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# Adenocarcinoma of the Stomach and Esophagus and Drinking Water and Dietary Sources of Nitrate and Nitrite

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## Abstract

We conducted a population-based case-control study of adenocarcinoma of the stomach and esophagus in Nebraska, U.S.A. Nitrate concentrations in public drinking water supplies were linked to residential water source histories. Among those using private wells at the time of the interview, we measured nitrate levels in water samples from wells. Dietary nitrate and nitrite were estimated from a food-frequency questionnaire. Among those who primarily used public water supplies (79 distal stomach, 84 esophagus, 321 controls), average nitrate levels were not associated with risk (highest versus lowest quartile: stomach OR=1.2, 95% CI [0.5–2.7]; esophagus OR=1.3, 95% CI [0.6–3.1]). We observed the highest ORs for distal stomach cancer among those with higher water nitrate ingestion and higher intake of processed meat compared with low intakes of both; however, the test for positive interaction was not significant (p=0.213). We did not observe this pattern for esophagus cancer. Increasing intake of nitrate and nitrite from animal sources was associated with elevated ORs for stomach cancer and with a significant positive trend in risk of esophagus cancer (P-trend=0.325 and 0.015, respectively). Larger studies with higher exposures to drinking water sources of nitrate are warranted to further evaluate N-nitroso compound precursors as risk factors for these cancers.

### Keywords

Nitrate; nitrite; stomach cancer; esophagus cancer; diet; drinking water

Nitrate contamination of water supplies can come from nitrogen fertilizer use, animal husbandry, nitrogen oxide pollutants in the air, poorly maintained septic systems, and other sources of human waste.[1] Ingestion of nitrate and nitrite under conditions likely to form N-nitroso compounds (NOCs), called endogenous nitrosation, is considered probably carcinogenic to humans based on sufficient evidence in animals and limited evidence from epidemiologic studies of dietary nitrite and stomach cancer.[2,3] Most studies of drinking water nitrate and stomach cancer are ecologic and results are mixed,[4] whereas studies of dietary

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nitrite intake are generally positive.[3,5] Few studies have been conducted to evaluate esophagus cancer and precursors of endogenous nitrosation, although many NOCs are potent animal carcinogens for the stomach, esophagus, and other organ sites. Nitrosation is inhibited by consumption of antioxidants in fruits and vegetables,[4] and increased with red meat,[6] indicating that these factors should also be considered.

## Methods

### Study Population

As previously described, we conducted a population-based case-control study of adenocarcinoma of the stomach and esophagus in 66 counties in eastern Nebraska, a state with elevated nitrate levels in many drinking water supplies.[7–9] Cases were white men and women age 21 or older, newly diagnosed between July 1, 1988, and June 30, 1993, identified from the Nebraska Cancer Registry and confirmed by histological review. At the same time, we enrolled a population-based series of brain cancer cases (gliomas).[9] Of the identified eligible cases, interviews were completed for 170 stomach and 137 esophagus cases, giving response rates of 79% and 88%, respectively. We analyzed distal stomach cancer (hereafter stomach cancer), which has somewhat different risk factors from cardia cancer.[10] The number of cardia cancers was too few to evaluate separately.

Controls were selected from a previous population-based case-control study of lymphatic and hematopoietic cancers in Nebraska,[11] and were re-interviewed at the time of this study (1992–1994). We selected a stratified random sample from the previous controls and over-sampled living controls to provide more power for analyses by respondent type. For the youngest cases, we had insufficient numbers of controls; therefore, new controls born in 1967–71 were identified from death certificates (n=20, deaths in 1988–93) and from random digit dialing (n=3) by the same methods as in the earlier study. Of the 606 eligible controls, 503 (83%) were successfully interviewed. The response rate in the original study was 87%, giving an overall control response rate of 72%.

Telephone interviews were conducted with subjects or their proxies for those who were deceased or too ill to participate. Proxy interviews were conducted for 80%, 76%, and 61% of stomach and esophagus cases and controls, respectively. The majority (≥79%) of proxies were the spouse or child. The study was approved by Institutional Review Boards at the National Cancer Institute and University of Nebraska Medical Center.

### Exposure Assessment

Interviewers obtained a residential and water source history and information about demographic factors, tobacco and alcohol use, pesticide use by farmers, occupational histories, medical conditions, and medication use. To assess dietary intake, we used the short Health Habits and History Questionnaire[12] with the addition of foods high in nitrate and nitrite. Nitrate and nitrite content of food items was determined from values in the literature as previously described.[9] We obtained nitrate concentrations for water utilities (1965–1985) from a database of monitoring data from Nebraska public water supplies.[9] Nitrate measurements were available for samples taken from the distribution system and at the groundwater wells. If available, we used the distribution measurements to calculate an annual mean nitrate level; otherwise, measurements from wells serving the utility in that year were averaged. For years with no nitrate measurements, we assigned an estimate based on the annual mean nitrate concentration for the utility in neighboring years. We calculated a weighted average where the weights were 1.0, 0.75, 0.5, and 0.25 depending on whether the annual mean was 1–2, 3–4, 5–6, or 7–9 years, respectively, from the year missing measurement data. Participants using a private well at the

interview home were asked to provide a water sample; 15 stomach cases (65% of eligible cases), 22 esophagus cases (78%) and 44 controls (61%) participated.

