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Nitrate Intake and the Risk of Thyroid Cancer and Thyroid Disease

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Abstract

Background—Nitrate is a contaminant of drinking water in agricultural areas and is found at high levels in some vegetables. Nitrate competes with uptake of iodide by the thyroid, thus potentially affecting thyroid function.

Methods—We investigated the association of nitrate intake from public water supplies and diet with the risk of thyroid cancer and self-reported hypothyroidism and hyperthyroidism in a cohort of 21,977 older women in Iowa who were enrolled in 1986 and who had used the same water supply for >10 years. We estimated nitrate ingestion from drinking water using a public database of nitrate measurements (1955–1988). Dietary nitrate intake was estimated using a food frequency questionnaire and levels from the published literature. Cancer incidence was determined through 2004.

Results—We found an increased risk of thyroid cancer with higher average nitrate levels in public water supplies and with longer consumption of water exceeding 5 mg/L nitrate-N (for ≤ 5 years at > 5 mg/L, relative risk [RR] = 2.6 [95% confidence interval (CI) = 1.1–6.2]). We observed no association with prevalence of hypothyroidism or hyperthyroidism. Increasing intake of dietary nitrate was associated with an increased risk of thyroid cancer (highest vs. lowest quartile, RR = 2.9 [1.0–8.1]; P for trend = 0.046) and with the prevalence of hypothyroidism (odds ratio = 1.2 [95% CI = 1.1–1.4]), but not hyperthyroidism.

Conclusions—Nitrate may play a role in the etiology of thyroid cancer and warrants further study.

Thyroid cancer is the most common malignancy of the endocrine system and the eighth most common cancer among women.¹ In the United States, the incidence of thyroid cancer has increased substantially since 1980, with an annual percentage increase of 6% during the period 1997–2003.² This increase may reflect better detection,³ although more recent analyses of US incidence data show that at least some of the increase has occurred for larger tumors and for men and women of all races and ethnicities,^{4,5} suggesting other factors besides detection.

Papillary thyroid cancer accounts for >70% of thyroid tumors in the United States. The only established risk factor is exposure to ionizing radiation, particularly in early childhood.¹ Some

epidemiologic studies have shown increased risk with goiter⁶ and number of pregnancies⁷ and lower risk with intake of fish and cruciferous vegetables.^{1,6}

Ingested nitrate inhibits thyroid uptake of iodide by binding to the sodium-iodide symporter on the surface of thyroid follicles. This reduces the levels of the thyroid hormones triiodothyronine (T₃) and thyroxine (T₄), which increases thyroid stimulating hormone (TSH). TSH controls thyroid hormone production through a negative feedback loop.^{8–11} Chronic stimulation of the thyroid gland by TSH can lead to proliferative changes in follicular cells, including hypertrophy and hyperplasia as well as neoplasia.^{12,13} There is some evidence from human studies that exposure to elevated nitrate levels in drinking water is associated with increased thyroid volume and increased frequency of subclinical thyroid disorders.^{14,15} Nitrate and nitrite are also precursors in the endogenous formation of N-nitroso compounds, which are potent animal carcinogens that cause thyroid and many other tumors in animal models.¹⁶ Ingestion of nitrate and nitrite has also been associated with increased risk of stomach, esophagus, and other cancers in some epidemiologic studies.¹⁷

Nitrate is a common contaminant of drinking water, particularly in agricultural areas where application of nitrogen fertilizers since the 1950s has resulted in increasing concentrations of nitrate in drinking water supplies.^{18–20} Nitrate is also a natural component of the diet, occurring at high levels in green leafy and certain root vegetables. There is some evidence that higher rates of fertilizer application increase nitrate levels in vegetables.²¹ For example, organically grown lettuce, which does not receive inorganic nitrogen fertilizer, has lower nitrate concentrations than conventionally grown lettuce.²² Thus, intensive agricultural practices may have increased exposure to nitrate from both dietary and drinking water sources.

