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Thyroid cancer risk and dietary nitrate and nitrite intake in the Shanghai Women's Health Study

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Abstract

Nitrate and nitrite are precursors in the endogenous formation of N-nitroso compounds and nitrate can disrupt thyroid homeostasis by inhibiting iodide uptake. We evaluated nitrate and nitrite intake and risk of thyroid cancer in the Shanghai Women's Health Study that included 73,317 women, aged 40–70 years enrolled in 1996–2000. Dietary intake was assessed at baseline using a food frequency questionnaire. During approximately 11 years of follow-up, 164 incident thyroid cancer cases with complete dietary information were identified. We used Cox proportional hazards regression to estimate relatives risks (RRs). We determined the nitrate and nitrite contents of foods using values from the published literature and focusing on regional values for Chinese foods. Nitrate intake was not associated with thyroid cancer risk (RR_{Q4} = 0.93; 95%CI: 0.42–2.07; p for trend = 0.40). Compared with the lowest quartile, women with the highest dietary nitrite intake had about a two-fold risk of thyroid cancer (RR_{Q4} = 2.05; 95%CI: 1.20–3.51;) but there was not a monotonic trend with increasing intake (p for trend= 0.36). The trend with increasing nitrite intake from animal sources was significant (p for trend = 0.02) and was stronger for nitrite from processed meats (RR_{Q4} = 1.96; 95%CI: 1.28–2.99; p for trend <0.01). Although we did not observe an association for nitrate as hypothesized, our results suggest that women consuming higher levels of nitrite from animal sources, particularly from processed meat, may have an increased risk of thyroid cancer.

Introduction

An increasing incidence of thyroid cancer has been reported worldwide, with an average increase of 48.0% among males and 66.7% among females in recent decades (1). The increases in thyroid cancer incidence include different parts of China, such as Hong Kong (1) and Tianjin (2). Considerable variation by geographic region has suggested that environmental, dietary, or lifestyle factors may play a role in thyroid cancer etiology. Only a few studies have investigated diet in relation to thyroid cancer (3–6).

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A recent review by the International Agency for Research on Cancer (7) of ingested nitrate and nitrite concluded that dietary nitrate and nitrite ingested under conditions likely to result in endogenous nitrosation (formation of N-nitroso compounds [NOC]) is probably carcinogenic to humans (group 2A) (7, 8). In the human body, nitrate is converted to nitrite primarily by oral bacteria. Primarily in the stomach, nitrite can react with amines, amides, or amino acids to produce NOCs, most of which are potent animal carcinogens. Vitamin C has been shown to be an effective inhibitor of *N*-nitroso compound formation (9, 10). Nitrate also competitively inhibits iodide uptake by the thyroid (11–13), possibly affecting thyroid hormone production and potentially resulting in thyroid tumor promotion (14–16). The impact of nitrate and nitrite intake on the risk of thyroid cancer is therefore of interest.

Nitrate is a natural component of plants and is found at high concentrations in leafy vegetables, such as lettuce and spinach, cabbage, celery, and some root vegetables, such as beets (17). Nitrite and nitrate are added to cured meats such as bacon, hot dogs, and ham to prevent the growth of spore-forming bacteria as well as to add color and flavor (18). Plant-based foods constitute a large part of the Chinese diet, including cruciferous vegetables such as cabbage, as well as dark green leafy vegetables (19). The Chinese dietary patterns, suggest that some Asian populations may experience higher exposure to dietary nitrate (19) relative to the Western populations where this hypothesis has been previously evaluated (20, 21).

Dietary and drinking water nitrate intake increased the risk of thyroid cancer among older women in an Iowa cohort (20), and higher intake of dietary nitrate increased the risk of thyroid cancer among men but not women in the NIH-AARP cohort (21). To date, this hypothesis has not been evaluated in a Chinese population. We subsequently evaluated the relationship between dietary nitrate and nitrite intake and thyroid cancer in the Shanghai Women's Health Study (SWHS), a prospective cohort study.

Methods

Study population

A detailed description of the SWHS cohort has been published elsewhere (22). Briefly, a roster of 81,170 women aged 40–70 years was obtained from the resident offices in seven communities located in urban Shanghai, China. The SWHS was conducted in these communities as the cancer incidence as well as age, education level, and occupations of the women are similar to the general population of urban Shanghai (22). A total of 75,221 (92.7%) women participated in the study and completed a baseline interview during 1996 to 2000. We excluded 279 who were found to be younger than age 40 or older than age 70 years, 1,490 women who had prior malignancies (except non-melanoma skin cancer) as reported at the baseline interview, and 10 women who were diagnosed with cancer (except non-melanoma skin cancer) within one month after the interview. We also excluded women who reported extreme caloric intake (>3500 kcal or <500 kcal per day). Our analysis included 73,317 women; follow up was through December 2009.

