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TRIHALOMETHANES IN DRINKING WATER AND THE RISK OF DEATH FROM KIDNEY CANCER: DOES HARDNESS IN DRINKING WATER MATTER?

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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 risk of development of kidney cancer and (2) determine whether hardness levels in drinking water modify the effects of TTHM on risk of kidney cancer induction. A matched case-control study was used to investigate the relationship between the risk of death attributed to kidney cancer and exposure to TTHM in drinking water in 53 municipalities in Taiwan. All kidney cancer deaths in the 53 municipalities from 1998 through 2007 were obtained. 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 and levels of hardness in drinking water were also collected. The municipality of residence for cancer cases and controls was presumed to be the source of the subject's TTHM and hardness exposure via drinking water. Relative to individuals whose TTHM exposure level was <4.9 ppb, the adjusted OR (95% CI) for kidney cancer was 0.98 (0.77–1.25) for individuals who resided in municipalities served by drinking water with a TTHM exposure ≥4.9 ppb. However, evidence of an interaction was noted between the use of soft water and drinking water TTHM concentrations. Increased knowledge of the interaction between hardness and TTHM levels in reducing risk of kidney cancer development will aid in public policy decision and establishing standards to prevent disease occurrence.

Chlorination is presently the most common procedure used for water treatment worldwide (Simmons et al. 2004). Chlorine reacts with naturally occurring organic materials in raw water to produce a variety of disinfection by-products (DBP), including trihalomethanes (THM), halogenated acetonitriles, halogenated acetic acids, haloketones, and haloaldehydes (Krasner et al. 1989). Trihalomethanes consist of four components: chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform. THM, the most common DBP, are routinely measured in public water supplies and thus

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serve as a useful marker of DBP in treated water.

Disinfection by-products were discovered in drinking water in 1974 (Bellar et al. 1974; Rook 1974). Since that time, a number of epidemiologic studies have determined the increased risk of cancer occurrence associated with DBP exposure. Among the cancer sites, elevated bladder cancer incidence is the most consistently associated with exposure to DBP (Cantor et al. 1987; 1998; Chang et al. 2007; King and 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).

Although much of the focus concerning the carcinogenic potential of DBP has centered on the bladder, kidney cancer has also been of some interest. There have been few studies investigating DBPs in drinking water in relation to kidney cancer, and results have provided inconclusive. Of the seven studies based on exposure to chlorinated water as a measure of DBP exposure, three found an association with increased kidney cancer occurrence (Gottlieb et al. 1982; Koivusalo et al. 1994; Yang et al. 1998) and four reported no significant association (Koivusalo et al. 1997; Wilkins and Comstock 1981; Young et al. 1981; Zierler et al. 1986).

Two studies used THM levels as a measurement of exposure to determine correlation between DBP exposure and kidney cancer risk development. Cantor et al. (1978) found that kidney cancer in males was positively correlated with levels of chloroform in drinking water. However, Vincent et al. (2004) did not observe an increase in kidney cancer risk associated with THM exposure. Koivusalo et al. (1998) used drinking water mutagenicity as a surrogate indicator of exposure to DBP and reported an exposure-response relation between estimated level of historical exposure to drinking water mutagenicity and elevated risk of kidney cancer incidence in men. The hardness of drinking water is determined predominantly by calcium and magnesium concentrations. Water hardness is expressed as the equivalent amount of calcium carbonate that could be formed from calcium and magnesium in solution. Hard water contains higher levels of both calcium and magnesium than soft water.

There is limited data regarding calcium and magnesium intake and correlation to renal-cell carcinoma. Three studies reported a significant protective effect of calcium intake on development of renal-cell carcinoma (Prineas et al. 1997; Hu et al. 2003; Chiu et al. 2011). Chou et al. (2004) noted a significant positive association between calcium intake and renal-cell carcinoma occurrence. However, Mellemgaard et al. (1996) found no significant relationship between calcium intake and renal-cell carcinoma. Low intake of magnesium was reported to be associated with increased risk of renal-cell carcinoma (Wolk et al. 1996). However, this finding was not supported by other studies (Chou et al. 1994; Prineas et al. 1997). No previous studies explored whether hardness levels in drinking water might modify the association between total trihalomethanes (TTHM) exposure and health outcomes. If substantial effect modification by hardness levels in drinking water exists, the true magnitude of the association between TTHM exposure and health outcomes may be obscured.

The objectives of this study were to (1) examine the relationship between TTHM levels in public water supplies and death attributed to kidney cancer and (2) determine whether hardness levels in drinking water modify the effects of TTHM on kidney cancer risk occurrence.

