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

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The possible association between the risk of kidney cancer development and the levels of calcium and magnesium in drinking water from municipal supplies was investigated in a matched cancer case-control study in Taiwan. All eligible kidney cancer deaths (1778 cases) of Taiwan residents from 1999 through 2008 were compared with deaths from other causes (1778 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 (TWSC). The control group consisted of individuals who died from other causes, and the controls were pair-matched to the cancer cases by gender, year of birth, and year of death. The adjusted odd ratios for death attributed to kidney cancer for individuals with higher calcium levels in their drinking water, as compared to the lowest tertile, were 0.89 (95% CI = 0.72–1.11) and 0.78 (95% CI = 0.62–0.98), respectively. The adjusted odd ratios were not statistically significant for the relationship between magnesium levels in drinking water and kidney cancer development. The results of the present study demonstrate that there may be a significant protective effect of calcium intake from drinking water against the risk of death due to kidney cancer.

In Taiwan, kidney cancer is the 14th leading cause of cancer mortality for males and the 13th for females (DOH, 2009). The age-adjusted mortality rate for kidney cancer was 2.5 per 100,000 among males and 2 per 100,000 among females in 2008. There is substantial geographic variation in incidence of kidney cancer mortality within the country (NHRI, 2005). This geographic distribution pattern is suggestive of the postulation that an environmental risk factor may play a role in the observed disease development.

Renal-cell cancer (RCC) represents 80–85% of all kidney cancers (Tavani & La Vecchia, 1997), and the incidence of this form of carcinoma has been increasing globally (Mathew et al., 2002). However, little is known regarding the etiology of kidney cancer. Smoking, obesity, and hypertension are the most consistently accepted causal risk factors for kidney cancer

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development (Mclaughlin & Lipworth, 2000; Lipworth et al., 2006).

The hardness of drinking water is determined predominantly by calcium and magnesium content. Drinking-water hardness is expressed as the equivalent amounts of calcium and magnesium present in water when compared to the standard known quantity of calcium carbonate. Hard water contains higher levels of calcium and magnesium than soft water.

Magnesium, which together with calcium is the main determinant of water hardness, may protect against deaths from cancer (Durlach et al., 1986, 1990). Two biologically plausible mechanisms are considered by which magnesium may prevent carcinogenesis. Intracellular magnesium may enhance the fidelity of DNA replication, or magnesium at the cell membrane may prevent changes that trigger the carcinogenic process (Blondell, 1980). It should be noted that support for these hypotheses is not yet conclusive. Wolk et al. (1996) reported that low intake of magnesium was associated with increased risk of renal-cell carcinoma development. However, this finding was not supported by other studies (Chow et al., 1994; Prineas et al., 1997). The association between calcium intake and risk of kidney cancer development was also inconclusive in previous epidemiologic studies. Two studies reported a significant protective effect of calcium intake on renal-cell carcinoma development (Prineas et al., 1997; Hu et al., 2003); one study noted a significant positive association between calcium intake and renal-cell carcinoma formation (Chou et al., 1994); and one study reported no marked relationship (Mellemgaard et al., 1996). In our previous studies, a significant protective association between drinking-water calcium levels and colorectal (Yang et al., 1997; Yang & Chiu, 1998), gastric (Yang et al., 1998), and breast cancer (Yang et al., 2000b) was noted. In contrast, a correlation between prostate (Yang et al., 2000a), ovary (Chiu et al., 2004), and esophageal cancer (Yang et al., 2002) and drinking-water calcium intake was not significant. It is of interest that water levels of magnesium are associated with a protective effect against gastric (Yang et al., 1998), breast (Yang et al., 2000b), ovary (Chiu et al., 2004), esophageal (Yang et al., 2002), and prostate cancer (Yang et al., 2000a) but not colorectal cancer (Yang et al., 1997; Yang & Chiu, 1998). The objective of this study was to examine the relationship between the levels of calcium and magnesium in drinking water and risk of death from kidney cancer.

