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Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study

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Abstract

During the past several decades, an increasing incidence of thyroid cancer has been observed worldwide. Nitrate inhibits iodide uptake by the thyroid, potentially disrupting thyroid function. An increased risk of thyroid cancer associated with nitrate intake was recently reported in a cohort study of older women in Iowa. We evaluated dietary nitrate and nitrite intake and thyroid cancer risk overall and for subtypes in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a large prospective cohort of 490,194 men and women, ages 50–71 years in 1995–1996. Dietary intakes were assessed using a 124-item food frequency questionnaire. During an average of 7 years of follow-up we identified 370 incident thyroid cancer cases (170 men, 200 women) with complete dietary information. Among men, increasing nitrate intake was positively associated with thyroid cancer risk (relative risk (RR) for the highest quintile versus lowest quintile RR=2.28, 95% CI: 1.29–4.04l; p-trend <0.001); however, we observed no trend with intake among women (p-trend=0.61). Nitrite intake was not associated with risk of thyroid cancer for either men or women. We evaluated risk for the two main types of thyroid cancer. We found positive associations for nitrate intake and both papillary (RR = 2.10; 95%CI: 1.09–4.05; p-trend=0.05) and follicular thyroid cancer (RR= 3.42; 95%CI: 1.03–11.4; p-trend=0.01) among men. Nitrite intake was associated with increased risk of follicular thyroid cancer (RR= 2.74; 95%CI: 0.86–8.77; p-trend=0.04) among men. Our results support a role of nitrate in thyroid cancer risk and suggest that further studies to investigate these exposures are warranted.

Introduction

During the past several decades, an increasing incidence of thyroid cancer has been observed worldwide (1–6). From the mid-1970s to 2005, the age-adjusted papillary thyroid cancer rates in the U.S. rose 158% from 4.7 to 12.1 per 100,000 among women and 106%

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from 1.9 to 3.9 per 100,000 among men (1). Although increased diagnosis probably accounts for some of the increase, other factors responsible for the rapid increase are currently unknown. The increased risk of thyroid cancer associated with ionizing radiation has been well established (7,8), but no other environmental exposures have been identified and consistent dietary associations have been limited to iodine deficiency (7,8).

Nitrate is a natural component of plants and is found at high concentrations in leafy vegetables, such as lettuce and spinach, and some root vegetables, such as beets (9). Nitrate is also a contaminant of drinking water and can be a major source of intake when levels are at or above the maximum contaminant level (MCL) of 10 mg/L nitrate-nitrogen (N) (approximately 45 mg/L as nitrate) (9–11). Nitrite and nitrate salts are added to cured meats such as bacon, hot dogs, and ham to prevent the growth of spore-forming bacterium as well as to add color and flavor (12).

Nitrate is of particular interest for thyroid cancer as nitrate competitively inhibits iodide uptake by the thyroid. Decreases in available iodide can result in lower production of the thyroid hormones T_3 and T_4, resulting in increased production of thyroid stimulating hormone (TSH). Based on findings from animal models, chronic TSH stimulation of the thyroid is thought to play a role in thyroid carcinogenesis (13). In addition, nitrate is reduced to nitrite by oral bacteria in human, and nitrite reacts with amines and amides *in vivo* to form nitrosamines and nitrosamides (collectively known as N-nitroso compounds (NOC)), potent animal carcinogens. Specific NOCs have been shown to cause thyroid tumors in animal studies (14). Most previous investigations into the association between nitrate and nitrite and human cancer have focused on gastrointestinal cancers, although the relationship with thyroid cancer risk is biologically plausible (15–20).

A positive association between nitrate intake and thyroid cancer was recently reported in the Iowa Women's Health Study (21). The investigators found that increasing intake of dietary and drinking water nitrate was associated with a significant increase in the risk of thyroid cancer (21). However, the study was limited to women and the analysis of dietary nitrate and thyroid cancer included only 40 cases. We further evaluate the hypothesis that nitrate ingestion is associated with thyroid cancer risk in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a large U.S. prospective cohort including a half a million people aged 50 to 71 years at baseline,. We also investigate the association with dietary nitrite intake to examine the hypothesis that dietary precursors of NOCs may increase thyroid cancer risk.

Methods

Study population

The NIH-AARP Diet and Health Study was initiated in 1995–1996 when an extensive baseline questionnaire was mailed to 3.5 million AARP members aged 50–71 years residing in one of 6 US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or 2 US metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) (22). This questionnaire ascertained information on usual dietary intake over the past 12 months, use of individual and multivitamin supplements, smoking history, alcohol intake, height and weight at baseline and other factors. A total of 617,119 persons returned the baseline questionnaire (17.6 %), and 567,169 questionnaires were determined to have been satisfactorily completed.

Among the 567,169 persons with satisfactory baseline questionnaires, we excluded those with duplicate questionnaires (n = 179), those who had died or moved out of the study area prior to baseline (n = 582), those who withdrew from the study (n = 6), those who had

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questionnaires completed by proxy respondents (*n* = 15,760), those who had been previously diagnosed with cancer except for nonmelanoma skin cancer (*n* = 51,205), and those with extreme values for total energy intake (beyond twice the interquartile range of Box-Cox log-transformed intake, corresponding to <415 kcal/day and >6,144 kcal/day for men and <317 kcal/day and >4,791 kcal/day for women; total *n* = 4,434). After these exclusions, 292,125 men and 198,069 women were available for analysis.

Cancer ascertainment

Incident, first primary thyroid cancer cases (*International Classification of Diseases for Oncology*, Third Edition (ICD-O-3) (23), codes C73) were identified through December 31, 2003, via linkage of the NIH-AARP cohort database to the databases of the 8 original plus three additional state cancer registries and the National Death Index Plus. The state cancer registries are certified by the North American Association of Central Cancer Registries as meeting the highest standard of quality (90% case ascertainment within 24 months of the close of the diagnosis year). In a validation study, we estimated that 90% of all cancer cases in our cohort were validly identified via linkage to state cancer registries, as compared with self-reports and medical records (24).

A total of 370 incident thyroid cancer cases were identified (170 in men and 200 in women) during an average of 7 years of follow-up. Papillary thyroid cancer (ICD-O-3 codes 8050, 8660, 8340, 8341, 8343, 8344, and 8350) was the most common histologic type, accounting for 114 (67%) cases in men and 144 (72%) of cases in women. Follicular carcinoma (ICD-O-3 codes 8290, 8330, 8331, 8332, and 8335) was the second most frequent type in men (n=30, 18%), followed by medullary (ICD-O-3 codes 8345, 8346, 8510) (n=10, 6%) and anaplastic (ICD-O-3 codes 8020, 8021, 8012, 8030, 8031, and 8032) 1 case; 1%) carcinomas. In women, follicular carcinoma accounted for 34 (17%) thyroid cancer cases, followed by 6 cases of medullary (3%) and 6 anaplastic (3%) carcinomas. The histology of 25 additional cases was not specified (7% of all cases).

