

# Drinking Water Source and Chlorination Byproducts

## II. Risk of Colon and Rectal Cancers

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We evaluated the association between chlorination byproducts and colon and rectal cancer risk in a population-based case-control study conducted in Iowa in 1986–1989. Data were gathered from 685 colon cancer cases, 655 rectal cancer cases, and 2,434 controls. We calculated odds ratios for the 560 colon cancer cases, 537 rectal cancer cases, and 1,983 controls for whom water exposure information was available for at least 70% of their lifetime. We estimated exposure to chlorination byproducts with two types of measures: duration of lifetime at residences served by chlorinated water and estimated lifetime trihalomethane exposure. For rectal cancer, we observed an association with duration of chlorinated surface water use, with adjusted odds ratios of 1.1, 1.6, 1.6, and 2.6 for 1–19, 20–39, 40–59, and  $\geq 60$  years of exposure, compared with no exposure. Rectal cancer risk was also associated with several differ-

ent measures of estimated lifetime trihalomethane exposure. For colon cancer and subsites, we detected no important increase in risk associated with duration of chlorinated surface water, nor with trihalomethane estimates. When we evaluated chlorination byproducts jointly with other factors, we found larger relative risk estimates for rectal cancer among subjects with low dietary fiber intake. The risk related to  $\geq 40$  years of exposure to a chlorinated surface water source was 2.4 (95% confidence interval = 1.5–4.0) for persons with low fiber intake and 0.9 (95% confidence interval = 0.4–1.8) for persons with high fiber intake, relative to the risk of persons with high-fiber diets and no exposure to chlorinated surface water. We observed a similar risk differential for low and high levels of physical activity. (Epidemiology 1998;9:29–35)

**Keywords:** colorectal neoplasms, drinking water, water source, chlorination, gender, trihalomethanes, diet, physical activity.

Chlorination byproducts result from the disinfection of drinking water with chlorine. The practice of adding chlorine to raw water supplies became widespread at the turn of the twentieth century, but it was not until the mid-1970s that Rook<sup>1</sup> and Bellar *et al*<sup>2</sup> independently observed that chlorine reacts with naturally occurring organic matter to form trihalogenated methanes (THMs). Subsequently, a U.S. Environmental Protection Agency survey<sup>3</sup> reported that chloroform, the most ubiquitous of the THMs, could be found in almost every treated drinking water supply. Treated surface water sources were shown to contain much higher levels of chlorination byproducts than treated groundwater sources, owing to the higher concentrations of organic

matter, such as humic and fulvic acids found in untreated surface water.

Epidemiologic assessment of the effects of chlorination byproducts started with several ecologic studies that compared aggregate cancer mortality or incidence rates of different communities by water source, THM levels, or chlorination status.<sup>4–13</sup> The results of these preliminary studies indicated that persons drinking chlorinated water, especially chlorinated water derived from surface sources, may be at increased risk of bladder, colon, and rectal cancers. Subsequent case-control studies, in which exposure was based on the residence reported on the death certificate, generally supported these positive findings for colon and rectal cancers,<sup>14–21</sup> but interpretation was limited, since a person's water exposure at the last residence does not necessarily represent tapwater exposures experienced in the past. Case-control interview studies of incident cases have the potential to overcome the limitations of the early studies, but relatively few have been conducted.<sup>22–24</sup> In a case-control interview study of incident colon cancer in Wisconsin, Young *et al*<sup>22</sup> did not observe an increase in colon cancer risk associated with lifetime THM exposure, but response rates were low (45% cases, 48% controls). Cragle *et al*<sup>23</sup> observed a positive association of colon cancer with chlorinated water consumption in persons over age 60 years; however, their results are difficult to interpret

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since their methods were not described in detail. A recent Canadian case-control incidence study, which examined both sites and collected comprehensive exposure data, reported an increased risk of colon cancer but not rectal cancer associated with chlorination byproducts.<sup>24</sup>

We conducted a case-control study in Iowa to examine the relation between ingestion of chlorination byproducts and risk of cancer. A companion paper describes our findings for bladder cancer.<sup>25</sup> Here, we report on the results from an analysis of the association between water source, estimated exposure to chlorination byproducts as represented by THMs, and risk of colon and rectal cancers.

## Methods

### STUDY POPULATION

We identified eligible cases through the State Health Registry of Iowa, the statewide tumor registry. Colon cancer cases were eligible if diagnosed during a 10-month period starting in March 1987. Eligible rectal cancer cases were diagnosed during a 24-month period starting in January 1986. Eligibility criteria for the 801 colon and 761 rectal cancer cases we identified included Iowa residency at diagnosis, age between 40 and 85 years, histologic confirmation, and no previous history of a malignant neoplasm. Control eligibility was restricted to Iowa residents between 40 and 85 years of age who were alive at the time of initial contact. We conducted control selection in two phases. We frequency-matched the first group of controls on sex and age in 5-year groups to the entire case group of six sites. We identified these controls from computerized tapes containing driver's license data for persons ages 40–64 years ( $N = 692$ ) and from U.S. Health Care Financing Administration tapes for persons ages 65–85 years ( $N = 1,166$ ). We added an additional 1,175 eligible controls by using similar techniques to match controls to additional bladder cancer cases diagnosed in 1988–1989, to yield a total of 3,033 eligible controls.

