Arch. Environ. Contam. Toxicol. 33, 336–340 (1997)

ARCHIVES OF
Environmental
Contamination
and Toxicology

Gastric Cancer Mortality and Drinking Water Qualities in Taiwan

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Received: 27 November 1996/Accepted: 16 April 1997

Abstract. The possible association between the risk of gastric cancer and nitrate and hardness in drinking water from municipal supplies was investigated in a matched case-control study in Taiwan. Data on gastric cancer deaths among eligible residents in Taiwan from 1987 through 1991 (6,766 cases) were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Controls were deaths from other causes (6,766 controls) and were matched individually to the cases by sex, year of birth, and year of death. Data on nitrate–nitrogen (NO_3–N) and hardness levels in drinking water throughout Taiwan were collected from the Taiwan Water Supply Corporation (TWSC). The municipality of residence for cases and controls was assumed to be the source of the subject's nitrate and hardness exposure via drinking water. There was no difference in gastric cancer rates between the groups with different levels of nitrate. The odds ratios (95% confidence interval) for death from gastric cancer was 0.95 (0.87–1.03) for the group with water nitrate levels between 0.23 and 0.44 mg/L, and 1.02 (0.93–1.11) for the group with nitrate levels greater than 0.45 mg/L. However, the results show a significant negative relationship between drinking water hardness and gastric cancer mortality. Odds ratios were 1.16 (1.07–1.26) and 1.65 (1.52–1.79), respectively, for exposure to moderately hard water and soft water compared with the use of hard water. This is an important finding for the Taiwan water industry and human health risk.

In Taiwan, gastric cancer is the third leading cause of cancer mortality for males and the sixth for females (DOH/ROC 1993a). The age-adjusted mortality rate for gastric cancer was 13.31 per 100,000 among males and 6.54 among females in 1993. There is substantial geographic variation in gastric cancer mortality within the country (DOH/ROC 1993b). Such a geographic distribution may suggest an environmental risk factor.

It has been suggested that a link exists between the levels of nitrate in drinking water and the mortality from stomach cancer (Hill *et al.* 1973; Jensen 1982; Harman 1983; Gilli *et al.* 1984; Dutt and Lim 1987; Xu 1981). However, other studies have failed to confirm such an association (Armijo *et al.* 1981; Davies 1980; Beresford 1985; Fraser and Chilvers 1981; Rademacher *et al.* 1992). The WHO (1985) concluded that no firm epidemiological evidence has been found linking gastric cancer to drinking water containing higher levels of nitrate, but a link cannot be ruled out due to the inadequacy of the data available.

The mechanisms are unclear, but hardness in drinking water has been suspected as another factor which is associated with stomach cancer (Malnasi *et al.* 1976; Turner 1962; Zemla 1980).

The objective of this study was to evaluate the risk of gastric cancer associated with nitrate and water hardness exposure in drinking water from municipal supplies in Taiwan.

Materials and Methods

Study Area

Taiwan is divided into 361 administrative districts, which will be referred to herein as municipalities. They are the units that will be subjected to statistical analysis. Excluded from the analysis were 30 aboriginal townships and 9 islets that had different life-styles and living environments. This elimination of unsuitable municipalities left 322 municipalities for the analysis.

Subject Selection

Data on all deaths of Taiwan residents from 1987 through 1991 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 sex, 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 gastric cancer deaths (International Classification of Disease, ninth revisions [ICD-9], code 151).

