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Calcium and Magnesium in Drinking Water and Risk of Death from Colon Cancer

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The possible association between the risk of colon cancer and the levels of calcium and magnesium in drinking water from municipal supplies was investigated in a matched case-control study in Taiwan. All eligible colon cancer deaths (1714 cases) of Taiwan residents from 1989 through 1993 were compared with deaths from other causes (1714 controls), and the levels of calcium and magnesium in drinking water of these residents were determined. Data on calcium and magnesium levels in drinking water throughout Taiwan were obtained from the Taiwan Water Supply Corporation. The control group consisted of people who died from other causes and the controls were pair-matched to the cases by sex, year-of-birth, and year-of-death. The adjusted odd ratios (95% confidence interval) were 0.79 (0.64–0.98) for the group with water calcium levels between 24.4 and 42.3 mg/liter and 0.58 (0.47–0.73) for the group with calcium levels of 42.4 mg/liter or more. The adjusted odd ratios were not statistically significant for the relationship between magnesium levels in drinking water and colon cancer. The results of the present study show that there is a significant protective effect of calcium intake from drinking water against colon cancer.

Key words: Colon cancer — Drinking water — Calcium — Magnesium — Epidemiology

In Taiwan, colon-rectum cancer is the fourth leading cause of cancer mortality for males and the sixth for females.[1] The age-adjusted mortality rate for colon cancer was 7.16 per 100,000 among males and 5.67 among females in 1993. There is substantial geographic variation in colon cancer mortality within the country.[2] Such a geographic distribution may suggest an environmental risk factor.

Dietary factors are now thought to be the most important etiologic factors in the development of colon cancer.[3] An increased risk of colon cancer has been attributed to diets high in fat and red meat and low in dietary fruits and vegetables.[4–7] Among the specific dietary components, calcium has been found to have a protective effect against colon cancer.[8–16] A possible protective effect of calcium against colon carcinogenesis has also been suggested by animal studies; calcium binds bile acids and fatty acids and may thus diminish their proliferative effect on the colon mucosa.[17–20] An alternative hypothesis, based on *in vitro* studies in human epithelial cells,[21] suggests that calcium might inhibit the proliferation of colonic epithelial cells directly by inducing terminal differentiation.

Magnesium, which, together with calcium, is the main determinant of water hardness, also protects against deaths from cancer. There are two biologically plausible mechanisms by which magnesium could prevent carcinogenesis. Intracellular magnesium may enhance the fidelity of DNA replication or magnesium at the cell membrane may prevent changes which trigger the carcinogenic process.[22]

Dietary calcium is the main source of calcium intake. In Taiwan, the mean daily intake of dietary calcium is 507 mg. This figure is only 81.9% of the recommended daily intake.[23] The major portion of magnesium intake is via food, and to a lesser extent via drinking water.[24] There are no available data for assessing the percentage contribution of drinking water to the total magnesium intake in Taiwan. Nonetheless, in the modern world, intake of dietary magnesium is often lower than the recommended dietary amounts of 6 mg/kg/day.[25] For individuals at the borderline of calcium and magnesium deficiency, waterborne calcium and magnesium can make an important contribution to their total daily intake.

The objective of this study was to study the relationship between the levels of calcium and magnesium in drinking water and death from colon cancer.

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 1989 through 1993 were obtained from the Bureau of Vital

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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 colon cancer deaths occurring in people between 50 and 69 years of age (International Classification of Disease, ninth revision [ICD-9], code 153).

A control group was formed using all other deaths, excluding those deaths which were associated with gastrointestinal disease. The deaths excluded were those caused by malignant neoplasm 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 code 578). Subjects who died from cardiovascular disease (ICD-9 codes 410–414) and cerebrovascular diseases (ICD-9 codes 430–438) were also excluded from the control group because of previously reported negative correlations with hardness (calcium or magnesium) levels in drinking water.[24, 26–32] A total of 26.16% of the eligible control candidates were excluded on the basis of these criteria. 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, the study subjects needed to have residence and place-of-death in the same municipality. For controls, the most frequent causes of death were liver cancer (9.1%), diabetes mellitus (8.4%), chronic liver disease and cirrhosis (7.9%), lung cancer (7.9%), respiratory diseases (7.4%), other forms of heart disease (ICD codes 420–429) (6.8%), and diseases of the genitourinary tract (4.1%).

Information on the levels of calcium and magnesium in each municipality's treated drinking water supply was obtained from the Taiwan Water Supply Corporation (TWSC),[33] to whom each waterworks is required to submit drinking water quality data, including the levels of calcium and magnesium. 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 and magnesium 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. Their details have already been described in earlier publications.[31, 32, 34] 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.[35] Data collected included the annual mean levels of calcium and magnesium 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 and magnesium exposure via drinking water. The levels of calcium and magnesium of that municipality were used as an indicator of exposure to those substances for an individual residing in that municipality.