### DATA COLLECTION

#### Case-Control Data

After obtaining physician consent for cases, we wrote to each identified study subject or next-of-kin explaining the purpose of the study, and we subsequently telephoned them to invite participation through completion of a postal questionnaire. The questionnaire included questions about residential and occupational histories, usual adult dietary habits, including fluid consumption, past medical conditions, history of familial cancer, usual physical activity, and other items. Subjects who at any time expressed reluctance in completing the detailed questionnaire were given the opportunity to respond to a shorter 15-minute telephone interview, which excluded detailed occupational history, food frequency questions, and other items not considered essential to the analysis of water quality and risk. Final response to

the mail questionnaire and telephone interview resulted in 685 colon cancer cases (85.5%), 655 rectal cancer cases (86.1%), and 2,434 controls (80.3%). Proxy interviews numbered 95 for colon cancer, 115 for rectal cancer, and 2 for controls.

#### Water Utility Data

In the spring and summer of 1987, we conducted a survey of all Iowa water utilities serving at least 1,000 persons and collected information from operators and data tapes concerning treatments and water sources used at each utility since its inception. The survey resulted in historical information collected from 280 utilities serving 345 Iowa communities with a total 1980 population of 1.94 million, approximately two-thirds of the 1980 total Iowa population.<sup>26</sup> From each utility, we collected finished water samples at the same representative point in the distribution system. We analyzed these samples for the presence of the four major THMs and other contaminants.

### EXPOSURE ASSESSMENT

We combined data from the personal questionnaire, the water utility survey, and the THM measurements of water samples to create indices of past exposure to chlorination byproducts for each respondent. For all utilities in the water utility survey, we estimated past THM levels by applying geometric mean THM values calculated from 1987 measurement data according to treatment type and water source. We estimated past exposure to chlorination byproducts for study subjects by linking residences reported on the questionnaire to the water utilities serving them by geographic location and year. We considered water from private wells to be nonchlorinated groundwater, and we assigned it an estimated THM level of 0.5  $\mu\text{g}$  per liter (half the detection limit). Using our linked data, we calculated several indices of lifetime exposure, including total lifetime THM exposure (gm), average lifetime THM concentration ( $\mu\text{g}$  per liter), and total number of years exposed to chlorinated surface water, chlorinated groundwater, and any chlorinated water (surface or ground).

### STATISTICAL METHODS

To decrease the potential bias introduced by subjects for whom lifetime exposure assessment was incomplete, we calculated odds ratios for all colon and rectal cancer cases and controls with identifiable water exposure data for at least 70% of their lifetime. Of the 685 colon cancer cases, 655 rectal cancer cases, and 2,434 controls, we included in the analyses 560 colon cancer cases (81.8%), 537 rectal cancer cases (82.0%) and 1,983 controls (81.5%). Among these respondents, approximately 5.5% of the total exposure years were missing information on water source and treatment, compared with over 50% of exposure years with missing information for the excluded subjects. Excluded subjects did not

differ much from the subjects included in the analysis with respect to age, sex, or subject status. Compared with the excluded subjects, subjects in the analysis subset were less likely to live in urban areas and less likely to have obtained a college degree, but the proportions of cases and controls with these characteristics were similar (results not shown).

We used unconditional multiple logistic regression models to estimate odds ratios for risk of colon and rectal cancers associated with duration at chlorinated ground and surface sources, various estimates of THM exposure, and tapwater consumption, while adjusting for potentially confounding factors. All models included age (four categories) and sex as adjustment factors. In analyses of water source and THM exposure and rectal cancer risk, we also adjusted for urbanicity as measured by average lifetime population size of places of residence (in thousands:  $\leq 2.5$ , 2.6–9.9, 10.0–49.9,  $\geq 50$ ). In tests for trend, we treated exposure variables as continuous. We also examined the joint effect of exposure to chlorinated surface water with various factors in relation to rectal cancer risk.

## Results

Among respondents with ascertainable water exposure for at least 70% of their lifetime, there were similar numbers of male and female colon cancer cases (50.5%

male), and a slight male excess of rectal cancer cases (59.2%). The proportion of cancer cases diagnosed after age 65 years was higher for colon (70.5%) than for rectal cancer (62.0%). The site-specific distribution in our population reflected national patterns in colon cancer rates by anatomical location,<sup>27</sup> with cancers of the sigmoid and descending colon dominating.