MATERIALS AND METHODS

Selection of Study Municipalities

Chlorination has been the major strategy for the disinfection of drinking water in Taiwan. Chlorine is currently added to approximately 92% of the nation's drinking water. The current Taiwan water system is rather simple. Residents obtain their drinking water from the public drinking water supply systems served by either the Taiwan Water Supply Corporation (TWSC), Taipei Water Supply Corporation, or nonmunicipal sources. The major sources of municipal

water supplies are almost all surface waters and are treated with chlorine. The nonmunicipal sources are mainly privately owned wells (groundwater) and are nonchlorinated (Yang et al. 1998).

Taiwan is divided into 361 administrative districts, which are referred to in this report as municipalities. 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). This elimination of unsuitable municipalities left 65 municipalities for this study. These 65 municipalities provided a unique opportunity to investigate the relationship between risk of kidney 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) were recorded. The renal cancer case group consisted of all eligible kidney cancer deaths occurring in individuals between 50 and 69 yr of age (International Classification of Disease, ninth revision [ICD-9], code 189).

The control group consisted of all other deaths excluding those deaths that were associated with genitourinary disease (codes 179–189, 580–629). Subjects who died from colon (Chen et al. 2005; Doyle et al. 1997; Kanarek and Young 1982; King et al. 2000; Young et al. 1981), rectal (Chen et al. 2005; Gottlieb et al. 1981; 1982; Gottlieb and Carr 1982; Hildesheim et al. 1998; Yang et al. 1998), pancreatic (Carlo and Mettlin 1980; Ijsselmuiden et al. 1992), lung (Cantor et al. 1978; Koivusalo et al. 1997; Yang et al. 1998), 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 renal cancer 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 liver cancer (11.7%), diabetes mellitus (10.1%), chronic liver disease and cirrhosis (7.4%), acute myocardial infarction (4.3%), and intracerebral hemorrhage (3.5%).

Drinking-Water TTHM Exposure Assessment

TTHM were used as a marker for DBP exposure in this study. Water samples were collected quarterly during each of the 2 years from each of the 65 municipalities. TTHM

were determined by gas chromatography/mass spectrometry (Taiwan EPA method: NIEA W785.51B) and consisted of chloroform, bromoform, BDCM, and DBCM. The sum of the concentrations of the four individual THM is the TTHM. Data on the annual levels of TTHM were obtained from 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 kidney cancer cases and controls were identified from the death certificate and presumed to be the source of the subjects' 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.

Water Hardness

Information on the levels of hardness in finished water in each municipality was obtained from the Taiwan Water Supply Corporation, to which each waterworks is required to submit drinking-water quality data, including hardness. 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 hardness on a routine basis using standard methods, it was presumed that analytical variability was minimal. Details have already been described in an earlier publication (Yang et al. 1999). Among the 65 municipalities, 12 were excluded as their drinking water sources were changed in the past decade. The final complete data consisted of hardness data from 53 municipalities. Hardness remains reasonably constant for long periods of time and is a quite stable characteristic of a municipality water supply (Bell and Doege 1984). Data collected were the annual mean levels of hardness for the year 1990. It was presumed that hardness levels in 1990 were a reasonable indicator of historical hardness exposure levels from drinking water (Yang et al. 1999).

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

Statistics

In the analysis, subjects were categorized into one of the two TTHM exposure categories: low (less than medium among controls; <4.9 ppb) and high (greater than or equal to medium among controls; ≥4.9 ppb). Conditional logistic regression was used to estimate the association between TTHM levels present in drinking water and risk for kidney cancer occurrence. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using the low exposure group as the referent group (Breslow and Day 1980). The association between drinking-water TTHM levels and risk for kidney cancer development was stratified by hardness levels in drinking water, which was previously shown to affect kidney cancer risk (Hu et al. 2003; Prineas et al. 1997; Wolk et al. 1996). Hardness was divided into three categories: water with less than 75 mg/L of $CaCO_3$ (soft); 75–150 mg/L of $CaCO_3$ (moderately hard); and above 150 mg/L of $CaCO_3$ (hard) (Sawyer et al. 2003). The analyses were performed using SAS software (version 9.2; SAS Institute, Inc., Cary, NC). All statistical tests were two-sided, and values of $p < .05$ were considered statistically significant.