High exposure to nitrate can cause methemoglobinemia in infants. For this reason, nitrate is regulated in public water supplies at a maximum contaminant level (MCL) of 10 mg/L as nitrate-nitrogen (N) (about 45 mg/L as nitrate). Acceptable daily intake values have also been set for dietary intake, with a particular focus on levels in baby foods. However, the regulatory limits for nitrate in food and water have not been extensively studied in relation to other health outcomes.²³ To date, epidemiologic studies of thyroid cancer risk have not evaluated nitrate intake in relation to thyroid cancer, and the literature on the relationship with thyroid conditions is limited. We investigated the association between incident thyroid cancer and prevalent hyperthyroidism and hypothyroidism in relation to nitrate intake from drinking water and dietary sources in a prospective cohort of older women in Iowa.

METHODS

Details of the study population have been described previously.^{24,25} Briefly, a questionnaire was mailed in 1986 to 98,030 women aged between 55 and 69 years who were randomly selected from Iowa driver's license files. A total of 41,836 women participated in the initial survey, and constitute the study cohort. There were slight demographic differences between respondents and nonrespondents,²⁵ with nonrespondents having slightly higher mortality from smoking-related cancers.^{25,26}

The initial interview contained questions about demographics, anthropometry, reproductive history, hormone use, family history of cancer, residence location, physical activity, smoking, alcohol consumption, and medical conditions. This included questions on whether the respondent had ever taken medication for hypothyroidism and hyperthyroidism, and whether they were currently taking medication for these conditions. The questionnaire also included a 126-item semi-quantitative food frequency questionnaire adapted from the 1984 Nurses Health Study.^{25,27} Nitrate intake from foods was calculated using the Harvard Nutrient Database

updated in 2008 for specific foods. Nitrate levels were assigned by computing means of published values weighted by consumption frequencies for the US population.

Information about the participants' usual source of drinking water was collected in the second follow-up questionnaire in 1989; a total of 36,127 women (89%) responded. Participants were asked the primary source of their drinking water at their current residence (municipal [public] water supply, private well, bottled water, or other) and how long they drank that type of water (<1 year, 1–5 years, 6–10 years, 11–20 years, >20 years, or unknown). Public supplies were the primary drinking water source (76% of women) followed by private wells (18%) and bottled water or another source (6%). Of women using the public supplies, 82% used the supply for >10 years and 70% used the supply for >20 years.

Drinking Water Analysis Cohort

We excluded women who reported cancer at the 1986 baseline (N = 3881) and women who did not respond to or died before the 1989 survey (N = 5076). To evaluate longer-term exposure to nitrate from drinking water, we excluded 7143 women who had used their public or private well supply for 10 years or less. Of the 25,736 remaining women, 20,300 used public supplies in 484 different communities and 5436 used private wells. As previously described,²⁴ we excluded women living in 47 communities that were served by multiple water sources and 41 communities for which no nitrate measurement data were available. After these exclusions, a total of 16,541 women were available for analysis of nitrate exposure from public water supplies. Together with the 5436 women who used private wells for >10 years, the drinking water analysis cohort numbered 21,977. For our analyses of dietary nitrate, we additionally excluded women who had unreasonable energy intakes (<600 or >5000 kcal/d) or had > 30 blank food items (n = 1326).

Nitrate Exposure Assessment for Water Supplies

A database of historical monitoring data for Iowa public water supplies consisted of measurements collected in each utility's water distribution system during 3 time periods (1955–1964, 1976–1982, and 1983–1988). All water samples had been analyzed at the University of Iowa Hygienic Laboratory. The 1955–1964 water samples were analyzed using the phenoldisulfonic acid spectrophotometry method,²⁸ whereas the 1976–1988 water samples were analyzed using the cadmium reduction method.²⁹ We computed several exposure metrics for each public supply, including the average nitrate concentration in the period 1955–1988 and the number of years the supply had measured levels at or above 5 mg/L nitrate-N (half the maximum contaminant level).