Trained interviewers administered detailed in-person interviews using a structured questionnaire to collect information on demographic characteristics, dietary habits, physical activity, disease and surgery history (including whether the participant has ever been diagnosed with hyperthyroidism or hypothyroidism), smoking, alcohol consumption, tea consumption, a lifetime residential and occupational history, family history of cancer (did not specify thyroid cancer), and reproductive history, and hormone use. Body measurements, including height, weight, and waist and hip circumferences, were also measured at baseline.

Cancer incidence and vital status were ascertained by biennale in-person follow-up interviews and through the Shanghai Cancer Registry. Cancer reporting is legally mandated in Shanghai, China. Medical charts and pathology slides were collected from diagnostic hospitals to verify the cancer diagnosis. A total of 164 incident thyroid cancer cases were identified during 11 years of follow-up. Nearly all cohort members were successfully followed, with the response rates for first in-person follow-up being 99.8% (2000–2002), second 98.7% (2002–2004), and third 96.7% (2004–2007). All possible incident cancer cases were verified by home visits. Medical charts from the referral hospitals were reviewed to verify the diagnosis, and pathological characteristics of the tumor were recorded. For subjects who had moved, the new address was requested from the neighborhood Community Office, local police department, or the Shanghai Resident Registry. Death certificate data from the Shanghai Vital Statistics Unit was collected to identify causes of death. Despite these efforts, we only had histology codes for 126 of the 164 cases. Of the 126 cases with codes, 14 thyroid cancers were the follicular type, 2 were the medullary type, and none were anaplastic tumors. Additionally, although participants are followed regularly for cancer outcomes, they are not routinely evaluated for thyroid disease.

Estimation of Dietary Nitrate and Nitrite

A comprehensive food frequency questionnaire was administered at the baseline interview. The 77-item food frequency questionnaire was developed for the SWHS population and was validated in the study population (23). Briefly, the investigators compared the FFQ intakes to multiple dietary recalls by contacting a subset of 200 study participants twice a month during a 12-month period to obtain the type and amount of foods that they consumed over the past 24 hours. The days of the 24-hour dietary recalls (24-HDR) were chosen to assure a balanced representation of weekdays and weekend days for each participant. All recalls were obtained by an unannounced in-person interview in the evening after dinner (around 19:00). At the end of the 1 year study, a second FFQ was administered. The investigators found that the SWHS FFQ reliably and accurately measured usual intake of most major nutrients and food groups, although total vegetable and fruit intake was overestimated. The authors suggested that over-reporting of seasonal vegetable and fruit consumption in the FFQ was the cause of the differences (23). As a result, carotene and vitamin C intake were significantly different between the FFQ and the 24 hour recall based on the Wilcoxon signed rank test (23). Nitrate and nitrite intake were not estimated.

For each food line item, participants were asked how frequently (daily, weekly, monthly, annually, or never) they consumed the food or food group during the past year in 5 predefined categories ranging from “not at all” to “everyday”. They were asked the amount of the food they typically consumed in liang (1 liang = 50 g). For seasonal food consumption, a subset of women (approximately 1,000) were asked about the number of months out of the year the food was eaten, and those results were used to calibrate intake of seasonal foods for all SWHS members. To calculate nutrient intakes, the intake amounts were multiplied by the nutrient content obtained from the Chinese Food Composition Tables (24) or for nitrate and nitrite from the published literature (described below) and summed across all foods.

We determined the nitrate and nitrite contents for 29 vegetables, 19 meats, 6 preserved foods (including 2 processed meat items), rice and noodles, 13 dessert and bean items, and 8 fruits using from values from the published literature. Our review of the literature focused on Chinese foods. If values for Chinese foods were unavailable for Shanghai, we used values from China in general and if those were unavailable we then chose values from other Asian countries. We only used values from Western countries if there was no published value for Asian areas. Nitrate and nitrite values for most vegetables were from a survey conducted in Shanghai (25), whereas values for most fruits (25), some processed meats (25), vegetables not reported by Zhou et al. (19), and rice (26) were from other studies in China. Values for fresh meat (27) and bread items (28), some fruits, such as apples, pears, grapes, peaches and strawberries (29), were from Western countries. When values were available from multiple studies, we calculated means weighted by the number of samples analyzed.

Foods with the highest nitrate levels were Chinese greens (1933 mg/kg) (25), cabbage/bok choy cabbage (1653 mg/kg), and green cabbage (1558 mg/kg) (25). Foods with the highest nitrite levels were smoked meat/bacon and salted meat/preserved meat (both 12.5 mg/kg) (26), eggplant (4.6 mg/kg) (19) and wax gourd (4.3 mg/kg) (19).