MATERIALS AND METHODS

Study Area and Subject Selection

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

Data on all deaths of Taiwan residents from 1999 through 2008 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), was recorded on computer tapes. The cancer case group consisted of all eligible kidney cancer deaths occurring in individuals between 50 and 69 yr of age (International Classification of Disease, ninth revision [ICD-9], code 189).

A control group was formed using all other deaths excluding those deaths that were associated with malignant neoplasm of genitourinary organs (codes 179–189) and diseases of the genitourinary system (codes 580–629). Subjects who died from malignant neoplasm of esophagus (code 150) (Yang et al., 2002), stomach (code 151) (Yang et al., 1998), colon (code 153) (Yang et al., 1997), rectum (code 154) (Yang & Chiu, 1998), pancreas (code 157) (Yang et al., 1999b), breast (code 174)

(Yang et al., 2000b), ovary (code 183) (Chiu et al., 2004), and prostate (code 185) (Yang et al., 2000a) and from those who died from cardiovascular disease (codes 410–414) (Yang et al., 1996), cerebrovascular diseases (codes 430–438) (Yang, 1998), diabetes mellitus (code 250) (Yang et al., 1999a), and hypertension (codes 401–405) (Yang & Chiu, 1999) were also excluded from the control group because of previously reported negative correlations with hardness (calcium or magnesium) levels in drinking water. Control subjects 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 case. For controls, the most frequent causes of death were liver cancer (15.4%), lung cancer (12.4%), chronic liver disease and cirrhosis (9.0%), motor vehicle traffic accident of unspecified nature (4.7%), and other ill-defined and unknown causes of morbidity and mortality (2.9%).

Calcium and Magnesium Levels

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, 1991), to which 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 spectrophotometric methods, it was postulated 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. Details have already been described in earlier publications (Yang et al., 1997, 1998, 2002). The final complete dataset consisted of drinking water quality information from 252 municipalities. Hardness (calcium and magnesium) remains reasonably constant for long periods of time and is a stable characteristic of a municipality's water supply (Bell, 1984). Data collected included the annual mean levels of calcium and magnesium for the year 1990. The municipality of residence for all cancer cases and controls was identified from the death certificate and 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 (RR) in relation to the calcium and magnesium levels in 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 & Day, 1980). Coefficients whose p values were $<.05$ were considered statistically significant.

RESULTS

In total, 1778 kidney cancer cases with complete records were collected for the period 1999–2008. Of the 1778 cases, 1034 were males and 744 females. The mean calcium concentration in the drinking water of the cancer cases was 34.3 mg/L (SD = 19.7). Controls had a mean calcium exposure of 35.5 mg/L (SD = 19.7). The mean magnesium concentration in the drinking water was 11.2 mg/L (SD = 7) for cancer cases, and 11.6 mg/L (SD = 7.5) for controls. Both cancer cases and controls had a mean age of 61.7. Cancer cases lived in municipalities in which 92.7% of the population was served by a waterworks. For controls this number was 91.5%. Cancer cases had a higher rate (43.6%) of living in metropolitan municipalities than controls (38.1%) (Table 1).

TABLE 1. Characteristics of the Study Population

Characteristics	Cancer cases	Controls
Total subjects	1778	1778
Enrollment municipality	252	252
Gender (%)		
Male	1034 (58.2)	1034 (58.2)
Female	744 (41.8)	744 (41.8)
Mean age in years (SD)	61.7 ± 5.7	61.7 ± 5.7
Mean calcium concentration (mg/L) (SD)	34.3 ± 19.7	35.5 ± 19.7
Mean magnesium concentration (mg/L) (SD)	11.2 ± 7.0	11.6 ± 7.5
Drinking water served by waterworks (%)	92.7 ± 15.7	91.5 ± 16.5
Marital status (%)		
Single	84 (4.6)	112 (6.1)
Married	1463 (79.6)	1368 (74.4)
Ever married	291 (15.8)	358 (19.5)
Urbanization level of residence (%)[a]		
Metropolitan	776 (43.6)	678 (38.1)
City	382 (21.5)	346 (19.5)
Town	376 (21.2)	489 (27.5)
Rural	244 (13.7)	265 (14.9)

