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CALCIUM AND MAGNESIUM IN DRINKING WATER AND RISK OF DEATH FROM RECTAL CANCER

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The possible association between the risk of rectal 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 rectal-cancer deaths (986 cases) of Taiwan residents from 1990 through 1994 were compared with a sample of deaths from other causes (986 controls), and the levels of calcium and magnesium in the 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 (TWSC). The control group consisted of people who died from other causes, and the controls were pair-matched to the cases by gender, year of birth and year of death. Compared with those with calcium levels below 22.0 mg/liter, the adjusted odd ratios (95% confidence interval) were 0.72 (0.53–0.98) for the group with water calcium levels between 22.0 and 40.8 mg/liter and 0.63 (0.45–0.87) for the group with calcium levels of 40.9 mg/liter or more. The adjusted odd ratios were not statistically significant for the relationship between magnesium levels in drinking water and rectal cancer. The results of the present study show that there may be a significant protective effect of calcium intake from drinking water on the risk of rectal cancer. *Int. J. Cancer* 77:528–532, 1998.

In Taiwan, colorectal cancer is the fourth leading cause of cancer mortality for males and females (Department of Health, Taiwan, 1995). The age-adjusted mortality rate for colorectal cancer was 11.38 per 100,000 among males and 8.48 among females in 1993. For rectal cancer alone, the mortality rate was 4.22 for males and 2.81 for females. There is substantial geographic variation in colorectal-cancer mortality within the country (Department of Health, Taiwan, 1993). Such a geographic distribution may suggest an environmental risk factor.

Dietary factors are now thought to represent important etiologic factors in the development of colorectal cancer (Doll and Peto, 1981). An increased risk of colorectal cancer has been attributed to diets high in fat and red meat and low in fruits and vegetables (Willet and MacMahon, 1984; Willet, 1989; Steinmetz and Potter, 1991; Potter *et al.,* 1993). In addition, calcium intake has been found to have a protective effect on colorectal cancer (Garland *et al.,* 1985; Sorenson *et al.,* 1988; Slattery *et al.,* 1988; Lipkin and Newmark, 1995; Kune *et al.,* 1987; Arbman *et al.,* 1992; Peters *et al.,* 1992; Lee *et al.,* 1989; Bostick *et al.,* 1993). A possible protective effect of calcium against colon carcinogenesis has been suggested by animal studies; calcium binds bile acids and fatty acids, and may thus diminish their proliferation on the colon mucosa (Wargovich *et al.,* 1983, 1984; Van der Meer and De Vries, 1985). An alternative hypothesis, based on *in vitro* studies in human epithelial cells (Buset *et al.,* 1986), suggests that calcium may 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 may protect against deaths from cancer (Durlach *et al.,* 1986, 1990). Two biologically plausible mechanisms are considered by which magnesium could prevent carcinogenesis: intracellular magnesium may enhance the fidelity of DNA replication, or magnesium may prevent changes that trigger the carcinogenic process (Blondell, 1980).

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 (Lee *et al.,* 1991). The major portion of magnesium intake is via food, and to a lesser extent via drinking water (Rubenowitz *et al.,* 1996). There are no available data for assessing the percentage contributed by drinking water to the total magnesium intake in Taiwan. Nonetheless, intake of dietary magnesium nowadays is often lower than the recommended dietary amounts of 6 mg/kg/day (Durlach, 1989). For individuals at the borderline of calcium and magnesium deficiency, waterborne calcium and magnesium may make an important contribution to their total daily intake.

We have found that there is a significant protective association between drinking-water calcium levels and colon and gastric cancer, whereas water levels of magnesium are associated with a protective effect against gastric cancer but not colon cancer (Yang *et al.,* 1997, 1998). Although cancers of the colon and rectum show some differences in their geographic and temporal distribution, it is common to discuss them together in terms of causation (Higginson *et al.,* 1992). The objective of this study was to examine the relationship between the levels of calcium and magnesium in drinking water and deaths from rectal cancer. This is one in a series of similar studies evaluating the relationship between calcium and magnesium in drinking water and risk of cancer at various sites.

MATERIAL AND METHODS

Study area

Taiwan is divided into 361 administrative districts, which will be referred to herein as municipalities. Of these, 30 aboriginal townships and 9 islets were excluded from our analyses, since their residents had substantially different life-styles and living environments. This elimination of unsuitable municipalities left 322 municipalities for analysis.

Subject selection

Data on all deaths of Taiwan residents from 1990 through 1994 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 rectal-cancer deaths occurring in people between 50 and 69 years of age [International Classification of Disease, 9th revision (ICD-9), code 154].