In addition to calculating dietary nitrite and nitrate from all foods, we calculated nitrite from plant, animal, and processed meat sources separately. Additionally, we computed the percent of total nitrate and nitrite intake that came from individual food line items. Because the major sources of nitrate were vegetables, which also contain beneficial nutrients such as vitamin C, we evaluated the correlation between nitrate intake and specific micronutrients. Nitrate intake was highly correlated with vitamin C (Pearson's r = 0.85), vitamin E (r = 0.53), folate (r = 0.65), and carotenes (r = 0.91). We evaluated the correlation with cruciferous vegetable intake as they are considered goitrogens and potential thyroid cancer risk factors (30) (r = 0.90).

Drinking water nitrate can constitute the majority of nitrate intake when levels are near or above the maximum contaminant level (31). Almost all of the participants in this study reported that they drank tap water from the Shanghai municipal water supply in the previous 10 years. Based on nitrate levels in the drinking water supplies in Shanghai in 2004, which were relatively low (<2 mg/L) (32), drinking water would be expected to contribute a small percent of total intake and it was not considered.

Statistical analysis

Person-years for each subject were calculated from the date of enrollment to the primary endpoint (diagnosis of cancer), death, or December 31, 2009, whichever came first. For the analysis of thyroid cancer risk, Cox proportional hazard models were employed to compute the relative risks (RRs) and 95% confidence intervals (CI). The proportional hazards assumption was tested and upheld in all analyses. Tests for linear trend were conducted using the median value of each quartile exposure category as a continuous variable in the model. Dietary variables were adjusted for energy intake using the nutrient density method (33), which expresses intake in units per 1000 calories.

For all models, we adjusted for age, total energy intake, and a history of thyroid disease. We evaluated the impact of risk factors sometimes associated with thyroid cancer, including education, smoking status, income, a family history of cancer, and body mass index, but their inclusion in the models did not result in a material change (>10%) in the thyroid cancer associations and are not presented. We further adjusted the thyroid cancer models for dietary vitamin C intake (mg/1,000kcals) (except for vitamin C interaction models), carotene, and folate in a second fully adjusted micronutrient model (hereafter "fully adjusted model"). We present the results for both the risk factor adjusted and the fully adjusted micronutrient models in table 4 but only refer to the results from the fully adjusted micronutrient models in the text.

We further evaluated risk for major sources of nitrate and nitrite including fruit, vegetable, and meat (including salted and preserved) food groups. We also considered thyroid cancer risk by cruciferous vegetables (cabbage, bok choy, turnips, cauliflower), beans (baby beans, dry beans, soybeans, yard long beans, and sprouts), leafy greens (spinach, green cabbage, Chinese cabbage, and asparagus lettuce), red vegetables (tomatoes), yellow/orange vegetables (carrots and sweet potatoes), and citrus fruits (tangerines, oranges, grapefruits). This allowed us to consider the possibility that nitrate or nitrite is acting as a proxy for intake of a particular food group. As their inclusion in the models did not result in a material change (>10%) in the thyroid cancer associations, none of these foods and food groups were included in the final presentation of results.

To evaluate the consistency of associations, we stratified by age (at or above/below the median age of 50 years), BMI (at or above/below median of 23.7 kg/m^2), and education (junior high school or fewer years of education; some high school or greater years of education). We stratified by red meat intake (at or above/below median 26.8/1,000kcals), and vitamin C intake (at or above/below median 51.3 mg/1,000kcals) to evaluate factors potentially affecting endogenous *N*-nitrosation. We assessed multiplicative interactions by adding the relevant cross-product term to main-effects models, with the p-value for interaction determined by a Wald test for the cross-product term.

All the analyses were performed in SAS 8.02 (SAS Institute Inc., Cary, NC). All tests were two-sided, with a significance level of 0.05.

Results

A total of 164 incident thyroid cancer cases were identified during an average of 9 years of follow-up. The baseline characteristics of the thyroid cancer cases were similar to the overall cohort (Table 1). The median dietary nitrate intake was 309 mg/day (IQR: 215 –413 mg/day) and the median daily nitrite intake was 1.4 mg/day (IQR: 1.1–1.8 mg/day). The median intake of nitrate from plant sources was 299 mg/day; whereas, median intake of nitrite from plant sources was 1.2 mg/day. The major contributors to nitrate intake were greens/Chinese greens, watermelon, and baby soybeans/fresh peas/fresh broad beans (medians: 42.7%, 12.5%, 4.2%, respectively) (Table 2). The major contributors to nitrite intake were watermelon, fresh bean curd, and salted/preserved vegetables (medians: 15.2%, 9.7%, and 9.1%, respectively). Salted preserved meat and smoked meat/bacon (e.g., all processed meats) contributed approximately 1.2% of total nitrite intake.