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

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Dietary intake

The dietary component of the baseline questionnaire asked about the frequency of consumption during the past 12 months and corresponding portion sizes of 124 food items, including 14 fruit and 23 vegetables, and fresh and processed meats. Participants were queried about their frequency of intake in 10 categories ranging from "never" to "2+ times per day" for foods and "never" to "6+ times per day" for beverages. Each line item was accompanied by 3 possible portion size categories. The food items, portion sizes, nutrient database, and pyramid food servings database were constructed using methods developed by Subar et al. (25) with national dietary data from the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) (26). The Pyramid Servings Database utilized a recipe file to disaggregate food mixtures into their component ingredients and assign them to food groups. The food frequency questionnaire was validated using two 24-hour recalls in a subset of the cohort (27).

The nitrite and nitrate content of over 3,000 foods were determined by conducting a review of the literature focusing on U.S. and Canadian foods and calculating means of the published values weighted by the number of samples analyzed (28,29). If values from U.S. or Canadian foods were unavailable, we used values from other Western countries. The nitrite and nitrate values for foods constituting a FFQ line item were combined by weighting the food-specific values by sex-specific intake amounts from the 1994–1996 CSFII (25). For

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example, the nitrate content of a line item was calculated using a weighted average of the nitrate content in the included foods where the weights were determined by intake amounts from the CSFII, specific for the age group and gender. Daily intakes of nitrate and nitrite were calculated by multiplying the frequency of consumption of each line item by its nitrate or nitrite content and summing over line items. In addition to calculating dietary nitrite and nitrate from all foods, we calculated nitrite from plant, animal, and processed meat sources separately.

The major contributors to nitrate intake were lettuce (34.4%), cooked spinach (10.2%), and broccoli (4.5%) and the major contributors to nitrite intake were cold cuts (7.2%), pasta (6.7%), and bread (6.5%). The sources were similar for men and women. Because the major sources of nitrate were vegetables, which also contain beneficial nutrients such as vitamin C, beta-carotene and folate, we evaluated the relationship of these micronutrients with nitrate intake in our study population. The correlations for intake of nitrate with vitamin C, beta-carotene, and folate among men were 0.36, 0.65, and 0.52, respectively, among men and 0.39, 0.64, and 0.60, respectively, among women. We also looked at the correlation of nitrate and cruciferous vegetables (broccoli, cauliflower, brussel sprouts, collard greens, and cabbage) as they are hypothesized to increase thyroid cancer risk. The correlation was 0.40 in both men and women.

Although information about the usual source of drinking water and tap water intake was not assessed for the cohort, we used the census tract location of a participant's residence at enrollment to estimate the likelihood that they may have been exposed to elevated nitrate concentrations via their drinking water supply in a Geographic Information System (GIS). First, residential addresses for all participants were geocoded to a census tract. Using ESRI's ArcInfo (Redlands, CA) GIS software, we then linked the census tract to a geospatial model developed by Nolan et al. (30) that predicts nitrate contamination of ground water used for drinking water across the continental United States. The predicted nitrate concentration represents average levels in an area of about 20 square km, which is the minimum size of the U.S. Geological Survey groundwater monitoring network. Ground water provides drinking water for more than one-half of the US population (31), and is the sole source of drinking water for many rural communities and some large cities. The model includes variables that are significant predictors of nitrate in ground water including nitrogen fertilizer and manure applications, the location of orchards/vineyards, aquifer rock type, and population density and provides a predicted nitrate concentration level (mg/L nitrate-N). Next, we calculated the area within each census tract that intersected areas estimated to have an average nitrate level ≥10 mg/L, the MCL. We identified for exclusion from some analyses, participants who resided in census tracts where ≥50% of the area was estimated to overlay groundwater with nitrate levels 10 mg/L or greater because their nitrate intake from water sources might have been substantial. Using this approach, we excluded approximately 11,764 study participants and 12 thyroid cancer cases (2.4% of the study population).

Statistical analysis

Person-years of follow-up for each participant accrued from the date of return of the baseline questionnaire to the date of thyroid cancer diagnosis, the date of moving out of the registry ascertainment area, death, or the end of the follow-up period. Cox proportional hazards models with person-years as the underlying time metric were used to estimate relative risks (RR) and 95% confidence intervals (CI) for thyroid cancer according to quintiles of intake of nitrate and nitrite. We also examined the associations between quartiles of nitrate and nitrite intake for the papillary and follicular thyroid cancer subtypes. Tests for linear trend were conducted using the median value of each exposure category as a continuous variable in the model. We evaluated total dietary nitrate and nitrite intake as well as the animal and plant sources of nitrite separately.

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Consumption of nitrate and nitrite intake (mg per day) was adjusted for energy intake using the nutrient density method (32), which expresses intake per 1000 calories of total caloric intake. All multivariate models were adjusted for age, smoking status (never, current, former), race (White, Black, other), family history of any cancer (yes, no), education (<12 years, 12 years or high school equivalent, some college, college graduate or postgraduate), and BMI (<25, 25–29.9, 30–34.9, ≥35 kg/m^2) as these factors have been shown to be associated with thyroid cancer risk in this and other study populations. We also present models additionally adjusted for vitamin C consumption (mg/day), beta-carotene consumption (mg/day) and folate consumption (mg/day) to evaluate the possibility that these micronutrients may be confounders of the association with nitrate and nitrite. We did not include cruciferous vegetable intake in the full micronutrient adjusted model as it did not result in a change in the risk estimate when included in the thyroid cancer risk factor model and it was not associated with an increased risk of thyroid cancer.

To evaluate the consistency of the associations, we stratified by age (at or above/below the median age of 62.6), body mass index (at or above/below median of 27), and education (high school or fewer years of education; some college or greater years of education). We stratified by smoking status (ever/never), vitamin C intake (at or above/below median 134.4mg), vitamin E intake (at or above/below median 7.9mg), and red meat intake (at or above/below median 51.1g) to evaluate factors potentially affecting nitrosation. We assessed multiplicative interaction by adding the relevant cross-product term to main-effects models in sex-specific analyses. We repeated our analyses in a sample restricted to those without potentially high intake of nitrate from drinking water.