To facilitate comparison between this and previous studies, we examined the risk associated with duration of exposure to chlorinated surface and groundwater sources. The percentage of years at nonchlorinated groundwater (public or private wells) was slightly higher for controls (56.4%) than for either colon (54.4%) or rectal (54.2%) cancer cases. In contrast, the percentage of years of exposure to chlorinated surface water was slightly higher for rectal cancer cases (13.8%) than for colon cancer cases (11.7%) or controls (11.1%). We present in Table 1 the results of the logistic regression analysis that examined risk with duration of exposure to chlorinated surface and chlorinated groundwater sources. After control for age, sex, duration at chlorinated ground sources, and population size, we observed a monotonic trend of increasing rectal cancer risk with duration at residences served by a surface chlorinated source. Subjects with more than 60 years of exposure at a surface chlorinated source were at more than twice the risk of developing rectal cancer than those with no years at a chlorinated surface source [odds ratio (OR) = 2.61; 95% confidence interval (CI) = 1.4–

5.0]. We observed no increase in colon

cancer risk associated with duration at a chlorinated surface water source.

When we examined duration of exposure to chlorinated groundwater, controlling for age, sex, and duration at chlorinated surface water sources, we found an indication of increased risks

for colon and rectal cancers (Table 1). Results from analyses examining duration of exposure for any chlorinated water (surface or ground) resembled the estimated risk observed for duration at chlorinated surface water sources for both sites. We observed similar risk patterns for both sites when we analyzed men and women separately. Further adjustment for the other potential confounding factors described in the Methods did not alter the risk estimates presented above.

In Table 2, we show results from analyses investigating associations with estimates of both cumulative lifetime THM exposure (gm) and average lifetime THM concentration ( $\mu\text{g}$  per liter). We detected no clear trend in colon cancer risk with either measure of THM exposure. In contrast, there was a trend of increasing rectal cancer risk with both increasing cumulative

TABLE 1. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Colon and Rectal Cancers by Duration at Residences Served by Chlorinated Surface Water, Chlorinated Groundwater, or Any Chlorinated Water

Duration (Years)	Controls	Colon Cancer		Rectal Cancer	
		Cases	OR* (95% CI)	Cases	OR*,† (95% CI)
Chlorinated surface water					
0‡	1,275	353	1.0	325	1.0
1–19	428	125	1.02 (0.8–1.3)	115	1.08 (0.8–1.4)
20–39	139	38	0.99 (0.7–1.5)	47	1.55 (1.1–2.2)
40–59	101	35	1.21 (0.8–1.8)	32	1.63 (1.0–2.6)
$\geq 60$	40	9	0.81 (0.4–1.7)	18	2.61 (1.4–5.0)
P (trend)			0.36		0.005
Chlorinated groundwater					
0‡	624	154	1.0	178	1.0
1–19	500	153	1.19 (0.9–1.5)	122	0.87 (0.7–1.1)
20–39	530	140	1.03 (0.8–1.3)	150	1.14 (0.9–1.5)
40–59	300	101	1.29 (1.0–1.7)	80	1.32 (0.9–1.9)
$\geq 60$	29	12	1.64 (0.8–3.3)	7	1.46 (0.6–3.6)
P (trend)			0.27		0.09
Any chlorinated water (surface or ground)					
0‡	449	118	1.0	119	1.0
1–19	431	107	0.89 (0.7–1.2)	101	0.88 (0.7–1.2)
20–39	499	137	0.99 (0.8–1.3)	136	1.11 (0.8–1.5)
40–59	478	160	1.19 (0.9–1.6)	136	1.41 (0.9–2.0)
$\geq 60$	126	38	1.01 (0.7–1.6)	45	2.13 (1.3–3.5)
P (trend)			0.13		0.0002

\* Odds ratios were calculated from logistic regression models including age (4 strata) and sex. Also, models of duration at chlorinated surface water included a variable for duration at chlorinated groundwater (5 strata), and models of duration at chlorinated groundwater included a variable for duration at chlorinated surface water (5 strata).

† Logistic regression models for rectal cancer also included average population size of lifetime residences (4 strata).

‡ Referent category.

**TABLE 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Colon and Rectal Cancers Associated with Estimated Lifetime Trihalomethane Intake**

Trihalomethane Exposure	Colon Cancer			Rectal Cancer	
	Controls	Cases	OR* (95% CI)	Cases	OR* (95% CI)
Total lifetime THM (gm)					
≤0.04†	681	179	1.0	153	1.0
0.05-0.12	485	127	0.96 (0.7-1.2)	125	1.25 (1.0-1.6)
0.13-0.34	292	70	0.86 (0.6-1.2)	76	1.28 (0.9-1.8)
0.35-1.48	291	94	1.19 (0.9-1.6)	87	1.52 (1.1-2.1)
1.49-2.41	97	14	0.52 (0.3-0.9)	33	1.87 (1.2-3.0)
≥2.42	97	31	1.13 (0.7-1.8)	30	1.64 (1.0-2.6)
Unknown	40	45		33	
P (trend)			0.54		0.08
Lifetime average THM concentration (µg/liter)					
≤0.7†	695	191	1.0	173	1.0
0.8-2.2	495	142	1.01 (0.8-1.3)	123	1.05 (0.8-1.4)
2.3-8.0	298	80	0.93 (0.7-1.3)	86	1.24 (0.9-1.7)
8.1-32.5	297	89	1.07 (0.8-1.4)	83	1.23 (0.9-1.7)
32.6-46.3	99	27	0.93 (0.6-1.5)	36	1.66 (1.1-2.6)
≥46.4	99	31	1.06 (0.7-1.6)	36	1.66 (1.1-2.6)
P (trend)			0.85		0.01

