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Dietary nitrate and nitrite intake and risk of non-Hodgkin lymphoma

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Abstract

Although established risk factors such as immunodeficiency and viral infections may be responsible for a portion of non-Hodgkin lymphoma (NHL) cases, the vast majority of NHL cases remain unexplained. The role of dietary nitrate and nitrite in NHL risk is of interest since they are precursors of N-nitroso compounds and nitrosoureas have been shown to induce B and T-cell lymphomas in animal studies. However, few studies have evaluated the potential association between consumption of nitrate and nitrite intake and NHL by subtype or chromosomal translocation status, and the results of these studies have been inconsistent. We estimated the dietary intake of nitrate and nitrite using a food frequency questionnaire in a population-based, case-control study of 348 cases and 470 controls conducted in Nebraska in 1999–2002. A non-significant excess risk of NHL was found among women who reported an intake of nitrite in the highest quartile compared to the lowest quartile (OR = 1.6; 95% CI: 0.8–2.9), particularly nitrite from animal sources (OR=1.9; 95% CI: 1.0–3.4). No significant associations were observed for nitrate or nitrite by NHL subtype. Although there were some increases in risk that support the N-nitroso hypothesis, they were not significant and do not confer strong evidence of an association.

Keywords

Non-Hodgkin lymphoma; nitrate; nitrite; diet

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies arising from lymphocytes (1–3). Although established risk factors such as immunodeficiency and viral infections may be responsible for a portion of NHL cases, the vast majority of NHL cases remain unexplained (1–3). The role of dietary nitrate and nitrite in NHL risk is of interest since these chemicals are precursors in the endogenous formation of N-nitroso compounds, including nitrosamines and nitrosoureas; the latter have been shown to induce B and T-cell lymphomas in animal studies (4–5). Nitrate and nitrite are common in typical American diets as 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 (6–9). Nitrite and nitrate salts are also 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 (6). Dietary intake of nitrate and nitrite has been demonstrated to result in the formation highly carcinogenic N-nitroso compounds (10–12).

There is some evidence from human epidemiologic studies that high dietary intake of nitrate and nitrite is associated with NHL risk (13–16). A cohort study of women in Iowa found that dietary nitrate was inversely associated with risk of NHL (13). In both the National Cancer Institute (NCI)-Surveillance Epidemiology and End Results (SEER) NHL study (15) and a case-control study conducted previously in Nebraska (16), the investigators found that dietary nitrite was associated with an increased risk of NHL, whereas dietary nitrate was associated with a lower risk of NHL. A case-control study of NHL in women in Connecticut reported no association between the risk of NHL overall and dietary nitrate intake, but a slightly increased risk of NHL with higher dietary nitrite intake (14). Emerging evidence suggests etiologic heterogeneity by NHL subtype, but to our knowledge, only a few studies have evaluated the association of nitrate and nitrite intake by NHL subtype. The case-control study in Connecticut found a significant positive trend for follicular lymphoma and nitrate and nitrite intake (14). Risk of T-cell lymphoma was also increased for the highest quartile of nitrite intake (14). In the only study that evaluated the association according to t(14;18)-defined subtypes of NHL (16), dietary nitrite was significantly associated with the risk of t(14;18)-positive NHL (OR = 2.8; 1.3–6.1). To further evaluate dietary sources of nitrate and nitrite as risk factors for NHL overall and for NHL subtypes, as defined by histology and molecular characteristics, we analyzed data in a population-based case-control study in Nebraska.

Methods

Study population

The study population and methods have been reported in detail elsewhere (17–19). Briefly, cases were identified by the statewide Nebraska Lymphoma Study Group Registry using a rapid case ascertainment system. Eligible cases had newly-diagnosed and histologically confirmed NHLs occurring between 1999 and 2002 and were residents of the 66 counties in eastern Nebraska, age 20–75 years, without infection with the human immunodeficiency virus (HIV) or prior history of malignancy (except cutaneous squamous cell or basal cell carcinomas). The cases were also required to be alive and mentally competent to participate.