We also tested whether nitrate and nitrite intake were log-linearly associated with risk of thyroid cancer by comparing a non-parametric regression curve obtained using restricted cubic splines with the linear model (33). The number and location of the knots were identified through a stepwise selection process. Nitrate and nitrite values above the 1^{st} percentile and below the 99^{th} percentile were included in the smoothing spline models; the reference point identified corresponded to the minimum nitrate or nitrite intake value, and four knots were used. The likelihood ratio test and visual inspection of the restricted cubic splines were used assess the continuous association.

For all comparisons, *P* values were 2-sided and an alpha level of $\alpha < 0.05$ indicated statistical significance.

Results

The unadjusted incidence of thyroid cancer overall in this population was 16.8 per 100,000 person-years (12.8 per 100,000 man-years among men and 23.4 per 100,000 woman-years among women). The mean dietary nitrate intake in the total study population was 88 mg/day (sd = 65 mg/day) and the mean daily nitrite intake was 1.2 mg/day (sd = 0.6 mg/day). The average intake of nitrate from plant sources was 83 mg/day (92.0 % of the total nitrate intake); whereas, average intake of nitrite from plant sources was 0.8mg/day (66.3% of the total nitrite intake). Men and women in the highest compared to the lowest quintile of nitrate intake reported lower energy intake, were more educated, more physically active, and were more likely to consume fruits and vegetables (Table 1).

Men and women in the highest versus the lowest quintile of nitrite intake were less likely to be white and to be current or recent smokers. Men and women in the highest quintile of nitrite intake tended to be more educated, more physically active, and more likely to consume fruits, vegetables, and processed meats than those in the lowest quintile (Table 1).

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In our analysis of thyroid cancer risk by quintiles of nitrate and nitrite intake, we observed a non-significant increase in the risk of thyroid cancer for men and women combined in the micronutrient adjusted models although the trend for nitrate was significant in the age-adjusted (p for trend = 0.01) and risk factor adjusted (p for trend = 0.01) models (Table 2). A significant interaction between dietary nitrate intake and risk of thyroid cancer by sex (p for interaction <0.01) was observed for all models. Among men, we identified a more than two-fold significantly increased risk of thyroid cancer in the highest intake quintile (Q5 vs. Q1 RR = 2.28; 95%CI: 1.29–4.04) in the fully adjusted micronutrient model, with a monotonic increase in thyroid cancer risk (p-trend <0.01) in both multivariate models. In contrast, among women, intake quintiles 2 through 5 were associated with a decreased risk of thyroid cancer risk although there was no trend with intake (p = 0.61) for all models. Nitrite intake was not associated with risk of thyroid cancer overall, or for either men or women in the age-adjusted or multivariate models (Table 2).

The spline analyses of the relative risk and 95% confidence interval for thyroid cancer in men and women demonstrated an increasing risk with increasing nitrate intake among men and a slight decrease in risk among women (Figure 1). A formal test for interaction by sex using multivariate regression confirmed that the trends by gender were different (p <0.01). We did not observe a significant change in risk for men or women with increasing nitrite intake or a difference in risk by gender for nitrite.

We evaluated the relationship between quartiles of nitrate and nitrite intake for the papillary (Table 3) and follicular subtypes (Table 4) of thyroid cancer. For the papillary type, we observed a borderline positive trend in risk (p for trend=0.05) and a significant association in the highest nitrate intake quartiles among men (RR = 2.10; 95%CI: 1.09–4.05) in the in micronutrient adjusted model (Table 3). The trend for increasing nitrate intake among in the age-adjusted and risk factor adjusted models was significant (p for trend <0.01 for both models) and the RRs were stronger (Q4 vs. Q1 RR = 2.90 and RR = 2.21, respectively). Among women, the RRs were below one for all nitrate intake quartiles for papillary thyroid cancer and no significant trends were observed in the age-adjusted or multivariate models.

We observed a more than 3-fold increased risk of follicular thyroid cancer among men in the high nitrate intake quartile (Q4 vs. Q1 RR = 3.42; 95%CI: 1.03–11.4; p for trend<0.01 in micronutrient adjusted model) (Table 4) in the age-adjusted and multivariate models. No change in follicular thyroid cancer risk was observed among women in the age-adjusted or multivariate models. For dietary nitrite, we observed elevated RRs for follicular thyroid cancer associated with the third and fourth intake quartiles in men and a positive trend in risk in the age-adjusted and multivariate models (p for trend = 0.04 in micronutrient adjusted model) (Table 4). The increase in follicular thyroid cancer risk from dietary nitrite in men appeared to be due to plant sources of nitrite (p for trend = 0.02 in micronutrient adjusted model) rather than animal sources of nitrite (p for trend = 0.37 in micronutrient adjusted model) (data not shown). The top five foods that together contributed 42.7% of intake of nitrite from plant sources in this cohort are pasta, rice/grains, white breads/rolls, hot breakfast cereals, and apples.

We stratified our analyses by age (median), education (no/some college), BMI (at or above/ below median), and physical activity (at or above/below 3–4 times per week) to assess the consistency of the association. Results were similar by levels of these factors for men and women (data not shown). Restricting our analyses to women who were post-menopausal resulted in no material change in risk. Because vitamins C and E and red meat intake affect endogenous formation of NOCs, we conducted analyses stratified by the median intake level of each of these dietary factors, but found no significant interactions.

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As smoking has also been shown to affect endogenous formation of NOCs (38), we stratified our analysis of nitrate and nitrite intake by never and ever smoking status (data not shown). A borderline significant interaction was found for smoking status and nitrite intake in women (p interaction = 0.05) in micronutrient adjusted model. Among female smokers, we found a significant trend of increasing risk of thyroid cancer in the full multivariate model (p for trend = 0.04), including RRs that increased from 1.08 (95%CI: 0.52–2.19) in the second quintile to 1.28 (95%CI: 0.65–2.52) in the third quintile, 1.52 (95%CI: 0.79–2.52) in the fourth quintile and 1.74 (0.92–3.32) in the highest quintile. In contrast, the RRs in never smoker women were all less than 1.0 with no significant trend in the full multivariate model. We did not observe a significant trend with nitrite intake in male smokers or non-smokers or among men and women combined.

The results were unchanged when we excluded the 2.5% of the study population who resided in census tracts where 50% of the study population had predicted drinking water nitrate levels greater than 10 mg/L.