Women in the highest quartile of nitrate intake reported higher intake of total calories than those in the lowest quartile and they consumed more vegetables and fruits (Table 3). Women in the highest quartile of nitrite intake tended to report a family history of cancer, to be less educated, and to consume more fruit, salted preserved meat, and smoked meat/bacon than those in the lowest nitrite intake quintile. Those in the highest quartiles of nitrate and nitrite had higher consumption of fiber, vitamins C and E, carotene and folic acid.

Compared to women in the lowest quartile of nitrate intake, risk of thyroid cancer was elevated in the 2nd intake quartiles (RR_{Q2} = 1.69; 95%CI: 1.07–2.68) but not in the 3rd and 4th intake quartiles (RR_{Q3} = 1.23; 95%CI: 0.71–2.15, RR_{Q4} = 0.93; 95%CI: 0.42–2.07; p for trend = 0.40) in the fully adjusted model (Table 4). Women in the highest compared to the lowest quartile of nitrite intake had a significant increased risk of thyroid cancer in the fully adjusted model (RR_{Q4} = 2.05; 95%CI: 1.20–3.51), although the trend was not significant (p for trend = 0.36). The increase in risk appeared to be due primarily to animal sources of nitrite (RR_{Q4} = 1.59; 95%CI: 1.00–2.52, p for trend = 0.02), particularly nitrite from processed meats (RR_{Q4} = 1.96; 95%CI: 1.28–2.99), and the trend was significant (p for trend <0.01). The results were similar when we stratified by age, BMI, and education.

The association between high nitrate and nitrite intake did not differ by high or low vitamin C or red meat intake, and we did not observe any statistically significant interactions for thyroid cancer in the fully adjusted micronutrient models (Table 5).

Discussion

In this large prospective cohort study of women in Shanghai, we did not observe an association between dietary nitrate intake and thyroid cancer as hypothesized. However, we did find an approximately 2-fold increased risk of thyroid cancer associated with the highest quartile of nitrite intake. The increased risk for nitrite intake was primarily due to intake from animal sources, particularly processed meats.

Our findings are not entirely consistent with what we observed previously for nitrate and nitrite intake in U.S. study populations. Specifically, in a cohort of older women in Iowa (the Iowa Women's Health Study), we found that 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) (20). Nitrite was not estimated. In another prospective cohort, the NIH-AARP Diet and Health Study, we found that increasing nitrate intake was positively associated with thyroid cancer risk (highest quintile versus lowest quintile RR=2.28, 95% CI: 1.29–4.04; p for trend <0.001) among men; however, we observed no trend with intake among women. In the NIH-AARP cohort, we did not find an association with nitrite intake and risk of thyroid cancer overall for either men or women although we did observe a positive association for follicular thyroid cancer and nitrite in men (21).

Nitrite and reactive nitrogen species react with nitrosatable compounds, mainly amines and amides (found in fish and meats), to form NOCs (9). Consumption of nitrate or nitrite from processed meats and fish should theoretically result in more exposure to NOCs than plant-based foods; our results for nitrite support this mechanism as the positive association we observed was strongest for processed meat sources of nitrite. As vegetables contain inhibitors of *in vivo N*-nitrosation such as vitamin C and polyphenols (9, 10, 34, 35), we might expect a lack of an association between plant sources of nitrate and nitrite and thyroid cancer if the risk is being increased via NOCs. In this study, nitrate and vitamin C intake were highly correlated and we did not observe an interaction between nitrate/nitrite and vitamin C intake and thyroid cancer risk. Future work addressing potential mechanisms of nitrate and nitrite effects on the thyroid is necessary.

The difference in the daily consumption of nitrate in this study population compared to Western populations is particularly notable. The median daily dietary nitrate among women in Shanghai was 300 mg/day, compared to a daily median of approximately 100 mg/day in U.S. study populations (20, 21). Chinese women appear to be experiencing much higher exposure than previously studied populations. In contrast, intake of nitrate and nitrite from processed meats is lower in women in this population compared to U.S. study populations (20, 21). Intake of animal sources of nitrite represented less than 13% of intake on average in the SWHS population compared to approximately 30% of nitrite intake in a Western population (13). Additionally, it should be noted that other animal sources such as milk (2.3%) and eggs (3.1%) made a greater contribution to nitrite intake than salted/preserved meats (1.2%). In contrast, processed meats can be a primary source of exposure to nitrite among Americans.

