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Nitrates in Drinking Water and Risk of Death from Rectal Cancer in Taiwan

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The relationship between nitrate levels in drinking water and rectal cancer development has been inconclusive. A matched case-control and nitrate ecology study was used to investigate the association between mortality attributed to rectal cancer and drinking-water nitrate exposure in Taiwan. All deaths due to rectal cancer of Taiwan residents from 1999 through 2003 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 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. Data on nitrate-nitrogen (NO_3-N) levels in drinking water throughout Taiwan were collected from Taiwan Water Supply Corporation (TWSC). The municipality of residence for cancer cases and controls was assumed to be the source of the subject's nitrate exposure via drinking water. The adjusted odds ratios for rectal cancer death for those with high nitrate levels in their drinking water, as compared to the lowest tertile, were 1.22 (0.98–1.52) and 1.36 (1.08–1.70), respectively. The findings of this study warrant further investigation of the role of nitrates in drinking water in the etiology of rectal cancer in Taiwan.

Nitrate in drinking water comes from numerous natural and synthetic sources, including wastewaters and agricultural and urban runoff. Nitrogen fertilizer is the largest contributor to anthropogenic nitrogen globally and has been implicated as the predominant source of drinking water nitrate in rural areas (Fields, 2004). The U.S. Environmental Protection Agency (EPA) established a maximum contaminant level (MCL) in drinking water of 10 mg/L as nitrate-N to protect infants from methemoglobinemia (Ward et al., 2005). However, the effectiveness of this regulatory limit for preventing other health risks such as cancer has not been adequately studied (De Roos et al., 2003).

Nitrates act as procarcinogens, interacting with amines and amides in the stomach and gut to form a variety of *N*-nitroso compounds (NOC) via a nitrosation process, after reduction in the saliva of nitrate to nitrite (Walker, 1990). Several studies support a direct relationship between nitrate intake and endogenous formation of NOC. High nitrate levels in drinking water are associated with increased excretion of *N*-nitrosoproline in urine (Mirvish et al., 1992; Moller et al., 1989), and nitrate administered via drinking water was found to be directly related to concentration of total NOC in feces (Rowland et al., 1991). In addition, populations with high rates of esophageal, gastric, and nasopharyngeal cancers excrete high levels of urinary *N*-nitrosoproline (Kamiyama et al., 1987; Lu et al., 1986; Yi et al., 1993). These results demonstrate a contribution of drinking-water nitrates to overall nitrosation and suggest that nitrate intake may be used as a surrogate for exposure of humans to NOC (De Roos et al., 2003).

Nitrosation also occurs in the large intestine (Bruning-Fann & Kaneene, 1993). NOC are potent animal carcinogens, inducing tumors at multiple organ sites including the rectum (Bogovski & Bogovski, 1981; Ward et al., 2005). NOC were found to induce tumors in every animals species tested, and it is likely that humans are also affected (Lijinsky, 1986; Ward et al., 2005). However, few epidemiologic studies have been conducted to address the association of nitrates in drinking water and cancer risk. The majority of investigations focused on gastric cancer and data are inconclusive (Forman, 1989; Cantor, 1997; Yang et al., 1998; Gulis et al., 2002).

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Our hypothesis derives from animal experiments in which rats (Mirvish et al., 1987) and hamsters (Germann et al., 1991) displayed higher rates of intestinal tumors after administration of NOC either from drinking water or by injection. Epidemiologic data concerning a link between drinking water nitrates and rectal cancer are limited. One ecologic study conducted in Slovakia found a positive association between drinking-water nitrates and rectal cancer (Gulis et al., 2002). Weyer et al. (2001) reported an inverse association between nitrate levels in drinking water and rectal cancer. Other studies found no association between rectal cancer and presence of nitrates (Geleperin et al., 1976; Jensen, 1982; Morales-Suarez-Varela et al., 1995; De Roos et al., 2003).