Discussion

In this large prospective cohort of AARP members, we found that higher intake of dietary nitrate was associated with an increased risk of thyroid cancer in men. The positive association among men was present for both the papillary and follicular subtypes. These findings were only modestly changed when we adjusted for micronutrients that were correlated with nitrate intake, demonstrating that the association with nitrate was unlikely due to other micronutrients in vegetables. The findings were also unchanged when we excluded persons for whom contaminated drinking water may have constituted a substantial portion of their nitrate intake. Nitrite intake was not clearly associated with risk of thyroid cancer overall for either men or women; however, we observed an increased risk of follicular thyroid cancer in the highest nitrite intake quartile among men and a significant trend. When we stratified our results by smoking status, we found evidence of a significant increase in thyroid cancer risk with elevated nitrite intake among female smokers.

Our finding of an increased risk of thyroid cancer with increasing nitrate intake **in men** is consistent with the recent report from a cohort of older women in Iowa (21) where a positive association between both dietary and drinking water nitrate ingestion and thyroid cancer risk was observed. A RR of 2.9 (95% CI: 1.0–8.1) with a significant trend (p-trend=0.046) was observed comparing those in the highest quartile of dietary nitrate intake to the lowest quartile (21). They also 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, RR = 2.6; 95% CI: 1.1–6.2). Given that the positive findings among women from the Iowa study are consistent with our findings among men, it is not clear why we observed no association with dietary nitrate among women. In both studies, leafy green vegetables (lettuce and spinach) were the major contributors to nitrate intake.

The gender difference we observed may be partially explained by differential dietary reporting errors between men and women in our study population. Studies have found that healthful attitudes, beliefs, and dietary habits were more strongly correlated with vegetable intake among women than among men (34,35) and that women over-reported foods perceived as healthy (35,36). In other studies of this cohort (37), the authors found that vegetable intake was not associated with risk of total cancer among women, but was associated with a significant decrease in risk in men. Misreporting of vegetable intake by women in our study could have led to exposure misclassification, resulting in an attenuated association.

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We did find evidence of an increased risk of thyroid cancer among female smokers with high nitrite intake. Endogenous nitrosation is known to be associated with tobacco smoking (38). We subsequently hypothesized that nitrate and nitrite intake may result in different thyroid cancer risk profiles in smokers compared to non-smokers. This is because thiocyanate, which is present in tobacco smoke, is a strong catalyst of nitrosation of amines (39). Our finding of an increased risk of thyroid cancer with increasing nitrite intake in female smokers is interesting. It is not clear why this was observed in women and not men. Although this has not been previously reported, and it could be due to chance, it is biologically plausible, and it suggests that the potential interaction of tobacco intake and NOC precursors should be evaluated in the future.

Factors associated with the detection of thyroid cancers are important to consider in the assessment of thyroid cancer risk due to the recent changes in technology and the greater availability of diagnostic tests in recent decades (1). It is notable that men and women in the highest nitrate intake quintile had more education, increased physical activity, increased fruit and vegetable intake, and lower caloric intake. These characteristics are indicative of a more health conscious lifestyle and may be correlated with increased utilization of medical services and increased detection of thyroid tumors. However, it is unlikely that detection bias would occur only among men as such a detection bias would likely be higher among women due to their increased healthcare utilization patterns (40). In addition, we observed similar results among men and women younger than 65 and 65 and older, when access to health care via Medicare is available to all Americans, suggesting that increased detection is not a substantial source of bias in our study population.

Drinking water nitrate can constitute the majority of nitrate intake at levels near or above the MCL (41). Information on the primary source of drinking water was not obtained in this study; however, our findings were not altered when we excluded individuals living in areas where nitrate contamination of ground water is highly probable. Although a limitation of our study is that we did not have surface water estimates to identify persons for exclusion, more than half of the US population obtains drinking water from groundwater sources (42). Furthermore, surface waters in areas with contaminated groundwater are also likely to be affected. Lack of individual level drinking water information likely resulted in some misclassification of nitrate exposure from drinking water. Future investigation in this area, if possible, should utilize a study design that captures drinking water intake of nitrate in addition to dietary intake.

The possibility that nitrate intake from both the water and diet may be correlated with exposure to pesticides is an important point to consider. Insecticides, herbicides, and fungicides have been previously reported to have thyroid disrupting effects through a variety of mechanisms (43,44). Animal studies have shown that exposure to various pesticides can change the levels of thyroid hormones as well as increase TSH levels (45). It would be expected that those consume high levels of vegetables, and therefore high nitrate intake, would also potentially experience have exposure to pesticides. Additionally, nitrate contamination in ground water often occurs in agricultural areas with high nitrogen-based fertilizer use; these areas would also likely have increased levels of pesticides in the water as well. Future studies in this area would be strengthened through evaluation of the body burden of pesticides using biological samples in addition to the consideration of the role of nitrate intake.

Strengths of this study include the use of a detailed questionnaire to assess dietary intake of nitrate and nitrite and the wide range of intake. Among participants in our study, median intake of nitrate in the highest quintile was over 5 times that in the lowest quintile for nitrate and over 3 times that in the lowest quintile for nitrite. Other strengths include the

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prospective nature of the study, completeness of follow-up, the relatively large number of thyroid cancer cases, and the ability to adjust for a large number of potential confounding variables including micronutrients in vegetables. The analysis of thyroid cancer risk by histologic type is also a strength of this study. Dietary intake based on FFQs is affected by measurement error, which, if nondifferential, could reduce an association. In this study diet was assessed later in life; however, it is possible that exposure at younger ages may be more important for risk of thyroid cancer.

In sum, we found an increased risk of thyroid cancer with increasing dietary nitrate intake among men. Additionally, dietary nitrite was associated with elevated risk of follicular thyroid cancer among men apparently due to plant sources of nitrite. Given the previous positive finding for nitrate in women, it is unclear why we observed an association in men but not women. Future investigation into this hypothesis should include populations for whom both drinking water source and dietary consumption data are available, as well as data on factors that affect nitrosation. Our findings suggest that dietary nitrate may be a risk factor for thyroid cancer.