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

TABLE 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Kidney Cancer Death by Calcium Levels in Drinking Water, 1999–2008

	Calcium, mg/L (median)		
Parameter	≤24.0 (7.5)	24.4–42.6 (34.6)	43.0–81.0 (57.0)
Number of cancer cases	575	652	551
Number of controls	517	662	599
Crude OR[a]	1.0	0.89 (0.76–1.05)	0.83 (0.71–0.98)
Adjusted OR[b]	1.0	0.89 (0.72–1.11)	0.78 (0.62–0.98)

[a]Odds ratio adjusted for age and gender.
[b]Adjusted for age, gender, marital status, urbanization level of residence, and magnesium levels in drinking water.

Table 2 shows the numbers of cancer cases and controls and OR in relation to calcium levels in their drinking water. The crude OR for death from kidney cancer was significantly lower for the group with the highest levels of calcium (0.83, 95% CI = 0.71–0.98). Adjustments for possible confounders only slightly altered the OR. The adjusted OR (95% CI) was 0.78 (0.62–0.98) for the group with water calcium levels of 43 mg/L or greater.

The OR in relation to magnesium levels in drinking water are shown in Table 3. The crude OR were lower than 1 for the two groups with high levels of magnesium in drinking water, but this inverse association was not statistically significant. However, when adjustments were made for potential confounders, magnesium intake from drinking water was positively, although not significantly, associated with increased risk for kidney cancer development.

DISCUSSION

This investigation used a death-certificate-based cancer case-control study and a drinking-water quality ecology study to examine the relationship between mortality attributed to kidney cancer and exposure to calcium and magnesium in drinking water in Taiwan. The results of the present study showed that elevated calcium intake from drinking water may exert a protective effect on the risk of death due to kidney cancer.

TABLE 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Kidney Cancer Death by Magnesium Levels in Drinking Water, 1999–2008

	Magnesium, mg/L (median)		
Parameter	≤7.8 (3.8)	8.1–13.3 (9.3)	13.4–41.3 (17.3)
Number of cancer cases	595	596	587
Number of controls	587	594	597
Crude OR[a]	1.0	0.99 (0.84–1.16)	0.97 (0.83–1.14)
Adjusted OR[b]	1.0	1.08 (0.87–1.33)	1.21 (0.96–1.52)

[a]Odds ratio adjusted for age and gender.
[b]Adjusted for age, gender, marital status, urbanization level of residence, and calcium levels in drinking water.

Before any firm conclusion based on such a mortality analysis is made, the completeness and accuracy of the death registration system need to be evaluated. Since it is mandatory to register death certificates at local household registration offices, the death registration in Taiwan is 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, malignant neoplasms, including kidney cancer, were found to be one of the most unequivocally classified causes of death in Taiwan (Chen & Wang, 1990). Because of the fatal outcome, it is believed that all kidney cancer cases exposed to either high or low levels of calcium and magnesium in drinking water currently have access to medical care regardless of geographical location.

Data on water hardness 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 several water sources and at various points in the distribution system. No municipalities were excluded because of changes in treatment practice (e.g., the use of water softeners) during the past decade. It was felt that the hardness (calcium and magnesium) levels in drinking water remained reasonably stable. It was therefore assumed that calcium and magnesium levels in 1990 were a reasonable indicator of historical calcium and magnesium exposure concentrations in drinking water.

Migration from a municipality of high calcium and magnesium exposure to one of low calcium and magnesium exposure or vice versa might have introduced misclassification bias and bias in the OR estimates (Gladen & Rogan, 1979; Polissar, 1980). Mobility is age dependent, and diseases usually occur with a higher incidence among older groups and closer to the location of the environmental “cause” (Polissar, 1980). However, neighboring water sources tend to possess similar chemical composition, and hence even if an individual moved, the change in exposure to calcium and magnesium in drinking water would probably not be significant provided that the old and new residences were relatively close to one another, which also reduces the uncertainty created by the fact that some residents consume water at their workplaces or elsewhere. Further, all subjects used in the present study were at least 50 yr of age. It is generally presumed that the elderly are more likely to remain in the same residence for a significant portion of their life span. Furthermore, urbanization levels were included as a control variable in the analysis. Since it is conceivable that municipalities with similar urbanization levels may have similar migration rates, this probably minimized the migration issue in our study.