Studies in Taiwan found that there is a significant positive association between nitrate levels in drinking water and risk of death from gastric (Yang et al., 1998) and bladder cancer (Chiu et al., 2007), whereas levels of nitrates in drinking water was not associated with risk of death from colon cancer (Yang et al., 2007). Although cancers of the colon and rectum show some differences in their geographic and temporal distribution, it is appropriate to discuss these cancers together in terms of causation (Higginson et al., 1992). Since epidemiologic evidence for a link between drinking-water nitrates and rectal cancer has been limited, and because there is a need for additional studies using new independent data from other populations, the present study was undertaken in Taiwan to explore further whether nitrate levels in drinking water correlate with an increased incidence of rectal cancer. This is one in a series of similar studies evaluating the relationship between nitrate levels in drinking water and risk of cancer development in various tissues.

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MATERIALS AND METHODS

Study Area

Taiwan is divided into 361 administrative districts, which are referred to herein as municipalities. These units were subsequently subjected to statistical analysis. Excluded from the analysis were 30 aboriginal townships and 9 islets, which had different lifestyles and living environments. The elimination of unsuitable municipalities yielded 322 municipalities.

Subject Selection

Data on all deaths of Taiwan residents from 1999 through 2003 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. The case group consisted of all eligible rectal cancer deaths occurring in individuals between 50 and 69 yr of age (International Classification of Disease, ninth revisions [ICD-9], code 154).

The control group consisted of all other deaths, excluding those deaths that were associated with gastrointestinal disease. The deaths excluded were those caused by malignant neoplasm of the stomach (ICD-9 code 151), malignant neoplasm of the small intestine, including duodenum (ICD-9 code 152), malignant neoplasm of the colon (ICD-9 code 153), malignant neoplasm of the 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 whose death was attributed to bladder (Morales Suarez-Varela, 1993; Weyer et al., 2001; Chiu et al., 2007), lung (Hoffmann et al., 1994), esophagus (Yang, 1980; Wu et al., 1993, Cantor, 1997), and head and neck (Andre et al., 1995; Herity et al., 1981) cancers and non-Hodgkin lymphoma (NHL) (Cantor, 1997; Gulis et al., 2002; Ward et al., 1996) were also excluded from the control group because of previously reported associations with nitrates or NOC exposures. 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. The most frequent causes of death among the controls were diabetes mellitus (13%), liver cancer (11%), chronic liver disease and cirrhosis (7%), acute myocardial infarction (5%), and acute but ill-defined cerebrovascular disease (3%).

Nitrate-Nitrogen Levels

Information on the levels of NO_3-N in each municipality's treated drinking water supply was obtained from the Taiwan Water Supply Corporation (TWSC) (TWSC/ROC, 1991), to which each waterworks is required to submit drinking-water quality data including the levels of nitrate. Four water samples, one for each season, were collected from each waterworks. The samples were analyzed by the waterworks lab using standard methods (cadmium reduction method). Since the lab examines nitrate levels on a routine basis using standard methods, it was presumed that analytical variability was not a confounding factor. 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. These details are given in earlier publications (Yang, 1998; Yang et al., 2000). The final complete data comprised NO_3-N results from 252 municipalities. Data collected were the annual mean levels of NO_3-N for the year 1990. The municipalities of residence for all cancer cases and controls were identified from the death certificate and assumed to be the source of the subjects' nitrate exposure via drinking water. The levels of nitrate of each municipality were used as an indicator of exposure to nitrate for an individual residing in that municipality.

Statistics

In the analysis, subjects were divided into tertiles according to the levels of nitrate and calcium in their drinking water.

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Conditional logistic regression was used to estimate the relative risk in relation to the nitrate levels in drinking water. Calcium levels in drinking water were included in the multiple regression analysis because our previous study reported a protective effect of calcium intake via drinking water against rectal cancer (Yang & Chiu, 1998). Odds ratio (ORs) and their 95% confidence intervals (95% CIs) were calculated using the group with the lowest exposure as the reference group (Breslow & Day, 1980). Values of $p < .05$ were considered statistically significant.

