Calcium and magnesium in drinking-water and risk of death from lung cancer in women

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Abstract. The possible association between the risk of lung cancer in women and the levels of calcium (Ca) and magnesium (Mg) in drinking-water from municipal supplies was investigated in a matched, case-control study in Taiwan. All eligible female lung cancer deaths (3,532 cases) of Taiwan residents, from 2000 through to 2008, were compared with deaths from other causes (3,532 controls), and the levels of Ca and Mg in drinking-water of these residents were determined. Data on Ca and Mg 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 sex, year of birth, and year of death. The adjusted odd ratios were not statistically significant for the relationship between Ca levels in drinking-water and lung cancer in women. The adjusted odd ratios for female lung cancer deaths for those with higher Mg levels in their drinking-water, as compared to the lowest tertile, were 0.82 (95% CI = 0.72-0.93) and 0.80 (95% CI = 0.69-0.93), respectively. The results of the present study show that there is a significant trend toward a decreased risk of lung cancer in women with increasing Mg levels in drinking-water.

Key words: lung cancer, drinking-water, calcium, magnesium, epidemiology

In Taiwan, lung cancer is the second leading cause of cancer mortality for males and the leading cause for females [1]. The age-adjusted mortality rate for lung cancer was 36.5 per 100,000 among males and 16.5 among females in 2008. There is substantial geographic variation in lung cancer mortality within the country [2]. Such a geographic distribution may suggest an environmental risk factor. The hardness of drinking-water is determined largely by its calcium (Ca) and magnesium (Mg) content. It is expressed as the equivalent amount of calcium carbonate that could be formed from the Ca and Mg in solution. Hard water contains higher levels of Ca and Mg than soft water. Mg, which together with Ca is the main determinant of water hardness, may protect against deaths from cancer [3, 4]. Two biologically

To cite this article: Cheng MH, Chiu HF, Tsai SS, Chen CC, Yang CY. Calcium and magnesium in drinking-water and risk of death from lung cancer in women. Magnes Res 2012; 25(3): 112-9 doi:10.1684/mrh.2012.0318
plausible mechanisms are considered by which Mg could prevent carcinogenesis. Intracellular Mg may enhance the fidelity of DNA replication or Mg on the cell membrane may prevent changes which trigger the carcinogenic process [5]. Nevertheless, support for these hypotheses is not yet widespread. There are sparse data regarding Mg intake and lung cancer risk. One study reported a protective effect of dietary Mg intake on lung cancer risk [6]; a second study reported a significant positive association between dietary Mg intake and lung cancer risk [7]; and a third study reported a statistically insignificant inverse association [8].

The association between Ca intake and lung cancer risk was also inconclusive in previous epidemiological studies. One study reported a significant, positive association between Ca intake and lung cancer risk [9]. However, two studies did not show any protective effect against lung cancer [8, 10].

The well-established evidence that cigarette smoking is a strong causal risk factor for lung cancer in women has been reviewed elsewhere (Ernster, 1996). However, most of the female lung cancer patients in Taiwan were nonsmokers [11]. The proportion of female lung cancer patients who smoked was less than 10% [12]. Further, recent data from the National Health Interview Survey in 2001 showed that the prevalence smoking was 4.2% for females [13]. We believe that the Taiwanese female population is an appropriate group for studies designed to investigate the relationship between the levels of Ca and Mg in drinking-water and the risk of death from lung cancer because of the very low prevalence of smoking. We have previously used this population to assess the relationship between the effect of air pollution and lung cancer [14-16].

The objective of this study was to study the relationship between the levels of Ca and Mg in drinking-water and risk of death from lung cancer in women.

Materials and methods

Study area and subject selection

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 nine 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 2000 through to 2008 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health that 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. The case group consisted of all eligible female lung cancer deaths occurring in individuals between 50 and 69 years of age (International Classification of Disease, ninth revisions [ICD-9], code 162). We excluded patients younger than age 50 because the characteristics of early-onset lung cancer are thought to be different from the more prevalent later-onset lung cancer. We excluded lung cancer cases older than age 70 because of the difficulty in obtaining matched control subjects for them. Controls were drawn from all other deaths excluding deaths due to neoplasms and diseases that were associated with respiratory problems ([ICD-9] codes 010-018 and 460-519). 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 main objective of the present study was to assess the effects, if any, of exposure to Ca or Mg in drinking-water on female lung cancer risk. In order to avoid possible confounding by occupational exposure, all analyses were restricted to cases and controls who were reported to be housewives on their death certificates. Figure 1 illustrates a flowchart of study subject selection.

