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MAGNESIUM IN DRINKING WATER MODIFIES THE ASSOCIATION BETWEEN TRIHALOMETHANES AND THE RISK OF DEATH FROM COLON CANCER

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The objectives of this study were to (1) examine the relationship between total trihalomethanes (TTHM) levels in public water supplies and death attributed to colon cancer and (2) determine whether magnesium (Mg) levels in drinking water modify the effects of TTHM on risk of colon cancer development. A matched case-control study was used to investigate the relationship between the risk of death attributed to colon cancer and exposure to total trihalomethanes (TTHM) in drinking water in 53 municipalities in Taiwan. All colon cancer deaths of the 53 municipalities from 1998 through 2007 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Controls were deaths from other causes and were pair-matched to the cancer cases by gender, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each cancer case. Data on TTHM levels in drinking water were collected from Taiwan Environmental Protection Administration. Information on the levels of Mg in drinking water was obtained from the Taiwan Water Supply Corporation. The municipality of residence for cancer cases and controls was presumed to be the source of the subject's TTHM and Mg exposure via drinking water. Relative to individuals whose TTHM exposure levels were <4.9 ppb, the adjusted odds ration (OR) (with 95% confidence interval [CI]) for colon cancer was 1.14 (1.01–1.28) for individuals who had resided in municipalities served by drinking water with a TTHM exposure ≥4.9 ppb. Evidence of an interaction between drinking-water TTHM and Mg intake via drinking water was noted. This is the first study to report an effect modification by Mg intake from drinking water in association between TTHM exposure and risk of colon cancer occurrence. Better knowledge of this modifying factor will help in public policymaking and setting health standards.

Chlorination is presently the most common procedure used for water treatment globally. Despite the effectiveness of chlorine in preventing morbidity and mortality due to waterborne pathogens, there remains concern about possible adverse health effects associated with chronic exposure to chlorination disinfection by-products (DBP) present in drinking water (Rice et al., 2009).

Chlorine reacts with naturally occurring organic materials in raw water to produce a variety of DBP, including trihalomethanes

(THM), halogenated acetonitriles, halogenated acetic acids, haloketones, and haloaldehydes (Krasner et al., 1989; Richardson et al., 2008). Trihalomethanes consist of four species: chloroform, bromodichloromethane (BDCM), dibromochloromethane, and bromoform. Trihalomethanes are the most common DBP and are routinely measured in public water supplies, making them a useful marker for levels of DBP in treated water.

Disinfection by-products were discovered in drinking water in 1974 (Rook, 1974; Bellar et al., 1974). Since then, a number of epidemiologic studies determined the risk of cancer development associated with DBP exposure. Among the cancer types, bladder cancer is the most consistently associated with exposure to DBP (Cantor et al., 1987, 1998; King & Marrett, 1996; Koivusalo et al., 1998; McGeehin et al., 1993; Morris et al., 1992; Vena et al., 1993; Villanueva et al., 2003, 2004, 2007; Zierler et al., 1988; Chang et al., 2007). A few studies investigated the association between DBP in drinking water and colon cancer; however the findings are inconclusive. Of the nine studies based on exposure to chlorinated water as a measure of DBP exposure, four found an association with increased incidence of colon cancer occurrence (Young et al., 1981; Kanarek & Young, 1982; Doyle et al., 1997; King et al., 2000), while five reported no significant association between colon cancer development and exposure to DBP (Gottlieb et al., 1981, 1982; Gottlieb & Carr, 1982; Hildesheim et al., 1998; Yang et al., 1998). Five studies used THM levels as a measurement of exposure to examine DBP exposure and risk of colon cancer development. Four studies did not observe an increase in colon cancer development associated with THM exposure (Lawrence et al., 1984; Young et al., 1987; Hildesheim et al., 1998; Vinceti et al., 2004). A study conducted in Ontario, however, reported a significant elevation in colon cancer frequency associated with cumulative exposure to THM (King et al., 2000).