\* Odds ratios were calculated from logistic regression models including age (4 strata) and sex. Logistic regression models for rectal cancer also included average population size of lifetime residences (4 strata).  
† Referent category.

and average THM exposure, after controlling for age, sex, and average population size. We noted similar effects when we examined men and women separately. Amount of tapwater consumed did not confound this effect, as it was not an independent risk factor in our population (data not shown). After adjustment for age and for sex, we observed little association between tapwater consumption and rectal cancer. We observed a slight decrease in colon cancer risk with increasing tapwater intake, with those who drank ≥2.9 liters per day

of tapwater at a 25% reduced risk of colon cancer compared with those who drank <1.5 liters per day. Adjustment for other potential confounding factors did not alter these estimates much. We also observed little difference in risk estimates when we restricted analyses to live subjects.

In addition to the estimates of lifetime exposure to chlorination byproducts presented in Tables 1 and 2, we also examined the association between colon and rectal cancer risk and various other temporal measures of exposure, including latency (time since first exposure), exposures in specific years, exposures in 20-year time windows, and lagged exposures. These measures were highly correlated in our study population, however, and results from these analyses did not yield any notable additional information and are not presented here.

We also examined associations with chlorination byproducts by colon and rectal subsites. Table 3 shows results for total lifetime THM exposure and for duration at chlorinated surface water. We observed no consistent increase in cancer risk with increasing THM exposure for the proximal, distal, or sigmoid colon. For cancer of the rectum alone (not including the rectosigmoid junction), which accounts for 66% of the rectal cancer cases, there was a trend in risk with increasing total THM intake, rising to a 90% increase for the highest THM level (OR = 1.89; 95% CI = 1.2-2.9). For the rectosigmoid junction, risk for any exposure was elevated, with

**TABLE 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Colon and Rectal Cancer Associated with Estimated Lifetime Total Trihalomethane Exposure and Years at Chlorinated Surface Water Sources by Cancer Subsite\***

Exposure	Proximal Colon		Mid-colon		Sigmoid Colon		Rectosigmoid Junction		Rectum		
	Controls	Cases	OR† (95% CI)	Cases	OR† (95% CI)	Cases	OR† (95% CI)	Cases	OR†,‡ (95% CI)	Cases	OR†,‡ (95% CI)
Total lifetime THM (gm)											
≤0.04§	681	65	1.0	34	1.0	75	1.0	43	1.0	110	1.0
0.05-0.12	485	46	0.90 (0.6-1.4)	29	1.18 (0.7-2.0)	49	0.92 (0.6-1.4)	49	1.72 (1.1-2.7)	76	1.08 (0.8-1.5)
0.13-0.34	292	30	1.01 (0.6-1.6)	11	0.70 (0.3-1.4)	27	0.82 (0.5-1.3)	31	1.83 (1.1-2.1)	45	1.08 (0.7-1.6)
0.35-1.48	291	34	1.20 (0.8-1.9)	21	1.37 (0.8-2.4)	38	1.16 (0.8-1.8)	32	1.91 (1.1-3.2)	55	1.37 (0.9-2.0)
≥1.49	194	17	0.81 (0.5-1.4)	10	0.96 (0.5-2.0)	17	0.78 (0.4-1.4)	16	1.49 (0.8-2.9)	47	1.89 (1.2-2.9)
Unknown	40	23		7		15		13		20	
P (trend)			1.00		0.28		0.78		0.97		0.04
Duration at chlorinated surface water (years)											
0§	1,275	134	1.0	68	1.0	142	1.0	111	1.0	214	1.0
1-19	428	52	1.24 (0.9-1.8)	27	1.11 (0.7-1.8)	45	0.90 (0.6-1.3)	46	1.21 (0.8-1.8)	69	0.99 (0.7-1.4)
20-39	139	13	0.86 (0.5-1.6)	8	1.02 (0.5-2.2)	17	1.06 (0.6-1.8)	14	1.15 (0.6-2.1)	33	1.54 (1.0-2.4)
40-59	101	10	0.84 (0.4-1.7)	8	1.35 (0.6-2.9)	15	1.28 (0.7-2.3)	8	0.91 (0.4-2.0)	24	1.66 (1.0-2.7)
≥60	40	6	1.26 (0.5-3.1)	1	0.43 (0.1-3.2)	2	0.43 (0.1-1.8)	5	1.49 (0.6-4.0)	13	2.50 (1.3-4.9)
P (trend)			0.55		1.00		0.68		0.86		0.01

\* Definitions of sites (*International Classification of Diseases*, 9th revision, codes): proximal (right-sided) colon: cecum (153.4), ascending (153.6), hepatic flexure (153.0); mid-colon: splenic flexure (153.7), descending (153.2), transverse (153.1); sigmoid colon (153.3); rectosigmoid junction (154.0); rectum (154.1). Other subsites (excluded from analyses) (N = 12): overlap (153.8), not otherwise specified (153.9).