For controls, the most frequent causes of death were diabetes mellitus (19.1%), chronic liver disease and cirrhosis (7.8%), intracerebral hemorrhage (5.4%), motor vehicle traffic accident of unspecified nature (5.2%).

Calcium and magnesium levels

Information on the levels of Ca and Mg in each municipality’s treated drinking-water supply was obtained from the Taiwan Water Supply Corporation [17], to whom each waterworks is
required to submit drinking-water quality data, including the levels of Ca and Mg. Four 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 Ca and Mg levels on a routine basis using spectrophotometric method, 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 [18-20]. The final, complete data consisted of drinking-water quality data from 252 municipalities. Hardness (Ca and Mg levels) remains reasonably constant for long periods of time and is a quite stable characteristic of a municipality’s water supply [21]. Data collected included the annual mean levels of Ca and Mg for the year 1990. We assumed that Ca and Mg levels in 1990 were a reasonable indicator of historical Ca and Mg exposure levels from drinking-water. 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 Ca and Mg exposure via drinking-water. The levels of Ca and Mg of that municipality were used as an indicator of exposure to hardness for an individual residing in that municipality.
Statistics

In the analysis, the subjects were divided into tertiles according to the levels of Ca and Mg in their drinking-water. Conditional logistic regression was used to estimate the relative risk in relation to the Ca and Mg levels in drinking-water. Odds ratio and their 95% confidence intervals (95% CIs) were calculated using the group with the lowest exposure as the reference group [22]. Coefficients whose P-values < 0.05 were considered statistically significant.

Results

A total of 3,532 female lung cancer cases with complete records were collected for the period from 2000-2008. The mean Ca concentration in the drinking-water for the cases was 32.9 mg/L (SD = 19.7). Controls had a mean Ca exposure of 35.6 mg/L (SD = 19.6). The mean Mg concentration in the drinking-water was 10.9 mg/L (SD = 7.2) for the cases, and 11.7 mg/L (SD = 7.6) for the controls. Both cases and controls had a mean age of 57.7. Cases lived in municipalities in which 92.9% of the population was served by a waterworks. For controls this number was 90.7%. Cases had a higher rate (46.4%) of living in metropolitan municipalities than the controls (38.1%) (table 1).

The crude ORs were significantly lower than 1.0 for the two groups with high levels of Ca in drinking-water, but when adjustment was made for potential confounders there was no difference between the groups with different levels of Ca (table 2).

After adjustment for potential confounders including age, sex, marital status, urbanization level of residence, and calcium levels in drinking-water, the adjusted ORs (95% CI) were 0.82 (0.72-0.93) for the group with water Mg levels between 8.3 and 14.1 mg/L and 0.80 (0.69-0.93) for the group with Mg levels of 14.3 mg/L or more.

Table 1. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>3,532</td>
<td>3,532</td>
</tr>
<tr>
<td>Enrollment municipality</td>
<td>252</td>
<td>252</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>57.7 ± 4.5</td>
<td>57.7 ± 4.5</td>
</tr>
<tr>
<td>50-54</td>
<td>1,004 (28.4%)</td>
<td>1,004 (28.4%)</td>
</tr>
<tr>
<td>55-59</td>
<td>1,137 (32.2%)</td>
<td>1,137 (32.2%)</td>
</tr>
<tr>
<td>60-64</td>
<td>1,315 (37.2%)</td>
<td>1,315 (37.2%)</td>
</tr>
<tr>
<td>65-69</td>
<td>76 (2.2%)</td>
<td>76 (2.2%)</td>
</tr>
<tr>
<td>Mean water calcium concentration mg/L (mean ± SD)</td>
<td>32.9 ± 19.7</td>
<td>35.6 ± 19.6</td>
</tr>
<tr>
<td>Mean water magnesium concentration mg/L (mean ± SD)</td>
<td>10.9 ± 7.2</td>
<td>11.7 ± 7.6</td>
</tr>
<tr>
<td>Drinking-water served by waterworks (%)</td>
<td>92.9 ± 16.2</td>
<td>90.7 ± 18.0</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>32 (0.9%)</td>
<td>14 (0.4%)</td>
</tr>
<tr>
<td>Married</td>
<td>2,798 (79.2%)</td>
<td>2,565 (72.6%)</td>
</tr>
<tr>
<td>ever married</td>
<td>702 (19.9%)</td>
<td>953 (27.0%)</td>
</tr>
<tr>
<td>Urbanization level of residence (%)b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metropolitan</td>
<td>1,637 (46.4%)</td>
<td>1,346 (38.1%)</td>
</tr>
<tr>
<td>city</td>
<td>803 (22.7%)</td>
<td>832 (23.6%)</td>
</tr>
<tr>
<td>town</td>
<td>745 (21.1%)</td>
<td>891 (25.2%)</td>
</tr>
<tr>
<td>rural</td>
<td>347 (9.8%)</td>
<td>463 (13.1%)</td>
</tr>
</tbody>
</table>

a) SD: standard deviation.