Magnesium (Mg) is an essential element that plays an important role in biological function in enzymatic processes, genomic stability, DNA repair, modulating cell proliferation, cell cycle progression, and cell differentiation (Hartwig, 2001; Larsson et al., 2005. Mori et al. (1993) demonstrated that Mg supplementation reduced the incidence of colon cancer in rats. Only a few epidemiologic studies investigated the relationship between Mg intake and risk of colon cancer development. A Swedish cohort study reported an inverse association between dietary Mg intake and colon cancer occurrence in women (Larsson et al., 2005). In the Iowa women's cohort study, an inverse association of dietary Mg intake with colon cancer development was found (Folsom & Hong, 2006). However, a recent Netherlands cohort study reported no significant relationship between Mg intake and frequency of colon cancer occurrence (van den Brandt et al., 2007). No previous studies explored whether Mg levels in drinking water modify the association between total THM (TTHM) exposure and colon cancer development. If substantial effect modification by Mg levels in drinking water exists, the true magnitude of the association between TTHM exposure and colon cancer development may be obscured. Further, better understanding of the modifying factors will help in public policy decisions, risk assessment, and setting exposure standards. The objective of this study was to (1) study the relationship between TTHM levels in public water supplies and mortality attributed to colon cancer and (2) determine whether Mg levels in drinking water modify the effects of TTHM on risk of colon cancer development.

MATERIALS AND METHODS

Selection of Study Municipalities

Chlorination has been the major strategy for the disinfection of drinking water in Taiwan and is currently added to approximately 92.04% of the nation's drinking water. The current Taiwan water system is rather simple. Residents obtain their drinking water either from the public drinking-water supply systems served by the Taiwan or Taipei Water Supply Corporation or from nonmunicipal sources.

The major sources of municipal water supplies are predominantly all surface waters that are treated with chlorine. The nonmunicipal sources are mainly privately owned wells (groundwater) and are not chlorinated (Yang et al., 1998).

A national survey of TTHM concentrations in the distribution systems of municipal drinking water was carried out in 96 municipalities by the Taiwan Environmental Protection Administration (EPA) in 2000 and 2002 (EPA/Taiwan, 2000, 2002). Among these 96 municipalities, 31 municipalities were excluded because they were supplied by more than one waterworks and the exact population served by each waterworks could not be determined (Yang et al., 2007; Chang et al., 2007). This elimination of unsuitable municipalities yielded 65 municipalities. These 65 municipalities provided a unique opportunity to investigate the relationship between risk for colon cancer development and levels of TTHM in Taiwan's drinking water.

Socioeconomic Factors

Each municipality in Taiwan was assigned to a degree-of-urbanization category from 1 to 8 based on the urban–rural classification of Tzeng and Wu (1986), which takes into account variables such as population density, age composition, economic activity and family income, educational level, environment, and health service-related facilities. A municipality with the highest urbanization score, such as the Taipei metropolitan area, was classified as category 1, whereas mountainous areas with the lowest score were assigned to category 8. The urbanization index used in this study serves as a proxy for a large number of explanatory variables such as socioeconomic status and differential exposures to environmental conditions, which are related to the etiology of mortality. For the analyses, the urban–rural classification was further divided into four levels: I, metropolitan (categories 1 and 2); II, city (categories 3 and 4); III, town (categories 5 and 6); and IV, rural (categories 7 and 8).

Subject Selection

Data on all deaths of Taiwan residents from 1998 through 2007 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is responsible for the death registration system in Taiwan. For each death, detailed demographic information including gender, year of birth, year of death, cause of death, place of death (municipality), and residential district (municipality) was recorded on computer tapes. The cancer case group consisted of all eligible colon cancer deaths occurring in people between 50 and 69 yr of age (International Classification of Disease, ninth revision [ICD-9], code 153).