As thyroid cancer is a common finding at autopsy (36), the opportunity for a detection bias in assessing risk factors for thyroid cancer is an important point to consider. In Shanghai all women have access to basic health care; therefore, a detection bias related to health care access is of less concern than in the United States. Nevertheless, higher levels of income and education can be a proxy for higher utilization of health care (37). We evaluated the association between educational level and nitrate and nitrite intake and found that more educated women had lower nitrite intake, particularly from processed meat sources, than less educated women. Therefore, it is unlikely that our positive findings for nitrite are due to differential detection of thyroid tumors by nitrite intake. A limitation of our study was that we did not have data on tumor size and we were unable to more directly evaluate the possible role of detection bias by comparing the associations for microcarcinomas (<1 cm) and larger size tumors; the incidence of smaller tumors would be expected to be most affected by screening.

As iodine deficiency can disrupt thyroid hormone production resulting in increased TSH release, the iodine status of the population is an important consideration. In past decades, there were many areas in China where iodine deficiency presented a major public health issue. However, salt has been iodized throughout China since 1996, and as a result, iodine intake has increased countrywide. Data from the Ministry of Health of China indicate that the median urinary iodine excretion, a measure of iodine intake, increased from 165 μg per liter in 1995 to 330 μg per liter in 1997 and stabilized at a similar level (306 μg per liter) in 1999 (38). According to the guidelines of the World Health Organization (WHO), after iodization measures were instituted, the levels of iodine intake in China were more than adequate. Additionally, as Shanghai is a seaside city, its residents consume high levels of fish and seafood, and subsequently iodine, and cases of iodine deficiency disease were extremely rare even before national iodination measures. As such, it is unlikely that iodine deficiency affected our findings. We also considered this point by attempting to look at cases in our study population by histologic type as relatively more follicular thyroid cancer cases occur in iodine deficient regions. Although the histologic data was incomplete, more than 85% of tumors with histology information were papillary tumors. The high number of papillary thyroid cancers is consistent with what has been observed in other iodine sufficient populations.

Our study had numerous strengths, including the use of a comprehensive questionnaire to assess dietary intake of nitrate and nitrite and the wide range of intake. Among participants in our study, the median intake of nitrate in the highest quartile was over three times that in the lowest quartile and for nitrite, the highest quartile was over two times that in the lowest quartile. Another strength is that we were able to estimate nitrate levels in most vegetables using values specific for Shanghai. This is important for accurate exposure assessment as women in this area tend to eat locally grown produce and the nitrate values vary substantially from province to province. For example, values for spinach ranged from 1112 mg/kg in Shanghai, to 1649 mg/kg in Hangzhou, to 1850 mg/kg in Chongqing, and to 2358 mg/kg in Beijing (25). Other strengths include the well-established cohort, the 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.

Limitations of our study include the fact that the assessment of dietary intake was limited to the year prior to baseline, which could result in misclassification of exposure if dietary intakes changed over time. Although our questionnaire was previously validated for macro- and micronutrients, a validation specifically for nitrate and nitrite is needed. Also, we did not have data on iodine or radiation exposure and were subsequently unable to consider the potential role of iodine or radiation exposure on our findings. Our adjustment for family history of cancer was also non-specific and would have been improved with information about family history of thyroid cancer, although family history of thyroid cancer is rare and unlikely to be an important confounder.

Although we did not observe an association for nitrate as hypothesized, our results suggest that women consuming higher levels of nitrite, especially from animal sources, may have an increased risk of thyroid cancer. The identification of nitrite as a potential risk factor is of interest as the known causes of thyroid cancer are currently limited to radiation exposure during childhood. This potential risk factor for thyroid cancer should be considered in additional studies.

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References

1. 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; 20(5):525–31. [PubMed: 19016336]
2. Qian B, He M, Dong S, Wang J, Chen K. Incidence and mortality of thyroid cancers in Tianjin from 1981 to 2001. Chin J Endocrinol Metab. 2005; 21:432–434.
3. Ron, E.; Schneider, AB. Thyroid Cancer. In: Schottenfeld, D.; Fraumeni, J., editors. Cancer Epidemiology and Prevention. 3. Oxford University Press; New York NY: 2006. p. 975-994.
4. Kilfoy BA, Zhang Y, Park Y, Holford TR, Schatzkin A, Hollenbeck A, Ward MH. Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study. Int J Cancer. 2011 Jul 1; 129(1):160–72. [PubMed: 20824705]
5. Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR. Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology. 2010 May; 21(3):389–95. [PubMed: 20335813]
6. Peterson E, De P, Nuttall R. BMI, Diet and Female Reproductive Factors as Risks for Thyroid Cancer: A Systematic Review. PLoS One. 2012; 7(1):e29177. Epub 2012 Jan 19. [PubMed: 22276106]
7. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Ingested nitrate and nitrite and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 2010; 94:1–464.
8. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Cogliano V. WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. Lancet Oncol. 2006; 7:628–9. [PubMed: 16900606]
9. Mirvish SS. Inhibition by vitamins C and E in vivo nitrosation and vitamin C occurrence in the stomach. Eur J Cancer Prev. 1996; 1:131–6. [PubMed: 8972308]
10. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal, and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett. 1995; 93:17–48. [PubMed: 7600541]
11. Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, Santini F, Crump K, Gibbs J. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid. 2004 Dec; 14(12): 1012–9. [PubMed: 15650353]
12. De Groef B, Decallonne BR, Van der Geyten S, Darras VM, Bouillon R. Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. Eur J Endocrinol. 2006 Jul; 155(1):17–25. [PubMed: 16793945]
13. Bruce, GM.; Peterson, MK.; Pleus, RC. Comparative contribution of perchlorate and antithyroid agents in American diets to iodide uptake inhibition. Paper presented at the 32nd Propellant Development & Characterization Subcommittee and 21st Safety & Environmental Protection Subcommittee Joint Meeting; Seattle, WA. 29 July 2004;
14. 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(5):873–877. [PubMed: 2029752]