Since the measure of effect in this investigation was mortality rather than incidence, migration during the interval between cancer diagnosis and death also needs to be considered. During this period, cancer diagnosis may influence a decision to migrate and possibly introduce bias. Data are not available for the differences in survival rates of kidney cancer patients between high and low calcium and magnesium exposure areas. If there was a trend toward migration to more urban areas or lower calcium and magnesium exposure areas because of proximity to medical care, for example, a spurious association between calcium and magnesium exposure and death due to kidney cancer would have been noted. Three aspects of this study presumably minimized this possibility. First, migration due to kidney 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. Second, urbanization level was included as a control variable in the analysis. Finally, the subjects in the present study were between the ages of 50 and 69 yr, and it was postulated that individuals in this age group are more likely to remain in the same residence and therefore that most of their life span was spent at the address as listed on the death certificate.

A significant protective effect against kidney cancer development was correlated with calcium intake from drinking water in the group with the highest levels of elemental intake, suggesting that only subjects with calcium intake via drinking water above a certain threshold received a beneficial effect with respect to risk of kidney cancer development. This finding is in agreement with previous studies in which calcium from food and dietary supplements was measured and shown to protect against renal carcinogenesis (Prineas et al., 1997; Hu et al., 2003). Epidemiologic studies reported that dietary calcium is inversely associated with blood pressure (McCarron et al., 1982, 1984; Ackley et al., 1983). In a meta-analysis, Cappuccio et al. (1995) showed that high dietary calcium intake lowered blood pressure. Dietary calcium is the main source of calcium intake; thus, it would seem reasonable to expect that intake of dietary calcium could reduce the risk of kidney cancer development, which is commonly associated with hypertension. In Taiwan, the mean daily intake of dietary calcium is 507 mg. This value is only 81.9% of the recommended daily intake (Lee et al., 1991). One may postulate that waterborne calcium may provide 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/L. This value would contribute, on average, 13.1% to an individual's total dietary calcium intake, given a daily consumption of 2 L water. Another reason why calcium in water might play a critical role is its higher bioavailability. Calcium may be similar to magnesium, which in water appears as hydrated ions and therefore is more easily absorbed from water than from food (Durlach, 1989; Theophanides et al., 1990). Our study appears to be the first investigation to report a possible protective effect of calcium intake via drinking water against kidney cancer development.

In the general population, the major portion of magnesium intake is via food, and to a lesser extent drinking water (Rubenowitz et al., 1996). 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 amounts of 6 mg/kg/d (Durlach, 1989). For individuals at the borderline of magnesium deficiency, waterborne magnesium is an important contribution to their total intake. In addition, the loss of magnesium from food is lower when food is cooked in magnesium-rich water (Haring & Delft, 1981). Another reason why magnesium in water may play a critical role is its higher bioavailability. 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 individuals who drink water with high magnesium levels could thus be crucial in the prevention of magnesium deficiency. Our results do not support the notion that magnesium exerts a protective effect against cancer development (Blondell, 1980). In fact in this study, magnesium intake from drinking water was positively, although not significantly, associated with higher risk of kidney cancer development, with an OR of 1.08 (0.87–1.33) and 1.21

(0.96–1.52), respectively, for the two higher magnesium levels. The reason for not finding a protective effect of magnesium on risk of kidney cancer development may be due to the fact that calcium and magnesium in drinking water are highly correlated (correlation coefficient is .68). This may create collinearity in the regression model, making it difficult to detect an independent effect of magnesium.

Smoking, obesity, and hypertension 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 demonstrate that drinking calcium-rich water regularly may exert a protective effect against development of kidney cancer. Future studies should increase the precision of the estimation of the individual's intake of calcium, via both food and water, and control for confounding factors, especially personal risk factors such as smoking, obesity, and hypertension, in attempting to correlate renal cancer risk development with drinking-water calcium and magnesium.