RESULTS

In total, 1118 rectal cancer cases with complete records were collected for the period of 1999–2003. Of the 1118 cases, 662 were males and 456 females (Table 1). The mean nitrate concentration in drinking water of the rectal cancer cases was 0.46 mg/L (SD = 0.45). Controls possessed a mean nitrate exposure of 0.43 mg/L (SD = 0.46). Both cancer cases and controls had a mean age of 61.7. Cancer cases lived in municipalities in which 90.7% of the population was served by a waterworks. For controls this number was 90.4%. Cancer cases had a quantitatively higher rate (35.8%) of living in metropolitan municipalities than controls (31.9%) (Table 1).

Table 2 shows the number of cancer cases and controls and ORs for rectal cancer in relation to nitrate levels in drinking water. The crude ORs were significantly higher than 1 for the group with the highest nitrate levels (1.27; 95% CI = 1.04–1.56). Adjustments for possible confounders only slightly altered the ORs. The adjusted ORs (95% CI) were 1.22 (0.98–1.52) for the group with water nitrate levels between 0.19 and 0.45 mg/L and 1.36 (1.08–1.70) for the group with nitrate levels of 0.48 mg/L or more. There was a significant trend toward an increased rectal cancer risk with increasing nitrate levels in drinking water.

TABLE 1
Characteristics of the Study Population

Characteristics	Cancer cases	Controls
Total subjects	1118	1118
Enrollment municipality	252	252
Gender (%)		
Male	662 (59.2)	662 (59.2)
Female	456 (40.8)	456 (40.8)
Mean age in years (SD)[a]	61.7 ± 5.5	61.7 ± 5.5
Mean NO_3-N concentation (mg/L)(SD)	0.46 ± 0.45	0.43 ± 0.46
Mean calcium concentration (mg/L)(SD)	35.5 ± 19.6	35.7 ± 18.4
Drinking water served by waterworks (%)	90.7 ± 17.8	90.4 ± 18.2
Urbanization level of residence (%)[b]		
Metropolitan	400 (35.8)	357 (31.9)
City	254 (22.7)	258 (23.1)
Town	312 (27.9)	317 (28.4)
Rural	152 (13.6)	186 (16.6)

[a]SD: standard deviation.

[b]Urbanization level of each municipality based on urban–rural classification scheme of Tzeng and Wu (1986).

DISCUSSION

This study uses a death-certificate-based case-control study to examine the relationship between rectal cancer mortality and nitrate exposure levels in drinking water in Taiwan. The results of the present study show that individuals who resided in the municipalities with highest levels of nitrate in drinking water were at a statistically significant increased risk for development for rectal cancer compared to individuals living in municipalities with the lowest nitrate levels, after controlling for possible confounders. Our findings are consistent with a recent report from Slovakia (Gulis et al., 2002) and are in contrast to previous reports (Geleperin et al., 1976; Jensen, 1982; Morales-Suarez-Varela et al., 1995; Weyer et al., 2001; De Roos et al., 2003).

Despite their inherent limitations (Morgenstern, 1982), studies of the ecological correlation between mortality and environmental exposures are used widely to generate or discredit epidemiological findings. Before any conclusion based on 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 very reliable. Although causes of death may be misdiagnosed and/or misclassified, this problem has been minimized through improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, malignant neoplasms, including rectal cancer, were reported to be one of the most unequivocally classified causes of death in Taiwan (Chen & Wang, 1990). Because of debilitating manifestations associated with rectal cancer, it is believed that patients exposed to either high or low levels of nitrate in drinking water are currently utilizing medical care regardless of geographical location.

Of greater concern is whether the relative levels of nitrate in the period around 1990 correspond to the relative levels found in periods 20–30 yr earlier. This is important since it is likely that exposure to causal factors would precede cancer mortality by at least 20 yr (the latency period for carcinogen exposure). The historical levels of nitrate are not available for the study areas. However, it is believed that the correlation between the nitrate levels of 1990 and those found 20–30 yr earlier might be high, since the use of nitrogen fertilizers has not changed over time in these study areas.