† Odds ratios were calculated from logistic regression models including age (4 strata) and sex.

‡ Logistic regression models for rectal cancers also included average population size of lifetime residences (4 strata).

§ Referent category.

**TABLE 4. Odds Ratios and 95% Confidence Intervals for Risk of Rectal Cancer Associated with Years at Chlorinated Surface Water Sources and Usual Fiber Intake, Usual Physical Activity, or Average Daily Tapwater Ingestion\***

	Duration at Chlorinated Surface Water (Years)			
	0	1-19	20-39	≥40
Dietary fiber intake				
Above median	1.0†	1.28 (0.9-1.9)	1.20 (0.6-2.3)	0.89 (0.4-1.8)
Below median	0.99 (0.7-1.3)	0.88 (0.6-1.3)	1.57 (0.9-2.7)	2.43 (1.5-4.0)
Usual physical activity (times/week)				
≥1	1.0†	0.96 (0.7-1.4)	0.89 (0.5-1.7)	1.16 (0.6-2.2)
<1, never	1.10 (0.8-1.4)	1.25 (0.9-1.8)	2.28 (1.4-3.8)	2.22 (1.3-3.7)
Average daily tapwater (liters/day)				
<2.1	1.0†	1.34 (0.9-1.9)	1.85 (1.1-3.1)	2.00 (1.2-3.3)
≥2.1	1.27 (0.9-1.6)	1.24 (0.9-1.8)	1.34 (0.8-2.3)	1.72 (1.0-3.0)

\* Odds ratios were calculated from logistic regression models including age (4 strata), sex, and average population size of lifetime residences (4 strata). Analyses excluded unknowns for lifetime trihalomethanes, fiber intake, usual physical activity, or average daily tapwater.

† Referent category.

no monotonic trend. We obtained similar results for subsites of the colon and rectum when we examined the effect of duration of exposure to chlorinated surface water. For cancer of the rectum alone, persons who consumed chlorinated surface water for  $\geq 60$  years were at a 150% increased risk of cancer compared with those with no years of exposure to chlorinated surface water (OR = 2.50; 95% CI = 1.3-4.5).

We also evaluated the association between rectal cancer and duration of exposure to chlorinated surface water jointly with other factors. In particular, we observed that both dietary fiber intake and physical activity modified the effect of chlorinated surface water ingestion on rectal cancer risk (Table 4). Among respondents who spent  $\geq 40$  years drinking chlorinated surface water and reported diets low in fiber, we observed almost a 150% increase in risk compared with persons consuming high-fiber diets and drinking either nonchlorinated or chlorinated groundwater (OR = 2.43; 95% CI = 1.5-4.0). Among respondents with a high-fiber diet, we observed no increase in risk associated with  $\geq 40$  years of exposure to chlorinated surface water (OR = 0.89; 95% CI = 0.4-1.8). We observed a similar risk pattern when we examined the joint effect of physical activity and exposure to chlorinated surface water. Respondents who exercised 1-4 times per month or less were at increased risk of rectal cancer associated with chlorinated surface water, whereas respondents who exercised with a frequency of at least 1 time per week were not. In contrast, we observed no interaction of amount of water consumed with exposure to chlorinated surface water. We conducted a similar analysis of our other measures of chlorination byproducts, namely estimated total and average THMs, and observed similar risk patterns for rectal cancer.

Among several other factors we evaluated as potential confounders, urbanicity was the only one associated with both disease and exposure (rectal cancer only). Other factors associated with colon and rectal cancer risk included a history of colitis, a family history of bowel

cancer, obesity, and dietary fat consumption. Dietary fiber was inversely associated with colon and rectal cancer risk. Education was associated with rectal cancer only, with decreased risks observed among those with a college education or more. We observed a weak association with smoking for colon but not rectal cancer, with increases in risk observed among past but not current smokers.

## Discussion

Although a few previous case-control mortality studies<sup>14,17-19</sup> support our reported association of chlorination byproducts and rectal cancer risk, it is difficult to compare our results directly with those of available studies. The

majority of case-control studies examining chlorinated water exposure and colon and rectal cancer risk used information from death certificates<sup>14-21</sup> and were limited by the way in which exposures were estimated and by an absence of data on potential confounders. Lawrence *et al*<sup>16</sup> estimated exposure over a 20-year period before death and did not observe an increase in colon or rectal cancer risk associated with chloroform exposure, but the number of rectal cancer cases was small (N = 76). Whereas several of these earlier mortality studies observed an increase in colon cancer risk associated with treated surface water or estimated THM exposure, our negative findings for colon cancer are supported by a more recent case-control incidence study<sup>22</sup> in which estimated lifetime THM exposures were evaluated. Our findings of an increased risk for rectal but not colon cancer associated with chlorination byproducts do not agree with results from a recent case-control incidence study conducted in Ontario, which found an increased risk of colon cancer but not rectal cancer associated with estimated past THM exposure.<sup>24</sup>

Our finding of differences in risk patterns for colon and rectal cancers associated with chlorination byproducts is consistent with suggestions of different etiologies for these tumors.<sup>27-31</sup> Differences in the epidemiology of cancers of the colon and rectum with respect to the distribution by age and sex have been reported<sup>27,30,31</sup> and are supported by our results. Further evidence for different etiologies for colon and rectal cancers is provided by diverging trends in colon and rectal incidence and mortality rates over time.<sup>27,31,32</sup> Differences for colon and rectal cancer risk have also been reported for dietary factors,<sup>29,33</sup> occupation,<sup>29,34,35</sup> and physical activity.<sup>29,36-38</sup> Epidemiologic evidence indicates that these two tumors have similar but not identical etiologies and should be examined as separate sites in most epidemiologic analyses.