A control group was formed using all other deaths excluding those deaths that were associated with gastrointestinal problems [*i.e.*, malignant neoplasm of small intestine (ICD-9 codes 152–154), gastric ulcer (ICD-9 code 531), duodenal ulcer (ICD-9 code 532), peptic ulcer, site

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unspecified (ICD-9 code 533), gastrojejunal ulcer (ICD-9 code 534), and gastrointestinal hemorrhage (ICD-9 code 578)]. Subjects who died from prostate (Morales *et al.* 1995a), bladder (Morales *et al.* 1995a, 1995b), lung (Hoffmann *et al.* 1994), esophageal (Yang 1980; Wu *et al.* 1993), and head and neck (Andre *et al.* 1995; Herity et al. 1981) cancer were also excluded from the control group because of previously reported associations with nitrate or N-nitroso compounds exposures. Control subjects were pair matched to the cases by sex, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case. To be eligible, both case and control subjects must have had residence and place of death in the same municipality.

Nitrate–Nitrogen and Hardness Levels

Information on the levels of nitrate–nitrogen (NO_3–N) and hardness in finished water in each waterworks was obtained from the Taiwan Water Supply Corporation (TWSC) (TWSC/ROC 1991), to whom each waterwork is required to submit drinking water quality data including the nitrate–nitrogen (NO_3–N) and hardness. Four finished water samples, one for each season, were collected from each waterworks. The samples were analyzed by the waterworks' laboratory office using the standard method. Since the laboratory office examines nitrate and hardness on a routine basis using a standard method, it was thought that the problems of analytical variability were minimal. Data collected were the annual mean NO_3–N and hardness for the year 1990. Among the 322 municipalities, 70 were excluded because they had more than one waterwork to supply the drinking water and the exact population served by each waterwork could not be determined. Their details are given in an earlier publication (Yang *et al.* 1996). The final complete data comprised data from 252 municipalities. The municipalities of residence for all cases and controls were identified from death certificates and were assumed to be the source of the subject's nitrate and hardness exposure via drinking water. The NO_3–N and hardness levels of that municipality were used as the indicator of that individual's nitrate and hardness exposure.

Statistics

In the analysis of the association between nitrate exposure and gastric cancer, the subjects were divided into tertiles according to the levels of nitrate in their drinking water. For the analysis of hardness, the subjects were divided into one of three mutually exclusive hardness 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 and McCarty 1978). Conditional logistic regression was used to estimate the odds ratios (ORs) and their 95% confidence interval (95% CI) in relation to the nitrate and hardness levels in drinking water (Breslow and Day 1980). Tests for trend were conducted using the method described by Mantel (1963). *P*-values < 0.05 were considered statistically significant.

Results

A total of 6,766 gastric cancer cases with complete records were collected for the period from 1987 to 1991. Of the 6,766 cases, 4,480 were males and 2,286 were females. The mean nitrate concentration for the gastric cancer cases ($n = 6766$) was 0.45 mg/L NO_3–N (SD = 0.43). Controls ($n = 6766$) had a mean NO_3–N exposure of 0.44 mg/L (SD = 0.44). Both cases and controls had a mean age of 65.2. Cases lived in municipalities in which 89.8% of the population was served by waterworks. For controls this number was 89.4%. Cases had a slightly higher rate (42.0%) of living in a metropolitan municipality than the controls (40.0%). There was no notable difference between cases and controls with regard to the urbanization levels of their residence (Table 1).

Table 2 shows the numbers of cases and controls and odds ratios in relation to the nitrate levels in their drinking water. The odds ratios (95% confidence interval) for death from gastric cancer was 0.95 (0.87–1.03) for the group with water nitrate levels between 0.23 and 0.44 mg/L, and 1.02 (0.93–1.11) for the group with nitrate levels greater than 0.45 mg/L. The odds ratios for death from gastric cancer were not significantly higher for the two groups with high levels of nitrate in the drinking water. Trend analyses also showed no statistically significant trend in risk of gastric cancer death with increasing nitrate levels.