An expert hematopathologist (D.D.W.) reviewed all cases and classified them according to the World Health Organization (WHO) classification of NHL (20). Of 529 live and eligible cases, 387 participated in the study (73.2% participation rate). Controls were selected by random digit dialing from the same 66 county area and were frequency matched to the cases by gender and 5-year age groups. Of 697 eligible controls, 535 participated in the study (76.8% participation rate). The study was approved by the Institutional Review Board of the University of Nebraska Medical Center. We obtained informed consent from each participant prior to the interview.

We obtained paraffin-embedded tumor blocks through the statewide Nebraska Lymphoma Study Group Registry and Tissue Bank for 175 of the 385 NHL cases (45.5%) in the parent case-control study. The other specimens were not available due to the length of time since case diagnosis, which exceeded the average time most hospitals and laboratories store their blocks (approximately 10–15 years). As previously described, tissue microarrays were prepared from archival paraffin-embedded tissue (17, 18). Four representative 0.6 mm cores were obtained from each case and inserted in a grid pattern into recipient paraffin blocks using a tissue arrayer (Beecher Instruments, Silver Spring, MD). Fluorescence in situ hybridization (FISH) studies were then performed on 4 micron tissue microarray sections. We used the commercially available LSI IGH/BCL2 dual color, dual fusion probe to define the t(14;18), and the centromeric enumeration probe of chromosome 18 to define the number of chromosome in the cells (Abbott-Vysis Inc., Downers Grove, IL). The t(14;18) status determined by FISH was validated by these two quality control measures. The upper limit for false-positive results for the t(14;18) probes is 5%. A minimum of 100 interphase nuclei were independently examined by two individuals, a cytotechnologist (S.J.) and an expert cytogeneticist (B.D.), for the presence of the t(14;18) and for chromosome 18 numbers. The agreement between the two readers was 100%. We compared the distribution of exposures of interest between NHL cases with available tumor blocks and those whose tumor blocks could not be retrieved. We found that the availability of tumor blocks did not differ by exposures of interest, including nitrate/nitrite.

Dietary assessment

We collected information on demographics and important medical, environmental, and lifestyle factors through telephone interviews. Following the completion of the telephone interview, we mailed the subjects a self-administered, modified version of the Block 1995 Revision of the Health Habits and History Questionnaire (21), which included additional foods high in nitrate (e.g., beets, celery, radishes, rhubarb) and separate questions about the various types of processed meats (baked ham [not including on sandwiches]; bacon; sausage [including Italian, German, Polish, breakfast]; hot dogs; ham, bologna, other lunch meats). This questionnaire has been validated by dietary records, and correlation coefficients for most nutrients are in the range of 0.5–0.6 although the validation did not include nitrate or nitrite (22).

The food frequency questionnaire included questions regarding the frequency of consumption of the various food groups including fruits and vegetables, dairy products, meats, breads, snacks, and beverages. For each food, subjects were asked to indicate their

usual portion from a selection of three serving sizes, and how often, on average, they had consumed that amount during the year before the interview. There were nine possible responses ranging from “never or less than once a month” to “every day.” Subjects were also asked about the regular use of multivitamins and eight single vitamin or mineral supplements, defined as at least one pill per week, over the past year.

Data analysis

We determined the nitrate and nitrite contents of the foods on the questionnaire from the literature, as described previously (23, 24). Daily intake of nitrate and nitrite was 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 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 top five contributors to nitrate intake in this study population were green salad (29.4%), celery (7.2%), baked potatoes (3.4%), bananas (1.6%), and cabbage/coleslaw (1.5%). The major contributors to nitrite intake were luncheon meats (4.6%), white bread (3.5%), baked ham (2.4%), sausage (2.1%), and bagels/English muffins (2.1%).

