Colon cancer and content of nitrates and magnesium in drinking water

Hui-Fen Chiu¹, Shang-Shyue Tsai², Trong-Neng Wu³,⁴, Chun-Yuh Yang⁴,⁵

¹ Department of Pharmacology, Kaohsiung Medical University, Kaohsiung; ² Department of Health Care Administration, I-Shou University, Kaohsiung County; ³ Graduate Institute of Environmental Health, China Medical University, Taichung; ⁴ Division of Environmental Health and Occupational Medicine, National Health Research Institute, Miaoli; ⁵ Institute of Public Health, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan

Correspondence: C.-Y. Yang, Institute of Public Health, College of Health Sciences, Kaohsiung Medical University, 100 Shih-Chuan 1st RD, Kaohsiung, Taiwan 80708
<chunyuh@kmu.edu.tw>

Abstract. The objective of this study was to explore whether magnesium levels (Mg) in drinking water modify the effects of nitrate on colon cancer risk. A matched case-control study was used to investigate the relationship between the risk of death from colon cancer and exposure to nitrate in drinking water in Taiwan. All colon cancer deaths of Taiwan residents from 2003 through 2007 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Controls were deaths from other causes and were pair-matched to the cases by gender, year-of-birth, and year-of-death. Information on the levels of nitrate-nitrogen (NO₃-N) and Mg in drinking water were collected from Taiwan Water Supply Corporation (TWSC). The municipality of residence for cases and controls was assumed to be the source of the subject’s NO₃-N and Mg exposure via drinking water. The results of our study show that there is a significant trend towards an elevated risk of death from colon cancer with increasing nitrate levels in drinking water. Furthermore, we observed evidence of an interaction between drinking water NO₃-N and Mg intake via drinking water. This is the first study to report effect modification by Mg intake from drinking water on the association between NO₃-N exposure and colon cancer risk.

Keywords: nitrate, drinking water, magnesium, colon cancer, effect modification

Nitrates in drinking water originate from numerous natural and man-made sources, including waste waters and agricultural and urban runoff. Nitrogen fertilizer is the largest contributor to anthropogenic nitrogen globally and has been implicated as an even more important source of drinking water nitrate in rural areas [1]. The U.S. Environmental Protection Agency (EPA) has established a maximum contaminant level (MCL) in drinking water of 10 mg/L as nitrate-N to protect infants from developing methemoglobinemia [2]. However, the effectiveness of this regulatory limit for preventing other health risks such as cancer has not been adequately studied [3].

Nitrates may act as a pro-carcinogen, interacting with amines and amides in the stomach to form a variety of N-nitroso compounds (NOC) (nitrosation), most of which are potent animal carcinogens [4], after the reduction of nitrate to nitrite in saliva [5]. Several studies support a direct relationship between nitrate intake and the endogenous formation of NOC. High nitrate levels in drinking water have been associated with increased excreted N-nitrosoproline levels in urine [6, 7]. Nitrate administered via drinking water was shown to be directly correlated with concentration of total NOC in feces [8]. In addition, populations with high rates of esophageal, gastric and nasopharyngeal cancer excrete high levels of N-nitrosoproline [9-11].
These results demonstrate a contribution of drinking water nitrates in nitrosation and suggest that nitrate intake may be used as a surrogate for exposure to target tissues to NOC [3].

NOC are potent animal carcinogens, inducing tumors at multiple organ sites including the colon [2, 12]. NOC were shown to produce tumors in several animal species tested, and it is likely that humans are also affected [2, 13]. However, few epidemiologic studies have been conducted to address the association of nitrates in drinking water with cancer risk and most of these studies focused on gastric cancer, with mixed results [14-17].

