

## Calcium, Magnesium, and Nitrate in Drinking Water and Gastric Cancer Mortality

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The possible association between the risk of gastric cancer and the levels of calcium, magnesium, and nitrate in drinking water from municipal supplies was investigated in a matched case-control study in Taiwan. Records of gastric cancer deaths among eligible residents in Taiwan from 1987 through 1991 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 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. Data on calcium, magnesium, and nitrate levels in drinking water throughout Taiwan were obtained from the Taiwan Water Supply Corporation. The municipality of residence of the cases and controls was assumed to be the source of the subject's calcium, magnesium, and nitrate exposure *via* drinking water. The subjects were divided into tertiles according to the levels of calcium, magnesium, and nitrate in their drinking water. The results of the present study show that there is a significant positive association between drinking water nitrate exposure and gastric cancer mortality. The present study also suggests that there was a significant protective effect of calcium intake from drinking water on the risk of gastric cancer. Magnesium also exerts a protective effect against gastric cancer, but only for the group with the highest levels.

Key words: Gastric cancer — Drinking water — Calcium — Magnesium — Nitrate

In Taiwan, gastric cancer is the third leading cause of cancer mortality for males and the sixth for females.<sup>1)</sup> 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.<sup>2)</sup> Such a geographic distribution may suggest an environmental risk factor.

A hypothesis linking nitrate intake and gastric cancer was presented in 1975<sup>3)</sup> and updated in 1988.<sup>4)</sup> Many epidemiological studies have indicated an association between nitrate levels of drinking water and mortality from stomach cancer.<sup>5–10)</sup>

Hardness in drinking water has also been suspected to be associated with stomach cancer.<sup>11–13)</sup> Animal studies indicate that salt-induced damage to the gastric mucosa might be inhibited by increased intake of calcium.<sup>14–16)</sup> A recent analytical epidemiologic study also found a possible protective effect of calcium against stomach cancer.<sup>17)</sup> There are two biologically plausible mechanisms 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.<sup>18)</sup> 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. In previous studies, however, calcium and magnesium data were not available.

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

### MATERIALS AND METHODS

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 which have different life-styles and living environments. This elimination of unsuitable municipalities left 322 municipalities for the analysis.

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 which 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 unspecified (ICD-9 code 533), gastrojejunal ulcer

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(ICD-9 code 534), and gastrointestinal hemorrhage (ICD-9 code 578). Subjects who died from prostate,<sup>19)</sup> bladder,<sup>19, 20)</sup> lung,<sup>21)</sup> esophageal,<sup>22, 23)</sup> and head and neck<sup>24, 25)</sup> cancer were also excluded from the control group because of previously reported associations with nitrate or *N*-nitroso compounds exposures. Subjects who died from cardiovascular and cerebrovascular diseases<sup>26–29)</sup> were also excluded from the control group because of previously reported associations with hardness levels (calcium and magnesium) in drinking water. 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. Each case and its matched control had residence and place-of-death in the same municipality.

Information on the levels of calcium, magnesium and nitrate-nitrogen (NO<sub>3</sub>-N), in each municipality's treated drinking water supply was obtained from the Taiwan Water Supply Corporation,<sup>30)</sup> to whom each waterworks is required to submit drinking water quality data including the levels of calcium, magnesium and nitrate. Four finished water samples, one for each season, were collected from each waterworks. The samples were analyzed by the waterworks laboratory office using standard methods. Since the laboratory office examines calcium, magnesium, and nitrate levels on a routine basis using standard methods, it was thought that the problem of analytical variability was minimal. Among the 322 municipalities, 70 were excluded as they were supplied by more than one waterworks and the exact population served by each waterworks could not be determined. The details were given in earlier publications.<sup>29, 31)</sup> The final data set consisted of drinking water quality data from 252 municipalities. Hardness (calcium and magnesium) remains reasonably constant for long periods of time and is a quite stable characteristic of a municipality's water supply.<sup>32)</sup> Data collected included the annual mean levels of calcium, magnesium, and nitrate for the year 1990. The municipality of residence for all cases and controls was identified from the death certificate and was assumed to be the source of the subject's calcium, magnesium, and nitrate exposure via drinking water. The levels of calcium, magnesium, and nitrate of that municipality were used as the indicator of that individual's exposure to those substances.

