been shown to initiate tumors when applied topically to mice; however, the trihalomethanes appear to exhibit tumor-promoting activity, as indicated by the induction of both regenerative hyperplasia and molecular markers of tumor promotion such as ornithine decarboxylase in animal bioassays.[43] Chloroform has not been shown to be mutagenic in *Salmonella,* but the other trihalomethanes have shown weak mutagenic potential by inducing base-pair substitutions.[7] While chlorination by-products other than the trihalomethanes may be more mutagenic,[44,45] their toxicology is less well characterized. It is also worth mentioning that there are many contaminants in water, particularly in surface water. Therefore, chloroform may serve as a surrogate measure of other contaminants that might be truly responsible for the observation in this study.

The morphological characteristics of colorectal epithelial tumors induced by

trihalomethanes in rodents are similar to those observed in human colorectal cancers.[46] All pathways of trihalomethane metabolism in animals lead to reactive intermediates that potentially interact with DNA. However, the carcinogenicity of trihalomethanes appears to be correlated with the production of recurrent cytotoxicity related to their metabolic activation by various cytochrome P450 isozymes.[46,47]

Finally, some limitations of this study need to be considered when interpreting the results. The residential history of study participants prior to the baseline questionnaire in 1986 was unavailable. Some misclassification of exposure may have occurred, since the exposure status for study participants was determined via their residence in 1986. Between 1986 and 1989, however, only 1.8% of cohort members indicated a change of residence. Together with previous estimates of the out-migration rate, this indicates that the exposure misclassification error due to lack of data on residential history for this cohort of older women is likely to be small. Because individual exposure status was defined only by past residence, misclassification of exposure could have occurred if a substantial number of cohort members lived in one community but used water from another community (e.g., workplace) as their main drinking water source. This is unlikely in our study, since our cohort members were all more than 55 years of age at baseline, and a majority of them were retirees, homemakers, or farmers. A second limitation is the lack of data on specific water consumption amounts for study participants. This prevented us from further quantifying intake levels of chlorination by-products by taking into consideration the variation in water consumption habits of individual cohort members. Random exposure misclassification in either of these instances, however, is likely to attenuate the estimated risk of disease.[48,49] Finally, this study was conducted only among women. It is unlikely, however, that the fundamental biology in colon carcinogenesis would be different for men than for women.

Conclusions

We found that women who resided in communities with surface water sources or drinking water with higher levels of chloroform were at significantly increased risk for cancer, particularly colon cancer. These findings are consistent with some, although not all, previous epidemiologic and animal studies and suggest that prolonged exposure to chlorination by-products in drinking water may be associated with an increased risk of cancer in humans. □

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References

1. Cantor KP. Epidemiologic studies of chlorination by-products in drinking water: an overview. In: Jolley RL, ed. *Water Chlorination: Environmental Impact and Health Effects.* 4th ed. Ann Arbor, Mich: Ann Arbor Scientific Publishers; 1983:1381–1397.
2. Bellar T, Lichtenberg J, Kroner R. The occurrence of organohalides in chlorinated drinking waters. Cincinnati, Ohio: US Environmental Protection Agency, Office of Research and Development, National Environmental Research Center; 1974.
3. Rook JJ. Formation of haloforms during chlorination of natural waters. *Water Treatment Examination.* 1974;23:234–243.
4. Rook JJ. Haloforms in drinking water. *J Am Water Works Assoc.* 1976;68:168–172.
5. Rook JJ. Chlorination reactions of fulvic acids in natural waters. *Environ Sci Technol.* 1977;11:478–482.
6. *Carcinogenesis Bioassay of Chloroform.* Bethesda, Md: Carcinogen Bioassay and Program Resources Branch, National Cancer Institute; 1976.
7. Dunnick J, Melnick R. Assessment of the carcinogenic potential of chlorinated water: experimental studies of chlorine, chloramine, and trihalomethanes. *J Natl Cancer Inst.* 1993;85:817–822.
8. Cantor K, Hoover R, Mason T, et al. Associations of cancer mortality with halomethanes in drinking water. *J Natl Cancer Inst.* 1978;61:979–985.
9. Alavanja M, Goldstein I, Susser M. A case-control study of gastrointestinal and urinary tract cancer mortality and drinking water chlorination. In: Jolley RL, Gorchev H, Hamilton DH Jr, eds. *Water Chlorination: Environmental Impact and Health Effects.* 2nd ed. Ann Arbor, Mich: Ann Arbor Scientific Publishers; 1978:395–409.
10. Wilkins J, Reiches N, Kruse C. Organic chemical contaminants in drinking water and cancer. *Am J Epidemiol.* 1979;110:420–448.
11. Wilkins J, Comstock G. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. *Am J Epidemiol.* 1981;114:178–190.
12. Young TB, Kanarek MS, Tsiatis AA. Epidemiologic study of drinking water chlorination and Wisconsin female cancer mortality. *J Natl Cancer Inst.* 1981;67:1191–1198.
13. Isacson P, Bean JA, Lynch C. Relationship of cancer incidence rates in Iowa municipalities to chlorination status of drinking water. In: Jolley RL, ed. *Water Chlorination: Environmental Impact and Health Effects.* 4th ed. Ann Arbor, Mich: Ann Arbor Scientific Publishers; 1983:1353–1364.
14. Lawrence C, Taylor P, Trock B, Reilly A. Trihalomethanes in drinking water and human colorectal cancer. *J Natl Cancer Inst.* 1984;72:563–568.
15. Cragle DL, Shy CM, Struba RJ, Siff EJ. A case-control study of colon cancer and water chlorination in North Carolina. In: Jolly RL, ed. *Water Chlorination Chemistry, Environmental Impact and Health Effects.* Chelsea, Mich: Lewis Publishers; 1985:153–159.
16. Cech I, Holguin A, Littell A, et al. Health significance of chlorination by-products in drinking water: the Houston experience. *Int J Epidemiol.* 1987;16:198–207.
17. Young T, Wolf D, Kanarek M. Case-control study of colon cancer and drinking water trihalomethanes in Wisconsin. *Int J Epidemiol.* 1987;16:190–197.
18. Cantor K, Hoover R, Hartge P, et al. Bladder cancer, drinking water source, and tap water consumption: a case-control study. *J Natl Cancer Inst.* 1987;79:1269–1279.
19. Zierler S, Feingold L, Danley RA, et al. Bladder cancer in Massachusetts related to chlorinated and chloraminated drinking water: a case control study. *Arch Environ Health.* 1988;43:195–200.
20. Flaten TP. Chlorination of drinking water and cancer incidence in Norway. *Int J Epidemiol.* 1992;21:6–15.
21. McGeehin MA, Reif JS, Becher JC, et al. Case-control study of bladder cancer and water disinfection methods in Colorado. *Am J Epidemiol.* 1993;138:492–501.
22. Morris R, Audet AM, Angelillo I, et al. Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health.* 1992;82:955–963.
23. Kushi LH, Sellers TA, Potter JD, et al. Dietary fat and postmenopausal breast cancer. *J Natl Cancer Inst.* 1992;84:1092–1099.
24. Folsom AR, Kaye SA, Sellers TA, et al. Body fat distribution and 5-year risk of death in older women. *JAMA.* 1993;269:483–487.
25. *Historical Community Water Supply and Treatment Data for the State of Iowa; Table 1 and Table 6.* 2nd ed. Iowa City, Iowa: Center for Health Effects of Environmental Contamination, University of Iowa; 1993.
26. Hoover R, Sprasser PH. Artificial sweeteners and human bladder cancer. *Lancet.* 1980;1:837–840.
27. *One Time Testing of Iowa's Regulated Drinking Water Supplies.* Iowa City, Iowa: Hygienic Laboratory, University of Iowa; 1989.
28. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B.* 1972;34:187–220.
29. Steinmetz K, Kushi L, Bostick R, et al. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol.* 1994;139:1–5.
30. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. *Cancer Res.* 1993;53:536–543.

31. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986;124: 17–27.
32. Sellers TA, Kushi LH, Potter JD, et al. Effect of family history, body fat distribution, and reproductive factors on risk of postmenopausal breast cancer. *N Engl J Med.* 1992;326:1323–1329.
33. Zheng W, Sellers TA, Doyle TJ, et al. Retinol, antioxidant vitamins and cancers of the upper digestive tract in a prospective cohort study of postmenopausal women. *Am J Epidemiol.* 1995;142:388–394.
34. Cerhan J, Wallace R, Folsom A, et al. Transfusion history and cancer risk in older women. *Ann Intern Med.* 1993;119:8–15.
35. Symons JM, Bellar TA, Carswell JK, et al. National Organics Reconnaissance Survey for Halogenated Organics. *J Am Water Works Assoc.* 1975;67:634–646.
36. Bostick R, Potter J, Sellers T, et al. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. *Am J Epidemiol.* 1993;137: 1302–1317.
37. Bostick R, Potter J, McKenzie D, et al. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res.* 1993;53:4230–4237.
38. Bostick R, Potter J, Kushi L, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women. *Cancer Causes Control.* 1994;5: 38–52.
39. Jo WK, Weisel C, Lioy PJ. Routes of chloroform exposure and body burden from showering with chlorinated tap water. *Risk Anal.* 1990;10:575–580.
40. Jo WK, Weisel C, Lioy PJ. Chloroform exposure and the health risk associated with multiple uses of chlorinated tap water. *Risk Anal.* 1990;10:581–585.
41. Levesque B, Ayotte P, LeBlanc A, et al. Evaluation of dermal and respiratory chloroform exposure in humans. *Environ Health Perspect.* 1994;102:1082–1087.
42. Nelemans PJ, Rampen F, Groenendal H. Swimming and the risk of cutaneous melanoma. *Melanoma Res.* 1994;4:281–286.
43. Pereira MA. Carcinogenicity of chlorination by-products: trihalomethanes. In: Jolley RL, ed. *Water Chlorination: Environmental Impact and Health Effects.* 4th ed. Ann Arbor, Mich: Ann Arbor Scientific Publishers; 1983:1165–1176.
44. Koivusalo M, Jaakkola J, Vartiainen T. Drinking water mutagenicity in past exposure assessment of the studies on drinking water and cancer: application and evaluation in Finland. *Environ Res.* 1994;64:90–101.
45. Koivusalo M, Jaakkola J, Vartiainen T. Drinking water mutagenicity and gastrointestinal and urinary tract cancers: an ecological study in Finland. *Am J Public Health.* 1994;84:1223–1228.
46. Melnick R, Dunnick J, Sandler D, et al. Trihalomethanes and other environmental factors that contribute to colorectal cancer. *Environ Health Perspect.* 1994;102:586–588.
47. Corley RA, Mendrala AL, Smith FA, et al. Development of a physiologically based pharmacokinetic model for chloroform. *Toxicol Appl Pharmacol.* 1990;103:512–527.
48. Flegal KM, Brownie C, Hass JD. The effects of exposure misclassification on estimates of relative risk. *Am J Epidemiol.* 1986;123:736–751.
49. Lynch CF, Woolson RF, O'Gorman T, Cantor KP. Chlorinated drinking water and bladder cancer: effect of misclassification on risk estimates. *Arch Environ Health.* 1989;44:252–259.