The food frequency questionnaire was completed by 348 of 387 cases (90%) and 470 of 535 controls (88%). Subjects who completed the food frequency questionnaire were slightly older than those who did not, but were similar in other characteristics such as education level, marital status, smoking status, and body mass index (19). Before analysis, we excluded 12 cases and 10 controls who reported implausible total calorie intakes (<800 kcal or >6,000 kcal for men, and <600 kcal or >5,000 kcal for women) or who left more than 20% of the items blank on the food frequency questionnaire, leaving 336 cases and 460 controls with complete dietary data. We used unconditional logistic regression to estimate the odds ratio (OR) and 95% confidence interval (CI) (26) to assess the association between the nitrate and nitrite variables and the risk of NHL.

The dietary intake variables were categorized into approximate quartiles, for overall NHL, or tertiles, for subtypes of NHL and for t(14;18), according to the distribution of consumption among the controls. We conducted analyses for two major subtypes of NHL, follicular lymphoma (including follicular lymphoma, grades 1–3, and diffuse follicle center lymphoma, grades 1/2) (n = 106) and diffuse large B-cell lymphoma (all types) (n = 87). We also evaluated the risk for t(14;18)-positive (n = 52) and -negative NHL groups (n = 104). The t(14;18)-positive and t(14;18)-negative analysis were conducted by evaluating the association of the groups independently with nitrate and nitrite intake.

Models were adjusted for the study matching factors of age (categorical) and gender (in overall models), and the potential confounders of marital status (current, not current), body mass index (normal, overweight, obese), education (less than high school, high school graduate, or more than high school), family history of cancer (yes, no), vitamins C (mg/1,000kcal), E (mg/1,000kcal), and total energy intake (kcal/day) (continuous). Other potential confounders were considered based on prior knowledge of the risk factors for

NHL, as well as change-in-estimate criteria (>10% change) (27). Factors such as farming status, physical activity, and use of hair dyes did not appreciably change the risk estimates, and therefore were not included in the final models. Dietary variables were adjusted for energy intake using the nutrient density method (28), which expresses intake in units per 1000 calories. Tests for linear trend were conducted using the continuous exposure variable in the model.

To evaluate the consistency of the associations for NHL overall, we stratified by age (at or above/below the median age of 61.4 years), body mass index (BMI) (at or above/below median of 26.9), and education (high school or fewer years of education/some college or greater years of education). We also stratified by smoking status (ever/never), vitamin C intake (at or above/below median 88.0 mg) and vitamin E intake (at or above/below median 9.2 mg) to evaluate factors potentially affecting nitrosation. The numbers were limited to stratify by these factors for NHL subtypes and by t14:18 status. We conducted the analysis using SAS version 9.1 (SAS Institute, Cary, NC) and report 2-sided p-values.

Results

The mean nitrate intake among cases was 100.3 mg/day (standard deviation (SD): 70.6 mg/day) and the mean nitrite intake was 1.4 mg/day (SD: 0.7 mg/day). The mean nitrate intake among controls was 103.0 mg/day (SD: 68.0 mg/day) and the mean nitrite intake was 1.3 mg/day (SD: 0.6 mg/day). Participants in the highest compared to the lowest quartile of energy adjusted nitrate intake tended to be older, were less likely to be smokers, were more educated, were more likely to have a family history of cancer, reported higher vegetable intake, and lower total daily calorie intake (Table 1). Participants in the highest versus the lowest quartile of nitrite intake were slightly older, were more likely to have a family history of cancer, greater body mass index, completed more years of education, reported higher intake of dairy products and processed meat, but similar total daily calorie intake (Table 1).

We found no association between the risk of NHL and dietary nitrate intake (Table 2). However, we found a slightly elevated risk of NHL among women (n = 52) had the highest intake of nitrite (highest vs. lowest quartile OR = 1.6; 95% CI: 0.8–2.9) with no positive significant trend. The risk of NHL was increased in women (n = 34) with high nitrite from animal products (OR = 1.9; 95% CI: 1.0–3.4) but not in women (n = 40) with high nitrite from plant sources of nitrite (OR = 0.8; 95% CI: 0.4–1.6). No increased risk of NHL was observed for men or women in the highest intake quartile of nitrite from processed meats or in the highest quartile of the sum of nitrate and nitrite from processed meats. The association between nitrate and nitrite intake overall and from plant, animal, and processed meat sources and the risk of NHL was not modified by vitamin C or vitamin E intake, or the lifestyle or demographic factors evaluated (data not shown).