b) The urbanization level of each municipality was based on the urban-rural classification scheme of Tzeng and Wu [41].
Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for female lung cancer death by calcium levels in drinking-water, 2000-2008.

<table>
<thead>
<tr>
<th>Calcium, mg/L (median)</th>
<th>(\leq 24.4) (14.9)</th>
<th>25.1-43.0 (34.8)</th>
<th>43.3-81.0 (57.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1,537</td>
<td>963</td>
<td>1,032</td>
</tr>
<tr>
<td>No. of controls</td>
<td>1,335</td>
<td>1,063</td>
<td>1,134</td>
</tr>
<tr>
<td>Crude odds ratio(^a)</td>
<td>1.0</td>
<td>0.78 (0.69-0.87)</td>
<td>0.78 (0.70-0.88)</td>
</tr>
<tr>
<td>Adjusted odds ratio(^b)</td>
<td>1.0</td>
<td>0.99 (0.85-1.14)</td>
<td>0.95 (0.81-1.10)</td>
</tr>
</tbody>
</table>

\(^a\) Odds ratio adjusted for age and sex.
\(^b\) Adjusted for age, sex, marital status, urbanization level of residence, and magnesium levels in drinking-water.

Table 3. Odds ratios (ORs) and 95% confidence interval (CIs) for female lung cancer death by magnesium levels in drinking-water, 2000-2008.

<table>
<thead>
<tr>
<th>Magnesium, mg/L (median)</th>
<th>(\leq 8.2) (3.8)</th>
<th>8.3-14.1 (9.3)</th>
<th>14.3-41.3 (17.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1,461</td>
<td>1,064</td>
<td>1,007</td>
</tr>
<tr>
<td>No. of controls</td>
<td>1,243</td>
<td>1,126</td>
<td>1,163</td>
</tr>
<tr>
<td>Crude odds ratio(^a)</td>
<td>1.0</td>
<td>0.80 (0.72-0.90)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Adjusted odds ratio(^b)</td>
<td>1.0</td>
<td>0.82 (0.72-0.93)</td>
<td>0.80 (0.69-0.93)</td>
</tr>
</tbody>
</table>

\(^a\) Odds ratio adjusted for age and sex.
\(^b\) Adjusted for age, sex, marital status, urbanization level of residence, and calcium levels in drinking-water.

\[X^2\] for trend = 28.93, \(p < 0.0001\) 

There was a significant trend toward a decreased female lung cancer risk with increasing Mg levels in drinking-water (\(X^2 = 28.93, p < 0.0001\)) (table 3).

**Discussion**

We have used a death certificate-based, case-control approach to examine the relationship between risk of death from lung cancer in women and Ca and Mg levels in drinking-water. There was a significant, protective, dose-response relationship between Mg, but not Ca levels and the risk of death from lung cancer in women.

Because it is mandatory to register death certificates at local household registration offices, the mortality statistics in Taiwan are considered to be highly accurate and complete [23]. Migration from a municipality of high Ca and Mg exposure to one of low Ca and Mg exposure or *vice versa* could have introduced misclassification bias and bias in the odds ratio estimate [24, 25]. Mobility is age-dependent, and diseases usually occur with a higher incidence among older groups and closer to the location of the environmental “cause” [25]. However, neighboring water sources tend to have similar chemical composition, and hence even if an individual had moved, the change in exposure to Ca and Mg 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 years of age. It is generally assumed 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 problem in our study.

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. Lung cancer has been reported
to have the worst five-year survival rate of all cancer sites [26]. During this period, the diagnosis of cancer may influence the decision to move and possibly introduce bias. Data are not available for the differences in survival rates of lung cancer patients between high and low Ca and Mg exposure areas. If there were a trend toward migration to more urban areas or lower Ca and Mg exposure areas because of proximity to medical care, for example, a spurious association between Ca and Mg exposure and female lung cancer death would result. Three aspects of this study presumably minimized this possibility. First, migration due to lung cancer diagnosis would be less likely for married females (about 79% of cases and 73% of controls were married), since for this cohort of decedents the spouse’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 ages for both cases and controls were between 50 and 69, and it was 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.