The control group consisted of all other deaths excluding those deaths that were associated with gastrointestinal diseases. The deaths excluded were those attributed to malignant neoplasms of stomach (ICD-9 code 151), malignant neoplasm of small intestine, including duodenum (ICD-9 code 152), malignant neoplasm of colon (ICD-9 code 153), malignant neoplasm of rectum, rectosigmoid junction, and anus (ICD-9 code 154), gastric ulcer (ICD-9 code 531), duodenal ulcer (ICD-9 code 532), peptic ulcer, site unspecified (ICD-9 code 533), gastrojejunal ulcer (ICD-9 code 534), and gastrointestinal hemorrhage (ICD codes 578). Subjects who died from bladder (Morris et al., 1992; King & Marrett, 1996; Cantor et al., 1998; Villanueva et al., 2003, 2004; Chang et al., 2007), kidney (Gottlieb et al., 1982; Yang et al., 1998; Wilkins et al., 1979; Cantor et al., 1978; Koivusalo et al., 1998), pancreatic (Carlo & Mettlin, 1980; IJsselmuiden et al., 1992), lung (Yang et al., 1998; Cantor et al., 1978; Koivusalo et al., 1997), and esophageal (Koivusalo et al., 1997) cancers were also excluded from the control group because of previously reported associations with chlorinated drinking-water use. Control subjects were pair matched to the cases by gender, year of birth, and year of death. A random sampling method was used to select one control from the set of possible controls for each case. The most frequent causes of death among the controls were diabetes mellitus (10.6%),

liver cancer (10.5%), chronic liver disease and cirrhosis (6.0%), acute myocardial infarction (3.7%), and breast cancer (3.6%).

Drinking-Water TTHM Exposure Assessment

TTHM levels were used as a marker for DBP in this study. Water samples were collected quarterly during each of the two years from each of the 65 municipalities. TTHM levels were determined by gas chromatography/mass spectrometry (Taiwan EPA method: NIEA W785.51B), and the TTHM consisted of chloroform, bromoform, BDCM, and dibromochloromethane. The sum of the concentrations of these four individual THM comprised the TTHM. Data on the annual levels of TTHM were obtained from the Environmental Protection Agency of Taiwan (EPA). Since the treatment practices have not changed over time in study areas, the average TTHM levels of the two years were used as a measure of exposure levels for the study municipalities.

The municipalities of residence for all colon cancer cases and controls were identified from the death certificate and presumed to reflect the source of the subject TTHM exposure via drinking water. The levels of TTHM of each municipality were used as an indicator of exposure to TTHM for an individual residing in that municipality. Dermal and inhalation route exposure contributions to TTHM were far less than from ingestion (Teuschler et al., 2004).

Magnesium Levels in Drinking Water

Information on the level of Mg in each municipality's treated drinking water supply was obtained from the Taiwan Water Supply Corporation, to which each waterworks is required to submit drinking water quality data, including the levels of Mg. Four finished water samples, one for each season, were collected from each waterworks. The samples were analyzed by the waterworks laboratory office using spectrophotometric methods. Since the

laboratory office examines Mg levels on a routine basis using standard methods, it was presumed that the problem of analytical variability was minimal. The experimental protocol details have already been described in earlier publications (Yang et al., 1997; Yang, 1998). Among the 65 municipalities, 12 were excluded as their drinking-water sources were changed in the past decade. The final complete data consisted of Mg results from 53 municipalities. Magnesium levels remained reasonably constant for long periods of time and the Mg level is a stable characteristics of a municipality's water supply (Bell & Doege, 1984). Data collected were the annual mean levels for Mg for the year 1990. It was assumed that Mg levels in 1990 were a reasonable indicator of historical Mg exposure levels from drinking water (Yang, 1998).

The municipality of residence for all cancer cases and controls was identified from death certificates and presumed to be the source of the subject's Mg exposure via drinking water. The levels of Mg of each municipality were used as an indicator of exposure to Mg for an individual residing in that municipality.