While the observed modification of the effect of chlorination byproducts on rectal cancer risk by physical activity and fiber intake may indicate an increased risk

associated with some correlated aspect of an unhealthy life-style, it is interesting to speculate on potential biological mechanisms. Although much of the recent evidence of the protective effect of physical activity is more consistent for colon cancer than for rectal cancer,<sup>36,38-42</sup> postulated mechanisms may also apply to rectal cancer. The increase in stool bulk resulting from high-fiber diets would dilute potential fecal carcinogens in the rectum as well as the colon. Likewise, the decrease in stool transit time resulting from a high-fiber diet or physically active life-style would reduce the amount of contact between potential carcinogens and both colon and rectal mucosa.<sup>37,43-45</sup>

We used various estimates of lifetime exposure to chlorination byproducts in drinking water in an attempt to improve our understanding of their potential carcinogenicity. Since levels of byproducts are much higher in surface water than in groundwater, duration of exposure to chlorinated surface water can be thought of as a marker for total lifetime exposure to chlorination byproducts. In an attempt to refine our assessment of exposure to these byproducts, we used THMs as a surrogate for the total byproduct mixture, and we estimated lifetime THM exposure in various ways. Our estimate of total lifetime THM intake assumes that it is the accumulation of the carcinogen in the body over a lifetime that is potentially detrimental. For the estimate of time-weighted average exposure, the carcinogenic effect is thought to arise from the effective concentration at the target organ. The effects of total lifetime amount and average concentration of THMs in the target organs could be different, and possibly dependent on the amount of tapwater ingested. In our study, however, years at chlorinated surface water sources and estimated lifetime THM levels were highly correlated, and we observed similar effects for each estimate of exposure to chlorination byproducts, with a slightly stronger effect observed for duration of exposure to chlorinated surface water over THM measures.

Possible explanations for the observed difference in effect between duration and estimated THM exposures are misclassification of estimated THM exposures, poor correlation of THMs with more important etiologic agents in the byproduct mixture, or both. We feel that our assessment of lifetime exposure to chlorination byproducts provided an improvement over exposure indices used by several previous studies because we measured exposure over each subject's lifetime rather than at a single time. Nevertheless, the application of current THM levels from our 1987 water supply survey to past residences receiving water with similar water source and treatment characteristics could have resulted in some misclassification of THM exposure levels. As a result of regulations issued in 1979 under the U.S. Safe Drinking Water Act, levels of THMs in finished drinking water were restricted to not more than 100 parts per billion, and the THM values from our 1987 Iowa water survey that were assigned to past residences could have underestimated actual pre-regulation THM levels that existed at the time the water was being consumed. Even though

1987 levels of THMs from surface water sources were lower than levels obtained from a similar water supply survey in 1979, THMs from surface sources remained consistently higher than concentrations in groundwater sources.

In addition to misclassification of estimated lifetime THM exposure, the existence of other, more important etiologic agents in treated drinking water cannot be discounted as an explanation for the observed differences between duration and THM measures. The suggestive pattern of increasing risk with years of exposure to chlorinated groundwater that we observed for both colon and rectum may indicate that duration is much more important than contaminant level, or that THMs and correlated byproducts are not the important causal agents since their levels are so much higher in chlorinated surface sources than in chlorinated ground sources. Since only one earlier study<sup>15</sup> examined chlorinated groundwater as a separate exposure, with no evidence of increased cancer risk, future studies should not be limited to THMs and treated surface water.

In addition to the development of lifetime exposure measures, high response rates (85.5% colon, 86.1% rectal, 80.3% controls) and extensive data on potential confounders are strengths of our study. In contrast to several earlier studies of chlorination byproducts and cancer risk,<sup>14,17-19</sup> in which control for confounding was minimal or absent, we were able to examine several variables as potential confounders and effect modifiers, including diet, family history of cancer, preexisting gastrointestinal conditions, education and income, body mass index, urbanicity, and frequency of physical activity. One variable that we identified as a confounder in our analyses was urbanicity or average population size of lifetime residences, which was positively correlated with levels of chlorination byproducts and negatively associated with rectal cancer. Adjustment for urbanicity increased the strength of the association between chlorination byproducts and rectal cancer risk. We observed no association of urbanicity with colon cancer.