Because nitrate monitoring data were limited before the mid-1960s, we restricted most analyses to individuals who used Nebraska public supplies after 1964. To reduce misclassification by unknown nitrate levels, mainly due to the use of private wells, we restricted the analyses to those with nitrate information (actual or imputed data) for 70% or more of their person-years after 1964 (79 stomach, 84 esophagus, 321 controls). We calculated the average nitrate level and the years of intake above the regulatory limit of ≥10 mg/L nitrate-nitrogen (hereafter mg/L nitrate). Water nitrate intake was estimated by multiplying tap water intake by the average nitrate level in public supplies. Dietary analyses were limited to those who had no more than 20% of food items with missing or don't know responses and nonmissing covariate information (104 distal stomach, 98 esophagus, 397 controls). We computed intake of animal and plant sources of nitrate and nitrite separately, and we summed animal nitrate and nitrite, which are additives to processed meats.

### Data Analysis

We evaluated quartiles (based on controls) of the average nitrate level in public supplies and of intakes of plant sources of dietary nitrate (primarily vegetables), plant sources of nitrite (primarily from breads and cereals), and animal sources of nitrite plus nitrate (from processed meats). We estimated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression, adjusting for gender, year of birth, and risk factors for stomach (education, smoking, alcohol) and esophagus cancer (smoking, alcohol, body mass index), which as a group changed the ORs in some models by more than 10%. The model for animal nitrate and nitrite and esophagus cancer was also adjusted for family history of gastrointestinal cancers due to a change in the results by more than 10% upon addition of this variable. Dietary analyses were additionally adjusted for total calories and nutrients significantly associated with these cancers.[7] We assessed effect modification of the average nitrate level in public supplies by vitamin C and red or processed meat intake using the continuous forms of the variables.

## Results

The overall study population and controls included in the public drinking water analyses have been previously described.[7–9] As expected, cases and controls in the public water analysis group had used Nebraska public water supplies for more years and private wells for fewer years than the overall study population. Those in the public drinking water analysis tended to have more years of formal education and fewer cases and controls had ever lived or worked on a farm. The analysis group and study population overall were similar with respect to a family history of cancer, the type of respondent providing the interview, and dietary intakes of nitrate, nitrite, carotenes and fiber (data not shown).

Duration of use of a public supply ≥10 mg/L was not associated with risk of either cancer (Table 1). Likewise, increasing intake quartiles of average nitrate in public supplies (range:<0.5–12 mg/liter) were not associated with a significant trend in risk of stomach or esophagus cancers (Table 1). Risk of both cancers was elevated in the second quartile largely due to elevated ORs among long-term Omaha residents who comprised the majority of subjects in that category of drinking water nitrate. Water nitrate intake computed from the average nitrate level in public supplies and usual tap water intake (range=0.2–39 mg/day) was not associated with risk (not shown). Odds ratios for stomach cancer were highest among those with higher average nitrate levels and higher processed meat intake compared with low intakes of both (>2.7mg/L nitrate/>30g/day processed meat: OR=2.0, 95% CI 0.8–4.8); however, the test for interaction between drinking water nitrate and processed meat intake was not significant (p for interaction=0.213). Excluding Omaha residents increased the OR for the highest water

nitrate/processed meat category (OR=2.7, 95% CI 0.8–9.8). This pattern was not apparent for esophagus cancer (p for interaction=0.98). Stratification by vitamin C and red meat intake revealed no clear pattern of effect modification for either cancer (not shown).

Higher intake of animal nitrite and nitrate was associated with elevated ORs for stomach cancer and increased ORs for esophagus cancer, with a significant trend (P-trend=0.015) (Table 2). We evaluated the joint effects of animal nitrate/nitrite and vitamin C intake using cutpoints at the median intake levels and observed no evidence for interaction (not shown). Plant sources of nitrite were not associated with either stomach or esophagus cancer. After adjusting for vitamin C intake and other nutrients, increasing intake of dietary nitrate from plant sources (which accounts for >90% of intake) was associated with elevated ORs for stomach cancer (Table 2); whereas ORs were not elevated in models without adjustment for vitamin C and the other nutrients (not shown). Esophageal cancer was not associated with plant sources of nitrate either before or after adjustment for other dietary nutrients.