RESULTS

In total, 500 kidney cancer cases with complete records were collected for the period 1998–2007. Of the 500 cases, 302 were males and 198 were females. Renal cancer cases had higher rates (61.8%) of residing in a metropolitan municipality than controls (51.6%) (Table 1). Of the renal cancer cases, 50.6, 37.2, and 12.2% lived at residences served by soft,

TABLE 1. Characteristics of the Study Population

Characteristics	Cancer cases ($n = 500$)	Controls ($n = 500$)
Enrollment, municipalities	53	53
Gender		
Male	302 (60.4%)	302 (60.4%)
Female	198 (39.6%)	198 (39.6%)
Age (yr)		
50–54	62 (12.4%)	62 (12.4%)
55–59	103 (20.6%)	103 (20.6%)
60–64	150 (30.0%)	150 (30.0%)
65–69	185 (37.0%)	185 (37.0%)
Marital status		
Single	23 (4.6%)	27 (5.4%)
Married	405 (81.0%)	356 (71.2%)
Ever married	72 (14.4%)	117 (23.4%)
Urbanization level of residence (%)[a]		
Metropolitan	309 (61.8%)	258 (51.6%)
City	88 (17.6%)	87 (17.4%)
Town	74 (14.8%)	110 (22.0%)
Rural	29 (5.8%)	45 (9.0%)
Hardness		
Hard[b]	61 (12.2%)	96 (19.2%)
Moderately hard[c]	186 (37.2%)	192 (38.4%)
Soft[d]	253 (50.6%)	212 (42.4%)

[a]The urbanization level of each municipality was based on the urban–rural classification scheme of Tzeng and Wu (1986).
[b]Total hardness: over 150 mg/L as $CaCO_3$.
[c]Total hardness: 75–150 mg/L as $CaCO_3$.
[d]Total hardness: 0–75 mg/L as $CaCO_3$.

moderately hard, and hard water, respectively, while 42.4, 38.4, and 19.2% of the controls received soft, moderately hard, and hard water, respectively.

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

TTHM levels (ppb)[a]	Cancer cases	Controls	OR (95% CI)[b]
Less than median (4.9)	258 (51.6%)	255 (51.0%)	1
Equal to or greater than median	242 (48.4%)	245 (49.0%)	0.98 (0.77–1.25)

[a]TTHM is total trihalomethanes.
[b]Adjusted for age, gender, marital status, and urbanization level of residence.

Table 2 shows the distribution of renal 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 kidney cancer was 0.98 (0.77–1.25) for individuals who resided in municipalities served by drinking water with a TTHM exposure ≥4.9 ppb.

The association of drinking water TTHM levels and kidney cancer stratified by hardness levels in drinking water was also assessed. The risk of kidney cancer occurrence associated with high TTHM levels (greater than or equal to median) was elevated among both those with moderately hard and individuals with soft water exposure. A positive interaction was observed between high TTHM levels and the use of soft water ($p < .05$ for multiplicative interaction term). A similar pattern in risk among low TTHM levels (less than median) was found. However, there was no significant indication of interaction with hardness levels (Table 3).

TABLE 3. Odds Ratios for Kidney Cancer in Relation to Levels of TTHM and Hardness in Drinking Water

	TTHM levels (ppb)					
	<4.9			≥4.9		
Water hardness	Cancer cases	Controls	OR[a] (95% CI)	Cancer cases	Controls	OR[a] (95% CI)
Hard[b]	46	65	1	15	31	0.88 (0.41–1.87)
Moderately hard[c]	22	28	1.18 (0.58–2.41)	164	164	1.16 (0.72–1.87)
Soft[d]	190	162	1.31 (0.81–2.16)	63	50	1.5 (0.85–2.68)

[a]Adjusted for age, gender, marital status, urbanization level of residence.
[b]Total hardness: over 150 mg/L as $CaCO_3$.
[c]Total hardness: 75–150 mg/L as $CaCO_3$.
[d]Total hardness: 0–75 mg/L as $CaCO_3$.
[e]The p value for interaction on the multiplicative scale <.05.

DISCUSSION

Our findings that TTHM in drinking water did not pose a significant risk for increased kidney cancer are in agreement with previous observations (Koivusalo et al. 1997; Vinceti et al. 2004; Wilkins and Comstock 1981; Young et al. 1981; Zierler et al. 1986). However, our findings contradict previous reports (Cantor et al. 1978; Gottlieb et al. 1982; Koivusalo et al. 1994; 1998; Yang et al. 1998). The basis for these inconsistencies is not known. All these studies, including our investigation, share common problems concerning exposure assessment methods. Instead of using a real individual exposure to TTHM, some type of surrogate for exposure was employed (Kukkula and Lofroth 1997). Our investigation estimated past TTHM levels by extrapolating exposure to recent TTHM levels while not taking into account type of treatment and residential histories. This is perhaps one basis for the variation in data from a negative to positive association. In addition, it is possible that TTHM levels correlated poorly with important etiological agents in the DBP mixtures (Hildesheim et al. 1998; King et al. 2000). A more basic reason for the inconsistent results may be that there is no causality between chlorinated drinking water and development of kidney cancer.