We had no nitrate measurement data for women using private wells, which are not regulated. Private wells are often located on farms near sources of nitrogen fertilizer applications.³⁰ The Iowa Statewide Rural Well Water Survey (1988–1989) estimated that 18% of rural private wells in Iowa had nitrate levels above 10 mg/L nitrate-N, but the concentrations varied greatly across the state and by well depth.^{30,31} We compared women who were well-water users with women using public supplies, with the lowest quartile of nitrate to determine the association of private well use with thyroid cancer and conditions.

Data Analysis

The cohort was traced annually for cancer incidence by linkage of personal identifiers to the State Health Registry of Iowa's cancer database, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.³² The mortality experience of the cohort was determined by linkage to Iowa death certificates, supplemented by linkage to the National Death Index. Each woman in the at-risk cohort was assigned person-years of follow-up from the date of return of the 1986 baseline questionnaire to the date of first cancer

diagnosis, date of emigration from Iowa, or date of death; if none of these occurred, follow-up was until 31 December 2004. During the 19 years of follow-up, 45 women in the drinking water analysis cohort were diagnosed with thyroid cancer (histologic type, 80% papillary and 18% follicular). The median time from enrollment to diagnosis was 9.3 years (interquartile range, 5.5–15.5 years). Among these 21,977 women, 3151 reported ever having hypothyroidism and 1009 reported ever having hyperthyroidism. A reported diagnosis of either thyroid condition was not associated with thyroid cancer risk.

We used Cox proportional hazards regression to compute relative risks (RRs) and 95% confidence intervals (CIs) for thyroid cancer. In the cross-sectional analysis of nonmalignant thyroid conditions, we used unconditional logistic regression to compute odds ratios (ORs) and 95% CIs for the prevalence of hyperthyroidism or hypothyroidism compared with women without the respective condition. We evaluated risk associated with nitrate intake from drinking water and dietary sources separately. Among those using public water supplies, we also calculated total nitrate intake by summing dietary and water nitrate intakes. Water nitrate intake was calculated by multiplying the average nitrate level in the public supply by 2 L/day (individual estimates of tap water intake were not obtained). For most women, nitrate intake came primarily from dietary sources. Dietary and total nitrate intakes were highly correlated (Spearman rank correlation, 0.95); therefore, we present results for dietary nitrate only.

We estimated the RR for quartiles of dietary nitrate intake using the lowest intake quartile as the reference category. Results for hypo- and hyperthyroidism associated with quintile cut points were similar to the quartile analysis and are not presented. We tested for trend using the median nitrate level in each category as a continuous variable in the models. To assess the association with nitrate concentrations in water supplies, we computed quartiles of the average nitrate level within a community during the years 1955–1988. We also computed the number of years women used a public supply with nitrate levels >5 mg/L nitrate-N in the same period. Analyses using tertiles of the average nitrate level in public supplies gave results similar to those obtained from the quartile analyses (data not shown).

Relative risks and odds ratios were adjusted for factors associated with risk of thyroid cancer or thyroid conditions in this study population, including age (continuous), vitamin C intake (<median and $\leq$ median), location of residence (farm, rural area, or town of population <1000, 1000–2499, 2500–9999, or $\geq$ 10,000), level of recreational physical activity (low, moderate, or high), education (<high school, high school, or college or vocational or graduate school), body mass index (kg/m^2), and smoking status (current, former, or never; Table 1). Variables that changed the risk estimates by >10% were included in the final models. We also evaluated potential effect modification by vitamin C (which inhibits endogenous nitrosation) by stratifying analyses of dietary and drinking water nitrate by the median intake level. We did not have comprehensive measurement data for other drinking water contaminants, such as disinfection by-products. However, adjustment for years using a chlorinated surface water source (water supplies that have elevated concentrations of disinfection by-products) did not alter the associations (data not shown).

