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Effect modification of the association between trihalomethanes and pancreatic cancer by drinking water hardness: Evidence from an ecological study

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ABSTRACT

The objective of this study was to examine the relationship between total trihalomethanes (TTHM) levels in public water supplies and risk of pancreatic cancer and to determine whether calcium (Ca) and magnesium (Mg) levels in drinking water modify the effects of TTHM on risk to develop pancreatic cancer. A matched case-control study was used to investigate the relationship between the risk of death attributed to pancreatic cancer and exposure to TTHM in drinking water in 53 municipalities in Taiwan. All pancreatic cancer deaths in 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 Ca and 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, Ca, and Mg exposure via drinking water. Relative to individuals whose TTHM exposure level < 4.9 ppb, the adjusted OR (95% CI) for pancreatic cancer was 1.01 (0.85–1.21) for individuals who resided in municipalities served by drinking water with a TTHM exposure > 4.9 ppb. There was no evidence of an interaction of drinking water TTHM levels with low Ca intake via drinking water. However, we observed evidence of an interaction between drinking water TTHM concentrations and Mg intake via drinking water. Our findings showed that the correlation between TTHM exposure and risk of pancreatic cancer is influenced by Mg in drinking water. Increased knowledge of the interaction between Mg and TTHM in reducing pancreatic cancer risk will aid in public policy making and standard setting.

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1. Introduction

Chlorination is presently the most common procedure used for water treatment worldwide (Simmons et al., 2004). 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.

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). THM consist of 4 species: chloroform, bromodichloromethane (BDCM), dibromochloromethane, and bromoform. THM 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.

DBPs were discovered in drinking water in 1974 (Rook, 1974; Bellar et al., 1974). Since that time, a number of epidemiologic studies have evaluated the cancer risk associated with DBPs exposure. Among the cancer sites, bladder cancer is the most consistently associated with exposure to DBPs (Morris et al., 1992;

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Cantor et al., 1998; Villanueva et al., 2003, 2004, 2007; Chang et al., 2007).

Although much of the focus concerning the carcinogenic potential of DBPs has centered on the bladder, pancreatic cancer has also been of some interest. Of the 9 studies based on exposure to chlorinated water as the measure of DBPs exposure, one reported a significant positive association between chlorinated drinking water and pancreatic cancer risk (IJsselmuiden et al., 1992); one reported a significant protective effect of chlorinated drinking water on pancreatic cancer risk (Kukkula and Lofroth, 1997); and 7 studies reported no association (Flaten, 1992; Gottlieb et al., 1982; Wilkins and Comstock, 1981; Koivusalo et al., 1997; Young et al., 1981; Zierler et al., 1986; Yang et al., 1998). Morris et al. (1992) found an odds ratio of 1.05 (95% *CI*=0.91–1.22) for pancreatic cancer in association with long-term consumption of chlorinated water in a meta-analysis. Two studies have used THM levels as a measurement of exposure to examine DBP exposure and pancreatic cancer risk. Vinceti et al. (2004) did not observe an increase in pancreatic cancer risk associated with THM exposure. In a recent study conducted in Canada, Do et al. (2005) also found no evidence of an association between exposure to THM in drinking water and the risk of pancreatic cancer.

The hardness of drinking water is determined largely by its content of calcium and magnesium. It 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 calcium (Ca) or magnesium (Mg) than soft water.

Yang et al. (1999) reported a significant inverse relation between drinking water hardness and pancreatic cancer risk. To date, only one epidemiologic study has examined the relation between dietary Mg intake and the risk of pancreatic cancer and no association was observed (Kesavan et al., 2010). There is evidence supporting a protective role for calcium against pancreatic cancer (Farrow and Davis, 1990; Ghadirian et al., 1991). One animal study also indicated that hyperproliferation in the pancreas of rodents was induced by feeding a low Ca Western-style diet (Xue et al., 1996). However, none of previous studies have explored whether Ca and Mg levels in drinking water might affect the association between total THM (TTHM) exposure and health outcome outcomes.