A pilot study conducted by Yang et al. (1998) found a significant positive association between consumption of chlorinated drinking water and elevated kidney cancer incidence. In our previous study, no attempt was made to quantify exposure to TTHM present in chlorinated water. The exposure assessment in that study was based on information about the chlorination portion (the fraction of the population in the municipality that is served by chlorinated water). An individual municipality was classified as a chlorinating municipality if more than 90% of the municipality population was served by chlorinated water. A nonchlorinating municipality was defined as one in which less than 5% of the municipality population received chlorinated water.

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

Mechanistic studies showed that THM induce aberrant crypt foci (ACF) primarily in the colon of rats when administered via either 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). These studies provide an important mechanistic link to a type of cancer associated with drinking-water exposure in humans (Richardson et al. 2007). No experimental study has examined the modulating effect of Ca and Mg on renal carcinogenesis specifically induced by THM. Nonetheless, our results suggest that Ca and Mg may act similar to folate, which inhibited ACF induced by TTHM, and therefore individuals who had low levels of Ca and Mg intake via drinking water may be at increased risk for kidney cancer formation.

TTHM were used as a marker of exposure to DBP, which is a complex of compounds with a variety of chemical and toxicologic properties, because they are the most prevalent DBP. Although chloroform accounts for a large proportion of the TTHM in most chlorinated water supplies including those of Taiwan (Hsu et al. 2001), toxicological evidence suggests that other DBP, such as brominated by-products and haloacetic acids, may exert greater carcinogenic potential (DeAngelo et al. 1996; Pegram et al. 1997). Results of the present study suggest

that lack of evidence of increased kidney cancer risk may be at least partially due to none differentiating exposure to various components of the THM mixture.

This study relied on municipality aggregate exposure data (measurements of TTHM levels in municipal tap water in the study municipality) to estimate individual exposure to TTHM. TTHM enter the body not only through ingestion, but also through inhalation and dermal routes (Whitaker et al. 2003). Epidemiologic studies only evaluated ingestion. However, evidence was provided that TTHM levels in drinking water serve as a reliable predictor of actual uptake to TTHM, although there is no apparent information on individual behaviors relating to exposure via other routes (Whitaker et al. 2003).

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 comprehensive. 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 kidney cancer, were found to be one of the most unequivocally classified causes of death in Taiwan (Chen and Wang 1990). Since kidney cancer is a potentially fatal disease, it is postulated that all patients with this disease in Taiwan would have had access to medical care regardless of their geographical location.

Migration from a municipality of high TTHM exposure to one of low TTHM exposure or vice versa may have introduced misclassification bias and bias in the OR estimate (Gladen and Rogan 1979; Polissar 1980). Mobility is age dependent, and diseases usually occur with a higher incidence among older groups and closer to the location of the environmental "cause" (Polissar 1980). However, neighboring water sources tend to share 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 old. It is generally assumed 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 differences in survival rates of kidney 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 kidney cancer death would have been noted. Three aspects of this study presumably minimized this possibility. First, migration due to kidney 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, and it was assumed that individuals in this age group are more likely to remain in the same residence and, therefore, that most of their life time was spent at the address as listed on the death certificate.

Of greater concern is whether the relative levels of TTHM in the period around 2000 correspond to the relative levels occurring in periods 20–30 yr earlier. This is important since it

is likely that exposure to causal factors would precede cancer mortality 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 2000 and levels in the previous 20–30 yr might be high since the treatment practices have not changed over time in study areas.

There are other risk factors for kidney 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 factor for kidney cancer is cigarette smoking (Schottenfeld and Fraumeni 1996). Since there is unfortunately no information available on this variable for individual study subjects, it could not be adjusted for directly in the analysis. However, there is no reason to believe that there would be any correlation between this variable and the levels of TTHM in drinking water. It is also unlikely that there would be a direct relationship between other risk factors and the level of TTHM in drinking water.

Exposure to TTHM was determined by linking each study subject's residence to their individual water source. However, it was not possible to calculate the exact amount of TTHM intake from water for individual subjects, because the quantity consumed at home or at other places could not be determined. However, evidence was provided that exposure to TTHM occurs mostly at home, because a large part of this uptake is through inhalation and dermal routes 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.

In summary, our data suggest that exposure to TTHM in drinking water at levels in this study is not associated with increased risk of death due to kidney cancer. Furthermore, the use of soft water was found to significantly modify the effects of TTHM exposure on kidney cancer risk. Better understanding of this modifying effect will help in establishing public policy and setting 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 cigarette smoking.

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