RESULTS

Of the 21,977 women in the drinking water cohort, 73% used a public water supply, 25% used a private well, and 2% used bottled water or another source. The distribution of demographic and other characteristics of the women by quartiles of dietary nitrate intake is shown in Table 1. Nitrate intake from drinking water among those using public supplies and the proportion of women using a private well as their drinking water source were similar across dietary nitrate quartiles. Higher dietary nitrate was associated with living in a town of population $\geq$ 10,000, a lower prevalence of current smoking, more years of education, a higher level of recreational

physical activity, and higher intakes of vitamin C and total calories. Age and average BMI were similar across quartiles of dietary nitrate intake. As previously reported,²⁴ the average nitrate concentration in public drinking water supplies was not associated with these factors.

Table 2 presents the associations between private well use, the nitrate concentration in public supplies, and incidence of thyroid cancer. There was little evidence for an association of thyroid cancer incidence with use of a private well as a drinking water source. However, increased mean nitrate concentration in public water supplies was associated with increasing risk of thyroid cancer (P for trend = 0.02). Compared with women in the lowest quartile, risk was elevated 2.2-fold (95% CI = 0.83–5.76) for the highest quartile. Risk was increased 2.6-fold (1.09–6.19) for the highest versus lowest category of years of use of a public water supply with nitrate levels >5 mg/L (P for trend = 0.04).

Increasing intake of nitrate from dietary sources was also associated with increasing risk of thyroid cancer (Table 3). The relative risk was 2.9 (1.00–8.11) for those in the highest versus lowest quartile of dietary nitrate (P for trend = 0.046).

We observed no association between the prevalence of hypothyroidism and hyperthyroidism with either the mean nitrate concentration in public water supplies or increasing years of nitrate levels >5 mg/L (Table 4). Use of a private well as a drinking water source was not associated with risk of either condition.

Increasing intake of nitrate from dietary sources was associated with increased prevalence of hypothyroidism (P for trend = 0.001; Table 5). Compared with those who had the lowest intake, there was a 24% higher prevalence of hypothyroidism among those in the highest intake quartile (95% CI = 1.10–1.40). There was no association with hyperthyroidism.

We evaluated drinking water and dietary nitrate intakes by the median intake level of total vitamin C from food and supplements because vitamin C inhibits endogenous nitrosation. Thus, risk associated with nitrate intake may be higher among those with lower vitamin C intakes. For hypothyroidism, the association with dietary nitrate intake was stronger among those with intakes of vitamin C below the median (P for trend = 0.02) than among those with higher intake (P for trend = 0.50); however, the test for multiplicative interaction was not significant (data not shown). There was no evidence of interaction between any of the nitrate exposure metrics and vitamin C for hyperthyroidism. Stratified analyses by other factors (including age, residence location, body mass index, smoking status, and education) showed no evidence of heterogeneity (data not shown).

Stratifying by median vitamin C intake, we observed somewhat stronger associations between dietary nitrate intake and thyroid cancer risk among those with lower vitamin C intake; however, the number of thyroid cancer cases was small in each group and the risks were unstable (data not shown).

DISCUSSION

We found a positive association between nitrate intake from public drinking water supplies and incidence of thyroid cancer. However, we observed no increased risk of thyroid cancer among users of private wells, for whom we had no measurement data. Drinking-water nitrate concentrations and private well use were not associated with thyroid conditions. Greater dietary nitrate intake was associated with an increased risk of thyroid cancer and a greater prevalence of hypothyroidism but not hyperthyroidism. These positive findings are of interest in light of the increasing incidence of thyroid cancer over the past decades, and the ubiquitous exposure to nitrate from dietary and drinking water sources—the latter occurring mostly in agricultural regions.