The objective of this study was to examine the relationship between TTHM levels in public water supplies and the risk of pancreatic cancer and to determine whether Ca and Mg levels in drinking water modify the effects of TTHM on risk of pancreatic cancer.

2. Materials and methods

2.1. Selection of study municipalities

Chlorination, the major strategy for the disinfection of drinking water in Taiwan, 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 either from the public drinking water supply systems served by the Taiwan or Taipei Water Supply Corporation or from non-municipal sources. In Taiwan, water sources are mostly (59.3%) drawn directly from rivers; the rest comes from groundwater and reservoirs, accounting for 21.7% and 19%, respectively (Hsu et al., 2001). The major sources of municipal water supplies are predominantly surface waters (78.3%) and treated with chlorine. The non-municipal 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 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 of pancreatic cancer development and levels of TTHM in Taiwan drinking water.

2.2. Socioeconomic factors

It has been found that mortality from cancer is associated with urbanization gradients (Greenberg, 1983). In this study, an urbanization index (Tzeng and Wu, 1986) was used to adjust for possible confounding resulting from different urbanization levels among the municipalities. The urbanization index used serves as a proxy for a large number of explanatory variables, such as population density, age composition, mobility, economic activity and family income, educational level, environment factors, and health service-related facilities, which are related to the etiology of mortality. A municipality with the highest urbanization score, such as the Taipei metropolitan area, was classified in category 1, whereas mountainous areas with the lowest score were assigned to category 8. This index has been used in our previous studies (Yang and Hsieh, 1998). For the analyses, the urban–rural classification was further sub-divided into 4 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).

2.3. 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 in charge of 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 on computer tapes. The case group consisted of all eligible pancreatic cancer deaths occurring in people between 50 and 69 years of age (International Classification of Disease, ninth revisions [ICD-9], code 157). In all, 1056 pancreatic cancer deaths with complete records satisfied this criterion.

The control group consisted of all other deaths excluding those deaths, which were associated with diseases of the digestive system (ICD-9 codes, 150–159, 520–579). Subjects who died from bladder (Morris et al., 1992; Cantor et al., 1998; Villanueva et al., 2003, 2004, 2007; Chang et al., 2007), kidney (Koivusalo et al., 1998; Gottlieb et al., 1982; Yang et al., 1998; Cantor et al., 1978), and lung (Koivusalo et al., 1997; Yang et al., 1998; Cantor et al., 1978) cancers were also excluded from the control group because of previously reported associations with chlorinated drinking water use. A total of 71,221 deaths satisfied this criterion. Control subjects were pair matched to the cases by sex, year of birth, and year of death. A case had an average of 67 appropriate controls who satisfied the criteria for matching. We used a random sampling method 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 (11.5%), liver cancer (9.5%), cerebrovascular disease (9.5%), ischemic hear disease (6.9%), chronic liver disease and cirrhosis (6.0%), diseases of respiratory system 5.6%), diseases of the genitourinary system (4.6%), and other forms of heart disease (4.3%).

2.4. Drinking water TTHM exposure assessment

TTHM levels were used as a marker for DBP exposure 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) which consisted of chloroform, bromoform, bromodichloromethane, and dibromochloromethane. The sum of the concentrations of the 4 individual THM comprise TTHM. Data on the annual levels of TTHM were obtained from EPA. Since the treatment practice (chlorination) and the water source have not changed in the past decade in study areas, the average TTHM levels of the two years were used as a measure of exposure levels for the municipalities examined.

The municipalities of residence for all pancreatic cancer cases and controls were identified from death certificates and assumed to be the source of the subject TTHM exposure via drinking water. The levels of TTHM in each municipality were used as an indicator of exposure to TTHM for an individual residing in that municipality.

2.5. Calcium and magnesium levels in drinking water

Information on the levels of Ca and Mg in each municipality treated drinking water supply was obtained from the Taiwan Water Supply Corporation (TWSC), to whom each waterworks is required to submit drinking water quality data, including levels of Ca and Mg. Four finished water samples, one for each season, were collected from each waterworks. Their details have already been described in earlier publications (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 Ca and Mg data from 53 municipalities. Hardness (Ca and Mg) remains reasonably constant for long periods of time and are quite

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