Statistics

In the analysis, the subjects were categorized into one of the two TTHM exposure categories: low (< medium among controls; <4.9 ppb) and high (≥ medium among controls; ≥4.9 ppb). Conditional logistic regression was used to estimate the association between TTHM levels present in drinking water and risk of colon cancer development. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were calculated using the low exposure group as the reference group (Breslow & Day, 1980). The association of drinking-water TTHM levels and risk of colon cancer occurrence stratified by Mg levels in drinking water was determined. The analyses were performed using SAS software (version 8.2; SAS Institute, Inc., Cary, NC). All statistical tests were two-sided and values of $p < .05$ were considered statistically significant.

RESULTS

In total, 2180 colon cancer cases with complete records were collected for the period of 1998–2007. Of the 2180 cases, 1239 were males and 941 females (Table 1). The majority of both cancer cases (79.2%) and controls (75.1%) were married. Cancer cases displayed a higher rate (63.1%) of living in metropolitan municipalities than controls (54.1%). Cancer cases (44.9%) were less likely to have lived at residence served by drinking water with higher levels ($\geq$5.9 mg/L) of Mg than controls (48.4%)(Table 1).

Table 2 shows the distribution of cancer cases and controls and OR with respect to levels of TTHM in drinking water. Relative to individuals whose TTHM exposure level <4.9 ppb, the adjusted OR (95% CI) for colon cancer incidence was 1.14 (1.01–1.28) for individuals who had resided in municipalities served by drinking water with a TTHM exposure $\geq$4.9 ppb.

The association between TTHM levels in drinking water and colon cancer risk among those with high ($\geq$ median) and low (< median) Mg intake via drinking water (Table 3) was determined. OR were significantly elevated in all categories of water TTHM and Mg intake compared to those with low water TTHM and high Mg intake. There was evidence of a significant interaction between drinking water TTHM and Mg intake (for multiplicative interaction term), in that there was a greater risk among those with high TTHM exposure and low Mg intake (OR = 1.60, 95% CI = 1.24–2.07) compared with those of similar TTHM exposure and high Mg intake (OR = 1.34, 95% CI = 1.09–1.66).

DISCUSSION

This investigation used a death-certificate-based cancer case-control study and a TTHM ecology study to examine the relationship

TABLE 1. Characteristics of the Study Population

Characteristics	Cancer cases (n = 2180)	Controls (n = 2180)
Enrollment municipality	53	53
Gender		
Male	1239 (56.8%)	1239 (56.8%)
Female	941 (43.2%)	941 (43.2%)
Age (yr)		
50–54	417 (19.1%)	417 (19.1%)
55–59	425 (19.5%)	425 (19.5%)
60–64	566 (26.0%)	566 (26.0%)
65–69	772 (35.4%)	772 (35.4%)
Marital status		
Single	113 (5.2%)	126 (5.8%)
Married	1726 (79.2%)	1638 (75.1%)
Ever married	341 (15.6%)	416 (19.1%)
Urbanization level of residence (%)[a]		
Metropolitan	1375 (63.1%)	1179 (54.1%)
City	346 (15.9%)	406 (18.6%)
Town	368 (16.9%)	442 (20.3%)
TTHM[b] levels (µg/L)		
Less than median (4.9)	1058 (48.5%)	1127 (51.7%)
Greater than or equal to median	1122 (51.5%)	1053 (48.3%)
Magnesium levels (mg/L)		
Less than median (5.9)	1202 (55.1%)	1126 (51.7%)
Greater than or equal to median	978 (44.9%)	1054 (48.4%)

[a]The urbanization level of each municipality was based on the urban–rural classification scheme of Tzeng and Wu (1986).

[b]TTHM is total trihalomethanes.