Our hypothesis is derived from animal experiments in which rats [18] and hamsters [19] had higher rates of intestinal tumors after administration of NOC either in drinking water or by injection. Given the biological plausibility for a role of NOC in the risk of development of colon cancer and widespread exposure to nitrates in the population, there is a surprising deficit of epidemiologic data concerning the possible association of nitrates in drinking water with colon cancer. One ecologic study conducted in Slovakia found a positive association between drinking water nitrates and colon cancer rates [16]. Other ecologic studies reported no association with colon cancer [20-22]. A prospective cohort study of Iowa women found that municipal drinking water nitrate levels were associated with an elevated risk of colon cancer that did not consistently increase with exposure [23]. De Roos et al. [3] conducted a case-control study in Iowa. No association of colon cancer with measures of nitrates in public water supplies, including average nitrate levels and the number of years with elevated average nitrate levels, was observed. However, a positive association was observed in a subpopulation of high meat or low vitamin C consumers [3]. From a case-control study conducted in Wisconsin women, McElroy et al. [24] reported that nitrate exposure from drinking water was not significantly associated with colorectal cancer risk overall. However, a 2.9-fold increased risk of proximal colon cancer was observed [24].

Magnesium (Mg) plays an important role in genomic stability, DNA repair, modulating cell proliferation, cell cycle progression, and cell differentiation [25, 26]. Mg supplementation has been demonstrated to reduce colon cancer risk in animal experiments [27]. However, there are only a few epidemiologic studies investigating the relationship between Mg intake and colon cancer risk. A Swedish cohort study reported an inverse association between dietary Mg intake and colon cancer risk in women [26]. In the Iowa women's cohort study, an inverse association of dietary Mg intake with colon cancer was found [28]. However, a recent Netherlands cohort study reported no relationship [29]. No previous studies have explored whether Mg levels in drinking water modify the association between NO3-N exposure and colon cancer. If a substantial effect modification by Mg levels in drinking water exists, the true magnitude of the association between NO3-N exposure and colon cancer may be obscured. Furthermore, better knowledge of the modifying factors will help in public policy making, risk assessment, and standard setting.

The objective of this study was to explore whether Mg levels in drinking water modify the effect of NO3-N on colon cancer risk.

Materials and methods

Study Area

Taiwan is divided into 361 administrative districts, which will be referred to herein as municipalities. Excluded from the analysis were 30 aboriginal townships and 9 islets which had different lifestyles and living environments (the diets of people in these municipalities are generally rich in fiber, antioxidants, and nitrosation inhibitors, which may yield beneficial properties and act in a way against colon carcinogenesis). This elimination of unsuitable municipalities yielded 322 municipalities.

In Taiwan, water sources are mostly (59.3%) drawn directly from rivers; the rest comes from groundwater and reservoirs, accounting for 21.7% and 19%, respectively [30]. The current Taiwan water system is rather simple. Residents obtain their drinking water either from the public drinking water supply systems served by the Taiwan or Taipei Water Supply Corporation or from non-municipal sources. The major sources of municipal water supplies are predominantly surface waters (78.3%) and are treated with chlorine. The non-municipal sources are mainly privately owned wells (groundwater) and are not chlorinated [31]. Chlorination, the major strategy for the disinfection of drinking water in Taiwan, is currently added to approximately 92.04% of the nation’s drinking water.

Socioeconomic factors

Each municipality in Taiwan was assigned to a degree-of-urbanization category from 1 to 8, based
on the urban-rural classification of Tzeng and Wu [32], which takes into account variables such as population density, age composition, economic activity and family income, educational level, environment, and health service-related facilities. A municipality with the highest urbanization score, such as the Taipei metropolitan area, was classified in category 1, whereas mountainous areas with the lowest score were assigned to category 8. The urbanization index used in this study serves as a proxy for a large number of explanatory variables such as socioeconomic status and differential exposures to environmental conditions, which are related to the etiology of mortality. For the analyses, the urban-rural classification was further divided into 4 levels: I, metropolitan (categories 1 and 2); II, city (categories 3 and 4); III, town (categories 5 and 6); and IV, rural (categories 7 and 8).

Subject selection

Data on all deaths of Taiwan residents from 2003 through 2007 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 colon cancer deaths occurring in subjects between 50 and 69 years of age (International Classification of Disease, ninth revisions [ICD-9], code 153). In all, 3,707 colon cancer deaths with complete records satisfied this criterion.