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References

1. Kilfoy BA, Devesa SS, Ward MH, Zhang Y, Rosenberg PS, Holford TR, Anderson WF. Gender is an age-specific effect modifier for papillary cancers of the thyroid gland. Cancer Epidemiol Biomarkers Prev. 2009 Apr; 18(4):1092–1100. [PubMed: 19293311]
2. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y. International patterns and trends in thyroid cancer incidence, 1973–2002. Cancer Causes Control. 2009 Jul; 20(5):525–531. Epub 2008 Nov 19. [PubMed: 19016336]
3. Colonna M, Grosclaude P, Remontet L, Schvartz C, Mace-Lesech J, Velten M, Guizard A, Tretarre B, Buemi AV, Arveux P, Esteve J. Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). European Journal of Cancer. 2002; 38:1762–1768. [PubMed: 12175693]
4. dos Santos Silva I, Swerdlow AJ. Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. The British Journal of Cancer. 1993; 67:330–340.
5. Montanaro F, Pury P, Bordoni A, Lutz J-M. Unexpected additional increase in the incidence of thyroid cancer among a recent birth cohort in Switzerland. European Journal of Cancer Prevention. 2006; 15:178–186. [PubMed: 16523016]
6. Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev. 2009 Mar; 18(3):784–791. 2009 Epub 2009 Feb 24. [PubMed: 19240234]
7. Ron, E.; Schneider, AB. Thyroid Cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006. p. 975-994.
8. New York: United Nations; 2000. United Nations Scientific Committee on the Effects of Atomic Radiation, Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2000 Report to the General Assembly, with scientific annexes, Vol 2: Effects.
9. Gangolli SD, van den Brandt PA, Feron VJ, Janzowsky C, Koeman JH, Speijers GJ, Spiegelhalder B, Walker R, Wisnok JS. Nitrate, nitrite and N-nitroso compounds. European Journal of Pharmacology. 1994; 292:1–38. [PubMed: 7867685]

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10. van Loon AJ, Botterweck AA, Goldbohm RA, Brants HA, van den Brandt PA. Nitrate intake and gastric cancer risk: results from the Netherlands cohort study. Cancer Letters. 1997; 114:259–261. [PubMed: 9103306]
11. McKnight GM, Duncan CW, Leifert C, Golden MH. Dietary nitrate in man: friend or foe? The British Journal of Nutrition. 1999; 81:349–358. [PubMed: 10615207]
12. Lück E. Chemical preservation of food. Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene 1 Abt Originale B, Hygiene. 1985; 180:311–318.
13. Hiasa Y, Kitahori Y, Kitamura M, Nishioka H, Yane K, Fukumoto M, Ohshima M, Nakaoka S, Nishii S. Relationships between serum thyroid stimulating hormone levels and development of thyroid tumors in rats treated with N-bis-(2-hydroxypropyl)nitrosamine. Carcinogenesis. 1991; 12:873–877. [PubMed: 2029752]
14. Lijinsky W. The anomalous biological activity of nitroso-2-oxopropyl compounds. Cancer Letters. 1991; 60:121–127. [PubMed: 1933836]
15. Boeing H. Epidemiological research in stomach cancer: progress over the last ten years. Journal of cancer research and clinical oncology. 1991; 117:133–143. [PubMed: 2036128]
16. Cantor KP. Drinking water and cancer. Cancer Causes & Control. 1997; 8:292–308. [PubMed: 9498894]
17. Forman D. Are nitrates a significant risk factor in human cancer? Cancer Surveys. 1989; 8:443–458. [PubMed: 2696589]
18. Hansson LE, Nyrén O, Bergström R, Wolk A, Lindgren A, Baron J, Adami HO. Nutrients and gastric cancer risk. A population-based case-control study in Sweden. International Journal of Cancer. 1994; 57:638–644.
19. Forman D. Dietary exposure to N-nitroso compounds and the risk of human cancer. Cancer Surveys. 1987; 6:719–738. [PubMed: 3330686]
20. van Loon AJ, Botterweck AA, Goldbohm RA, Brants HA, van den Brandt PA. Nitrate intake and gastric cancer risk: results from the Netherlands cohort study. Cancer Letters. 1997; 114:259–261. [PubMed: 9103306]
21. Ward MH, Kilfoy BK, Weyer P, Wang A, Cerhan JR. Nitrate Intake and the Risk of Thyroid Cancer and Thyroid Disease. Epidemiology. 2010 Mar 23.
22. S Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, Hurwitz PE, Coyle L, Schussler N, Michaud DS, Freedman LS, Brown CC, Midthune D, Kipnis V. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. American Journal of Epidemiology. 2001; 154:1119–1125. 2001. [PubMed: 11744517]
23. World Health Organization. International Classification of Diseases for Oncology. 2001.
24. Michaud DS. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Registry Manage. 2005; 32:70–75.
25. Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, Schatzkin A. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. American Journal of Epidemiology. 2000; 152:279–286. [PubMed: 10933275]
26. Friday, JB. MyPyramid Equivalents Database for USDA Survey Food Codes, 1994–2002 USDA, ARS, Community Nutrition Research Group. 2006.
27. Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, Brown CC, Butcher MS, Mouw T, Leitzmann M, Schatzkin A. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. Public Health Nutrition. 2008; 11:183–195. [PubMed: 17610761]
28. Ward MH, Cerhan JR, Colt JS, Hartge P. Risk of non-Hodgkin lymphoma and nitrate and nitrite from drinking water and diet. Epidemiology. 2006 Jul; 17(4):375–382. [PubMed: 16699473]
29. Ward MH, Cantor KP, Riley D, Merkle S, Lynch CF. Nitrate in public water supplies and risk of bladder cancer. Epidemiology. 2003; 14:183–190. 2003. [PubMed: 12606884]
30. Nolan BT, Hitt KJ. Vulnerability of shallow groundwater and drinking-water wells to nitrate in the United States. Environmental Science & Technology. 2006; 40:7834–7840. [PubMed: 17256535]