TABLE 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Colon Cancer Death in Relation to TTHM Levels in Drinking Water, 1998–2007

TTHM levels	Cancer cases	Controls	OR (95% CI)[a]
<4.9 (µg/L)	1058 (48.5%)	1127 (51.7%)	1.00
≥4.9 (µg/L)	1122 (51.5%)	1053 (48.3%)	1.14 (1.01−1.28)

[a]Adjusted for age, gender, marital status, and urbanization level of residence.

TABLE 3. Odds Ratios for Colon Cancer by TTHM Level and Magnesium Level in Drinking Water

	TTHM levels (µg/L)					
	<4.9			≥4.9		
Magnesium levels (mg/L)	Cancer cases	Controls	OR[a] (95% CI)	Cancer cases	Controls	OR[a] (95% CI)
≥5.9	201	282	1.00	777	772	1.34 (1.09−1.66)
<5.9	857	845	1.31 (1.06−1.62)	345	281	1.60[b] (1.24−2.07)

[a]Adjusted for age, gender, marital status, urbanization level of residence.
[b]The p value for interaction on the multiplicative scale is <.05.

between mortality attributed to colon cancer and exposure to TTHM in drinking water in Taiwan. A higher intake of drinking water TTHM (≥4.9 ppb) was associated with an increased risk of colon cancer development. Further, there was evidence of an interaction between drinking water TTHM with lower intake of Mg in drinking water.

One ecologic study (Vinceti et al., 2004) and four analytical epidemiologic studies (Lawrence et al., 1984; Young et al., 1987; Hildesheim et al., 1998; King et al., 2000) examined exposure to TTHM through public water supplies and risk of colon cancer occurrence. An ecologic study in Guastalla, northern Italy, did not find higher standardized mortality ratio (SMR = 1) of colon cancer in subjects using public water supplies with high TTHM (39.7 ppb in tap water immediately after the chlorination and 70.7 ppb in tap water 24 h after chlorination). A cancer case-control study of colon cancer in Wisconsin indicated that TTHM in drinking water did not pose a significant risk of colon cancer development (Young et al., 1987). OR for exposure to the middle (100–300 mg) and highest (>300 mg) category of lifetime cumulative TTHM were 1.05 (95% CI = 0.66–1.68) and 0.93 (95% CI = 0.55–1.57) respectively. A cancer case-control study of colon cancer in Iowa, Hildesheim et al. (1998), detected no increase frequency

in colon cancer risk associated with TTHM. In a cancer case-control study of colon cancer in New York State, cumulative chloroform exposure was estimated by the application of a statistical model to operational records from the individual water treatment facilities. No marked effect of cumulative chloroform exposure was seen (Lawrence et al., 1984). A cancer case-control study of colon cancer conducted in Ontario, however, reported that chronic (≥35 yr) exposure to a THM level of ≥75 ppb was associated with a twofold rise in colon cancer occurrence among males (King et al., 2000).

Our findings of an increased risk of colon cancer development associated with TTHM exposure are supported by a recent cancer case-control study conducted in Ontario (King et al., 2000). Our findings, however, do not agree with results of the findings of previous epidemiologic studies (Lawrence et al., 1984; Young et al., 1987; Hildesheim et al., 1998; Vinceti et al., 2004). The reason for these inconsistencies remains unknown. All of the mentioned studies, including our study, have common problems concerning the exposure assessment methods. Instead of using a real individual exposure to TTHM, some type of surrogate for exposure has always been employed (Kukkula & Lofroth, 1997). Some studies estimated past exposure to TTHM

by modeling water-supply characteristics and recent measurements of TTHM (Lawrence et al., 1984; Young et al., 1987; Hildesheim et al., 1998; King et al., 2000). Our study estimated past TTHM levels by extrapolating recent TTHM levels but not taking into account type of treatment and residential histories. This is perhaps one reason for the wide variation in results from a negative to positive association. In addition, it is possible that TTHM levels correlate poorly with the important etiological agents in the DBP mixtures (King et al., 2000). A more basic reason for the inconsistent results may be that there is no causality between chlorinated drinking water and risk of colon cancer development (Kukkula & Lofroth, 1997).