Table 3 shows the results by major subtypes. No significant association was observed for nitrate or nitrite intake with any of the NHL subtypes evaluated. Likewise, there were no significant associations between nitrate or nitrite intake and the risk of either t(14;18)-positive or -negative NHL (Table 4). However, we found a non-significant elevated risk of t(14;18)-positive NHL associated with the highest tertile of nitrite intake (OR = 1.6; 95% CI:

0.8–3.3). The subtype and t(14;18) status results for nitrate and nitrite intake were not modified by vitamin C or vitamin E intake, or by the lifestyle or demographic factors (including gender) evaluated (data not shown).

Discussion

This is one of the first studies to evaluate the association between dietary nitrate/nitrite and risk of NHL by subtype and by t(14;18) status. While we found no apparent increased risk of NHL with increasing intake of nitrate or nitrite among men and women combined, we found a modest elevated risk of NHL among women who reported higher intake of nitrite, particularly nitrite from animal sources. Dietary intake of nitrate and nitrite was not associated with either t(14;18)-positive or –negative NHL in the study population.

Our results are somewhat different than findings from prior studies of dietary nitrate and nitrite and NHL. However, our daily intake estimates of nitrate and nitrite intake are consistent with those reported in the NCI-SEER NHL case-control study (15), in which the same food frequency questionnaire was used. Specifically, the median daily nitrite intake in the current study was 1.2 mg/day compared to 0.91 mg/day in the NCI-SEER study. Similarly, the median daily intake of nitrate in our study was 102 mg/day compared to 114 mg/day in the NCI-SEER study. In both the NCI-SEER (15), the investigators found that dietary nitrite was associated with a higher risk of NHL among men and women (N cases = 458) combined (highest quartile: OR = 3.1; 95%CI: 1.7–5.5). Similarly, in the prior Nebraska case-control study (16), the investigators also found that dietary nitrite was associated with a higher risk of NHL (OR = 2.8; 95% CI: 1.3–6.1) among men and women combined (N cases = 147). In a case-control study of NHL among Connecticut women (N cases = 594), higher dietary nitrite intake was associated with an elevated risk of NHL overall (OR = 1.4; 95% CI: 0.9–2.2); the association was due to nitrite was from animal sources (14). In our study, we found a marginally significant increase in risk among women in the highest quartile of nitrite intake from animal sources but no association among men.

Few studies have evaluated risk by NHL subtype. In the Connecticut case-control study, analyses of nitrite intake by NHL subtype revealed a significant positive trend with nitrite intake from animal sources for FL and DLBCL (14). In contrast, we did not find an association for either subtype in our study population overall nor in men and women separately. In a previous study of NHL in Nebraska that evaluated dietary intakes by presences of t(14;18) translocations (16), risk of t(14;18)-positive NHL was elevated for the highest versus the lowest approximate tertile of dietary nitrite intake (OR = 2.8; 95% CI: 1.3–6.1). In our study, the association was not strong, but we observed a non-significant increased risk of t(14;18)-positive NHL in the highest tertile of nitrite intake (OR = 1.6; 95% CI: 0.8–3.3).

Consistent with our finding, no association was observed for intake of dietary nitrate and NHL in the Iowa cohort (13) or Connecticut case control study (14), or for NHL subtype in the case-control study (14). However, an inverse association was reported for NHL with increasing nitrate intake in the NCI-SEER study (15). In the previous report on nitrate and nitrite and t(14;18) (16), dietary nitrate was weakly associated with a lower risk of t(14;18)-

negative NHL. In this study, we observed no change in risk with increasing nitrate intake for t(14;18)-positive or -negative NHL.