The control group consisted of all other deaths excluding those deaths which were associated with gastrointestinal diseases. The deaths excluded were those caused by malignant neoplasms of stomach (code 151), malignant neoplasm of small intestine, including duodenum (code 152), malignant neoplasm of colon (code 153), malignant neoplasm of rectum, rectosigmoid junction and anus (code 154), gastric ulcer (code 531), duodenal ulcer (code 532), peptic ulcer, site unspecified (code 533), gastrojejunal ulcer (code 534), and gastrointestinal hemorrhage (code 578). Subjects who died from bladder [23, 33], lung [34], esophagus [14, 35, 36], liver [37], head and neck [38, 39] cancers, and non-Hodgkin lymphoma (NHL) [14, 16, 40] were also excluded from the control group because of previously reported associations with nitrate or NOC exposure. 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 amongst the controls were Diseases of the respiratory system (16.1%), diabetes mellitus (12.3%), cerebrovascular diseases (11.3%), chronic liver disease and cirrhosis (7.2%), ischemic heart disease (5.7%), diseases of the genitouriinary system (5.4%), breast cancer (3.6%), and motor vehicle traffic accidents of unspecified nature (3.5%).

Nitrate-nitrogen (NO$_3$-N) and Mg levels

Information on the levels of NO$_3$-N and Mg in each municipality’s treated drinking water supply was obtained from the Taiwan Water Supply Corporation (TWSC) [41], to which each waterworks is required to submit drinking water quality data, including the levels of nitrates and Mg. 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 (cadmium reduction method and spectrophotometric method, respectively). Since the laboratory office examines nitrate and Mg 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 had more than one supply of drinking water and the exact population served by each could not be determined. Their details are provided in earlier publications [17, 24, 42]. The final complete data comprised NO$_3$-N and Mg data from 252 municipalities. Mg remains reasonably constant for long periods of time and is quite a stable characteristic of a municipality’s water supply [43]. Data collected were the annual mean levels of NO$_3$-N and Mg for the year 1990. The municipalities of residence for all cases and controls were identified from the death certificate and it was assumed that drinking water was the source of the subjects’ nitrate and Mg exposure via drinking water. The levels of NO$_3$-N and Mg of each municipality were used as an indicator of exposure to NO$_3$-N and Mg for an individual residing in that municipality.

Statistics

In the analysis, the subjects were categorized into one of the three NO$_3$-N exposure categories: low (the lowest 50th percentile among controls; < 0.027 mmol/L); medium (50th-75th percentile among controls; 0.028-0.041 mmol/L); and high (above the
75th percentile among controls; 0.043-0.204 mmol/L). Conditional logistic regression was used to estimate the association between NO$_3$-N levels present in drinking water and colon cancer risk. Odds ratio (OR) and their 95% confidence intervals (95% CI) were calculated using the low exposure group as the reference group [44]. The association between drinking water NO$_3$-N levels and risk of colon cancer was stratified by Mg levels in drinking water. The analyses were performed using the SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina). All statistical tests were two-sided and values of p < 0.05 were considered statistically significant.

**Results**

A total of 3,707 colon cancer cases with complete records were collected for the period of 2003-2007. The majority of both cases and controls were married. Cases had a higher rate of living in metropolitan municipalities than controls. Both cases and controls lived in municipalities in which more than 90% of the population was served by a waterworks. The mean NO$_3$-N concentration in the drinking water was 0.032 mmol/L for the cases and 0.031 mmol/L for the controls. Cases were less likely to have lived in residences served by drinking water with high levels (≥ 0.39 mmol/L) of Mg than the controls (table 1). The distribution of nitrate and Mg levels by municipalities are presented in table 2.