A control group was formed comprising all other deaths, excluding those deaths associated with gastrointestinal disease. The deaths excluded were those caused by malignant neoplasms of

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the stomach (ICD-9 code 151), small intestine, including duodenum (ICD-9 code 152), colon (ICD-9 code 153), 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 codes 578). Subjects who died from cardiovascular disease (ICD-9 codes 410–414) and cerebrovascular disease (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 (Rubenowitz *et al.,* 1996; Biorck *et al.,* 1965; Morris *et al.,* 1961; Schroeder, 1960; Leoni *et al.,* 1985; Rylander *et al.,* 1991; Yang *et al.,* 1996; Yang, 1998). Control subjects were pair-matched to the cases by gender, year of birth and year of death. Each matched control was selected randomly from the set of possible controls for each case. The most frequent causes of death among the controls were diabetes mellitus (9.3%), liver cancer (8.1%), lung cancer (8.0%), chronic liver disease and cirrhosis (7.4%), other forms of heart disease (ICD codes 420–429) (7.3%), respiratory diseases (7.0%) and diseases of the genito-urinary tract (4.6%). To be eligible, all study subjects had to have residence and place of death in the same municipality.

Calcium and magnesium levels in drinking water

Information on the levels of calcium and magnesium in each municipality's treated drinking-water supply was obtained from the Taiwan Water Supply Corporation (1991), to which each waterworks is required to submit drinking-water-quality data, including levels of calcium and magnesium. Four finished water samples, one for each season, were collected from each waterworks, after analysis by the laboratory offices of each waterworks using standard methods. Since all laboratory offices examine 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 (Yang *et al.,* 1996, 1997, 1998; Yang, 1998). The final complete data 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 (Sharrett *et al.,* 1984). 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.

Statistics

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 of death from rectal cancer in relation to the calcium and magnesium levels in the drinking water. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using the group with the lowest exposure as the reference group (Breslow and Day, 1980).

RESULTS

A total of 986 rectal-cancer deaths with complete records were collected for the period from 1990–1994. Of these, 602 (61%) were males.

The mean calcium level in the drinking water of cases was 31.4 mg/liter (SD = 19.6). Controls (n = 986) had a mean calcium exposure of 35.1 mg/liter (SD = 19.6). The mean magnesium concentrations in the drinking water were 10.3 mg/liter (SD = 7.1) and 11.2 mg/liter (SD = 7.6) for cases and controls respectively. Cases and controls alike had a mean age of 61.4. Cases lived in municipalities in which 91.4% of the population was served by a waterworks. For controls, this proportion was 89.8%. Cases had a higher rate (43.6%) of living in metropolitan municipalities than the controls (38.0%) (Table I).

Table II shows the numbers of cases and controls and OR in relation to calcium and magnesium levels in the drinking water. The OR for death from rectal cancer were significantly lower for the 2 groups with high levels of calcium in their drinking water. Adjustments for possible confounders only slightly altered the OR. There was a significant trend toward decreased rectal-cancer risk with increasing calcium levels in drinking water ($\chi^2 = 17.73$, $p < 0.0001$). The crude OR were significantly protective for the group with the highest magnesium level (0.75, 95% CI 0.61–0.94), but after adjustment 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 approach to examine the relationship between rectal-cancer mortality and calcium and magnesium levels in the drinking water in Taiwan. There was a significant protective dose-response relationship between calcium but not magnesium levels and risk of rectal cancer.

Despite their inherent limitations (Morgenstern, 1982), studies of the ecological correlation between mortality and environmental exposures have been used widely to generate or discredit epidemiological hypotheses. Before any conclusion based on such a mortality analysis is made, however, the completeness and accuracy of the death-registration system should be evaluated. Death registration in Taiwan is complete, since it is mandatory to register deaths at local household registration offices and since the household registration information is verified annually by a door-to-door survey. Although causes of death may be misdiagnosed and/or misclassified, the problem has been minimized through the improvement in verification and classification of causes of death in Taiwan since 1972. Furthermore, Taiwan is a small island with a convenient communications network, and the accessibility of medical-service facilities is comparable among study municipalities. Differences in mortality between the municipalities in this study do not appear to result from systematic differences in recording and codification.

TABLE I – CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Cases	Controls	*p* value
Total subjects	986	986	
Enrollment municipality	252	252	
Gender (%)			
male	602 (61.1)	602 (61.1)	
female	384 (38.9)	384 (38.9)	
Mean age in years (SD)[1]	61.4 ± 5.4	61.4 ± 5.4	
Mean calcium concentration (SD)	31.4 ± 19.6	35.1 ± 19.6	0.000
Mean magnesium concentration (SD)	10.3 ± 7.1	11.2 ± 7.6	0.003
Drinking water served by waterworks (%)	91.4 ± 15.8	89.8 ± 17.0	0.11
Urbanization level of residence (%)[2]			
metropolitan	430 (43.6)	375 (38.0)	
city	207 (21.0)	183 (18.6)	
town	236 (23.9)	279 (28.3)	
rural	113 (11.5)	149 (15.1)	0.03

[1]SD, standard deviation.–[2]The urbanization level of each municipality was based on the urban-rural classification scheme of Tzeng and Wu (1986).