REFERENCES

Ackley, S., Barrett-Connor, E., and Suarez, L. 1983. Dairy products, calcium and blood pressure. *Am. J. Clin. Nutr*. 38:457–461.

Bell, J. A. 1984. *Drinking water and human health*. Chicago: American Medical Association.

Blondell, J. M. 1980. The anticarcinogenic effect of magnesium. *Med. Hypoth*. 6:863–871.

Breslow, N. E., and Day, N. E. 1980. *Statistical methods in cancer research*, vol. I, *The analysis of case-control studies*. Lyon: International Agency for Research on Cancer.

Cappuccio, F., Elliot, P., Allender, P. S., Pryer, P. A., and Cutler, J. A. 1995. Epidemiologic association between dietary calcium intake and blood pressure: A meta-analysis of published data. *Am. J. Epidemiol*. 142: 935–945.

Chen, C. J., and Wang, C. J. 1990. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res*. 50:5470–5474.

Chiu, H. F., Chang, C. C., and Yang, C. Y. 2004. Magnesium and calcium in drinking water and risk of death from ovarian cancer. *Magnesium Res*. 17:28–34.

Chou, W. H., Gridley, G., McLaughlin, J. K., Mandel, J. S., Wacholder, S., Blot, W. U., Niwa, S., and Fraumeni, J. F. 1994. Protein intake and risk of renal cell cancer. *JNCI* 86:1131–1139.

Department of Health, Taiwan. 2009. *Statistics of causes of death*. Taipei: DOH.

Durlach, J. 1989. Recommended dietary amounts of magnesium: Mg RDA. *Magnesium Res*. 2:195–203.

Durlach, J., Bara, M., Guiet-Bara, M., and Colley, P. 1986. Relationship between magnesium, cancer and carcinogenic or anti-cancer metals. *Anticancer Res*. 6:1353–1362.

Durlach, J., Bara, M., and Guiet-Bara, A. 1990. Magnesium and its relationship to oncology. *Metal Ions Biol. Systems* 26:549–578.

Gladen, B., and Rogan, W. 1979. Misclassification and the design of environmental studies. *Am. J. Epidemiol*. 109:607–616.

Haring, B. S., and Delft, V.W. 1981. Changes in the mineral composition of food as a result of cooking in hard and soft waters. *Arch. Environ. Health* 36:33–35.

Hu, J., Mao, Y., and White, K. 2003. Diet and vitamin or mineralsupplements and risk of renal cell carcinoma in Canada. *Cancer Causes Control* 14:705–714.

Lee, N. Y., Chu, Y. C., Chang, C. P., Shieh, M. J., and Kao, M. D. 1991. Dietary survey in Taiwan area, 1986–1988. *J. Chin. Nutr. Soc*. 16:39–60.

Lipworth, L., Tarone, R. E., and McLaughlin, J. K. 2006. The epidemiology of renal cell carcinoma. *J. Urol*. 176:2353–2358.

Mathew, A., Devesa, S. S., Fraumeni, J. F., and Chow, W. H. 2002. Global increases in kidney cancer incidence, 1973–1992. *Eur. J. Cancer Prev*. 11:171–178.

McCarron, D., Morris, C., and Cole, C. 1982. Dietary calcium in human hypertension. *Science* 217:267–269.

McCarron, D., Morris, C., Holly, J., and Stanton, J. 1984. Blood pressure and nutrient intake in the United States. *Science* 224:1392–1398.

McLaughlin, J. K., and Lipworth, L. 2000. Epidemiologic aspects of renal cell cancer. *Semin. Oncol*. 27:115–123.

Mellemgaard, A., McLaughlin, J. K., Overvad, K., and Olsen, J. H. 1996. Dietary risk factors for renal cell carcinoma in Denmark. *Eur. J. Cancer* 4:673–682.

National Health Research Institutes. 2005. *Atlas of health in Taiwan*. Taipei: NHRI.

Polissar, L. 1980. The effect of migration on comparison of disease rates in geographic studies in the United States. *Am. J. Epidemiol.* 111:175–182.