Table 3 shows the distribution of cases and controls and OR with respect to the levels of NO$_3$-N in drinking water. The crude OR was significantly higher than 1.0 for the group with the highest levels of nitrate in their drinking water. Adjustments for possible confounders only slightly altered the ORs. The adjusted ORs (95% CI) were 1.02 (0.90-1.15) for the group with water nitrate levels between 0.028 and 0.041 mmol/L and 1.16 (1.04-1.30) for the group with nitrate levels of 0.043 mmol/L or more. There was a significant trend towards an elevated

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cancer cases (n = 3,707)</th>
<th>Controls (n = 3,707)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment municipality</td>
<td>252</td>
<td>252</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- male</td>
<td>2,087 (56.3%)</td>
<td>2,087 (56.3%)</td>
</tr>
<tr>
<td>- female</td>
<td>1,620 (43.7%)</td>
<td>1,620 (43.7%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 50-54</td>
<td>736 (19.9%)</td>
<td>736 (19.9%)</td>
</tr>
<tr>
<td>- 55-59</td>
<td>732 (19.7%)</td>
<td>732 (19.7%)</td>
</tr>
<tr>
<td>- 60-64</td>
<td>913 (24.6%)</td>
<td>913 (24.6%)</td>
</tr>
<tr>
<td>- 65-69</td>
<td>1,326 (35.8%)</td>
<td>1,326 (35.8%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- single</td>
<td>177 (4.7%)</td>
<td>214 (5.8%)</td>
</tr>
<tr>
<td>- married</td>
<td>2,927 (78.0%)</td>
<td>2,747 (74.1%)</td>
</tr>
<tr>
<td>- ever married</td>
<td>603 (16.3%)</td>
<td>746 (20.1%)</td>
</tr>
<tr>
<td>Urbanization level of residence (%)b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- metropolitan</td>
<td>1669 (45.0%)</td>
<td>1417 (38.2%)</td>
</tr>
<tr>
<td>- city</td>
<td>808 (21.8%)</td>
<td>802 (21.7%)</td>
</tr>
<tr>
<td>- town</td>
<td>834 (22.5%)</td>
<td>931 (25.1%)</td>
</tr>
<tr>
<td>- rural</td>
<td>396 (10.7%)</td>
<td>557 (15.0%)</td>
</tr>
<tr>
<td>Drinking water served by waterwork (%)</td>
<td>92.94 ± 15.68</td>
<td>91.32 ± 16.98</td>
</tr>
<tr>
<td>NO$_3$-N level (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- median</td>
<td>0.027</td>
<td>0.027</td>
</tr>
<tr>
<td>- mean ± SDf</td>
<td>0.032 ± 0.033</td>
<td>0.031 ± 0.034</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mean±SDf</td>
<td>0.45 ± 0.30</td>
<td>0.48 ± 0.32</td>
</tr>
<tr>
<td>- &lt; median (0.39)</td>
<td>2,238 (60.4%)</td>
<td>2,071 (55.9%)</td>
</tr>
<tr>
<td>- ≥ median</td>
<td>1,469 (39.6%)</td>
<td>1,636 (44.1%)</td>
</tr>
</tbody>
</table>

a There are water analyses in this table.

b The urbanization level of each municipality was based on the urban-rural classification scheme of Tzeng and Wu (1986).

c Standard deviation.
risk of death from colon cancer with increasing nitrate levels in drinking water.

We evaluated the association between NO₃-N levels in drinking water and colon cancer risk among those with high (≥ median) and low (< median) Mg intake via drinking water (Table 4). There was a suggestion of interaction between drinking water nitrate and Mg intake, in that individuals with the highest NO₃-N exposure and low Mg intake from drinking water had a 1.47-fold increased risk of colon cancer, whereas those with the highest NO₃-N exposure whose drinking water Mg intake was above the median had no statistically significant increased risk. Statistically significant interaction was observed only for the highest NO₃-N exposure group when we included Mg levels as a continuous variable. We found that there was a 2.5% (95% CI = 0.8%-4.3%) decrease in the risk of colon cancer per 1 mg/L of Mg increase in drinking water for the highest NO₃-N exposure group.

Table 2. Distribution of nitrate and magnesium levels by municipalities.