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31. Solley WB, Pierce RR, Perlman HA. Estimated Use of Water in the United States in 1990. U.S. Geological Survey Circular. 1993:1081. 1993.
32. WC, W. Nutritional epidemiology. New York Oxford University Press; 1998.
33. Durrleman S, Simon R. Flexible regression models with cubic splines. Statistics in Medicine. 1989; 8:551–561. [PubMed: 2657958]
34. Satia JA, Kristal AR, Patterson RE, Neuhouser ML, Trudeau E. Psychosocial factors and dietary habits associated with vegetable consumption. Nutrition. 2002; 18:247–254. [PubMed: 11882398]
35. Trudeau E, Kristal AR, Li SE, Patterson RE. Demographic and Psychosocial Predictors of Fruit and Vegetable Intakes Differ: Implications for Dietary Interventions. Journal of the American Dietetic Association. 1998; 98:1412–1417. [PubMed: 9850109]
36. Subar AF, Kipnis V, Troiano RP, Midthune D, Schoeller DA, Bingham S, Sharbaugh CO, Trabulsi J, Runswick S, Ballard-Barbash R, Sunshine J, Schatzkin A. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. American Journal of Epidemiology. 2003; 158:1–13. [PubMed: 12835280]
37. George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J, Schatzkin A, Hollenbeck A, Subar AF. Fruit and vegetable intake and risk of cancer: a prospective cohort study. The American Journal of Clinical Nutrition. 2009; 89:347–353. [PubMed: 19056579]
38. Boyland E, Walker SA. Effect of thiocyanate on nitrosation of amines. Nature (Lond.). 1974; 248:601–602. [PubMed: 4824029] Hoffman D, Bunnemann KD. Endogenous formation of, V nitroso proline in cigarette smokers. Cancer Res. 1983; 43:5570–5574. [PubMed: 6616484]
39. Nishiyama, RHLG.; Thompson, NW. The prevalence of small papillary thyroid carcinomas in 100 consecutive necropsies in an American population. New York: Grune & Stratton; 1977. p. 123-125.
40. Sampson RJWL, Bahn RC, Kurland LT. Occult thyroid carcinoma in Olmsted County, Minnesota:prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. Cancer. 1974; 34
41. Owens GM. Gender differences in health care expenditures, resource utilization, and quality of care. Journal of Managed Care Pharmacy. 2008; 14:2–6. 2008. [PubMed: 18439060]
42. Chilvers C, Inskip H, Caygill C, Bartholomew B, Fraser P, Hill M. A survey of dietary nitrate in well-water users. Int J Epidemiol. 1984; 13:324–331. [PubMed: 6490303]
43. Boas M, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. Eur J Endocrinol. 2006; 154(5):599–611. [PubMed: 16645005]
44. Zoeller RT. Environmental chemicals impacting the thyroid: targets and consequences. Thyroid. 2007; 17(9):811–817. [PubMed: 17956155]
45. Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. Thyroid. 8(9): 827–856. (199). [PubMed: 9777756]

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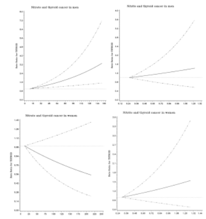

Figure 1. Estimated relative risk and 95% confidence bands for thyroid cancer among men and women

The Y-axis exhibits the relative risk of thyroid cancer and the X-axis exhibits intake of nitrate (panels on left) or nitrite (panels on right). The upper panels illustrate the relationship between continuous nitrate and nitrite intake and thyroid cancer in men and the lower panels illustrate the relationship between continuous nitrate and nitrite intake and thyroid cancer in women.

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Table 1

Baseline characteristics of the NIH-AARP Diet and Health Study cohort by quintiles of nitrate and nitrite intake

			Nitrate					Nitrite				
Sex	**Parameter**	**Characteristics**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
	Number of thyroid cancer cases		**63**	**67**	**60**	**74**	**106**	**59**	**78**	**72**	**74**	**87**
	Energy adjusted quintile median mg/ 1000kcal		19.4	29.9	40.9	57.4	94.8	0.5	0.6	0.7	0.7	0.9
	Unajusted quintile median mg/day		29.6	49.8	70.2	100.9	166.8	0.6	0.9	1.1	1.4	1.9
Men	N = 292,125											
	Age		61.7	62.1	62.3	62.3	62.4	61.6	62	62.2	62.4	62.6
	Race	Non-hispanic white (%)	91.8	93.1	93.1	92.7	91.6	93.5	94.2	93.7	92.5	88.1
		Non-hispanic black (%)	3.2	2.6	2.4	2.6	2.6	3.1	2.5	2.5	2.5	3
		Hispanic, Asian, Pacific Islander, American Indian, Alaskan Native, or unknown (%)	5	4.3	4.5	4.8	5.9	3.4	3.4	3.8	5	9
	Positive family history of cancer (%)		46.8	47.2	47	47.2	46.3	47.1	47.5	47.4	47.1	45.5
	Currently married (%)		81.3	85.8	86.7	86.1	85.6	81.5	86	86.5	86.6	84.7
	Body mass index (kg/m2)		27.3	27.4	27.3	27.3	27	27.2	27.4	27.4	27.3	27
	Smoking history	Never smoker (%)	25.5	29.5	30.8	30.7	31.2	23.7	29.2	30.4	31.5	32.3
		Former smoker (%)	53.4	56.2	57.2	58.3	59.3	55.8	56.3	56.7	56.9	57
		Current smoker or quit <1 year ago (%)	17.1	10.5	8	7.1	5.5	16.5	10.8	9.2	7.9	6.4
	Education, college graduate or post graduate (%)		34.9	43.3	47.4	49.9	52.9	41.9	45.4	45.5	45.4	44.8
	Vigorous physical activity, >5 times per week		16.5	19.2	21.7	24.4	28.6	18.5	19.6	20.7	22.4	26.1
	Dietary Intakes	Energy (kcal/d)	2200.8	2036.7	1973.7	1954.9	1775.5	2249	2031.7	1987.4	1932.7	1825.6
		Vegetables (servings/1,000kcal)	2.5	3.4	4.1	4.9	6.3	3.4	3.8	4	4.2	4.7
		Fruit (servings/1,000kcal)	2.3	2.8	3.1	3.4	3.7	2.7	2.8	3	3.1	3.4
		Processed Meat (g/1000kcal)	13.2	12.9	12	11	9.4	8.1	10.5	11.9	13.5	16.6
		Vitamin C (mg/1,000kcal)	61.4	76.9	87.3	97.8	118.2	76.2	81.5	84.2	87.5	96.0
		Vitamin E (mg/1,000kcal)	4.2	4.7	4.9	5.1	5.7	4.3	4.9	5	5	5
		Beta carotene (mg/1,000kcal)	985.4	1582.6	2091.6	2705.1	4150.2	1363	1781.6	2049.6	2360.9	3115.5
		Folate (mg/1,000kcal)	187	213	229.1	246.7	290.7	184.3	214.6	230.1	244.2	269.2