15. Tajtakova M, Semanova Z, Tomkova Z, Szökeova E, Majoros J, Radikova Z, Sebökova E, Klimes I, Langer P. Increased thyroid volume and frequency of thyroid disorders signs in schoolchildren from nitrate polluted area. Chemosphere. 2006; 62:559–564. [PubMed: 16095667]
16. van Maanen JM, van Dijk A, Mulder K, de Baets MH, Menheere PC, van der Heide D, Mertens PL, Kleinjans DC. Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicology Letters. 1994; 72:365–374. [PubMed: 8202954]
17. 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]
18. National Academy of Sciences. Committee on Nitrite and Alternative Curing Agents in Food. Part 1. National Academy Press; Washington, DC: 1981. The health effects of nitrate, nitrite and N-nitroso compounds.
19. Zhong Z, Hu C, Wang M. Nitrate and nitrite in vegetables from north China: content and intake. Food Additives & Contaminants. 2002; 19:1125–1129. [PubMed: 12623672]
20. Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR. Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology. 2010; 21:389–95. [PubMed: 20335813]
21. Kilfoy BA, Zhang Y, Park Y, Holford TR, Schatzkin A, Hollenbeck A, Ward MH. Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP diet and health study. Int J Cancer. 2010; 129(1):160–72. [PubMed: 20824705]
22. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A. The Shanghai Women's Health Study: design, and baseline characteristics. Am J Epidemiol. 2005; 162(11):1123–1131. [PubMed: 16236996]
23. Shu XO, Yang G, Jin F, Liu D, Kushi L, Wen W, Gao YT, Zheng W. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. Eur J Clin Nutr. 2004; 58(1):17–23. [PubMed: 14679362]
24. Yang, YX.; Wang, GY.; Pan, XC. China Food Composition Tables 2002. Beijing, China: Beijing University Medical Press; 2002.
25. Zhou ZY, Wang MJ, Wang JS. Nitrate and nitrite contamination in vegetables in China. Food Rev Int. 2000; 16:61–76.
26. Yuan Y, Zhang T, Yuan T, Wang Y, Zheng H, Zhang B. Survey of nitrite content in foods from north-east China. Food Add Contam. 2010
27. MAFF UK Food Surveillance Information Sheets. MAFF, 1998 – 1997 Total Diet Study NITRATE AND NITRITE. Number 163 October 1998. Ministry of Agriculture, Fisheries and Food; London, UK: 1998.
28. Selenka F, Brand-Grimm D. Nitrate and nitrite in human food calculation of thedaily intake and its range (authors transl). Zentralbl Bakteriol [Orig B]. 1976; 162(5–6):449–66.
29. Susin J, Kmecl V, Gregorcic A. A survey of nitrate and nitrite content of fruit and vegetables grown in Slovenia during 1996–2002. Food Addit Contam. 2006; 23:385–90. [PubMed: 16546884]
30. Truong T, Baron-Dubourdieu D, Rougier Y, Guénel P. Role of dietary iodine and cruciferous vegetables in thyroid cancer: a countrywide case-control study in New Caledonia. Cancer Causes Control. 2010; 21(8):1183–92. [PubMed: 20361352]
31. 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]
32. Yang HJ, Shen ZM, Zhang JP, Wang WH. Water quality characteristics along the course of the Huangpu River (China). J Environ Sci (China). 2007; 19(10):1193–8. [PubMed: 18062417]
33. Willett, WC. Nutritional epidemiology. New York: Oxford University Press; 1998.
34. Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F, Negri E. Red meat intake and cancer risk: a study in Italy. Int J Cancer. 2000; 86:425–8. [PubMed: 10760833]
35. Bartsch H, Frank N. Blocking the endogenous formation of N-nitroso compounds and related carcinogens. IARC Sci Publ. 1996; 139:189–201. [PubMed: 8923031]