Total THM levels were used as a marker of exposure to DBP, which is a complex mixture of compounds with a variety of chemical and toxicologic properties; THM are the most prevalent DBP (Villanueva et al., 2004). Therefore, the same level of TTHM did not necessarily represent the same mixture in all studies (Villanueva et al., 2004; Richardson et al., 2008). Although chloroform accounts for a large proportion of TTHM in most chlorinated water supplies including Taiwan (Hsu et al., 2001), toxicological evidence suggests that other DBP, such as brominated by-products and haloacetic acids, may exert greater carcinogenic potential (Pegram et al., 1997; DeAngelo et al., 1996, 1999; King et al., 2000; Claxton et al., 2008). In a study with positive associations (King et al., 2000), the OR increased to twofold higher levels, which is greater than our OR estimation (OR = 1.14). If the positive findings were not spurious, the difference in observed risk for colon cancer occurrence may be due to geographic differences in the composition of DBP mixtures (Cantor, 1997). Brominated by-products and haloacetic acids were detected in Ontario water supplies and may be responsible for the observed greater effects in the study of King et al. (2000).

In this study, municipality aggregate exposure data (measurements of TTHM levels in municipal tap water in the study municipality) were relied upon to estimate individual exposure to TTHM. Total THM permeate the body not only through ingestion, but also through inhalation and dermal absorption (Whitaker et al., 2003). Epidemiologic studies only evaluated ingestion. However, evidence was provided that TTHM levels in drinking water are a reliable predictor of actual uptake to TTHM even though there is no information on individual chemical behaviors (Whitaker et al., 2003).

An additional advantage of our study was that Taiwan Water Supply Corporation provided drinking-water quality data including Mg levels. The risk of colon cancer occurrence associated with higher TTHM levels was elevated among those with lower Mg intake from drinking water. Our findings demonstrate that it is important to consider the levels of Mg in drinking water in the evaluation of the relationship between TTHM exposure and risk of colon cancer development. To our knowledge, this is the first study to report an effect modification by Mg intake from drinking water in the correlation between TTHM exposure and colon cancer risk.

Mechanistic studies showed that THM induce aberrant crypt foci (ACF) primarily in the colon of rats when administered either via drinking water or gavage (DeAngelo et al., 2002; Geter et al., 2004; Richardson et al., 2007). A diet lacking folate significantly increased the frequency of ACF induced by bromoform relative to that of a normal diet in rats (Geter et al., 2005; Richardson et al., 2007). Our study results suggest that Mg may act similarly to folate, which inhibited ACF induced by TTHM, and therefore individuals who had low levels of Mg intake via drinking water may be at increased risk of colon cancer development.

Despite their inherent limitations (Morgenstern, 1982), studies of ecological correlation between mortality and environmental exposures are widely used to generate or discredit epidemiological hypotheses. Before any conclusion based on such a mortality analysis is made, the completeness and accuracy of the death registration system need to be evaluated. Since it is mandatory to register death certificates at local household

registration offices, the death registration in Taiwan is reliable and complete. Although causes of death may be misdiagnosed and/or misclassified, the problem has been minimized through the improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, malignant neoplasms, including colon cancer, were found to be one of the most unequivocally classified causes of death in Taiwan (Chen & Wang, 1990). Because of their fatal outcome, it is believed that all colon cancer cases exposed to either high or low levels of TTHM in drinking water were all currently able to have access to medical care regardless of geographical location.