<table>
<thead>
<tr>
<th>Magnesium (mmol/L)</th>
<th>NO₃-N level (mmol/L)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.007 (25th percentile)</td>
<td>0.008-0.027 (25th-50th percentile)</td>
</tr>
<tr>
<td>0.06-0.29 (25th percentile)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>0.30-0.41 (25th-50th percentile)</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>0.42-0.65 (50th-75th percentile)</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>0.66-1.72 (above 75th percentile)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>64 (25.4%)</td>
<td>73 (29.0%)</td>
</tr>
</tbody>
</table>

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for colon cancer death in relation to nitrate levels in drinking water, 2003-2007.

<table>
<thead>
<tr>
<th>NO₃-N, mmol/L (median)</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Crude ORb</th>
<th>Adjusted ORc</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.027 (0.004)</td>
<td>1,921</td>
<td>2,052</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.028-0.041 (0.031)</td>
<td>730</td>
<td>732</td>
<td>1.07 (0.94-1.20)</td>
<td>1.22 (1.01-1.36)</td>
</tr>
<tr>
<td>&gt; 0.043 (0.071)</td>
<td>1,056</td>
<td>923</td>
<td>1.22 (1.01-1.36)</td>
<td>1.16 (1.04-1.30)</td>
</tr>
</tbody>
</table>

Table 4. Odds ratios for colon cancer by levels of nitrate and Mg in drinking water.

<table>
<thead>
<tr>
<th>Magnesium (mmol/L)</th>
<th>NO₃-N level (mmol/L)</th>
<th>Cases</th>
<th>Controls</th>
<th>ORb (95%CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>ORb (95%CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>ORb (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.027 (0.003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 0.39</td>
<td>590</td>
<td>677</td>
<td>1.00</td>
<td></td>
<td>252</td>
<td>294</td>
<td>0.96 (0.78-1.17)</td>
<td>627</td>
<td>624</td>
<td>1.04 (0.88-1.23)</td>
</tr>
<tr>
<td>&lt; 0.39</td>
<td>1331</td>
<td>1375</td>
<td>1.03 (0.89-1.18)</td>
<td></td>
<td>478</td>
<td>438</td>
<td>1.09 (0.91-1.30)</td>
<td>429</td>
<td>299</td>
<td>1.47 (1.21-1.78)</td>
</tr>
</tbody>
</table>

a There are water analyses in this table.
b Adjusted for age, gender, marital status, urbanization level of residence.
c p value for interaction on the multiplicative scale < 0.05.
Discussion

This study used a death-certificate-based case-control study to examine whether Mg levels in drinking water modify the effects of NO$_3$-N in drinking water on colon cancer risk. We found that the risk of colon cancer associated with high NO$_3$-N levels in drinking water was elevated among those with low Mg intake from drinking water.

Our findings suggest that it might be important to consider the levels of Mg in drinking water in the evaluation of the relationship between NO$_3$-N exposure and colon cancer risk. To our knowledge, this is the first study to report an effect modification by Mg intake from drinking water in the association between NO$_3$-N exposure and colon cancer risk. Antioxidants that inhibit endogenous nitrosation include vitamin C and alpha-tocopherol, which can reduce nitrite to NO [45]. Our study results suggest that Mg may be like vitamin C and alpha-tocopherol, which inhibited endogenous nitrosation caused by the intake of nitrate from drinking water, and therefore individuals who had low levels of Mg intake via drinking water may be at increased risk of exposure to NOC and colon cancer.

Despite their inherent limitations [46], studies of the ecological correlation between mortality and environmental exposures have been widely used to generate or discredit epidemiological hypotheses. Before any 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 colon cancer, were reported to be one of the most unequivocally classified causes of death in Taiwan [47]. Because of a fatal outcome, it is believed that all colon cancer cases from high or low levels of NO$_3$-N and Mg exposure in drinking water had access to medical care, regardless of geographical location, in recent years.

Of greater concern is whether the relative levels of nitrate in the period around 1990 correspond to the relative levels of nitrates in the period 20-30 years prior to 1990. This is important since it is likely that exposure to causal factors would precede cancer mortality by at least 20 years (the latency period for carcinogen exposure). Nitrate contamination in public water supplies in Taiwan was due principally to the use of nitrogen fertilizers in areas of arable farming [48]. The historical levels of nitrates are not available for the study areas. However, it is believed that the correlation between the levels of 1990 and levels of 20-30 years ago would be high since a municipality’s urban development is gradual (the agricultural areas decreased gradually). Therefore we feel that the nitrate levels in 1990 were a reasonable indicator of historical levels occurring over the past 20-30 years.