36. Valle LA, Kloos RT. The prevalence of occult medullary thyroid carcinoma at autopsy. J Clin Endocrinol Metab. 2011; 96:E109–13. [PubMed: 20943788]

37. Liu GG, Zhao Z, Cai R, Yamada T, Yamada T. Equity in health care access to: assessing the urban health insurance reform in China. Soc Sci Med. 2002 Nov; 55(10):1779–94. [PubMed: 12383462]

38. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Tong Y, Wang W, Gao T, Li C. Effect of iodine intake on thyroid diseases in China. N Engl J Med. 2006 Jun 29; 354(26):2783–93. [PubMed: 16807415]

Table 1

Baseline Characteristics of the Cohort by Thyroid Cancer Status, Shanghai Women's Health Study

	Total Cohort (n = 73,317)	Thyroid Cancer Cases (n= 164)
Age at cohort entry, years, mean (SD)	52.0 (9.1)	50.1 (8.4)
Education, %		
Elementary school or lower	21	13
Middle school	37	36
High school	28	35
College or higher	14	16
Cancer in first-degree relative, %	25.3	33.5
Diabetes, %	4.3	3.7
Any alcohol intake, %	2	0.7
Ever smoker, %	2.8	1.2
Total caloric intake, kcal/day, mean (SD)	1,685.1 (407.5)	1,716.4 (470.5)
Body mass index, mean (SD)	23.4 (3.2)	23.1 (2.5)
Total physical activity, metabolic equivalent tasks-hours/week, mean (SD)	106.6 (45.1)	101.1 (47.3)

Table 2

Percent contribution to total daily intake of nitrate and nitrite for participants in the SWHS

Foods contributing to median nitrate intake	%	Foods contributing to median nitrite intake	%
Greens/Chinese Greens	42.7	Watermelon	15.2
Watermelon	12.5	Fresh bean curd	9.7
Baby soy beans, fresh peas, fresh broad beans	4.2	Salted vegetables, preserved vegetables	9.1
Winter melon	4.1	Winter melon	7.8
Chinese cabbage/bok choi cabbage	3.4	Noodles, steamed bread, and other wheat foodstuffs	6.0
Cucumber, luffa	3.2	Apples	5.9
Snow peas	3.1	Rice	5.1
Green cabbage	3.0	Vegetarian meat (other bean curd, fried, etc.)	5.0
Celery	2.7	Pears	3.7
Yard long bean	2.2	Desserts	3.4

Table 3

Means and proportions for baseline characteristics of the SWHS cohort by quartiles of nitrate and nitrite intake (N = 73,317)

		Nitrate				Nitrite			
Parameter	**Characteristics**	**Q1**	**Q3**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Energy adjusted quintile median mg/1000kcal		108.6	164.2	217.6	250.9	0.62	0.81	0.95	1.12
Unadjusted quintile median mg/day		165.8	257.8	350.6	506.8	0.89	1.27	1.61	2.14
Age (mean)		53	51.7	51.5	51.9	53.9	51.8	51.2	51.1
Positive family history of cancer (%)		24.5	25.6	25.3	25.7	25.7	25.4	26.1	26.4
Currently married (%)		87.9	90	90.1	87.3	85.6	89.5	90.7	89.5
Body mass index (kg/m2)		23.1	23.3	23.5	23.9	23.2	23.3	23.4	23.8
Smoking history	Ever smoker (%)	3.8	2.5	2.2	2.6	4.4	2.5	1.8	2.4
Education, highschool or more (%)		26.3	19.7	18.8	20.7	34	20.3	16.5	14.7
Vigorous physical energy expend		8.2	8	8	8.1	8.7	8	7.9	7.8
Dietary Intakes	Energy (kcal/day)	1491.5	1625.5	1726.2	1897.3	1398.6	1587.9	1734.4	2019.7
	Vegetables (servings/1,000kcal)	13	13.6	13.8	14.2	13.5	13.6	13.7	13.8
	Cruciferous Vegetables (g/1,000kcal)	23.5	41.7	60.5	103.3	45.9	51.8	58.6	72.6
	Fruit (servings/1,000kcal)	4.4	5.4	5.9	6.6	3.5	5.2	6.2	7.4
	Salted preserved meat (servings/1,000kcal)	0.79	0.86	0.87	0.87	0.6	0.75	0.84	1.19
	Smoked meat/bacon (servings/1,000kcal)	0.34	0.41	0.4	0.41	0.18	0.31	0.4	0.68
	Meat (g/1,000kcal)	29.8	30.7	30	27.8	29.3	31	30.2	27.8
	Fat (g/1,000kcal)	16.5	17.4	17.4	17.8	15.1	17.3	18	18.8
	Fiber (g/1,000kcal)	4.9	9.4	11.1	14.6	7.8	9.3	11.2	15
	Protein (g/1,000kcal)	37.1	39.2	40.4	42.2	36	39.3	40.8	42.8
	Iron (mg/1,000kcal)	9.7	10.6	11.3	12.6	9.9	10.7	11.3	12.3
	Vitamin C (mg/1,000kcal)	48.2	75.5	99.9	151.3	56.3	77.8	99.3	144.3
	Vitamin E (mg/1,000kcal)	8.3	10.7	12.7	16.6	7.9	10.2	12.7	18.2
	Carotene (mg/1,000kcal)	837	1305	1729	2623	1157	1445	1705	2188
	Folic acid (mg/1,000kcal)	142	162	179	211	146	166	179	204