Migration from a municipality of high TTHM to one of low TTHM exposure or vice versa may have introduced misclassification bias and bias in the OR estimate (Gladen & Rogan, 1979; Polissar, 1980). Mobility is age dependent, and diseases usually occur with a higher incidence among older subjects and closer to the location of the environmental "cause" (Polissar, 1980). However, neighboring water sources tend to possess similar chemical composition, and hence even if an individual moved, the change in exposure to TTHM in drinking water would probably not be significant provided that the old and new residences were relatively close to one another, which also reduces the uncertainty created by the fact that some residents consume water at their workplaces or elsewhere. Further, all subjects used in the present study were at least 50 yr of age. It is generally presumed that the elderly are more likely to remain in the same residence for a significant portion of their life span. Furthermore, urbanization levels were included as a control variable in the analysis. Since it is conceivable that municipalities with similar urbanization levels may have similar migration rates, this probably minimized the migration problem in our study.

Since the measure of effect in this study is mortality rather than incidence, migration during the interval between cancer diagnosis and death must also be considered. During this period, cancer diagnosis may influence a decision to migrate and possibly introduce bias. Data are not available for the differences in survival rates of colon cancer patients between high and low TTHM exposure areas. If there was a trend toward migration to more urban areas or lower TTHM exposure areas because of proximity to medical care, for example, a spurious association between TTHM exposure and death attributed to colon cancer would have been noted. Three aspects of this study presumably minimized this possibility. First, migration due to colon cancer diagnosis would be unlikely, since for this cohort of decedents the subject's occupational status would weigh against a move requiring a job change late in life. Second, urbanization level was included as a control variable in the analysis. Finally, the subjects in the present study were between the ages of 50 and 69 yr, and it was presumed that individuals in this age group are more likely to remain in the same residence; therefore, most of their lifetime was spent at the address listed on the death certificate.

Of greater concern is whether the relative levels of TTHM in the period around 2000 correspond to the relative chemical levels occurring in periods 20–30 yr earlier. This is important since it is likely that exposure to causal factors would precede mortality due to cancer by at least 20 yr (the latency period for carcinogen exposure). The historical levels of TTHM are not available for the study areas. However, it is possible that the correlation between the levels of year 2000 and levels in the previous 20–30 yr might be high since treatment practices have not changed over time in study areas.

There are a number of major risk factors for colon cancer that need to be taken into account when investigating the possibility of an additional factor (drinking-water TTHM exposure). On the basis of scientific knowledge from epidemiologic studies, the most important risk factors for colon cancer development are physical activity, and meat and fat consumption (Schottenfeld & Fraumeni, 1996). There is unfortunately no information available on this variable for an individual study subject, and thus it was not possible to adjust for this directly

in the analysis. However, there is no reason to believe that there would be any correlation between these confounders and levels of TTHM in drinking water. It is also unlikely that there would be a direct relationship between other risk factors and TTHM levels in drinking water.

Exposure to TTHM was determined by linking each study subject's residence to the person's individual water source. However, it was not possible to calculate the precise amount of TTHM intake from water for individual subjects, because the quantity consumed at home or other places could not be determined. However, evidence was provided that exposure to TTHM occurs predominantly at home, because a large part of this uptake is through inhalation and dermal absorption that occur during bathing, showering, and cleaning dishes (Whitaker et al., 2003). Nonetheless, data on individual exposure were thus still characterized by a lack of precision. However, this misclassification of exposure is most likely to be nondifferential (i.e., unrelated to cases and controls), which would reduce the magnitude of association (effect estimates are likely to be biased toward the null) rather than introduce a positive bias in the association.

In summary, our data suggest that exposure to TTHM in drinking water at levels in this study is likely to be a risk for colon cancer development, although the levels in this study were far lower than those reported in other studies. Further, it was found that Mg in drinking water significantly modified the effects of TTHM exposure on colon cancer risk. Better knowledge of this modifying factor will help in public policymaking and setting health standards. Future studies should increase the precision of the estimation of the individual's exposure to TTHM and control for confounding factors, especially personal risk factors such as physical activity and meat and fat consumption.

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