Published in final edited form as:
Cancer Causes Control. 2010 June ; 21(6): 889–896. doi:10.1007/s10552-010-9517-6.

Risk of Non-Hodgkin Lymphoma and Nitrate and Nitrite from the Diet in Connecticut Women

Briseis A. Kilfoy[1], **Mary H. Ward**[1], **Tongzhang Zheng**[2], **Shelia Zahm**[1], **Theodore R. Holford**[2], **Peter Boyle**[3], **Ping Zhao**[4], **Min Dai**[4], **Brian Leaderer**[2], and **Yawei Zhang**[2]

[1] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

[2] Yale School of Public Health, Yale University, New Haven, CT, USA

[3] International Prevention Research Institute, Lyon, France

[4] China's National Cancer Institute, Beijing, China

Abstract

The incidence of non-Hodgkin lymphoma has substantially increased during the past several decades, and although established risk factors such as immunodeficiency and viral infection may be responsible for a portion of the cases, the vast majority of the NHL cases remain unexplained. Dietary nitrate and nitrite intake are exposures of particular interest for non-Hodgkin lymphoma risk as they have been shown to cause lymphomas in animal studies and there is growing evidence of adverse impact in the epidemiological literature. We investigated NHL risk in general and by subtype in relation to dietary nitrate and nitrite intake in a population-based case-control study of 1,304 women in Connecticut. Nitrate and nitrite intake was assessed using a 120-item food frequency questionnaire. We found no association between risk of NHL and dietary nitrate and a slightly increased risk of NHL for higher dietary nitrite intake (OR = 1.37; 95% CI: 1.04–1.79). The risk was significantly increased for diffuse large B-cell lymphoma (OR = 1.61; 95% CI: 1.08–2.42), follicular lymphoma (OR = 1.61; 95% CI: 1.02–2.54), and T-cell lymphoma (OR = 2.38; 95% CI: 1.12–5.06). Animal products containing nitrite appear to be driving the risk for DLBC lymphoma and follicular lymphoma, whereas the risk for T-cell lymphoma is being driven by plant products. Our results confirm a previous finding for nitrite intake and highlight the importance of evaluating NHL risk by histologic type. We conclude that these results should be replicated in a larger study with data on water consumption as well as diet.

Keywords

Non-Hodgkin lymphoma; nitrate and nitrite; diet

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies arising from lymphocytes throughout the body (1–3). The histologic types can be divided into aggressive and indolent types, formed from either B-cells or T-cells (3). It has been estimated that

Address for correspondence and reprints: Dr. Briseis A. Kilfoy, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, EPS, Room 8111, 6120 Executive Boulevard, Bethesda, MD 20852-7244. Phone: 301-435-2358; Fax: 301-402-1819. kilfoyb@mail.nih.gov.

65,980 individuals will be diagnosed with NHL and 19,500 will die from NHL in the United States in 2009 (4). Although established risk factors such as immunodeficiency and viral infection may be responsible for a portion of the cases, the vast majority of the NHL cases remain unexplained.

Nitrate and nitrite are precursors in the formation of N-nitroso compounds (NOCs), a class of genotoxic compounds most of which are animal carcinogens and which can act systemically (5). Specific NOCs have been shown to cause lymphomas in animal studies (6). 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 (5). 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 (7). Ingestion of nitrate and nitrite at the acceptable daily intake level results in increased urinary excretion of N-nitroso compounds (8). Although most previous investigations into the association between nitrate and nitrite and human cancer have focused on gastrointestinal cancers (9–12), the relationship with non-Hodgkin lymphoma is biologically plausible and of interest.

One cohort and three case-control studies previously evaluated dietary nitrate, and nitrite and non-Hodgkin lymphoma risk, however the results were not consistent (13–16). It was concluded that the results should be followed up in a larger study. Investigation of other dietary and nutrient intakes in this study population has been conducted previously (16). An increased risk of NHL was previously associated with higher consumption of animal protein, saturated fat, and carbohydrates. An increased risk was also observed for higher consumption of eggs and dairy products (including milk and butter products) and white bread. A decreased risk was observed for greater intake of dietary fiber, tomatoes, broccoli, squash, cabbage, cauliflower, onions, leeks, mixed lettuce salad with vegetables, dark bread, tortillas, popcorn, citrus fruits, apples, and pears (17). Intake of nitrate and nitrite was not estimated from the questionnaire previously. We therefore evaluated dietary sources of nitrate and nitrite as risk factors for NHL and NHL subtypes in a population-based case-control study of females in Connecticut.