Table 4

Relative risks (RR) and 95% confidence intervals (CI) according to quartiles of nitrate or nitrite intake and thyroid cancer in the Shanghai Women's Health Study

	median (mg/1,000kcal)	Thyroid Cancer (n= 164)				
Nitrate		Cases	RR *	95% CI	RR &	95% CI
Quartile 1	109	34	1.00	(ref)	1.00	(ref)
Quartile 2	164	56	1.81	1.18–2.76	1.69	1.07–2.68
Quartile 3	218	41	1.44	0.92–2.28	1.23	0.71–2.15
Quartile 4	251	33	1.32	0.82–2.14	0.93	0.42–2.07
p-value for trend			0.37		0.40	
Nitrite						
Quartile 1	0.6	32	1.00	(ref)	1.00	(ref)
Quartile 2	0.8	51	1.60	1.03–2.51	1.64	1.04–2.58
Quartile 3	0.9	31	1.05	0.64–1.73	1.09	0.65–1.85
Quartile 4	1.1	50	1.91	1.22–3.00	2.05	1.20–3.51
p-value for trend			0.19		0.36	
Plant sources of nitrite						
Quartile 1	0.5	37	1.00	(ref)	1.00	(ref)
Quartile 2	0.7	47	1.32	0.85–2.03	1.30	0.83–2.02
Quartile 3	0.8	39	1.19	0.75–1.86	1.15	0.71–1.87
Quartile 4	1.0	41	1.37	0.88–2.15	1.30	0.76–2.4
p-value for trend			0.37		0.70	
Animal sources of nitrite						
Quartile 1	0.1	30	1.00	(ref)	1.00	(ref)
Quartile 2	0.1	35	1.03	0.63–1.69	1.03	0.63–1.68
Quartile 3	0.1	48	1.41	0.88–2.26	1.35	0.84–2.16
Quartile 4	0.2	51	1.59	1.01–2.56	1.59	1.00–2.52
p-value for trend			0.02		0.02	
Processed meat sources of nitrite						
Quartile 1	0.0	59	1.00	(ref)	1.00	(ref)
Quartile 2	0.0	19	0.81	0.48–1.36	0.77	0.46–1.31
Quartile 3	0.0	49	1.17	0.80–1.72	1.20	0.81–1.75

	median (mg/1,000kcal)	Thyroid Cancer (n= 164)				
Quartile 4	0.1	37	1.92	1.26–2.93	1.96	1.28–2.99
p-value for trend			<0.01		<0.01	

*Adjusted for age (continuous), total energy intake (continuous), education, and history of thyroid disease& Adjusted for age (continuous), total energy intake (continuous), education, history of thyroid disease, vitamin C, carotene, and folate intake.

Table 5

Relative risks (RR) and 95% confidence intervals (CI) according to joint intake of nitrite or nitrate and vitamin C and risk of thyroid cancer

Joint intake Nitrite and/or nitrate/vitamin C	Low/high	Low/low	High/high	High/low	p interaction
Thyroid Cancer					
Dietary vitamin C, median intake†	117.4	58.8	117.4	58.8	
Nitrate, total, median intake†	134.2	134.2	244.1	244.1	
Number of cases	17	47	37	13	
Multivariate RR (95% CI)‡	1.00	0.98 (0.54–1.77)	0.93 (0.52–1.68)	1.03 (0..46–2.29)	0.77
Nitrite, total, median intake†	0.71	0.71	1.05	1.05	
Number of cases	16	44	38	16	
Multivariate RR (95% CI)‡	1.00	1.12 (0.62–2.04)	1.13 (0.63–2.03)	1.16 (0.56–2.41)	0.83

* Low-high distinctions based on median intake values.

† mg/1,000 kcal per day.

Adjusted for age (continuous), total energy intake (continuous), education, and history of thyroid disease.