Two epidemiologic studies^{14,15} among populations with sufficient iodine intake have provided some evidence that nitrate ingestion via drinking water is associated with subclinical hypothyroidism and hypertrophy of the thyroid. The hypothesized mechanism is inhibition of iodide uptake due to competitive binding to the sodium-iodide symporter on the surface of thyroid follicles. Nitrate levels in drinking water supplies have been associated with increased thyroid volume,^{14,15} increased TSH levels,¹⁴ and other signs of subclinical thyroid disorders.¹⁵

We did not observe an increased risk of hyperthyroidism or hypothyroidism in relation to nitrate exposure from public water supplies. However, dietary nitrate accounted for the majority of nitrate intake in this study population. The association between dietary nitrate intake and hypothyroidism was stronger among those with lower vitamin C intakes, suggesting that this dietary pattern (which is associated with endogenous formation of *N*-nitroso compounds¹⁷) rather than the nitrate level alone may be important. Still, this may be a chance finding. Our analysis of thyroid conditions was limited to self-reported medication use for these prevalent conditions; we did not have more objective or alternative measures of thyroid dysfunction such as thyroid hormone levels, thyroid weight, or ultrasonography data. We did not have information about iodine intake; however, the US National Health and Nutrition Examination Survey (NHANES I, 1971–1974) showed adequate to excessive dietary iodine intake in the US population.³³

To our knowledge, these associations for thyroid cancer have not been reported in an epidemiologic study previously and suggest that nitrate intake may be an important area for future research. Although based on a small number of cases, our results are consistent with animal data showing that chronic TSH stimulation of the thyroid gland from nitrate exposure can lead to proliferative changes in follicular cells, including hypertrophy and hyperplasia. Alternatively, *N*-nitroso compound formation may be a mechanism because about 5% of ingested nitrate is reduced to nitrite in vivo, thus serving as a precursor in the *N*-nitroso formation. Specific *N*-nitroso compounds cause thyroid and other cancers in animal studies.¹⁶

Strengths of this study include the prospective design and our historical database in which all samples were analyzed by the same laboratory. Additionally, we were able to reduce exposure misclassification by excluding communities with varying nitrate levels due to multiple sources. Other strengths include rapid and complete cancer ascertainment through the Iowa SEER registry, low population mobility, and information about several potential confounders.

There were several limitations to our exposure assessment. We ascertained the drinking water source only at the residence in 1989, and not for prior residences. An unknown proportion of women may have been consuming some portion of their drinking water from another source, particularly if they were employed in another town. Only 33% of women were employed outside the home in 1986.²⁴ On the basis of the 1990 US census data for Iowa,³⁴ 68% of workers lived and worked in the same town and, therefore, would have been served by the same public supply. Use of other water sources with different nitrate levels would be expected to be nondifferential and, therefore, is most likely to attenuate associations.

Nitrate concentrations can be substantially higher in private wells than public supplies because private wells are not regulated. However, concentrations in private wells vary depending on depth, construction, aquifer characteristics, and other factors,¹⁸ making private well use a poor surrogate for nitrate exposure. We did not have information on the usual amount of tap water intake, which may also have resulted in nondifferential misclassification.

Finally, although the exposure of interest was nitrate in drinking water, we could not evaluate other potential contaminants in drinking water, such as pesticides and perchlorate; the latter is a known inhibitor of iodide uptake by the thyroid cells,¹¹ which may be of etiologic importance.

In a recent survey of private wells across the state³⁵ perchlorate was detected in only 1 well, indicating that contamination is not common in Iowa.