Methods

Study population

The study population has been described in detail elsewhere (17, 18). Briefly, cases were histologically confirmed, incident NHL patients diagnosed in Connecticut between 1996 and 2000, restricted to women aged 21–84 at diagnosis, without previous diagnosis of cancer except nonmelanoma skin cancer, and alive at the time of interview. Out of 832 eligible NHL cases, 601 (72%) cases completed in-person interviews, and of those 594 completed the food frequency questionnaire. Participants were slightly older than non-participants, with mean ages of 67 and 62, respectively. The race distribution was similar between participants and non-participants.

Pathology slides or tissue blocks were obtained from the hospitals where the cases were diagnosed. The specimens were reviewed by two independent study pathologists. All NHL cases were classified according to the World Health Organization (WHO) classification system (19, 20), including 187 cases of diffuse large B-cell lymphoma (DLBCL), 134 cases of follicular lymphoma (FL), 66 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 40 cases of marginal zone B-cell lymphoma (MZBL), 44 cases of T/NK-cell lymphoma (T-cell), and 123 cases of other rare and unspecified subtypes.

Population-based controls with Connecticut addresses were recruited using random digit dialing methods (RDD) for those below age 65 years and files provided by the Centers for

Medicare and Medicaid Service (CMS) were used to recruit those aged 65 years or older, and were frequency matched to cases by age (±5 years). The participation rates were 69% for RDD controls and 47% for CMS controls. The distribution of age and race between participants and non-participants was similar. Out of 717 controls, we excluded 7 controls with dietary information missing, yielding 710 controls for final analysis.

The study was approved by the Human Subjects Research Review Committee at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. Written and informed consent was obtained from all subjects.

Interviews

In-person interviews were conducted by trained personnel using a standardized questionnaire to collect demographic information and other major known or suspected NHL risk factors, such as family history of cancer, pesticide exposure, medical history, smoking, alcohol consumption, UV radiation and hair-coloring products use. Dietary intake was assessed using a mailed self-administered semiquantitative food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center (Seattle, Washington), in which subjects were asked to characterize their usual diet in the year prior to being interviewed. The FFQ collects data on consumption frequency and portion size for approximately 120 foods including 19 vegetables, 11 fruits, and fresh and processed meats. Participants were queried about their frequency of intake in 9 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 (small, medium, or large). The questionnaire had been validated previously (21).

We determined the nitrate and nitrite contents of the foods on the questionnaire from the literature, as described previously (22, 23). Daily intakes of nitrate and nitrite were calculated by multiplying the frequency of consumption of each food by the nitrate or nitrite content of the food and summing across all food items. Intake was computed separately for animal and plant sources. We also evaluated intake of nitrate and nitrite from processed meat sources separately, which included both red and white meat sources of sausage, luncheon meats, cold cuts, ham, and hotdogs. The major contributors to nitrate intake in this study population were lettuce (17.5%), fruit (peaches, nectarines, and plums) (9.3%), and melon (watermelon and honeydew) (9.0%) and the major contributors to nitrite intake were rice and noodles (8.3%), lunch meats (7.1%), and fresh meat (beef, pork, or lamb) (6.8%).

Statistical analysis

Intake of nitrate and nitrite was divided into high and low intake according to the median consumption (mg/day for nitrate and nitrite) in controls. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the relative risk of NHL and NHL subtypes in relation to nitrate and nitrite consumption categories. Statistical analyses were performed using the SAS system, version 9.1 (SAS Institute, Cary, NC).

All models were adjusted for age, family history of NHL, total daily energy intake, vitamin C intake, vitamin E intake, and protein intake. Total energy intake was examined for extreme values (upper and lower 1.0% and 5.0%) and exclusion of these subjects did not result in material changes for the observed associations. We examined the associations between nitrate and nitrite intake and NHL overall as well as for NHL subtypes. To evaluate the consistency of the association, we stratified by at or above/below the median age of 61.4, body mass index (at or above/below median of 25), 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 103.5 mg), vitamin E intake

(at or above/below median 6.4 mg), and total protein intake (at or above/below median 57.4 mg) to evaluate factors potentially affecting nitrosation.

Results

Selected demographic characteristics of cases and controls were compared (Table 1). Cases and controls were similar with respect to age, race, reported family history of NHL, smoking status and total energy intake. However, cases tended to consume less alcohol, more calories, and have a higher BMI. The mean nitrate intake among cases was 116.5 mg/day (SE: 83.0 mg/day) and mean nitrite intake was 1.2 mg/day (SE: 0.6 mg/day). The mean nitrate intake among controls was 112.1 mg/day (SE: 75.1 mg/day) and mean nitrite intake was 1.1 mg/day (SE: 0.5 mg/day).