An investigation of dietary food groups and nutrient intakes in this study population was reported previously (19). Higher intake of green leafy vegetables and cruciferous vegetables, which contain high levels of nitrate were associated with a lower risk of NHL (19). When nitrate consumption comes mainly from dietary sources, in which vegetables are the primary contributors to intake, other bioactive substances, including antioxidants and other beneficial chemicals such as flavonoids (31, 32) are also consumed. Many high nitrate foods are also rich sources for fiber and vitamin C which has been hypothesized to be protective against NHL (33) as was also observed in this study population previously (19).

The strengths of our study include expert pathology review of the cases using the WHO classification, high response rates (73.2% for cases and 76.8% for controls), and inclusion of only newly-diagnosed and histologically-confirmed cases of NHL that occurred in a defined time period in a single geographic area. In addition, rapid case ascertainment was used to minimize survival bias in the cases. We were also able to make extensive adjustment for potential confounders including other dietary factors and physical activity.

Consideration must also be given to potential limitations in the present study that may have influenced the observed associations. First, we do not have information on nitrate exposure from drinking water sources. Nitrate is present as a contaminant in drinking water especially in rural areas, and can be a major source of intake when levels are at or above the maximum contaminant level (MCL) of 10 mg/L nitrate-N (36). In this study population, approximately 90% of the study participants resided in areas on public water supplies which would have municipal water supplies. However, low levels of nitrate exposure from drinking water in Nebraska have been shown to impact NHL risk previously (37), although a study in Iowa found no association for public supplies (15). In addition, although our dietary questionnaire has been found to accurately capture habitual dietary intake, the accuracy of measuring dietary constituents using a food frequency questionnaire remains a concern, particularly in a case-control study. There may also be some degree of misclassification due to the NHL in the period before the diagnosis that may alter the dietary pattern of patients and may influence recall and the reporting of usual diet one year before diagnosis. We also had limited numbers to stratify the subtype and t(14;18) status results to clearly identify the role of potential effect modifiers such as gender.

In summary, we found a modest increase in the risk of NHL overall in women who consume elevated levels of nitrite, particularly nitrite from animal sources. No significant associations were observed for nitrate or nitrite by NHL subtype. Although there were some increases in risk that support the N-nitroso hypothesis, that the formation of highly carcinogenic N-nitroso compounds induce lymphomas, they were not significant and do not confer strong evidence of an association. To our knowledge, only one prior study has evaluated these associations by NHL subtype and only one study by t(14;18) status. Our finding of no association with nitrate or nitrite by major subtypes conflicts with a previous report for FL (15). Our finding for nitrite and t(14;18)-positive NHL confers some support for the prior observation (16). Future studies with larger sample sizes are warranted to further clarify the

potential nitrate/nitrite and NHL association by subtypes and according to molecular classifications.

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Means and proportions of baseline characteristics of the Nebraska NHL study by quartiles of nitrate and nitrite intake