In the analysis, the subjects were divided into tertiles according to the levels of calcium, magnesium, and nitrate in drinking water. Conditional logistic regression was used to estimate the relative risk in relation to the nitrate levels in drinking water. Odds ratios and their 95% confidence intervals (95% CIs) were calculated using the group with the lowest exposure as the reference group.<sup>33)</sup> Coefficients with *P* values <0.05 were considered statistically significant.

## RESULTS

A total of 6766 gastric cancer cases with complete records was collected for the period of 1987–1991. Of the 6766 cases, 4480 were males and 2286 were females. The mean nitrate concentration for the gastric cancer cases (*n*=6766) was 0.45 mg/liter NO<sub>3</sub>-N (SD=0.43). Controls (*n*=6766) had a mean NO<sub>3</sub>-N exposure of 0.44 mg/liter (SD=0.44). The mean calcium concentration for the gastric cancer cases was 30.4 mg/liter (SD=19.2). Controls had a mean calcium exposure of 34.3 mg/liter (SD=19.0). The mean magnesium concentration for the gastric cancer cases was 10.2 mg/liter (SD=7.2). Controls had a mean magnesium exposure of 11.2 mg/liter (SD=7.5). 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 a waterworks. For controls this number was 89.4%. Cases had a slightly higher rate (42.0%) of living in metropolitan municipalities than the controls (36.9%) (Table I).

Table II shows the numbers of cases and controls and the odds ratios in relation to nitrate levels in their drinking water. The odds ratios for death from gastric cancer were not significantly lower or higher for the two groups with high levels of nitrate in the drinking water. However,

Table I. Characteristics of the Study Population

Characteristics	Cases	Controls
Total subjects	6766	6766
Enrollment municipality	252	252
Sex (%)		
male	4480 (66.2)	4480 (66.2)
female	2286 (33.8)	2286 (33.8)
Mean age in years (SD) <sup>a)</sup>	65.2±13.0	65.2±13.0
Mean nitrate-nitrogen (NO <sub>3</sub> -N) concentration (mg/liter) (SD)	0.45±0.43	0.44±0.44
Mean calcium concentration (mg/liter)(SD)	30.4±19.2	34.3±19.0
Mean magnesium concentration (mg/liter) (SD)	10.2±7.2	11.2±7.5
Drinking water served by waterworks (%)	89.8±5.3	89.4±5.5
Urbanization level of residence (%) <sup>b)</sup>		
metropolitan	2841 (42.0)	2706 (40.0)
city	1405 (20.8)	1421 (21.0)
town	1649 (24.3)	1719 (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 scheme of Tzeng and Wu.<sup>52)</sup>

Table II. Odds Ratios (ORs) and 95% CIs for Gastric Cancer Death by Nitrate Levels in Drinking Water, 1987–1991

	Nitrate, <sup>a)</sup> mg/liter (median)		
	≤0.22 (0.04)	0.23–0.44 (0.37)	≥0.45 (0.67)
No. of cases	2109	2126	2531
No. of controls	2079	2249	2438
Crude odds ratio	1.0	0.95 (0.87–1.03) <sup>b)</sup>	1.02 (0.93–1.11)
Adjusted odds ratio <sup>c)</sup>	1.0	1.10 (1.00–1.20)	1.14 (1.04–1.25)

a) Expressed as mg/liter as NO<sub>3</sub>-N.

b) 95% confidence intervals in parentheses.

c) Adjusted for urbanization level of residence, calcium, and magnesium levels in drinking water.

Table III. ORs and 95% CIs for Gastric Cancer Death by Calcium Levels in Drinking Water, 1987–1991

	Calcium, mg/liter (median)		
	≤20.2 (7.5)	22.0–38.7 (32.8)	39.5–81 (53.4)
No. of cases	2523	2142	2101
No. of controls	1914	2277	2575
Crude odds ratio	1.0	0.71 (0.65–0.77) <sup>a)</sup>	0.61(0.56–0.66)
Adjusted odds ratio <sup>b)</sup>	1.0	0.77 (0.69–0.88)	0.70(0.62–0.80)

a) 95% confidence intervals in parentheses.

b) Adjusted for urbanization level of residence, nitrate, and magnesium levels in drinking water.

when adjustments were made for possible confounders the odds ratios were significantly higher. The adjusted odd ratios (95% CI) were 1.10 (1.00–1.20) for the group with water nitrate levels between 0.23 and 0.44 mg/liter and 1.14 (1.04–1.25) for the group with nitrate levels of 0.45 mg/liter or more when compared to the group with the lowest levels.