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Sex	Parameter	Characteristics	Nitrate Q1	Nitrate Q2	Nitrate Q3	Nitrate Q4	Nitrate Q5	Nitrite Q1	Nitrite Q2	Nitrite Q3	Nitrite Q4	Nitrite Q5
Women	N = 198,069											
	Age		61.5	61.8	61.9	62	61.8	61.4	61.8	61.9	62	62.1
	Race	Non-hispanic white (%)	88.1	89.6	90.3	89.5	89	89.2	91.1	90.6	90.1	86.3
		Non-hispanic black (%)	6.4	5.7	5.4	5.5	5.5	7.2	5.3	5.3	5.1	5.5
		Hispanic, Asian, Pacific Islander, American Indian, Alaskan Native, or unknown (%)	5.5	4.7	4.4	5	5.5	3.6	3.6	4.1	4.8	8.2
	Positive family history of cancer (%)		50.5	51.4	51.5	51.2	50.9	50.9	50.9	51.9	51.5	50.4
	Currently married (%)		38.1	43.1	45.6	46.2	45.4	40.7	45	46.3	46.3	43
	Body mass index (kg/m2)		27.2	27.1	27	26.9	26.5	26.7	26.9	27	27	26.6
	Smoking history	Never smoker (%)	42.1	45.3	46.1	45	42.1	36.1	42.8	45.1	46.9	47.7
		Former smoker (%)	30.5	35.2	36.9	39.6	43.3	35.7	37.4	38.6	39.2	39.8
		Current smoker or quit <1 year ago (%)	23.6	16.3	13.6	12	10.7	14.5	16.4	13	10.5	8.4
	Education, college graduate or post graduate (%)		20.1	25.6	29	32.1	35.1	25.1	27.9	30	31	33.9
	Vigorous physical activity, >5 times per week		10.5	12.3	14.3	16.6	21.7	12.4	14.1	14.9	16.8	21.3
	Dietary Intakes	Energy (kcal/d)	1701.1	1623.4	1602.3	1572.2	1461.2	1663	1608.4	1590.7	1559.4	1460.7
		Vegetables (servings/1,000kcal)	1.9	2.7	3.3	4	5.6	2.9	3.4	3.7	4	4.8
		Fruit (servings/1,000kcal)	2.1	2.5	2.9	3.2	3.5	2.7	2.8	2.9	3.1	3.3
		Processed Meat (g/1000kcal)	9.7	9.5	8.8	8.1	6.7	6.3	7.7	8.4	9.0	9.5
		Vitamin C (mg/1,000kcal)	68	82.2	93.5	105.9	129.7	91.6	93.2	97.6	102.8	119.3
		Vitamin E (mg/1,000kcal)	4.4	4.8	5	5.3	5.9	4.7	5.2	5.2	5.3	5.5
		Beta carotene (mg/1,000kcal)	1099.4	1763.7	2329	3067.8	4897.3	1794	2330.6	2704.5	3174.2	4550.6

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Table 2

Relative risks (RRs) and 95% confidence intervals (CIs) for thyroid cancer in relation to quintiles of nitrate and nitrite intake among men and women overall and by gender: The NIH-AARP Diet and Health Study

	Quintile of intake					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
NITRATE						
Overall						
Median Intake	19.4	29.9	40.9	57.4	94.8	
Number of cases	63	67	60	74	106	
Age-adjusted RR[1]	1.00	1.01	0.87	1.04	1.41	0.01
95% CI	(ref)	0.72–1.43	0.61–1.24	0.74–1.45	1.02–1.93	
Multivariate RR[2]	1.00	0.98	0.84	0.99	1.33	0.01
95% CI	(ref)	0.70–1.39	0.58–1.20	0.70–1.39	0.96–1.85	
Multivariate RR[3]	1.00	0.96	0.80	0.92	1.18	0.15
95% CI	(ref)	0.68–1.36	0.56–1.15	0.64–1.32	0.80–1.73	
Men						
Median Intake	19.4	29.9	40.9	57.4	94.8	
Number of cases	27	34	28	36	45	
Age-adjusted RR[1]	1.00	1.38	1.27	1.84	2.91	<.01
95% CI	(ref)	0.83–2.29	0.75–2.15	1.12–3.03	1.80–4.69	
Multivariate RR[2]	1.00	1.29	1.15	1.65	2.57	<.01
95% CI	(ref)	0.77–2.14	0.67–1.96	0.99–2.75	1.57–4.21	
Multivariate RR[3]	1.00	1.26	1.10	1.54	2.28	<.01
95% CI	(ref)	0.75–2.10	0.64–1.90	0.90–2.63	1.29–4.04	
Women						
Median Intake	19.4	29.9	40.9	57.4	94.8	
Number of cases	36	33	32	38	61	
Age-adjusted RR[1]	1.00	0.71	0.56	0.56	0.76	0.60
95% CI	(ref)	0.44–1.14	0.35–0.91	0.36–0.89	0.48–1.10	
Multivariate RR[2]	1.00	0.71	0.57	0.57	0.75	0.75

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	Quintile of intake					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
95% CI	(ref)	0.44–1.14	0.35–0.92	0.36–0.91	0.49–1.15	
Multivariate RR[3]	1.00	0.70	0.55	0.55	0.69	0.61
95% CI	(ref)	0.43–1.13	0.34–0.90	0.34–0.89	0.42–1.15	
NITRITE						
Overall						
Median Intake	0.5	0.6	0.7	0.7	0.9	
Number of cases	59	78	72	74	87	
Age-adjusted RR[1]	1.00	1.28	1.17	1.18	1.37	0.13
95% CI	(ref)	0.92–1.80	0.83–1.65	0.84–1.67	0.98–1.91	
Multivariate RR[2]	1.00	1.25	1.12	1.13	1.28	0.28
95% CI	(ref)	0.89–1.76	0.79–1.59	0.80–1.59	0.92–1.80	
Multivariate RR[3]	1.00	1.28	1.16	1.17	1.32	0.26
95% CI	(ref)	0.91–1.80	0.81–1.65	0.82–1.67	0.92–1.91	
Men						
Median Intake	0.5	0.6	0.7	0.7	0.9	
Number of cases	28	40	37	25	40	
Age-adjusted RR[1]	1.00	1.49	1.43	1.00	1.68	0.15
95% CI	(ref)	0.92–2.42	0.88–2.34	0.58–1.72	1.04–2.73	
Multivariate RR[2]	1.00	1.34	1.26	0.87	1.48	0.40
95% CI	(ref)	0.82–2.21	0.75–2.09	0.50–1.53	0.88–2.48	
Multivariate RR[3]	1.00	1.36	1.26	0.86	1.36	0.26
95% CI	(ref)	0.83–2.24	0.75–2.12	0.48–1.53	0.78–2.37	
Women						
Median Intake	0.5	0.6	0.7	0.7	0.9	
Number of cases	31	38	35	49	47	
Age-adjusted RR[1]	1.00	1.10	0.96	1.27	1.15	0.45
95% CI	(ref)	0.69–1.78	0.59–1.56	0.81–2.00	0.73–1.81	
Multivariate RR[2]	1.00	1.04	0.89	1.17	1.07	0.62
95% CI	(ref)	0.65–1.68	0.54–1.45	0.74–1.85	0.67–1.72	