Increased diagnosis has been suggested as an explanation for the rise in thyroid cancer incidence during the past decades.^{3,36} However, increases in papillary thyroid cancer, the major histologic type, occurred for all racial and ethnic groups and for local, regional, and distant diseases, suggesting that increases in diagnosis cannot explain all of the increase in incidence.^{4,5} Access to medical care can affect diagnosis rates, although all of the women were of age at least 65 years at the last follow-up and so were covered by Medicare. Women with higher dietary nitrate intake were less likely to be current or past smokers, were more educated, and engaged in more physical activity than women with lower nitrate intake. These factors, which are indicative of a healthy lifestyle, did not differ by level of nitrate in public water supplies.²⁴ If a healthy lifestyle, including the consumption of high nitrate vegetables, was associated with increased use of health care screening for thyroid cancer, screening bias might partly explain the positive association with dietary nitrate intake, but not with drinking water nitrate concentrations. Due to the limited number of thyroid cancer cases, it was not possible to stratify by educational level, smoking status, or physical activity to evaluate the consistency of the association across subgroups of the population; however, education, smoking, and physical activity were not confounders.

In summary, we found that nitrate ingestion from dietary and drinking water sources was associated with an increased risk of thyroid cancer. Furthermore, our results suggest that higher intake of dietary nitrate is associated with hypothyroidism. Our findings for thyroid cancer were based on small numbers of cases; larger studies will be required to confirm or refute our observations and to evaluate the potential interactions between nitrate ingestion and factors that affect rates of endogenous nitrosation. Ascertainment of incident thyroid conditions to establish the timing of the association between nitrate ingestion and hypothyroidism would be preferable to self-reported information about these conditions. Our findings are novel and are biologically plausible. Given the increase in thyroid cancer incidence during the past decades, without an identifiable cause, a possible role for nitrate should be considered in future epidemiologic studies of thyroid cancer and thyroid conditions.

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TABLE 1

Baseline Characteristics of Women in the Drinking Water Analysis Cohort by Dietary Nitrate Intake Quartiles^a (n = 20,651)

Characteristic	Dietary Nitrate Intake (mg/d Nitrate-N)			
	≤17.4	17.4–27.7	27.8–41.1	>41.1
Nitrate intake from dietary sources (mg/d nitrate-N); median	12.4	22.4	33.7	53.8
Nitrate intake from drinking water (mg/d nitrate-N); ^b median	2.3	1.9	2.2	2.1
Using private wells; %	24.2	25.7	24.3	25.1
Total nitrate intake within quartiles (mg/d nitrate-N); ^a median	15.8	26.2	37.2	57.2
Age (years); mean (SD)	61.3 (4.2)	61.3 (4.2)	61.4 (4.2)	61.7 (4.2)
Residence location; %				
Farm	18.6	20.6	19.7	19.3
Rural area (not a farm)	6.6	6.2	6.1	6.1
Town with population <1000	8.6	6.8	7.2	7.0
Town with population 1000–2499	11.2	9.1	9.3	9.2
Town with population 2500–10,000	16.6	16.8	15.1	14.6
Town with population >10,000	37.8	39.9	42.1	43.2
Smoking status; %				
Current smoker or quit <1 year ago	17.0	14.6	13.9	11.8
Former smoker	17.6	19.5	19.4	22.6
Never	63.9	64.7	65.4	64.3
College graduate or postgraduate; %	30.4	39.2	43.7	50.0
BMI (kg/m ²); mean (SD)	26.8 (5.1)	26.9 (5.0)	26.9 (5.0)	27.0 (5.0)
High level of recreational physical activity; %	17.0	22.0	26.6	34.3
Energy (kcal/day); median	1436	1649	1802	1986
Vitamin C (mg/day); median	132	169	196	250

^aExcludes those with inadequate dietary information; assumes consumption of 2 L/day of tap water.

^bWomen using public water supplies (N = 15530); assumes consumption of 2 L/day of tap water.