We found no association between risk of NHL and dietary nitrate intake (Table 2). However, we did identify a significantly increased risk of NHL among those who reported relatively higher intake of nitrite (OR = 1.37; 95% CI: 1.04–1.79). The risk of NHL from relatively higher nitrite intake appears to be driven by animal products as the OR for nitrite from animal sources is 1.35 (95% CI: 1.05–1.75) compared to an OR of 1.11 (95% CI: 0.86–1.44) for plant product sources of nitrite.

When we stratified our data by subtype, we found no association between any NHL subtype and nitrate intake (Table 3). However, higher nitrite intake was associated with a significant increase in risk of DLBCL (OR = 1.61; 95% CI: 1.08–2.42), follicular lymphoma (OR = 1.61; 95% CI: 1.02–2.54), and T-cell lymphoma (OR = 2.38; 95% CI: 1.12–5.06) compared to controls. Animal products containing nitrite appear to be driving the risk for DLBC lymphoma (OR = 1.69; 95% CI: 1.14–2.49) and follicular lymphoma (OR = 1.79; 95% CI: 1.15–2.79), whereas the risk for T-cell lymphoma is being driven by plant products (OR = 2.38; 95% CI: 1.12–5.06).

When we stratified high and low nitrate intake by the median vitamin C and vitamin E intake, as well as by protein, we observed a significant interaction ($p = 0.02$) for vitamin E for NHL overall, but the results remained non-significant (Table 4). However, when we evaluated the stratified results for nitrite intake, we found that the highest risk of NHL associated with nitrite intake was among those who consumed low amounts of vitamin C (OR = 1.76; 95% CI: 0.96–3.22). In contrast, we identified the highest risk for nitrite intake among those who consumed higher amounts of vitamin E (OR = 1.52; 95% CI: 1.15–2.00) and protein (OR = 1.33; 95% CI: 0.82–2.17). We also observed a significant interaction for vitamin E intake and nitrite ($p = 0.04$), but not for vitamin C or protein intake.

As was observed for NHL overall, when we stratified high and low nitrate intake by the median vitamin C and vitamin E intake, as well as by protein, we did not observe an interaction for any of the NHL subtypes with the exception of follicular lymphoma (Table 5). We found that the risk of follicular lymphoma was increased (OR = 1.67; 95% CI: 1.05–2.64) for those who reported high nitrate intake and high vitamin E intake. We also found an increased risk of DLBC lymphoma (OR = 1.84; 95% CI: 1.24–2.71) and T-cell lymphoma (OR = 1.81; 95% CI: 1.03–3.94) among those who reported high nitrite intake and high vitamin C intake. Among those who reported high vitamin E intake, we found an increased risk of DLBC lymphoma (OR = 2.12; 95% CI: 1.24–2.71) and follicular lymphoma (OR = 1.99; 95% CI: 1.28–3.11) for those who report high nitrite intake.

To evaluate the consistency of the association for nitrite intake and NHL overall as well as NHL subtype, we stratified our results by smoking status, median BMI, and median age. Our results were not changed materially when stratified by these factors (not shown).

Discussion

We found no association between risk of NHL and dietary nitrate and a slightly increased risk of NHL with dietary nitrite intake. The risk was significantly increased for DLBC lymphoma, follicular lymphoma, and T-cell lymphoma. Animal products containing nitrite appeared to account for the risk of DLBC lymphoma and follicular lymphoma, whereas the risk for T-cell lymphoma was mainly due intake from plants and plant-based products. There was evidence of an interaction with intake of vitamin E for NHL overall and for the follicular histologic type.

In a previous population-based case-control study of NHL and dietary nitrate and nitrite in SEER centers in Iowa, Detroit, Seattle, and Los Angeles (14), investigators found that dietary nitrate was inversely associated with risk of NHL (OR highest quartile = 0.54; 95%CI: 0.34–0.86). However, dietary nitrite intake was associated with increasing risk of NHL (highest quartile: 3.1; 1.7–5.5), a somewhat stronger association that we identified in our study. They determined that the increased risk for nitrite was largely due to intake of bread and cereal sources or plant sources of nitrite; whereas, we found that nitrite from animal sources was positively associated with NHL overall, and the DLBCL and follicular lymphoma subtypes. The median daily intake in our study was similar to the values reported in the NCI-SEER study (median nitrate intake: 114 mg/day, median nitrite intake: 0.91 mg/day) despite the fact that our study was restricted to women. The NCI-SEER results are consistent with a case-control study conducted previously in Nebraska (23) where investigators found that dietary nitrite was associated with a higher risk of t(14;18)-positive NHL, whereas dietary nitrate was weakly associated with a lower risk of t(14;18)-negative NHL. The investigators of the Nebraska study also found that the increased risk of t(14;18)-positive NHL was due to nitrite intake from cereal.