	Quintile of intake					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
Multivariate RR[3]	1.00	1.09	0.95	1.28	1.19	0.40
95% CI	(ref)	0.67–1.78	0.58–1.58	0.79–2.06	0.71–1.98	

[1] Adjusted for entry age

[2] Adjusted for entry age, sex (overall model), smoking status, calories, race, family history, education, BMI, physical activity, and alcohol use

[3] Additionally adjusted for vitamin C, beta-carotene, and folate

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Table 3

Relative risks (RRs) and 95% confidence intervals (CIs) for papillary thyroid cancer in relation to quartiles of nitrate and nitrite intake in sex-stratified multivariate analyses: The NIH-AARP Diet and Health Study

	Quartile of intake				
	Q1	Q2	Q3	Q4	p-trend
NITRATE					
Men					
Median Intake	20.8	33.7	50.1	87.1	
Number of cases	21	31	31	31	
Age-adjusted RR[1]	1.00	1.67	1.93	2.90	<.01
95% CI	(ref)	0.96–2.90	1.10–3.36	1.41–4.28	
Multivariate RR[2]	1.00	1.57	1.79	2.21	<.01
95% CI	(ref)	0.90–2.74	1.02–3.14	1.25–3.90	
Multivariate RR[3]	1.00	1.56	1.74	2.10	<.05
95% CI	(ref)	0.88–2.74	0.97–3.14	1.09–4.05	
Women					
Median Intake	20.8	33.7	50.1	87.1	
Number of cases	30	30	33	51	
Age-adjusted RR[1]	1.00	0.75	0.65	0.79	0.64
95% CI	(ref)	0.45–1.24	0.40–1.07	0.50–1.24	
Multivariate RR[2]	1.00	0.74	0.65	0.80	0.73
95% CI	(ref)	0.44–1.23	0.39–1.07	0.50–1.28	
Multivariate RR[3]	1.00	0.72	0.63	0.74	0.60
95% CI	(ref)	0.43–1.21	0.37–1.05	0.43–1.28	
NITRITE					
Men					
Median Intake	0.5	0.6	0.7	0.9	
Number of cases	29	34	26	25	
Age-adjusted RR[1]	1.00	1.23	0.99	1.01	0.84
95% CI	(ref)	0.75–2.03	0.58–1.68	0.59–1.72	

	Quartile of intake				
	Q1	Q2	Q3	Q4	p-trend
Multivariate RR[2]	1.00	1.09	0.83	0.83	0.37
95% CI	(ref)	0.65–1.80	0.48–1.44	0.47–1.46	
Multivariate RR[3]	1.00	1.12	0.86	0.81	0.35
95% CI	(ref)	0.67–1.88	0.49–1.51	0.44–1.48	
Women					
Median Intake	0.5	0.6	0.7	0.9	
Number of cases	32	27	35	50	
Age-adjusted RR[1]	1.00	0.76	0.93	1.22	0.18
95% CI	(ref)	0.46–1.27	0.57–1.49	0.78–1.91	
Multivariate RR[2]	1.00	0.70	0.83	1.10	0.35
95% CI	(ref)	0.42–1.17	0.51–1.35	0.70–1.725	
Multivariate RR[3]	1.00	0.73	0.88	1.20	0.35
95% CI	(ref)	0.43–1.23	0.53–1.46	0.73–1.98	

[1] Adjusted for entry age

[2] Adjusted for entry age, sex (overall model), smoking status, calories, race, family history, education, BMI, physical activity, and alcohol use

[3] Additionally adjusted for vitamin C, beta-carotene, and folate

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Table 4

Relative risks (RRs) and 95% confidence intervals (CIs) for follicular thyroid cancer in relation to quartiles of nitrate and nitrite intake in sex-stratified multivariate analyses: The NIH-AARP Diet and Health Study

	Quartile of intake				
	Q1	**Q2**	**Q3**	**Q4**	**p-trend**
NITRATE					
Men					
Median Intake	20.8	33.7	50.1	87.1	
Number of cases	5	8	4	13	
Age-adjusted RR[1]	1.00	1.78	1.03	4.24	<.01
95% CI	(ref)	0.58–5.44	0.28–3.83	1.51–11.9	
Multivariate RR[2]	1.00	1.72	0.99	4.07	<.01
95% CI	(ref)	0.56–5.32	0.26–3.75	1.40–11.8	
Multivariate RR[3]	1.00	1.64	0.90	3.42	<.01
95% CI	(ref)	0.53–5.12	0.23–3.52	1.03–11.4	
Women					
Median Intake	20.8	33.7	50.1	87.1	
Number of cases	9	7	8	10	
Age-adjusted RR[1]	1.00	0.57	0.51	0.50	0.27
95% CI	(ref)	0.21–1.53	0.20–1.32	0.20–1.24	
Multivariate RR[2]	1.00	0.59	0.54	0.54	0.35
95% CI	(ref)	0.22–1.60	0.20–1.41	0.21–1.39	
Multivariate RR[3]	1.00	0.58	0.51	0.47	0.28
95% CI	(ref)	0.21–1.59	0.19–1.39	0.16–1.39	
NITRITE					
Men					
Median Intake	0.5	0.6	0.7	0.9	
Number of cases	6	4	8	12	
Age-adjusted RR[1]	1.00	0.69	1.44	2.28	0.04
95% CI	(ref)	0.20–2.46	0.50–4.17	0.85–6.09	

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	Quartile of intake				
	Q1	Q2	Q3	Q4	p-trend
Multivariate RR[2]	1.00	0.80	1.75	2.91	0.02
95% CI	(ref)	0.21–2.91	0.56–5.46	0.97–8.75	
Multivariate RR[3]	1.00	0.80	1.75	2.74	0.04
95% CI	(ref)	0.22–2.95	0.55–5.57	0.86–8.77	
Women					
Median Intake	0.5	0.6	0.7	0.9	
Number of cases	9	8	10	7	
Age-adjusted RR[1]	1.00	0.78	0.91	0.58	0.33
95% CI	(ref)	0.30–2.03	0.37–2.25	0.22–1.57	
Multivariate RR[2]	1.00	0.81	0.96	0.65	0.48
95% CI	(ref)	0.31–2.14	0.38–2.44	0.23–1.83	
Multivariate RR[3]	1.00	0.82	0.97	0.63	0.49
95% CI	(ref)	0.31–2.20	0.37–2.55	0.21–1.95	

[1]Adjusted for entry age

[2]Adjusted for entry age, sex (overall model), smoking status, calories, race, family history, education, BMI, physical activity, and alcohol use

[3]Additionally adjusted for vitamin C, beta-carotene, and folate