We observed a significant, protective, dose-response effect of drinking-water Mg levels on the risk of lung cancer in women, with an OR of 0.82 and 0.80 for the two groups with the highest levels of Mg in their drinking-water. This finding is consistent with a previous study in which Mg from food was measured [6]. Our study, however, appears to be the first investigation to report a possible protective effect of Mg intake via drinking-water against lung cancer in women. The potential mechanisms by which Mg may protect against lung cancer include its role in maintaining genetic stability [27], regulation of cell proliferation [28], and protection against inflammation [29, 30] and oxidative stress [31].

In the general population, the major portion of Mg intake is via food, and to a lesser extent via drinking-water [32]. There are no data available in the present study for assessing the percentage that drinking-water contributes to the total Mg intake. Nonetheless, in the modern-day world, intake of dietary Mg is often lower than the recommended amounts of 350 mg/day [33]. If the mean daily dietary intake of Mg is 280 mg/day (80% of the recommended dietary amounts) in Taiwan, and assuming that people drank an average of 2 L of water per day, the percentage of the Mg contribution for residents in areas with the highest water Mg levels (median, 17.4 mg/L) is about 12.43% (34.8/280). The percentages are 6.64% (18.6/280) for the group residing in areas with water Mg levels between 8.3 and 14.1 mg/L (median, 9.3 mg/L) and 2.71% (7.6/280) for the group in areas with water Mg levels of 8.2 mg/L or less (median, 3.8 mg/L). The relative contribution of water Mg would be even more important for persons with lower dietary intakes of Mg.

The question has been raised of how the relatively small intake of Mg via water, about 10% of the intake, can have a critical significance to the amount of Mg in the body. However, a review which dealt with waterborne Mg at a level of about 10% of the total daily Mg intake supported this hypothesis [34]. It may be that Mg in water, which occurs as hydrated ions, is more easily absorbed than Mg in food [33, 35]. It is also possible that waterborne Mg could correct insufficient dietary Mg levels [36]. In addition, the loss of Mg from food is lower when the food is cooked in Mg-rich water [37]. Nutritionists and pharmacologists should conduct studies using quantitative pharmacokinetic models to examine how waterborne Mg could have such a marked effect when it constitutes only a small percentage of total intake [34].

Cigarette smoking has been documented as the most important risk factor for lung cancer [26]. There is unfortunately no information available on individual smoking habits and thus it could not be adjusted for in the analysis. However, there is no reason to believe that there would be any correlation between this variable and the levels of Mg in drinking-water. Furthermore, as mentioned earlier, the prevalence of smoking in females is very low in Taiwan. We think that the degree to which not controlling for this variable may have affected our results is small, if it existed at all.

There are other risk factors, not included in this study, which may play a role in the etiology of lung cancer, such as passive smoking [38] and radon [39, 40]. To our knowledge, radon is of no relevance in the Taiwan area. Moreover, there is no reason to believe that there would be any correlation between these risk factors and the levels of Mg in drinking-water. It is postulated that the degree to which not controlling for these variables may have affected our results is negligible.

Inherent in this study design were the assumptions that cases and controls were exposed to Ca and Mg associated with the “usual place of residence” recorded on the death certificate and that
these individuals spent most of their daily life in the residential municipality. The probability that these assumptions were true was maximized by the imposition of two sample restrictions. First, males were eliminated from the sample. For this cohort of decedents (2000-2008), males were more likely to have been employed outside the residential municipality than were females and thus to have had significant Ca and Mg intake from drinking-water outside their usual residential municipality. Second, females with occupations outside the home were not included in this study and thus a confounding effect of occupational exposure is unlikely. For this cohort of decedents, housewives were thus likely to have had Ca and Mg intake via drinking-water only from their residential municipality.

In conclusion, the results of the present study show that there is a significant trend toward a decreased risk of lung cancer in women with increasing Mg levels in drinking-water. Future studies should increase the precision of the estimation of an individual’s intake of Mg, both via food and water, and control for confounding factors, especially personal risk factors such as smoking and passive smoking.

Disclosure

Financial support: This study was partly supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-100-2314-B-037-023-MY2). Conflict of interest: none.

References