An explanation for the null findings in this study for NHL risk and nitrate intake may be due to the presence of nitrosation inhibitors in vegetables or other nutrients that are hypothesized to decrease the risk of NHL. In both animal and human experiments, vitamin C and vitamin E have been shown to inhibit the in vivo formation of N-nitroso compounds from nitrite (24). Specifically, as dietary nitrate is mostly of vegetable origin, and vegetables are known to contain inhibitors of *in vivo* nitrosation, other antioxidants, and other beneficial chemicals such as flavanoids (25, 26), our findings for nitrate may be due to the protective effect of vegetables in the diet. This explanation has been pointed to in several epidemiologic studies that have reported either no association or inverse associations between dietary nitrate intake and human cancers (28–30).

When nitrate is consumed as part of a normal diet containing vegetables, other bioactive substances are concomitantly consumed. Previously in this study population (17), a decreased risk of NHL was associated with greater intake of dietary fiber, tomatoes, broccoli, squash, cabbage, cauliflower, onions, leeks, mixed lettuce salad with vegetables, dark bread, tortillas, popcorn, citrus fruits, apples, and pears. An investigation of vegetables, fruits, and antioxidants, and NHL in the NCI-SEER study (31), also demonstrated an inverse association between NHL risk and higher intake of all vegetables combined, but particularly with the green leafy and cruciferous vegetables. There are many potential explanations for the protective effect. Fiber, found in vegetables, breads, and beans, among other foods, has been hypothesized to be protective against NHL as the alimentary fibers are thought the affect the dilution, absorption, and/or breakdown of fat and animal protein in the gut, either directly or indirectly by modifying the gut microflora composition (32). Vegetables, particularly green leafy vegetables, which would also be high in nitrate, are also a good source of folate which is involved in pathways of DNA synthesis, repair, and methylation reactions (32, 33). Cruciferous vegetables in particular, such as broccoli, cauliflower, and

cabbage, contain glucoinolates which are converted in vivo to isothiocyanates, compounds which are potent inducers of carcinogen detoxifying enzymes (34). Furthermore, many high nitrate vegetables, such as spinach and kale, as well as carrots and tomatoes, contain high levels of carotenoids and anti-oxidant related nutrients which are known to scavenge ROS molecules (35), and may also enhance DNA repair activity by modifying gene expression distinct from their direct antioxidant properties (36). In other words, elevated intake of foods high in nitrate may have a variety of protective effects that may affect NHL risk.

The increased risk of NHL overall, as well as for DLBCL, follicular, and T-cell lymphoma, was observed among those who had high estimated nitrite intake. The increased risk observed for dietary nitrite consumption and NHL risk is supported by some animal studies. One potential explanation is that N-nitrosoureas have been shown to induce B and T-cell lymphomas in animal studies where it was concluded that the system may be an effective means of inducing B cell lymphoma with a carcinogen. However, in theory, the conversion of both nitrate and nitrite to nitrosamines would be affected by inhibitors of nitrosation, such as vitamin C and vitamin E, but the significant increases in risk are observed among those with the highest levels of consumption of these nutrients. This finding is inconsistent with the hypothesized impact of the nitrosation inhibitors on the association between nitrite intake and cancer risk; in short, the fact that we didn't see an interaction with vitamin C suggests that the evidence doesn't confer strong support the NOC hypothesis.

Previously in this study population (17), an increased risk of NHL was associated with higher consumption of animal protein and saturated fat. An increased risk was also observed for higher consumption of eggs and dairy products (including milk and butter products) and white bread (17). An alternative explanation for the increased risk observed among those who consumed high levels of nitrite from animal sources is that many foods high in nitrite, such as meat products, are also a source of zinc which has widespread action on different enzymes, peptides, transcriptional factors, and cytokines involved in various physiological steps of immune development and reactivity (37). Investigators have previously suggested chronic hyperstimulation of the immune system and increased immune unresponsiveness by proteins and fats as an etiologic mechanism for lymphoma (38, 39). In other words, its possible that the consumption of many animal products estimated to be high in nitrite may have an adverse impact on NHL risk due alternative biologic pathways rather than via NOCs.

A limitation of this project is that nitrate is also present as a contaminant in drinking water and can be a major source of intake when levels are at/above maximum contaminant level (MCL) of 10 mg/L nitrate-N (40). However, we did not have data on water intake. Though nitrate is typically a contaminant of drinking water in rural areas, and Connecticut is not an area that is typically reported as having nitrate contamination of their groundwater (41). In addition, dietary intake based on FFQs is affected by measurement error, which, if nondifferential, could reduce an association. Furthermore, a primary limitation of our study is that the sample size is modest and the number of cases in several histologic subgroups was small. The study sample was also limited to women and may be non-generalizable to the entire population. The response rate in our study was also moderate and could potentially result in biased risk. The positive findings in our report require replication in larger studies with greater power.