Table 3 shows the distribution of cases and controls with respect to levels of hardness in drinking water. 33.9, 32.5, and 33.6% of the cases lived at residences served by soft, moderately hard, and hard water, respectively, while 25.0, 34.0, and 41.0% were so served by the controls. The estimated odds ratios and 95% confidence intervals are shown also in Table 3. Relative to individuals whose hardness exposure level was more than 150 mg/L (hard water), the odds ratios was 1.16 (95% CI = 1.07–1.26) for persons who had resided in places served by hardness exposure level between 75 and 150 mg/L (moderately hard water), and 1.65 (95% CI = 1.52–1.79) for persons who had resided in places served by hardness exposure level less than 75 mg/L (soft water). The chi-square test for trend ($\chi^2 = 33.59$, $p < 0.0001$) indicates a statistically significant increasing trend in the odds of gastric cancer with decreasing levels of hardness.

Discussion

This study uses a death certificate–based case-control study and a drinking water quality ecology study to examine the relationship between gastric cancer mortality and nitrate and hardness exposure from drinking water in Taiwan. The results of the present study show that there is no significant association between drinking water nitrate exposure and gastric cancer mortality, but there is significant negative association between drinking water hardness and gastric cancer mortality.

Studies on the association between mortality and environmental exposures have been used widely to generate and falsify epidemiological hypotheses, despite their inherent limitations (Morgenstern 1982). The completeness and accuracy of the death registration system should be evaluated before any conclusion based on the mortality analysis is made. In Taiwan, it is mandatory to register death certificates at local household registration offices, and, since the household registration information is verified annually through a door-to-door survey, the death registration is very 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, Taiwan is a small island with a convenient communication network, and the accessibility of medical service facilities is comparable among study municipalities. Mortality data differences between the municipalities in this

Table 1. Characteristics of the study population

Characteristics	Cases	Controls
Total subjects	6,766	6,766
Enrollment municipality	252	252
Sex (%)		
male	4,480 (66.2)	4,480 (66.2)
female	2,286 (33.8)	2,286 (33.8)
Mean age in years (SD)[a]	65.2 ± 13.0	65.2 ± 13.0
Mean nitrate–nitrogen (NO_3–N) concentration (SD)[a]	0.45 ± 0.43	0.44 ± 0.44
Drinking water served by waterworks (%)	89.8 ± 5.3	89.4 ± 5.5
Urbanization level of residence (%)[b]		
metropolitan	2,841 (42.0)	2,706 (40.0)
city	1,405 (20.8)	1,421 (21.0)
town	1,649 (24.3)	1,719 (25.4)
rural	871 (12.9)	920 (13.6)

[a] SD: standard deviation
[b] The urbanization level of each municipality was based on the urban-rural classification of Tzeng and Wu (1986)

Table 2. Odds ratios (ORs) and 95% confidence intervals (CI) for gastric cancer by drinking water nitrate levels in Taiwan, 1987–1991

Nitrate (median)[a]	No. of Cases	No. of Controls	OR (CI)[b]
≤0.22 (0.04)	2,109 (31.2%)	2,079 (30.7%)	1.00
0.23–0.44 (0.37)	2,126 (31.4%)	2,249 (33.2%)	0.95 (0.87–1.03)
≥0.45 (0.67)	2,531 (37.4%)	2,438 (36.1%)	1.02 (0.93–1.11)
			χ^2, trend = 0.60
			$p = 0.44$

[a] Expressed as mg/L as NO_3–N
[b] Odds ratio adjusted for age and sex

Table 3. Odds ratios (ORs) and 95% confidence intervals (CI) for gastric cancer by drinking water hardness levels in Taiwan, 1987–1991

Hardness	No. of Cases	No. of Controls	OR (CI)[d]
Hard[a]	2,275 (33.6%)	2,773 (41.0%)	1.00[e]
Moderately hard[b]	2,197 (32.5%)	2,299 (34.0%)	1.16 (1.07–1.26)
Soft[c]	2,294 (33.9%)	1,694 (25.0%)	1.65 (1.52–1.79)
			χ^2, trend = 33.59
			$P < 0.0001$

[a] Total hardness: over 150 mg/L as $CaCO_3$
[b] Total hardness: 75–150 mg/L as $CaCO_3$
[c] Total hardness: 0–75 mg/L as $CaCO_3$
[d] Odds ratio adjusted for sex and age
[e] Hard water exposure as reference group

study do not appear to result from systematic differences in recording and codification of deaths.