Nitrate levels in private wells ranged from <0.5 mg/L to 67 mg/L. Compared with <0.5 mg/L, ORs for stomach cancer (adjusted for age, gender, and duration of farming) were elevated for 0.5–4.5mg/L (OR=4.7, 95% CI 0.5–41; 7 cases, 18 controls), and >4.5mg/L (OR=5.1, 95% CI 0.5–52; 4 cases, 13 controls); whereas, ORs were non-significantly inverse for esophagus cancer (>4.5mg/ L OR=0.5, 95% CI 0.1–2.9; 8 cases; 13 controls).

## Discussion

We found no overall association between intake of nitrate from public water supplies and stomach or esophagus cancer. Based on small numbers, stomach cancer risk was elevated among those with elevated nitrate concentrations in their private wells. We observed a significant positive trend in risk of esophageal cancer with increasing intake of nitrite plus nitrate from animal sources. We observed elevated odds ratios for distal stomach cancer associated with increasing ingestion of animal nitrite/nitrate and plant sources of nitrate, which did not reach statistical significance.

Cross-sectional studies in humans support a relationship between water nitrate ingestion and endogenous formation of NOCs in the gastrointestinal tract.[13–15] However, there have been few individual-based studies of NOC precursors in relation to risk of stomach and esophagus cancers. Most epidemiologic studies of drinking water nitrate and stomach cancer were ecologic and results were mixed.[16] A cohort study in the Netherlands[17] found no association between stomach cancer risk and quintiles of water nitrate intake determined from public supply levels and tap water intake; average intake from water was 1.3 mg nitrate-N/day. Public supply nitrate levels were not associated with stomach cancer in a death certificate-based case-control study in Wisconsin.[18] No individual-based studies evaluated drinking water nitrate and esophagus cancer, and the few ecologic studies that have been conducted were not informative.[2] Our study population had exposures to drinking water nitrate that were mostly below the regulatory limit and the small numbers of cases with high water nitrate exposure limited our ability to evaluate risk among subgroups likely to have higher endogenous nitrosation.

Our findings of positive associations for stomach and esophagus cancers with higher intake of animal sources of nitrate and nitrite are consistent with most previous studies. A cohort study in Europe found an elevated risk for distal stomach cancer associated with endogenous nitrosation estimated from the iron content of ingested meat, and evidence for an interaction with vitamin C and *Helicobacter pylori*.[19] A cohort study in the Netherlands[17] found increased risk for stomach cancer associated with the highest quartile of dietary nitrite ingestion, although risk was attenuated after adjustment for vitamin C and intake of other nutrients. A cohort study in Finland[20] found no association between dietary nitrite intake and stomach cancer. The Dutch

and Finnish cohorts did not evaluate effect modification between nitrite and dietary antioxidants. Most case-control studies of dietary nitrite or nitrosamine intake and stomach cancer found positive associations with risk.[5] Case-control studies in Korea,[21] Italy,[22] and the United States[23] evaluated the joint effects of dietary nitrite and vitamin C or other antioxidants and found the highest risk among those with higher nitrite and lower antioxidant intake, subgroups of the population that would be expected to have higher rates of endogenous nitrosation. The combined effects of dietary nitrite and vitamin C were also evaluated in the two case-control studies of esophagus cancer that evaluated dietary nitrite ingestion;[23,24] both studies found evidence for a positive association with nitrite intake and a significant interaction with vitamin C. In our study, we did not observe effect modification of the animal nitrate/nitrite association by vitamin C intake; however, we had limited power to evaluate interactions.

Strengths of our analysis include the high response rates among cases and controls, a lifetime water source history, a historical nitrate database for public water supplies, and our ability to estimate nitrate intake from diet and drinking water. Furthermore, we had information on many important risk factors for these cancers. Our study had several limitations. Most notably, the small numbers of cases with elevated water nitrate exposure limited our ability to evaluate risk among subgroups likely to have higher endogenous nitrosation. We lacked information on *Helicobacter pylori*, which is an established risk factor for stomach cancer and may be an important effect modifier for NOC exposure. Most interviews were conducted with proxies who were close relatives and would therefore be expected to accurately report residence histories. However, proxy responses would likely result in greater errors for dietary estimates and if non-differential, the effect would be to attenuate risk estimates.

In summary, we found no association between ingestion of nitrate from public drinking water supplies and risk of stomach and esophagus cancers. Although based on small numbers of exposed cases, ORs for stomach cancer were elevated among private well users with higher nitrate levels. Dietary nitrite and nitrate intake from animal sources was associated with significantly increased risk for esophageal cancer and elevated risk for stomach cancer. Larger studies in populations with higher exposures to drinking water nitrate, and information on dietary intakes and *H. pylori* infection are warranted to further evaluate the NOC hypothesis and stomach and esophagus cancers.