Our study has several strengths. It was population-based and included incident cases that were histologically confirmed. Furthermore, strengths of this study include the use of a detailed questionnaire to assess intake of different types of foods that contain nitrate and nitrite that resulted in a wide range of variation in dietary intake of nitrate and nitrite. The ability to evaluate effect modification by vitamin C and vitamin E intake, meat intake, and

smoking status, as well as a large number of other potential confounding variables was also a strength of this study.

In sum, our results suggest that nitrite intake increases the risk of NHL overall including DLBC lymphoma, follicular lymphoma, and T-cell lymphoma. Our null findings for nitrate are consistent with previous findings and may be explained by the concomitant consumption of nitrosation inhibitors. In addition, we found that animal sources of nitrite appear to be more relevant than plant sources of nitrite for the more common histologic types. However, the lack of an interaction with vitamin C suggests that alternative pathways should be explored. Future investigation into this hypothesis would be strengthened with a larger sample size with sufficient power to evaluate interaction with factors affecting nitrosation by histologic type.

Acknowledgments

This research was supported by grant CA62006 from the National Cancer Institute (NCI), the Intramural Research Program of the NCI, National Institutes of Health (NIH) and Fogarty training grant 1D43TW008323 01 from the NIH. This publication was made possible by CTSA Grant number UL1 RR024139 from the National Center for Research Resources (NCRR), a component of the NIH, and NHL roadmap for medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR.

References

1. Grulich AE, Vajdic CM. The epidemiology of non-Hodgkin lymphoma. Pathology. 2005; 37(6): 409–19. [PubMed: 16373224]
2. Groves FD, et al. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. Journal of the National Cancer Institute. 2000; 92(15):1240–51. [PubMed: 10922409]
3. The Non-Hodgkin's Lymphoma Classification, P., A Clinical Evaluation of the International Lymphoma Study Group. Classification of Non-Hodgkin's Lymphoma. 1997. p. 3909-3918.
4. Society AC, American Cancer Society. Cancer Facts and Figures 2009. Atlanta, GA: 2009.
5. Gangolli SD, et al. Nitrate, nitrite and N-nitroso compounds. European Journal of Pharmacology. 1994; 292(1):1–38. [PubMed: 7867685]
6. Bogovski P, Bogovski S. Animal species in which *N*-nitroso compounds induce cancer. Int J Cancer. 1981; 27:471–474. [PubMed: 7275353]
7. Luck E. [Chemical preservation of food]. Zentralblatt fur Bakteriologie, Mikrobiologie und Hygiene. 1. Abt Originale B, Hygiene. 1985; 180(2–3):311–8.
8. McKnight GM, et al. Dietary nitrate in man: friend or foe? The British journal of nutrition. 1999; 81(5):349–58. [PubMed: 10615207]
9. Forman D. Are nitrates a significant risk factor in human cancer? Cancer surveys. 1989; 8(2):443–58. [PubMed: 2696589]
10. Fraser P, et al. Nitrate and human cancer: a review of the evidence. International Journal of Epidemiology. 1980; 9(1):3–11. [PubMed: 6252106]
11. Hansson LE, et al. Nutrients and gastric cancer risk. A population-based case-control study in Sweden. International journal of cancer. 1994; 57(5):638–44.
12. van Loon AJ, et al. Nitrate intake and gastric cancer risk: results from the Netherlands cohort study. Cancer Letters. 1997; 114(1–2):259–61. [PubMed: 9103306]
13. Weyer PJ, et al. Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. Epidemiology. 2001; 12(3):327–38. [PubMed: 11338313]
14. Ward MH, et al. Risk of non-Hodgkin lymphoma and nitrate and nitrite from drinking water and diet. Epidemiology. 2006; 17(4):375–82. [PubMed: 16699473]
15. Ward MH, et al. Drinking water nitrate and the risk of non-Hodgkin's lymphoma. Epidemiology. 1996; 7(5):465–71. [PubMed: 8862975]