Of greater concern is whether the relative levels of nitrate and hardness in the period around 1990 correspond to the relative levels in periods 10–20 years previously. This is important since it is likely that exposure to causal factors would precede cancer mortality by at least 20 years (the latency period for carcinogen exposure). Some information on historical levels of nitrate and hardness was available for the study areas in 1980. The correlation between 1980 and 1990 nitrate and hardness levels for the study areas were reasonably high ($r = 0.86$ and 0.85, respectively). Nitrate and hardness data were supplied by the Water Quality Research Center of the Taiwan Water Supply Corporation, which conducts routine water analyses to assess suitability of water for drinking from both the sources and at various points in the distribution system. Also, the waterworks in each municipality received a questionnaire requesting information on whether any changes had occurred in the water supply or the treatment of the water during the past history. No municipalities were excluded because changes in water quality (*e.g.*,, the use of water softeners) had been occurred during the past few decades. It was felt that the nitrate and hardness levels have remained reasonably constant in drinking water. We therefore assumed that nitrate and hardness levels in 1990 were a reasonable indicator of historical nitrate and hardness exposure levels from drinking water.

Migration from a municipality of high nitrate and hardness exposure to one of low nitrate and hardness exposure, or vice versa, could have introduced misclassification bias and bias in the odds ratio estimate (Gladen and Rogan 1979; Polissar 1980). However, migrant studies have indicated that susceptibility to gastric cancer is strongly related to place of birth (early life exposures) and much less to place of later residence (Coggon *et al.* 1990). It is unfortunate that place-of-birth information was not available for the data set, and the use of the place-of-death information as the surrogate measure inevitably introduces bias to some extent. The individuals included in the present study were subjects whose residence and place of death were in the same municipality. In the event of a death in Taiwan, there is a social custom that the decedent's family always considers the death to occur in the municipality where he was born. Therefore, the decedent's residence, place of birth, and place of death are likely to be listed as the same municipality. We believe that this ameliorates the migration problem. Also, gastric cancer is a disease of old age, and it is assumed that the elderly are more likely to remain in the same residence during the last 20 years of their life (Rademacher *et al.* 1992).

The principal sources of dietary nitrate are drinking water and foods (White 1975; Walker 1975). The hypothesis that high nitrate ingestion may increase the risk of gastric cancer has led to concern over rising levels of nitrate in drinking water, but with little consideration to whether nitrate in water makes a major contribution to total nitrate intake. A study has indicated that when the concentration of waterborne nitrate is high, drinking water contributes substantially to total nitrate intake (Chilvers *et al.* 1984), and the potential for nitrite and N-nitroso compound formation may be increased. There are no available data for assessing the diet of the individual subjects in the present study. Moller *et al.* (1989) have reported a mean daily intake (excluding drinking water) of 37-mg nitrate through food in Denmark. Assuming that this figure is valid for Taiwan, drinking water would contribute, on average, 2.4% to the total nitrate intake in our 252 municipalities in Taiwan, given a daily consumption of 2 L of water. Since nitrate concentrations in Taiwan are so low and the contribution from drinking water to the total dietary intake may be rather small, our study does not provide evidence to support the drinking water nitrate–gastric cancer hypothesis.

There has recently been public concern over the possible nitrate contamination in public water supplies in Taiwan, due principally to the increasing use of inorganic fertilizers in areas

of arable farming. This makes it pertinent to examine the available evidence for an association between drinking water nitrate ingestion and gastric cancer. The nitrate concentration in drinking water in Taiwan is below the guideline value recommended by the World Health Organization (1984) of 10 mg/L. However, there is no scientific evidence to justify firm conclusions about the safety of any concentration of nitrate in water with regard to gastric cancer risk. Forman (1989) notes that although environmental nitrate exposure probably plays a role in the development of gastric cancer, it may not serve as a rate-limiting factor.