Table III shows the numbers of cases and controls and odds ratios in relation to calcium levels in their drinking water. The odds ratios for death from gastric cancer were significantly lower for the two groups with high levels of calcium in the drinking water. Adjustments for possible confounders only slightly altered the odds ratios. The adjusted odd ratios (95% CI) were 0.77 (0.69–0.88) for the group with water calcium levels between 22.0 and 38.7 mg/liter and 0.70 for (0.62–0.80) for the group with calcium levels of 39.5 mg/liter or more.

The odds ratios in relation to magnesium levels in drinking water are shown in Table IV. These odds ratios were also significantly lower than 1 for the higher magnesium levels, but when adjustment was made for possible confounders only the group with the highest levels (≥11.8 mg/liter) had a significantly lower odds ratio (0.86, 95% CI 0.76–0.98).

## DISCUSSION

We have used a death certificate-based case-control study and a drinking water quality ecology study to examine the relationship between gastric cancer mortality and calcium, magnesium, and nitrate exposure from drinking water in Taiwan. The results of the present study show that there is a significant positive association between drinking water nitrate exposure and gastric cancer mortality, and that there is a significant protective effect of calcium intake from drinking water on the risk of gastric cancer. Magnesium also appears to have a protective effect against gastric cancer, when the groups with the highest vs. the lowest tertiles of intake are compared. This study employed methodology similar to that used in our previous study.<sup>31)</sup> The results of our previous study showed that calcium, but not magnesium, intake from drinking water has a significant protective effect against colon cancer.

Despite their inherent limitations,<sup>34)</sup> studies on the ecological correlation between mortality and environmental exposures have been used widely to generate or discredit epidemiological hypotheses. The completeness and accuracy of a death registration system should be evaluated before any conclusion based on mortality analysis is made. In the event of death in Taiwan, the decedent's family is

Table IV. ORs and 95% CIs for Gastric Cancer Death by Magnesium Levels in Drinking Water, 1987–1991

	Magnesium, mg/liter (median)		
	≤7.0 (3.6)	7.3–11.6 (8.9)	11.8–41.3 (16.3)
No. of cases	2480	2143	2143
No. of controls	2027	2079	2660
Crude odds ratio	1.0	0.84 (0.77–0.91) <sup>a)</sup>	0.65 (0.60–0.71)
Adjusted odds ratio <sup>b)</sup>	1.0	1.01 (0.90–1.13)	0.86 (0.76–0.98)

a) 95% confidence intervals in parentheses.

b) Adjusted for urbanization level of residence, nitrate and calcium levels in drinking water.

required to obtain a death certificate from the hospital or local community clinic, which then must be submitted to the household registration office in order to cancel the decedent's household registration. The death certificate is required in order to have the decedent's body buried or cremated. Since the death certificates have to be completed by physicians and it is mandatory to register death certificates at the local household registration offices, and since the household registration information is verified annually through a door-to-door survey, the death registration in Taiwan 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, as in other countries,<sup>35)</sup> malignant neoplasms, including gastric cancer, have been reported to be one of the most unequivocally classified causes of death in Taiwan.<sup>36)</sup> Because of its fatal outcome, it is believed that all gastric cancer cases from rural or urban areas in Taiwan have had access to medical care, regardless of geographic location, in recent years.

Of greater concern is whether the relative levels of calcium, magnesium and nitrate 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 of changes in water quality

(e.g., the use of water softeners) during the past few decades. We, therefore, assumed that drinking water nitrate and hardness levels in 1990 were a reasonable indicator of historical levels.