16. Chiu BC, Dave BJ, Ward MH, Fought AJ, Hou L, Jain S, Gapstur S, Evens AM, Zahm SH, Blair A, Weisenburger DD. Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. Cancer Causes Control. 2008 Oct; 19(8):859–67. Epub 2008 Apr 2. [PubMed: 18386141]
17. Zheng T, et al. Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. Am J Epidemiol. 2004; 159(5):454–66. [PubMed: 14977641]
18. Morton LM, et al. Cigarette smoking and risk of non-Hodgkin lymphoma subtypes among women. Br J Cancer. 2003; 89(11):2087–92. [PubMed: 14647142]
19. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood. 1997; 89(11):3909–18. [PubMed: 9166827]
20. Harris NL, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999; 17(12):3835–49. [PubMed: 10577857]
21. Willett, W.; Lenart, E. Nutritional epidemiology. Oxford University Press; New York, NY: 1998. Reproducibility and validity of food-frequency questionnaires.
22. Ward MH, Zahm SH, Weisenburger DD, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer causes & control. 1994; 5:422–432. [PubMed: 7999964]
23. Ward MH, Cantor KP, Riley D, et al. Nitrate in public water supplies and risk of bladder cancer. Epidemiology. 2003; 14:183–190. [PubMed: 12606884]
24. Mirvish S. Effects of vitamins C and E on N-nitroso compound formation, carcinogenesis, and cancer. Cancer. 1986; 58:1852–1850.
25. Frankenfeld CL, Cerhan JR, Cozen W, Davis S, Schenk M, Morton LM, Hartge P, Ward MH. Dietary flavonoid intake and non-Hodgkin lymphoma risk. Am J Clin Nutr. 2008 May; 87(5): 1439–45. [PubMed: 18469269]
26. Cutler GJ, Nettleton JA, Ross JA, Harnack LJ, Jacobs DR Jr, Scrafford CG, Barraj LM, Mink PJ, Robien K. Dietary flavonoid intake and risk of cancer in postmenopausal women: the Iowa Women's Health Study. Int J Cancer. 2008 Aug 1; 123(3):664–71. [PubMed: 18491403]
27. Brambilla G, Martelli A. Genotoxic and carcinogenic risk to humans of drug-nitrite interaction products. Mutation research. 2007; 635:17–52. [PubMed: 17157055]
28. 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]
29. Forman D. Dietary exposure to N-nitroso compounds and the risk of human cancer. Cancer surveys. 1987; 6:719–738. [PubMed: 3330686]
30. Ward MH, Cantor KP, Riley D, et al. Nitrate in public water supplies and risk of bladder cancer. Epidemiology. 2003; 14:183–190. [PubMed: 12606884]
31. Kelemen LE, Wang SS, Lim U, Cozen W, Schenk M, Hartge P, Li Y, Rothman N, Davis S, Chanock SJ, Ward MH, Cerhan JR. Vegetables- and antioxidant-related nutrients, genetic susceptibility, and non-Hodgkin lymphoma risk. Cancer Causes Control. 2008 Jun; 19(5):491–503. Epub 2008 Jan 17. [PubMed: 18204928]
32. Blount BC, Mack MM, Wehr CM, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage; implications for cancer and neuronal damage. Proc Natl Acad Sci USA. 1997; 1994:3290–5. [PubMed: 9096386]
33. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. J Nutr. 2000; 130:129–32. [PubMed: 10720158]
34. Steinkellner H, Rabot S, Freywald C, et al. Effects of cruciferous vegetables and their consitituents on drug metabolizing enzymes involved in their bioactivation of DNA-reactive dietary carcinogens. Mutat Res. 2001; 480(1):285–97. [PubMed: 11506821]
35. Moller P, Loft S. Interventions with antioxidants and nutrients in relaiton to oxidative damage and repair. Mut Res. 2004; 551:79–89. [PubMed: 15225583]
36. Astley SB, Hughes DA, Wright AJ, Elliott RM, Southon S. DNA damage and susceptibility to oxidative damage in lymphocytes: effects of carotenoids in vitro and in vivo. Br J Nutr. 2004; 91:53–61. [PubMed: 14748938]
37. Dreosti IE. Zinc and the gene. Mut Res. 2001:161–7. [PubMed: 11295161]

38. Cunningham AS. Lymphomas and animal-protein con- sumption. Lancet. 1976; 2:1184–6. [PubMed: 63007]
39. Schwartz RS. Another look at immunologic surveillance. New Engl J Med. 1975; 293:181–3. [PubMed: 1094290]
40. Chilvers CIH, Caygill C, et al. A survey of dietary nitrate in well-water users. Int J Epidemiol. 1984; 13:324–331. [PubMed: 6490303]
41. 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]

Table 1

Descriptive characteristics of non-Hodgkin Lymphoma cases and controls among Connecticut women, 1995–2001