Regarding water hardness, there are no distinctly defined guidelines as to what constitutes a hard or soft water supply. A generally accepted classification is water with less than 75 mg/L of $CaCO_3$ is considered soft, 75–150 mg/L is moderately hard, and above 150 mg/L is hard (Sawyer and McCarty 1978). Three past studies that investigated gastric cancer risk and drinking water hardness were ecologic in design and reported positive associations between gastric cancer mortality and the use of soft water (Malnasi *et al.* 1976; Turner 1962; Zemla 1980). Our study used a case-control approach based on death certificate records. Exposure was defined in this study as the hardness of the drinking water source serving the address listed on the death certificate. The current study estimates a 65% excess of gastric cancer mortality in areas with soft water compared with areas with hard water, and a 16% excess for moderately hard water compared to hard water. Other studies (Malnasi *et al.* 1976; Turner 1962; Zemla 1980) have reported only correlation coefficients and not risk estimates as a function of exposure.

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 the calcium and magnesium in solution. Animal studies indicate that salt-induced damage to the gastric mucosa might be inhibited by increasing intake of calcium (Lipkin and Newmark 1985). A recent analytical epidemiologic study also reports a possible protective effect of calcium against stomach cancer (You *et al.* 1988). Two biologically plausible mechanisms are considered by which magnesium could prevent carcinogenesis. Intracellular magnesium may enhance the fidelity of DNA replication or magnesium on the cell membrane may prevent changes which trigger the carcinogenic process (Blondell 1980). Although the results from toxicologic studies offer a biologic rationale for the associations found here, we still have great difficulty in explaining why the hardness concentration in drinking water should affect gastric cancer mortality, when the relationship between hardness content (calcium or magnesium) of water and of food is considered. If the amounts of hardness in water have effect on gastric cancer mortality, the larger amounts in foods would have a greater effect. It appears to us that it is more reasonable to regard hardness as an ''indicator'' of something else, possibly a causal agent. The softer waters are originally acidic in character and could well contain amounts of a number of organic substances greatly in excess of the levels present in the harder waters. The various organic constituents of drinking water might play a role (Turner 1962). Also, soft water is more corrosive than hard water and promotes the dissolution of cadmium, lead, and other toxic substances from the plumbing system into the drinking water (Westendorf and Middleton 1979). All of these problems will require further study.

There are a number of major risk factors for gastric cancer which should be taken into account when investigating the possible role of an additional factor (drinking water nitrate or hardness exposure). On the basis of scientific knowledge from the epidemiologic study carried out in Taiwan, the most important risk factors for gastric cancer are cigarette smoking, alcohol drinking, green tea drinking as well as consumption of salted meat, cured meat, smoked food, fried food, and fermented beans (Lee *et al.* 1990). Unfortunately, there is no information available on these variables for individual study subjects, and they could not be adjusted for directly in the analysis. If the association between these potentially confounding variables on the one hand and stomach cancer risk on the other is not as strong as the one that has been observed for water hardness, adjustment of these variables will not qualitatively change the conclusion.

In summary, the present study has found no significant association between nitrate levels in drinking water and mortality from gastric cancer in Taiwan. The present study also suggests that a 65% excess risk of mortality from gastric cancer was found in relation to the use of soft water and a 16% excess with the use of moderately hard water compared with the use of hard water. The elevated risk was statistically significant, but evidence is presently not available to establish conclusively that water hardness may prevent gastric cancer. Future studies should investigate the individual's intake of hardness and chemicals, both via food and water, and control for confounding factors, especially personal risk factors such as smoking, alcohol drinking, green tea drinking and diet habits. Due to this uncertainty, it is not possible to recommend specific remedial measures.

Acknowledgment. This study was partly supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-86-2314-B-037-089).

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