TABLE 2

Association Between Nitrate Concentrations in Public Drinking Water Supplies and Incident Thyroid Cancer, 1986–2004

Drinking Water Source	No. Person-Years	No. Cases	RR (95% CI) ^a	Test for Trend
Private well	85,630	12	1.13 (0.83–3.66)	—
Public supply (mean nitrate concentration [mg/L nitrate-N])				
<0.36 ^b	63,293	6	1.00	
0.36–1.00	62,933	3	0.50 (0.13–2.01)	
1.01–2.46	62,268	6	1.17 (0.37–3.66)	
>2.46	63,114	13	2.18 (0.83–5.76)	<i>P</i> = 0.02
Public supply (years >5 mg/L nitrate-N)				
0 ^b	172,742	17	1.00	
1–4	43,350	3	0.70 (0.20–2.36)	
≥5	35,515	8	2.59 (1.09–6.19)	<i>P</i> = 0.040

^a Adjusted for age, vitamin C intake, and residence location.

^b Reference category.

TABLE 3Association Between Dietary Nitrate and Thyroid Cancer,^a 1986–2004

Dietary Nitrate (mg/day Nitrate-N)	Person-Years	No. Cases	RR (95% CI) ^b	Test for Trend
≤17.4 ^c	77,806	6	1.00	
17.5–27.7	86,270	10	1.65 (0.59–4.61)	
27.8–41.1	89,707	10	1.69 (0.58–4.84)	
>41.1	83,454	14	2.85 (1.00–8.11)	<i>P</i> = 0.046

^aExcludes those with inadequate dietary information.^bAdjusted for age, total calories, vitamin C intake, and residence location.^cReference category.

TABLE 4

Association Between Nitrate Concentrations in Public Drinking Water Supplies and Prevalent Hypothyroidism and Hyperthyroidism, 1986

Drinking Water Source	Hypothyroidism		Hyperthyroidism	
	No. Cases	OR (95% CI) ^a	No. Cases	OR (95% CI) ^b
Private well	674	0.99 (0.81–1.20)	209	0.86 (0.70–1.05)
Public supply (mean nitrate concentration [mg/L nitrate-N])				
<0.36 ^c	590	1.00	188	1.00
0.36–1.00	587	0.99 (0.88–1.13)	189	1.01 (0.82–1.24)
1.01–2.46	567	0.95 (0.83–1.08)	169	0.88 (0.71–1.09)
>2.46	600	0.98 (0.86–1.11)	182	0.98 (0.79–1.21)
Test for trend		<i>P</i> = 0.81		<i>P</i> = 0.86
Public supply (years >5 mg/L nitrate-N)				
0 ^c	1583	1.00	514	1.00
1–4	385	0.96 (0.85–1.08)	108	0.83 (0.67–1.03)
≥5	376	1.06 (0.93–1.20)	106	1.01 (0.82–1.26)
Test for trend		<i>P</i> = 0.47		<i>P</i> = 0.88

^a Adjusted for age, body mass index, residence, education, and smoking status; excludes 672 women with unknown hypothyroidism status.

^b Adjusted for age, body mass index, education, and smoking status; excludes 820 women with unknown hyperthyroidism status.

^c Reference category.

TABLE 5

Association Between Dietary Nitrate and Prevalent Hypothyroidism And Hyperthyroidism, 1986

Dietary Nitrate (mg Nitrate-N/day)	Hypothyroidism		Hyperthyroidism	
	No. Cases	OR (95% CI) ^a	No. Cases	OR (95% CI) ^b
≤17.4 ^c	613	1.00	228	1.00
17.5–27.7	765	1.13 (1.01–1.27)	233	0.90 (0.75–1.09)
27.8–41.1	826	1.19 (1.06–1.33)	241	0.89 (0.73–1.08)
>41.1	814	1.24 (1.10–1.40)	235	0.88 (0.72–1.08)
Test for trend		<i>P</i> = 0.001		<i>P</i> = 0.30

^a Adjusted for age, total calories, body mass index, residence, education, and smoking status; excludes 672 women with unknown hypothyroidism status.

^b Adjusted for age, total calories, body mass index, education, and smoking status; excludes 820 women with unknown hyperthyroidism status.

^c Reference category.