Migration from a municipality of high nitrate and Mg exposure to one of low nitrate and Mg exposure or vice versa may have introduced misclassification bias and bias in OR estimates [49, 50]. Mobility is age dependent, and diseases usually occur with a higher incidence amongst older groups and proximate to the location of the environmental “cause” [50]. However, neighboring water sources tend to possess similar chemical composition [51], and hence even if an individual moved, the change in exposure to nitrate and Mg in drinking water would probably not be significant provided that the old and new residence 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 for the present study were at least 50 years old. 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, urbanizational 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.

Intake of nitrate from drinking water and dietary sources may result in increased exposure to NOC through endogenous nitrosation [6, 7]. The principal dietary nitrate sources are vegetables. Vegetables also contain vitamin C and other nitrosation inhibitors [45], and therefore, high intakes may not result in high rates of formation of NOC [52]. Dietary intakes of red and processed meat are of particular importance in the formation of fecal NOC [53, 54]. There is unfortunately no information available for assessing the dietary nitrate sources from vegetables and meat for individual study subjects in this study. However, there is no reason to believe that there would be any correlation between the sources of dietary nitrate and the levels of nitrate in drinking water. Furthermore, Chivers et al. [55] indicated
that when the concentration of waterborne nitrate is high, drinking water contributes substantially to total nitrate intake and the potential for nitrite and NOC formation may be increased. It is thus proposed that individuals with a higher daily nitrate intake from drinking water and lower intakes of nitrosation inhibitors may be at an elevated risk of colon cancer.

Screening has been shown to be effective in reducing the incidence of, and mortality from colorectal cancer [56]. Unfortunately, there is no information available on the prevalence of screening utilization for individual municipality studies and therefore it could not be adjusted for directly in the analysis. If colon cancer screening is correlated with the levels of nitrate in drinking water, a spurious association between nitrate exposure and colon cancer death could result. However, there is no reason to believe that there would be any correlations between the habits of undergoing colon cancer screening and nitrate levels in drinking water. Nonetheless, this is a limitation that should be considered.

Some potential limitations of this study need to be noted. The information on nitrate or Mg concentrations in drinking water was not obtained individually from the subjects, but estimated from their concentrations in the public drinking water supply of their residential municipality. The lifetime residential history and the identification of the primary drinking water source (municipal water supply or private well water) of each subject are also not available even though both cases and controls lived in municipalities in which more than 90% of the population were served by a waterworks (92.94% and 91.32% for cases and controls, respectively). Our study may thus have been limited by potential exposure misclassification. While these sources of misclassification are important, such misclassification of exposure is most likely to be non-differential (i.e., unlikely to be associated colon cancer), which would reduce the magnitude of association rather than introduce a positive bias in the association. Furthermore, our results might have been confounded by the fact that no information on other potential risk factors, such as physical activity, meat and fat consumption, was available [57]. However, there is no reason to believe that there would be any correlation between these risk factors and the levels of nitrates and Mg in drinking water.

The nitrate concentration in drinking water in Taiwan is below the guideline value recommended by the World Health Organization [58] of 10 mg/L. This guideline was not based on estimates of cancer risk. In addition, there is no scientific evidence to justify firm conclusions about the safety of any concentration of nitrate in water with regard to cancer risk. Forman [15] noted that although environmental nitrate exposure probably plays a role in the development of cancer, it does not show a rate-limiting effect.

In summary, our data suggest that Mg in drinking water modified the effects of nitrate exposure on colon cancer risk. Future studies should increase the precision of the estimation of an individual's intake of nitrates and Mg, through both food and water, and control for confounding factors, especially personal risk factor such as physical activity, and meat and fat consumption.

Financial support and disclosure

This study was supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-97-2314-B-037-006-MY3).

None of the authors has any conflict of interest to disclose.

References