Prineas, R. J., Folsom, A. R., Zhang, Z. M., Sellers, T. A., and Potter, J. 1997. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. *Epidemiology* 8:31–36.

Rubenowitz, E., Axelsson, G., and Rylander, R. 1996. Magnesium in drinking water and death from acute myocardial infarction. *Am. J. Epidemiol*. 143:456–462.

Rylander, R., Bonevik, H., and Rubenowitz, E. 1991. Magnesium and calcium in drinking water and cardiovascular mortality. *Scand. J. Work Environ. Health* 17: 91–94.

Taiwan Water Supply Corporation. 1991. *The statistical data of water quality Taiwan*. Taichung: TWSC.

Tavani, A., and La Vecchia, C. 1997. Epidemiology of renal cell carcinoma. *J. Nephrol*. 10:93–106.

Theophanides, T., Angiboust, J. F., and Polissiou, M. 1990. Possible role of water structure in biological magnesium systems. *Magnesium Res*. 3:5–13.

Tzeng, G. H., and Wu, T. Y. 1986. Characteristics of urbanization levels in Taiwan districts. *Geograph. Res*. 12:287–323.

Wolk, A., Gridley, G., Niwa, S., Lindblad, P., McCredie, M., Mellemgaard, A., Mandel, J. S., Wahrendorf, J., McLaughlin, J. K., and Adami, H. O. 1996. International renal cell cancer study. VII. Role of diet. *Int. J. Cancer* 65:67–73.

Yang, C. Y. 1998. Calcium and magnesium in drinking water and risk of death cerebrovascular disease. *Stroke* 29: 411–414.

Yang, C. Y., and Chiu, H. F. 1998. Calcium and magnesium in drinking water and risk of death from rectal cancer. *Int. J. Cancer* 77:528–532.

Yang, C. Y., and Chiu, H. F. 1999. Calcium and magnesium in drinking water and the risk of death from hypertension. *Am. J. Hypertens*. 12:894–899.

Yang, C. Y., Chiu, J. F., Chiu, H. F., Wang, T. N., Lee, C. H., and Ko, Y. C. 1996. Relationship between water hardness and coronary mortality in Taiwan. *J. Toxicol. Environ. Health* 49:1–9.

Yang, C. Y., Chiu, H. F., Chiu, J. F., Tsai, S. S., and Cheng, M. F. 1997. Calcium and magnesium in drinking water and risk of death from colon cancer. *Jpn. J. Cancer Res*. 88:928–933.

Yang, C. Y., Cheng, M. F., Tsai, S. S., and Hsieh, Y. L. 1998. Calcium, magnesium, and nitrate in drinking water and gastric cancer mortality. *Jpn. J. Cancer Res*. 89: 124–130.

Yang, C. Y., Chiu, H. F., Cheng, M. F., Tsai, S. S., Hung, C. F., and Tseng, Y. T. 1999a. Magnesium in drinking water and the risk of death from diabetes mellitus. *Magnesium Res*. 12:131–137.

Yang, C. Y., Chiu, H. F., Cheng, M. F., Tsai, S. S., Hung, C. F., and Tseng, Y. T. 1999b. Pancreatic cancer mortality and total hardness in Taiwan's drinking water. *J. Toxicol. Environ. Health A* 56:361–369.

Yang, C. Y., Chiu, H. F., Tsai, S. S., Cheng, M. F., Lin, M. C., and Sung, F. C. 2000a. Calcium and magnesium in drinking water and the risk of death from prostate cancer. *J. Toxicol. Environ. Health A* 60:17–26.

Yang, C. Y., Chiu, H. F., Cheng, B. H., Hsu, T. Y., Cheng, M. F., and Wu, T. N. 2000b. Calcium and magnesium in drinking water and the risk of death from breast cancer. *J. Toxicol. Environ. Health A* 60: 231–241.

Yang, C. Y., Chiu, H. F., Tsai, S. S., Wu, T. N., and Chang, C. C. 2002. Magnesium and calcium in drinking water and the risk of death from esophageal cancer. *Magnesium Res*. 15:215–222.