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**TABLE 1**

**Odds Ratios and 95% Confidence Intervals for Adenocarcinoma of the Distal Stomach and Esophagus and Nitrate Concentrations in Nebraska Public Water Supplies (1965–1984)[a]**

| | Stomach Cancer | | | | Esophagus Cancer | | |
|---|---|---|---|---|---|---|---|
| | Controls | Cases | OR[b] | (95% CI) | Cases | OR[c] | (95% CI) |
| Nitrate in drinking water | | | | | | | |
| Years >10 mg/L nitrate-N | | | | | | | |
| 0 | 218 | 54 | 1.0 | | 57 | 1.0 | |
| 1–8 | 55 | 12 | 1.0 | (0.5–2.0) | 12 | 0.8 | (0.4–1.8) |
| 9+ | 48 | 13 | 1.1 | (0.5–2.3) | 15 | 0.9 | (0.4–1.9) |
| P for trend: | | | 0.672 | | | 0.384 | |
| Average nitrate level 1965–1984 (mg/L nitrate-N) | | | | | | | |
| <2.45 | 80 | 17 | 1.0 | | 17 | 1.0 | |
| 2.45–<2.58 | 80 | 29 | 2.1 | (1.0–4.4) | 27 | 2.1 | (1.0–4.6) |
| 2.58–4.32 | 80 | 16 | 1.2 | (0.5-2.6) | 21 | 1.2 | (0.5–2.7) |
| >4.32 | 81 | 17 | 1.2 | (0.5–2.7) | 19 | 1.2 | (0.6–2.7) |
| P for trend | | | 0.946 | | | 0.519 | |

[a] Includes those with 70% or more of their person-years after 1964 with Nebraska public water supply nitrate estimates;

[b] Odds ratios adjusted for year of birth, gender, education, smoking, alcohol;

[c] Odds ratios adjusted for year of birth, gender, body mass index, smoking, alcohol.

**TABLE 2**

**Odds Ratios and 95% Confidence Intervals for Adenocarcinoma of the Distal stomach and Esophagus and Nitrate and Nitrite from Dietary Sources[a]**

| | Distal Stomach Cancer | | | | Esophagus Cancer | | |
|---|---|---|---|---|---|---|---|
| | Controls | Cases | OR[b] | (95% CI) | Cases | OR[c] | (95% CI) |
| Diet nitrite and nitrate from animal sources (mg/day nitrate plus nitrite) | | | | | | | |
| <3.8 | 99 | 19 | 1.0 | | 14 | 1.0 | |
| 3.8–<5.7 | 99 | 31 | 1.6 | (0.8–3.2) | 17 | 0.7 | (0.3–1.6) |
| 5.7–<8.3 | 99 | 25 | 1.8 | (0.8–3.8) | 28 | 1.7 | (0.7–4.1) |
| 8.3+ | 100 | 29 | 1.6 | (0.7–3.7) | 39 | 2.2 | (0.9–5.7) |
| P for trend | | | 0.352 | | | 0.015 | |
| Diet nitrite from plant sources (mg/day nitrite) | | | | | | | |
| <0.36 | 94 | 23 | 1.0 | | 23 | 1.0 | 1.0 |
| 0.36–<0.52 | 102 | 22 | 1.1 | (0.4–2.7) | 28 | 1.1 | (0.5–2.3) |
| 0.52–<0.67 | 101 | 29 | 0.8 | (0.3–2.2) | 17 | 0.6 | (0.2–1.3) |
| 0.67+ | 100 | 30 | 1.1 | (0.3-3.4) | 30 | 1.0 | (0.4–2.4) |
| P for trend | | | 0.275 | | | 0.438 | |
| Diet nitrate from plant sources (mg/day nitrate-nitrogen) | | | | | | | |
| <16.9 | 99 | 24 | 1.0 | | 29 | 1.0 | |
| 16.9–<26.2 | 99 | 28 | 1.2 | (0.6–2.5) | 27 | 0.9 | (0.5–1.8) |
| 26.2–<38.8 | 99 | 26 | 1.4 | (0.7–2.9) | 18 | 0.6 | (0.3–1.3) |
| >38.8 | 100 | 26 | 1.6 | (0.7–3.6) | 24 | 0.8 | (0.3–1.8) |
| P for trend | | | 0.266 | | | 0.121 | |

[a] Excluded those with >20% unknown foods;

[b] Odds ratios adjusted for year of birth, gender, education, smoking, alcohol, total calories, vitamin C, fiber, carbohydrate;

[c] Odds ratios adjusted for year of birth, gender, body mass index, smoking, alcohol, total calories, vitamin A, folate, riboflavin, zinc, protein, carbohydrate.