In the analysis, the subjects were divided into tertiles according to the levels of calcium and magnesium in their drinking water. Conditional logistic regression was used to estimate the relative risk in relation to the calcium and magnesium levels in drinking water. Odds ratio and 95% confidence intervals (95% CIs) were calculated using the group with the lowest exposure as the reference group.[36] P-values of <0.05 were considered statistically significant.

RESULTS

A total of 1,714 colon cancer cases with complete records were collected for the period 1989–1993. Of the

Table I. Characteristics of the Study Population

Characteristics	Cases	Controls
Total subjects	1,714	1,714
Enrollment municipality	252	252
Sex (%)		
male	937 (54.7)	937 (54.7)
female	777 (45.3)	777 (45.3)
Mean age in years (SD)[a]	61.3±5.4	61.3±5.4
Mean calcium concentration (SD)	32.2±19.1	36.8±19.7
Mean magnesium concentration (SD)	10.9±7.6	11.6±7.5
Drinking water served by waterworks (%)	91.6±14.9	88.7±18.0
Urbanization level of residence (%)[b]		
metropolitan	708 (41.3)	635 (37.0)
city	375 (21.9)	307 (17.9)
town	437 (25.5)	488 (28.5)
rural	194 (11.3)	284 (16.6)

a) SD, standard deviation.
b) The urbanization level of each municipality was based on the urban-rural classification scheme of Tzeng and Wu.[42]

Table II. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Colon Cancer Death by Calcium Levels in Drinking Water, 1989–1993

	Calcium, mg/liter (median)		
	≤24.0 (9.2)	24.4–42.3 (34.6)	42.4–81.0 (57.0)
No. of cases	649	576	489
No. of controls	488	568	658
Crude odds ratio[a)]	1.0	0.76 (0.65–0.90)	0.56 (0.48–0.67)
Adjusted odds ratio[b)]	1.0	0.79 (0.64–0.98)	0.58 (0.47–0.73)
		χ^2 for trend =47.47, $P<0.0001$	

a) Odds ratio adjusted for age and sex.
b) Adjusted for age, sex, urbanization level of residence, and magnesium levels in drinking water.

Table III. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Colon Cancer Death by Magnesium Levels in Drinking Water, 1989–1993

	Magnesium, mg/liter (median)		
	≤7.3 (3.8)	7.4–13.3 (9.1)	13.4–41.3 (17.3)
No. of cases	632	567	515
No. of controls	555	527	632
Crude odds ratio[a)]	1.0	0.94 (0.80–1.11)	0.72 (0.61–0.84)
Adjusted odds ratio[b)]	1.0	1.08 (0.89–1.30)	1.06 (0.85–1.32)
		χ^2 for trend=1.74, $P>0.05$	

a) Odds ratio adjusted for age and sex.
b) Adjusted for age, sex, urbanization level of residence, and calcium levels in drinking water.

1,714 cases, 937 were males and 777 were females. The mean calcium concentration in the drinking water of the cases was 32.2 mg/liter (SD=19.1). Controls (n= 1,714) had a mean calcium exposure of 36.8 mg/liter (SD=19.7). The mean magnesium concentration in the drinking water was 10.9 mg/liter (SD=7.6) for the cases, and 11.6 mg/liter (SD=7.5) for the controls. Both cases and controls had a mean age of 61.3. Cases lived in municipalities in which 91.6% of the population was served by a waterworks. For controls this number was 88.7%. Cases had a higher rate (41.3%) of living in metropolitan municipalities than the controls (37.0%) (Table I).

Table II shows the numbers of cases and controls and odds ratios in relation to calcium levels in drinking water. The odds ratios for death from colon cancer were significantly lower for the two groups with high levels of calcium in their drinking water. Adjustments for possible confounders only slightly altered the odds ratios. The adjusted odd ratios (95% CI) were 0.79 (0.64–0.98) for the group with water calcium levels between 24.4 and 42.3 mg/liter and 0.58 (0.47–0.73) for the group with calcium levels of 42.4 mg/liter or more. There was a significant trend toward a decreased colon cancer risk with increasing calcium levels in drinking water (χ^2= 47.47, $P<0.0001$).

The odds ratios in relation to magnesium levels in drinking water are shown in Table III. The crude odds ratios were significantly lower than 1 for the group with the highest magnesium level (0.72, 95% CI 0.61–0.84), but when adjusted for calcium levels, there was no difference between the groups with different levels of magnesium.

DISCUSSION

In this study, we used a death certificate based case-control protocol and drinking water quality data to examine the relationship between colon cancer mortality and calcium and magnesium intake from drinking water in Taiwan. The results show that there is a significant protective effect of calcium intake from drinking water against colon cancer.