Migration from a municipality of high nitrate and hardness exposure to one of low calcium, magnesium, and nitrate exposure or *vice versa* could have introduced misclassification bias and bias in the odds ratio estimate.<sup>37, 38)</sup> 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.<sup>39)</sup> 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 probably 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 have occurred in the municipality where the person 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 likely to remain in the same residence during the last 20 years of their life.<sup>40)</sup>

The principal sources of dietary nitrate are drinking water and foods.<sup>41, 42)</sup> 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 as to whether nitrate in water makes a major contribution to total nitrate intake. A previous study has indicated that when the concentration of waterborne nitrate is high, drinking water contributes substantially to total nitrate intake,<sup>43)</sup> 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; however, based on findings from a study by Chilvers *et al.*,<sup>43)</sup> we assumed that water is an important consideration in determining environmental exposure to nitrate.

There has recently been public concern over 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. Our study provides evidence to support the hypothesis that there is a positive association between drinking water nitrate levels and gastric cancer. The nitrate concentration in drinking water in Taiwan is below the guideline value of 10 mg/liter recommended by the World Health Organization.<sup>44)</sup> 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<sup>45)</sup> 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.

Our finding of a significant protective of calcium intake from drinking water agrees with three past studies which were ecologic in design and which reported positive associations between gastric cancer mortality and the use of soft water.<sup>11-13)</sup> These studies<sup>11-13)</sup> 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. In these studies, however, data on calcium and magnesium levels were not available. Our study used a case-control approach based on death certificate records. Exposure was defined in this study as the calcium and magnesium levels of the drinking water source serving the address listed on the death certificate. Lee *et al.*<sup>46)</sup> reported a mean daily intake of 507 mg calcium through food in Taiwan. This figure is only 81.9% of the recommended daily intake. One may hypothesize that waterborne calcium can make an important contribution to the total daily intake for subjects with insufficient calcium intake. The mean calcium concentration in drinking water of Taiwan is 32.4 mg/liter. This figure would contribute, on average, 12.8% to an individual's total dietary calcium intake, given a daily consumption of 2 liters of water.

In the general population, the major portion of magnesium intake is via food, and to a lesser extent via drinking water (in Sweden, generally less than 5 percent is from drinking water).<sup>28)</sup> There are no available data for assessing the percentage that drinking water contributes to the total magnesium intake in the present study. Nonetheless, in the modern-day world, intake of dietary magnesium is often lower than the recommended dietary amount of 6 mg/kg/day.<sup>47)</sup> For individuals at the borderline of magnesium deficiency, waterborne magnesium can make an important contribution to their total intake. In addition, the loss of magnesium from food is lower when the food is

cooked in magnesium-rich water.<sup>48)</sup> The contribution of water magnesium among persons who use water with high magnesium levels could thus be crucial in the prevention of magnesium deficiency. The fact that a significant protective effect of magnesium intake via drinking water was found in the group with the highest levels of intake suggests that only subjects with magnesium intake via drinking water above a certain level receive a beneficial effect on their risk of stomach cancer.

Another reason why both calcium and magnesium in water can play a critical role is their higher bioavailability. Magnesium appears as hydrated ions in water and is therefore more easily absorbed from water than from food, and the situation may be similar for calcium.<sup>49, 50)</sup>

There are a number of major risk factors for gastric cancer in Taiwan, including cigarette smoking and consumption of alcohol, green tea, salted or cured meat, smoked or fried food and fermented beans,<sup>51)</sup> which should be taken into account when investigating the possible role of drinking water quality. These risk factors represent possibly important confounders in the present study. There is unfortunately no information available on these variables for individual study subjects and they could not be adjusted for directly in the analysis. However, there is no reason to believe that there would be any correlation between these confounders and the levels of nitrate, calcium, and magnesium of the water.<sup>27)</sup> Also, if the association between these potentially confounders on the one hand and stomach cancer risk on the other is not as strong as the one that has been observed for nitrate, calcium, and magnesium, adjustment for these variables will not qualitatively change the conclusion.

In conclusion, this study supports the hypothesis that there is a positive association between levels of nitrate in drinking water and mortality from stomach cancer. The present study also suggests that there is a significant protective effect of calcium and magnesium intake from drinking water on the risk of gastric cancer. Our study appears to be the first investigation to report a possible protective effect of calcium and magnesium intake via drinking water against stomach cancer. Future studies should investigate the individual's intake of calcium, magnesium, and nitrate, both via food and water, and control for confounding factors, especially personal risk factors such as smoking, alcohol use, green tea drinking and dietary habits.

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