TABLE II – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR RECTAL-CANCER DEATH, BY CALCIUM AND MAGNESIUM LEVELS IN DRINKING WATER, 1990–1994

	Number of cases	Number of controls	Crude OR[1]	Adjusted OR[2]
Calcium, mg/liter (median)				
≦20.2 (7.5)	374	288	1.00	1.00
22.0–40.8 (34.6)	311	332	0.71 (0.57–0.89)	0.72 (0.53–0.98)
40.9–79.2 (54.8)	301	366	0.63 (0.50–0.78)	0.63 (0.45–0.87)
				χ^2 for trend = 17.73
				$p < 0.0001$
Magnesium, mg/liter (median)				
≦7.0 (3.6)	340	297	1.00	1.00
7.3–11.6 (9.1)	326	320	0.89 (0.71–1.11)	1.12 (0.84–1.49)
11.8–41.3 (16.9)	320	369	0.75 (0.61–0.94)	1.11 (0.80–1.54)
				χ^2 for trend = 1.81
				$p > 0.05$

[1]OR adjusted for age and gender.–[2]Adjusted for age, gender, urbanization level of residence.

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 was reasonably high (r = 0.85). Hardness data were supplied by the Water Quality Research Center of the Taiwan Water Supply Corporation, which conducts routine water analyses to assess the suitability of water for drinking from the different water sources and at various points in the distribution system. In addition, the waterworks in each municipality received a questionnaire requesting information on any changes that had occurred in the water supply or the treatment of the water during the previous 20 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 had 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 or bias in our OR estimates (Gladen and Rogan, 1979; Polissar, 1980). 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, the decedent's family, according to social custom, always considers the death to have occurred in the municipality where he/she was born. Therefore, the decedent's residence, place of birth and place of death are likely to be listed as the same municipality, though place-of-birth information was not available for this data set. We believe that this minimized the migration problem in our data.

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 colorectal 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 (Potter *et al.,* 1993). During this period, cancer diagnosis may influence a decision to migrate and possibly introduce bias. Although data are not available for different survival rates of rectal-cancer patients in metropolitan areas and in country areas, a difference in survival rate for rectal cancer between metropolitan and country areas might tend to cause rectal-cancer patients to migrate to urban areas, leading to a spurious association. Three aspects of this study presumably minimized 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 were between the ages of 50 and 69, and it was assumed that individuals in this age group were more likely to have remained in the same residence and, therefore, that most of their lives had been spent at the address given on the death certificate.

We observed a significant protective dose-response effect of drinking-water calcium levels on the risk of rectal cancer, with OR of 0.72 and 0.63 for the 2 groups with the highest levels of calcium in their drinking water. The mean calcium concentration in Taiwan's drinking water is 33.3 mg/liter. This figure would contribute, on average, 13.1% to an individual's total dietary calcium intake, given a daily consumption of 2 liters of water. Another reason why calcium in water might play a critical role is its higher bio-availability. Calcium may be like magnesium, which in water appears as hydrated ions and is therefore more easily absorbed from water than from food (Durlach, 1989; Theophanides *et al.,* 1990).

We here report a possible protective effect of calcium intake, via drinking water, against rectal cancer, but this finding is consistent with many studies in which calcium from food and dietary supplements was measured. However, some studies have not found a protective effect from dietary calcium intakes (Tuyns *et al.,* 1988; Negri *et al.,* 1990; Freudenheim *et al.,* 1990; Benito *et al.,* 1991; Boutron *et al.,* 1996; Martinez *et al.,* 1996). The possibility that a protective effect in those studies may have been masked by unmeasured differences in calcium intakes from drinking water cannot be excluded.

In the general population, the major proportion of magnesium intake is via food, and to a lesser extent via drinking water (Rubenowitz *et al.,* 1996). No data in the present study enable assessment of the percentage that drinking water contributes to total magnesium intake. However, the average current intake of dietary magnesium is often lower than the recommended dietary amounts of 6 mg/kg/day (Durlach, 1989). 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 (Haring and Delft, 1981). Another reason why magnesium in water can play a critical role is its higher bio-availability. Magnesium in water appears as hydrated ions, which are more easily absorbed than magnesium in food (Durlach, 1989; Theophanides *et al.,* 1990). 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 (Blondell, 1980). In fact, in this study, after adjustment for calcium, magnesium intake

from drinking water was even positively, although not significantly, associated with the risk of rectal cancer, with OR of 1.12 (0.84–1.49) and 1.11 (0.80–1.54) respectively for the 2 higher magnesium levels. The reason for not finding a protective effect of magnesium on risk of rectal cancer may be because calcium and magnesium in the drinking water are highly correlated (correlation coefficient 0.66). This may create co-linearity in the regression model, making it difficult to detect an independent effect of magnesium.

Physical activity and consumption of meat and fat 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 (Rylander *et al.*, 1991).

In conclusion, the results of the present study show that drinking calcium-rich water regularly may exert a protective effect on the risk of rectal cancer. Future studies of calcium intake and rectal cancer should include estimates of calcium intake from drinking water as well as from diet and supplements.

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