Despite their inherent limitations,[37)] studies on the 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. Since 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 in Taiwan is very complete. Although causes of death may be misdiagnosed and/or misclassified, the problem has been minimized through improvements in the verification and classification of causes of death in Taiwan since 1972. Furthermore, Taiwan is a small island with a good communication network, and the accessibility of medical service facilities is comparable among study municipalities. Mortality data differences between the municipalities in this study do not appear to result from systematic differences in recording and codification.

Some information on the levels of water hardness was available for the study areas in 1980. The correlation between 1980 and 1990 hardness levels for the study areas is reasonably high ($r=0.85$). Hardness data were supplied by the Water Quality Research Center of the TWSC, which conducts routine water analyses to assess the suitability of water for drinking from the water sources and at various points in the distribution system. In addition, 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 twenty years. No municipalities were excluded because of changes in water quality (e.g., the use of water softeners) during the past few decades. It was felt that the hardness (calcium and magnesium) levels in drinking water have remained reasonably stable. We, therefore, assumed that calcium and magnesium levels in 1990 were a reasonable indicator of historical calcium and magnesium exposure levels from drinking water.

Migration from a municipality of high calcium and magnesium exposure to one of low calcium and magnesium exposure or *vice versa* could have introduced misclassification bias and bias in the odds ratio estimate.[38, 39] 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 he was born. Therefore, the decedent's residence, place-of-birth, and place-of-death are likely to be listed as the same municipality, even though place-of-birth information was not available for this data set. We believe that this ameliorates the migration problem.

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. The 5-year survival rate for colon cancer has been reported to be as low as 55% in the United States and developed countries and is one of the poorest among all cancer sites.[7] During this period, cancer diagnosis may influence a decision to migrate and possibly introduce bias. Although data are not available for the difference of survival rate of colon cancer patients between metropolitan areas and country areas, if, for example, there was a differential survival rate for colon cancer between metropolitan areas and country areas, a tendency for colon cancer patients to migrate to urban areas might exist, leading to a spurious association. Three aspects of this study are considered to minimize this possibility. First, migration due to 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. Next, urbanization level was included as a control variable in the analysis. Finally, the study subjects in the present study were between the ages of 50 and 69, and it is assumed that the elderly are more likely to remain in the same residence and, therefore, that most of their life time was spent at the address listed on the death certificate.

There was significant protective effect of calcium intake from drinking water on the risk of colon cancer, with odds ratios of 0.79 and 0.58 for the two groups with high levels of calcium in drinking water. Many previous studies have reported an inverse relation between calcium intake and colon cancer.[8–16] Dietary calcium is the main source of calcium intake. In Taiwan, the mean daily intake of dietary calcium is 507 mg. This figure is only 81.9% of the recommended daily intake.[23] One may hypothesize that waterborne calcium makes an important contribution to the total daily intake for subjects with insufficient calcium intake. The mean calcium concentration in Taiwan's drinking water is 33.3 mg/liter. This figure would contribute, on average, 6.6% to an individual's total dietary calcium intake, given a daily consumption of 2 liters of water. Another reason why calcium in water can play a critical role is its higher bioavailability. Calcium may be like magnesium, which in water appears as hydrated ions and is therefore more easily absorbed from water than from food.[25, 40] Our study appears to be the first investigation to report a possible protective effect of calcium intake via drinking water against colon cancer.

In the general population, the major portion of magnesium intake is via food, and to a lesser extent via drinking water.[24] There are no available data in the present study for assessing the percentage that drinking water contributes to the total magnesium intake. Nonetheless, in the modern-day world, intake of dietary magnesium is often lower than the recommended dietary amount of 6 mg/kg/day.[25] For individuals at the borderline of magnesium deficiency, waterborne magnesium can make an important contribution to total intake. In addition, the loss of magnesium from food is lower when the food is cooked in magnesium-rich water.[41] Another reason why magnesium in water can play a critical role is its higher bioavailability. Magnesium in water appears as hydrated ions, which are more easily absorbed than magnesium in food.[25, 40] The contribution of water magnesium among persons who drink water with high magnesium levels could thus be crucial in the prevention of magnesium deficiency. Our results do not support the hypothesis that magnesium exerts a protective effect against cancer.[22] In fact, in this study, magnesium intake from drinking water was even positively, although not significantly, associated with the risk of colon cancer, with an odds ratio of 1.08 (0.89–1.30) and 1.06 (0.85–1.32), respectively, for the two higher magnesium levels. The reason for not finding a protective effect of magnesium on risk of colon cancer may be because calcium and magnesium in the drinking water are highly correlated (the correlation coefficient is 0.65). This may create collinearity in the regression model, making it difficult to detect the effect of magnesium.

Physical activity, meat and fat consumption 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 calcium and magnesium of the water.[30]

In conclusion, the results of the present study show that there is a significant protective effect of calcium intake from drinking water against colon cancer. Future studies should increase the precision of the estimation of the individual's intake of calcium, both via food and water, and control for confounding factors, especially personal risk factors such as physical activity, and meat and fat consumption.

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