The exclusion of respondents from an analysis is always a concern, owing to the bias that it could introduce. We restricted our population because full lifetime exposure data were not available for all subjects. We had little data on water sources outside Iowa and were thus unable to assess exposures at non-Iowa municipal water supplies. There was little evidence, however, that the results were biased by restricting the analysis to the 80% of all subjects for whom we could account for at least 70% of lifetime water exposure. Data collected from proxy interviews are another potential source of bias in epidemiologic analyses. In our study sample, however, risk estimates from analyses limited to live subjects only did not differ much from estimates presented here.

In summary, our rectal cancer results are consistent with the findings of increased risk observed in several ecologic and case-control mortality studies. The lack of association between chlorination byproducts and colon cancer found here is consistent with the results observed in studies conducted by Young *et al*<sup>22</sup> and Lawrence *et*

al<sup>16</sup> in which exposure data were collected over an extended period of time, but different from a Canadian study<sup>24</sup> with respect to both colon and rectal cancer risk. Recent evidence indicates that certain classes of byproducts, such as brominated compounds, halogenated acetic acids, and chlorinated hydroxyfuranones, may be more harmful than the THMs.<sup>46-49</sup> We believe that future studies should include water quality indicators to reflect differences in levels of these compound classes, to the extent feasible.

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### References

- Rook JJ. Formation of haloforms during chlorination of natural waters. *J Soc Water Treat Exam* 1974;23:234-243.
- Bellar TA, Lichtenberg JJ, Kroner RC. The occurrence of organohalides in chlorinated drinking waters. *J Am Water Works Assoc* 1974;66:703-706.
- Symons JM, Bellar TA, Carswell JK. National organics reconnaissance survey for halogenated organics in drinking water. *J Am Water Works Assoc* 1975;67:634-647.
- Page T, Harris RH, Epstein SS. Drinking water and cancer mortality in Louisiana. *Science* 1976;193:55-57.
- DeRouen TA, Diem JE. Relationships between cancer mortality in Louisiana drinking-water source and other possible causative agents. In: Hiatt HH, Watson JD, Winsten JA, eds. *Origins of Human Cancer. Book A. Incidence of Cancer in Humans*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977;331-345.
- Kuzma RJ, Kuzma CM, Buncher CR. Ohio drinking water source and cancer rates. *Am J Public Health* 1977;67:725-729.
- Bean JA, Isacson P, Hausler WJ, Kohler J. Drinking water and cancer incidence in Iowa. I. Trends and incidence by source of drinking water and size of municipality. *Am J Epidemiol* 1982;116:912-923.
- Kool HG, Van Kreijl CF, Van Kranen HJ, De Greef E. Toxicity assessment of organic compounds in drinking water in the Netherlands. *Sci Total Environ* 1981;18:135-153.
- Cantor KP, Hoover R, Mason TJ, McCabe LJ. Associations of cancer mortality with halomethanes in drinking water. *J Natl Cancer Inst* 1978;61:979-985.
- Hogan MD, Chi P-Y, Hoel DG. Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. *J Environ Pathol Toxicol* 1979;2:873-887.
- Carlo GL, Mettlin CJ. Cancer incidence and trihalomethane concentrations in a public drinking water system. *Am J Public Health* 1980;70:523-525.
- Isacson P, Bean JA, Lynch C. Relationship of cancer incidence rates in Iowa municipalities to chlorination status of drinking water. In: Jolley RL, Brungs WA, Cotruvo JA, Cumming RB, Mattice JS, Jacobs VA, eds. *Water Chlorination: Environmental Impact and Health Effects*. vol. 4. Ann Arbor, MI: Ann Arbor Science Publishers, 1983;1353-1363.
- Zierler S, Danley RA, Feingold L. Type of disinfectant in drinking water and patterns of mortality in Massachusetts. *Environ Health Perspect* 1986;69:275-279.
- 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*. vol. 2. Ann Arbor, MI: Ann Arbor Science Publishers, 1977;395-409.
- Brenniman GR, Vasilomanolakis-Lagos J, Amsel J, Namekata T, Wolff AH. Case-control study of cancer deaths in Illinois communities served by chlorinated or nonchlorinated water. In: Jolley RL, Brungs WA, Cumming RB, eds. *Water Chlorination: Environmental Impact and Health Effects*. vol. 3. Ann Arbor, MI: Ann Arbor Science Publishers, 1980;1043-1057.
- Lawrence CE, Taylor PR, Trock BJ, Reilly AA. Trihalomethanes in drinking water and human colorectal cancer. *J Natl Cancer Inst* 1984;72:563-568.
- Gottlieb MS, Carr JK, Clarkson JR. Drinking water and cancer in Louisiana: a retrospective mortality study. *Am J Epidemiol* 1982;116:652-667.
- Gottlieb MS, Carr JK, Morris DT. Cancer and drinking water in Louisiana: colon and rectum. *Int J Epidemiol* 1981;10:117-125.