Characteristic	Cases (n=594)	Controls (n=710)	P
Age (years), mean ± SD	62.28 ± 13.75	61.41 ± 14.31	0.265
Race n(%)			0.246
White	546 (95.0)	661 (93.1)	
African-American	18 (3.0)	24 (3.4)	
Other	12 (2.0)	25 (3.5)	
Family history of NHL n(%)			0.099
No	385 (98.5)	706 (99.4)	
Yes	9 (1.5)	4 (0.6)	
Smoking Status n(%)			0.869
Never	265 (44.6)	320 (45.1)	
Ever	329 (55.4)	390 (54.9)	
Alcohol Intake n(%)			0.049
Never	226 (38.0)	233 (32.8)	
Ever	368 (62.0)	477 (67.2)	
Education n(%)			0.016
High school or less	259 (43.6)	263 (37.0)	
Some college or higher	335 (56.4)	447 (63.0)	
Body Mass Index, mean ± SD (weight (kg)/height $(m)^2$)	26.20 ± 5.75	25.38 ± 5.01	0.007
Energy intake (kcal/day), mean ± SD	1712.2 ± 602.15	1628.1 ± 595.88	0.012
Nitrate intake (mg/day), mean ± SD	116.50 ± 83.0	112.08 ± 75.11	0.313
Nitrite intake (mg/day), mean ± SD	1.17 ± 0.58	1.10 ± 0.51	0.021
Protein intake (mg/day), mean ± SD	63.07 ± 23.29	61.26 ± 23.75	0.167
Vitamin C (mg/day), mean ± SD	112.58 ± 56.57	107.75 ± 51.85	0.108
Vitamin E (mg/day), mean ± SD	7.32 ± 3.61	7.12 ± 3.57	0.200

Table 2

Multivariate adjusted* association of nitrate and nitrite with non-Hodgkin lymphoma, Connecticut women 1995–2001

	NHL Overall			
	Controls (no.)	**Cases (no.)**	**OR**	**95% CI**
Nitrate (mg/day)				
Low	352	274	1.00	
High	355	317	1.09	0.86, 1.39
Nitrite (mg/day)				
Low	349	248	1.00	
High	355	345	**1.37**	**1.04, 1.79**
Nitrite from plants (mg/day)				
Low	355	267	1.00	
High	355	327	1.11	0.86, 1.44
Nitrite from animals (mg/day)				
Low	355	253	1.00	
High	355	341	**1.35**	**1.05, 1.75**

*Adjusted for age, family history of cancer, calories, vitamin C intake, vitamin E intake, and protein intake

Table 3

Multivariate adjusted* association of nitrate and nitrite with non-Hodgkin lymphoma, Connecticut women 1995–2001

		Major B-cell subtypes														
		DLBCL (n=184)			Follicular (n=130)			CLL/SLL (n=66)			Marginal Zone (n=40)			T-cell (n=44)		
	Controls (no.)	Cases (no.)	OR	95% CI	Cases (no.)	OR	95% CI	Cases (no.)	OR	95% CI	Cases (no.)	OR	95% CI	Cases (no.)	OR	95% CI
Nitrate (mg/day)																
Low	352	90	1.00		53	1.00		34	1.00		24	1.00		22	1.00	
High	355	96	0.9	0.63, 1.28	80	1.43	0.94,2.16	32	1.26	0.72, 2.20	16	0.69	0.34, 1.41	22	1	0.52, 1.93
Nitrite (mg/day)																
Low	349	64	1.00		52	1.00		42	1.00		18	1.00		16	1.00	
High	355	122	**1.61**	**1.08, 2.42**	82	**1.61**	**1.02, 2.54**	24	0.65	0.34, 1.25	22	1.57	0.71, 3.45	**28**	**2.38**	**1.12,5.06**
Nitrite from plants (mg/day)																
Low	355	84	1.00		54	1.00		35	1.00		23	1.00		17	1.00	
High	355	103	0.9	0.62, 1.32	80	1.4	0.90, 2.16	31	1.18	0.65, 2.13	17	0.76	0.35, 1.63	27	1.83	0.90,3.71
Nitrite from animals (mg/day)																
Low	355	65	1.00		50	1.00		39	1.00		19	1.00		24	1.00	
High	355	122	**1.69**	**1.14, 2.49**	54	**1.79**	**1.15, 2.79**	27	0.83	0.45, 1.54	21	1.19	0.55, 2.53	20	0.9	0.43, 1.89
p for trend																

*Adjusted for age, family history of cancer, calories, vitamin C intake, vitamin E intake, and protein intake

Table 4

Multivariate adjusted association of nitrate and nitrite stratefied by vitamin C intake, vitamin E intake, and protein intake