Migration from a municipality of high nitrate exposure to one of low chemical exposure or vice versa may have introduced misclassification bias and bias in the ORs estimate

TABLE 2
Odds ratios (ORs) and 95% Confidence Intervals (CIs) for Death Attributed to Rectal Cancer and Correlation With Nitrate Levels in Drinking Water, 1999–2003

	Nitrate, mg/L (median)		
	≤0.18 (0.00)	0.19–0.45 (0.38)	0.48–2.85 (0.72)
Number of cancer cases	333	382	403
Number of controls	378	384	356
Crude odds ratio[a]	1.0	1.13 (0.92–1.39)	1.27 (1.04–1.56)
Adjusted odds ratio[b]	1.0	1.22 (0.98–1.52)	1.36 (1.08–1.70)
χ^2 for trend = 5.76, p = .02			

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

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(Gladen & Rogan, 1979; Polissar, 1980). Mobility is age dependent, and diseases usually occur with a higher incidence among older groups and near 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 quantity of nitrate in drinking water was probably not 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. In addition, all subjects used for the present study were at least 50 yr old, and 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 migration as a confounder 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 needs also 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 rectal cancer patients between high and low exposure areas. If there was a trend toward migration to more urban or lower nitrate exposure areas because of proximity to medical care, for example, a spurious association between nitrate exposure and rectal cancer death may have existed. Three aspects of this study presumably minimized this possibility. First, migration due to rectal cancer diagnosis would be unlikely, since for this cohort of decedents the subject's occupational status would weigh against a move requiring a change in development 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 assumed 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 listed on the death certificate.

Intake of nitrates from drinking water and dietary sources may produce increased exposure to NOC through endogenous nitrosation (Mirvish et al., 1992; Moller et al., 1989). The principal dietary nitrate sources are vegetables. Vegetables also contain vitamin C and other nitrosation inhibitors (Bartsch et al., 1988), and therefore, high nitrate intake may not result in high rates of formation of NOC (Coss et al., 2004). Dietary intakes of red and processed meat are of particular importance in the formation of fecal NOC (Bingham, 1999; Bingham et al., 2002). There is unfortunately no information available for assessing the dietary nitrate sources from vegetables and meat for individual study subjects in Taiwan. 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, a study has indicated that when the concentration of waterborne nitrate is high, drinking water contributes substantially to total nitrate intake (Chilvers et al., 1984), and consequently the potential for nitrite and NOC may be increased. It is thus proposed that individuals with higher daily nitrate intake from drinking water and lower intake of nitrosation inhibitors may be at a greater risk for development of rectal cancer.

There are a number of major risk factors for induction of rectal cancer that need to be taken into account when investigating the possibility of additional confounding factors. Based on epidemiologic studies, the most important risk factors for rectal cancer development are physical activity, and meat and fat consumption (Schottenfeld & Fraumeni, 1996). There is unfortunately no information available on these variables for an individual study subject and thus they could not be adjusted for directly in this analysis. However, there is no reason to believe that there would be any correlation between these confounders and the levels of nitrate in drinking water. It is also unlikely that there would be a direct relationship between other risk factors and the level of nitrates in drinking water.

The exposure to nitrates was determined by linking each study subject's residence to their individual water source. However, it was not possible to calculate the exact nitrate intake from water for individual subjects, because the amount

of water consumed at home or at other places could not be determined. Data on individual exposure were thus still characterized by a lack of precision.

The nitrate concentration in drinking water in Taiwan is below the guideline values recommended by the World Health Organization (1984) of 10 mg/L. This guideline was not based on estimates of cancer risk. Further, there is no scientific evidence to justify firm conclusions about the safety of any concentration of nitrates in water with regard to cancer risk development. Forman (1989) noted that although environmental nitrate exposure probably plays a role in the development of cancer, it does not exhibit a rate-limiting effect.

In summary, this study showed that exposure to nitrates in drinking water at levels reported in Taiwan may increase rectal cancer risk development. The findings of this study warrant further investigation of the role of nitrates in drinking water in the etiology of rectal cancer. Future studies should increase the precision of the estimation of the individual's intake of nitrates, through both food and water, and control for confounding factors, especially personal risk factors such as physical activity and meat and fat consumption.

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