- Gottlieb MS, Carr JK. Case-control cancer mortality study and chlorination of drinking water in Louisiana. *Environ Health Perspect* 1982;46:169-177.
- 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.
- Kanarek MS, Young TB. Drinking water treatment and risk of cancer death in Wisconsin. *Environ Health Perspect* 1982;46:179-186.
- Young TB, Wolf DA, Kanarek MS. Case-control study of colon cancer and drinking water trihalomethanes in Wisconsin. *Int J Epidemiol* 1987;16:190-197.
- Cragle DL, Shy CM, Struba RJ, Siff EJ. A case-control study of colon cancer and water chlorination in North Carolina. In: Jolley RL, Bull RJ, Davis WP, Katz S, Roberts MH Jr, Jacobs VA, eds. *Water Chlorination: Chemistry, Environmental Impact and Health Effects*. vol. 5. Chelsea, MI: Lewis Publishers, 1985;153-160.
- Marrett LD, King WD. Great Lakes Basin Cancer Risk Assessment: A Case-Control Study of Cancers of the Bladder, Colon, and Rectum. Ottawa: Bureau of Chronic Disease Epidemiology, Health Canada, 1995.
- Cantor KP, Lynch CF, Hildesheim M, Dosemeci M, Lubin J, Alavanja M, Craun GF. Drinking water source and chlorination byproducts. I. Risk of bladder cancer. *Epidemiology* 1997;9:21-28.
- Lynch CF, Gleaves M. Historical Community Water Supply and Treatment Data for the State of Iowa. Iowa City: Center for Health Effects of Environmental Contamination, University of Iowa, 1990.
- Schottenfeld D, Winawar SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. Philadelphia: WB Saunders, 1996;813-840.
- Weisburger JH. Causes, relevant mechanisms, and prevention of large bowel cancer. *Semin Oncol* 1991;18:316-336.
- Peters RK, Garabrant DH, Yu MC, Mack TM. A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. *Cancer Res* 1989;49:5459-5468.
- Kune S, Kune GA, Watson L. The Melbourne colorectal cancer study: incidence findings by age, sex, site, migrants, and religion. *Int J Epidemiol* 1986;15:483-493.
- Funkhouser E, Cole P. Declining mortality rates for cancer of the rectum in the United States: 1940-1985. *Cancer* 1992;70:2597-2601.
- Cancer in Iowa: 1973-1992. Iowa City: State Health Registry of Iowa, University of Iowa Press, 1995.
- Gerhardsson de Verdier M, Longnecker CP. Eating frequency: a neglected risk factor for colon cancer? *Cancer Causes Control* 1992;3:77-81.
- Arbman G, Axelson O, Fredriksson M, Nilsson E, Sjödal R. Do occupational factors influence the risk of colon and rectal cancer in different ways? *Cancer* 1993;72:2543-2549.
- Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM. Occupational exposures and cancer of the colon and rectum. *Am J Ind Med* 1992;22:291-303.
- Lee IM, Paffenbarger RS Jr, Hsieh C-c. Physical activity and risk of developing colorectal cancer among college alumni. *J Natl Cancer Inst* 1991;83:1324-1329.
- Sternfeld B. Cancer and the protective effect of physical activity: the epidemiological evidence. *Med Sci Sports Exerc* 1992;24:1195-1209.
- Gerhardsson de Verdier M, Steineck G, Hagman U, Rieger A, Norell SE. Physical activity and colon cancer: a case-referent study in Stockholm. *Int J Cancer* 1990;46:985-989.
- Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. *Am J Epidemiol* 1984;119:1005-1014.
- Vena JE, Graham S, Zielzny M, Swanson MK, Barnes RE, Nolan J. Lifetime occupational exercise and colon cancer. *Am J Epidemiol* 1985;122:357-365.
- Slattery ML, Schumacher MC, Smith KR, West DW, Abd-Elghany N. Physical activity, diet, and risk of colon cancer in Utah. *Am J Epidemiol* 1988;128:989-999.
- Dosemeci M, Hayes R, Vetter R, Hoover RN, Tucker M, Engin K, Unsal M, Blair A. Occupational physical activity, socio-economic status and risks of fifteen cancer sites in Turkey. *Cancer Causes Control* 1993;4:313-321.
- Howe GR, Benito E, Castelleto R, Cornee J, Esteve J, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, et al. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992;84:1887-1896.
- Levin B. Nutrition and colorectal cancer. *Cancer* 1992;70:1723-1726.
- Greenwald P. Colon cancer overview. *Cancer* 1992;70:1206-1215.
- Pegram RA, Andersen ME, Warren SH, Ross TM, Claxton LD. Glutathione S-transferase-mediated mutagenicity of trihalomethanes in *Salmonella typhimurium*: contrasting results with bromodichloromethane and chloroform. *Toxicol Appl Pharmacol* 1997;144:183-188.
- Bull RJ, Sanchez IM, Nelson MA, Larson JL, Lansing AJ. Liver tumor induction in B6C3F1 mice by dichloroacetate and trichloroacetate. *Toxicology* 1990;63:341-359.
- DeAngelo AB, Daniel FB, Most BM, Olson GR. The carcinogenicity of dichloroacetic acid in the male Fischer 344 rat. *Toxicology* 1996;114:207-221.
- Meier JR, Blazak WF, Knohl RB. Mutagenic and clastogenic properties of 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone: a potent bacterial mutagen in drinking water. *Environ Mol Mutagen* 1987;10:411-424.