	Low Nitrate			High Nitrate				Low Nitrite			High Nitrite		
	Controls	**Cases**		**Controls**	**Cases**			**Controls**	**Cases**		**Controls**	**Cases**	
Vitamin C*							Vitamin C						
High	258	270	1	166	159	1.12 (0.86–1.47)	High	258	189	1	162	169	1.34 (1.02–1.77)
Low	173	125	0.86 (0.65–1.14)	26	16	0.74 (0.38–1.42)	Low	181	134	0.98 (0.74–1.30)	21	28	1.76 (0.96–3.22)
p-interaction						0.39	p-interaction						0.11
Vitamin E&							Vitamin E						
High	385	317	1	135	125	1.14 (0.86–1.52)	High	382	281	1	142	157	1.52 (1.15–2.00)
Low	172	140	1.09 (0.82–1.44)	16	12	1.15 (0.53–2.50)	Low	174	150	1.29 (0.98–1.69)	6	5	1.42 (0.43–4.75)
p-interaction						0.02	p-interaction						0.04
Protein #							Protein						
Low	340	278	1	103	94	1.03 (0.74–1.43)	Low	343	262	1	89	83	1.11 (0.78–1.59)
High	224	185	0.74 (0.54–1.02)	41	35	0.91 (0.56–1.49)	High	233	202	0.90 (0.65–1.25)	39	45	1.33 (0.82–2.17)
p-interaction						0.65	p-interaction						0.69

*Adjusted for age, family history of cancer, calories, vitamin E intake, and protein intake

&Adjusted for age, family history of cancer, calories, vitamin C intake, and protein intake

#Adjusted for age, family history of cancer, calories, vitamin C intake, and vitamin E intake

Cancer Causes Control. Author manuscript; available in PMC 2011 May 3.

Table 5

Multivariate adjusted association of nitrate and nitrite stratefied by vitamin C intake, vitamin E intake, and protein intake

	Low Nitrate			High Nitrate				Low Nitrite			High Nitrite		
	Controls	**Cases**		**Controls**	**Cases**			**Controls**	**Cases**		**Controls**	**Cases**	
DBLCL							**DLBCL**						
Vitamin C*							Vitamin C*						
High	258	68	1	166	50	1.11 (0.75–1.64)	High	258	48	1	162	67	**1.84 (1.24–1.71)**
Low	173	39	0.81 (0.53–1.23)	26	4	0.59 (0.20–1.74)	Low	181	41	1.06 (0.74–1.30)	21	7	1.36 (0.54–3.42)
p-interaction						0.32	p-interaction						0.36
Vitamin E&							Vitamin E&						
High	385	108	1	135	37	1.02 (0.66–1.56)	High	382	79	1	142	61	**2.12 (1.44–3.14)**
Low	172	41	1.03 (0.68–1.57)	16	1	na	Low	174	46	**1.52 (1.00–2.31)**	6	0	na
p-interaction						0.67	p-interaction						0.68
Protein #							Protein #						
Low	340	86	1	103	28	0.96 (0.59–1.59)	Low	343	68	1	89	32	1.51 (0.92–2.49)
High	224	63	0.65 (0.40–1.03)	41	10	0.76 (0.36–1.61)	High	233	71	1.01 (0.62–1.66)	39	15	1.54 (0.77–3.05)
p-interaction						0.99	p-interaction						0.89
Follicular							**Follicular**						
Vitamin C*							Vitamin C*						
High	258	44	1	166	41	1.32 (0.85–2.03)	High	258	36	1	162	42	1.54 (0.98–2.41)
Low	173	23	0.70 (0.42–1.17)	26	4	0.80 (0.27–2.43)	Low	181	27	0.89 (0.54–1.46)	21	7	1.93 (0.76–4.95)
p-interaction						0.37	p-interaction						<0.01
Vitamin E&							Vitamin E&						
High	385	64	1	135	36	**1.67 (1.05–2.64)**	High	382	59	1	142	42	**1.99 (1.28–3.11)**
Low	172	31	1.23 (0.76–2.01)	16	3	1.50 (0.41–5.42)	Low	174	33	1.39 (0.86–2.23)	6	0	na
p-interaction						<0.01	p-interaction						<0.01
Protein #							Protein #						
Low	340	60	1	103	23	1.11 (0.64–1.91)	Low	343	61	1	89	15	0.82 (0.44–1.54)
High	224	38	0.65 (0.38–1.12)	41	11	1.25 (0.60–2.61)	High	233	42	0.76 (0.44–1.30)	39	15	1.76 (0.88–3.51)

	Low Nitrate			High Nitrate				Low Nitrite			High Nitrite		
	Controls	Cases		Controls	Cases			Controls	Cases		Controls	Cases	
p-interaction						0.98	p-interaction						0.86

*Adjusted for age, family history of cancer, calories, vitamin E intake, and protein intake

&Adjusted for age, family history of cancer, calories, vitamin C intake, and protein intake

#Adjusted for age, family history of cancer, calories, vitamin C intake, and vitamin E intake