Table 1

Parameter	Characteristics	Nitrate				Nitrite			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Density adjusted quartile median (mg/day)		22.0	39.1	57.5	106.1	0.5	0.6	0.7	0.9
Unadjusted quartile median (mg/day)		46.5	80.5	110.9	178.5	0.9	1.2	1.5	1.7
Mean age (years)		53.2	56.9	60.8	63.0	55.9	57.0	59.9	60.5
Positive family history of cancer (%)		51.4	47.7	56.0	62.0	52.8	58.3	48.9	55.8
Currently married (%)		73.0	69.7	73.2	74.9	74.0	75.1	73.9	67.9
Body mass index (kg/m ²)		28.0	27.2	27.4	27.9	27.2	27.3	27.9	28.1
Smoking history, ever smoker (%)		53.5	51.1	42.4	46.9	53.5	47.6	47.3	47.7
Education, more than highschool (%)		49.3	58.4	61.6	60.4	49.5	62.4	58.7	57.2
Vigorous physical activity, >5 times per week		0.6	0.5	0.6	0.7	0.5	0.7	0.6	0.7
Dietary Intakes	Energy (kcal/day)	2123.1	2054.3	1923.3	1720.1	1916.4	1914.3	2076.4	1951.7
	Meat (servings/1,000kcal)	1.1	1.2	1.2	1.3	1.1	1.1	1.3	1.3
	Vegetables (servings/1,000kcal)	1.0	1.3	1.6	2.1	1.4	1.5	1.5	1.7
	Dairy products (servings/1,000kcal)	0.9	0.9	0.9	1.0	0.7	0.9	0.9	1.1
	Fat (servings/1,000kcal)	2.0	1.9	1.9	1.7	2.2	2.0	1.8	1.6
	Fruit (servings/1,000kcal)	0.5	0.7	0.9	1.1	0.7	0.8	0.8	0.9
	Grain (servings/1,000kcal)	2.7	2.9	2.8	2.7	2.3	2.7	2.9	3.2
	Processed meat (g/1,000kcal)	13.0	11.7	11.4	11.2	6.8	9.8	13.1	17.6
	Fiber (g/1,000kcal)	0.5	0.7	0.8	0.9	0.5	0.7	0.8	0.9
	Folate (mg/1,000kcal)	172.8	191.3	196.5	216.5	171.9	186.9	198.1	216.4
	Iron (mg/1,000kcal)	6.5	7.0	7.3	7.8	6.5	7.0	7.4	7.7
	Vitamin C (mg/1,000kcal)	83.6	94.2	98.7	114.0	85.7	93.9	102.4	106.1
	Vitamin E (mg/1,000kcal)	9.8	11.1	10.7	10.0	10.2	10.2	11.0	10.2

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) according to quartiles of nitrate or nitrite intake and NHL in Nebraska

		Controls		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Nitrate												
Quartile 1	22.2	115	100	1.0	(ref)		67	1.0	(ref)	33	1.0	(ref)
Quartile 2	38.2	115	83	0.9	0.6–1.3		49	0.8	0.5–1.4	34	1.0	0.3–1.1
Quartile 3	55.5	114	80	0.9	0.6–1.3		38	0.8	0.5–1.4	42	1.0	0.6–1.7
Quartile 4	88.3	115	72	0.8	0.5–1.3		32	0.7	0.4–1.3	40	1.0	0.5–1.9
p-value for trend				0.6				0.2			0.6	
Nitrite												
Quartile 1	0.49	114	82	1.0	(ref)		51	1.0	(ref)	31	1.0	(ref)
Quartile 2	0.61	115	90	1.2	0.8–1.8		47	1.0	0.6–1.7	43	1.4	0.7–2.6
Quartile 3	0.71	116	68	0.8	0.5–1.3		45	0.9	0.5–1.5	23	0.8	0.4–1.6
Quartile 4	0.86	114	95	1.3	0.8–1.9		43	1.0	0.6–1.8	52	1.6	0.8–2.9
p-value for trend				0.4				0.9			0.2	
Nitrite from Plant Sources												
Quartile 1	0.26	115	82	1.0	(ref)		51	1.0	(ref)	31	1.0	(ref)
Quartile 2	0.34	115	98	1.2	0.8–1.8		63	1.3	0.8–2.2	35	1.1	0.6–2.1
Quartile 3	0.41	114	91	1.2	0.8–1.9		42	1.0	0.5–1.7	49	1.7	0.9–3.1
Quartile 4	0.53	115	64	0.9	0.6–1.4		30	1.0	0.5–1.9	34	0.8	0.4–1.6
p-value for trend				0.9				0.9			0.8	
Nitrite from Animal Sources												
Quartile 1	0.16	115	74	1.0	(ref)		37	1.0	(ref)	37	1.0	(ref)
Quartile 2	0.23	114	88	1.3	0.8–1.9		50	1.1	0.6–1.9	38	1.5	0.8–2.7
Quartile 3	0.29	115	76	1.0	0.7–1.6		42	0.9	0.5–1.7	34	1.1	0.6–2.0
Quartile 4	0.41	115	97	1.3	0.8–1.9		57	0.9	0.5–1.6	40	1.9	1.0–3.4
p-value for trend				0.3				0.9			0.1	
Nitrite from Processed Meat Sources												
Quartile 1	0.02	115	75	1.0	(ref)		35	1.0	(ref)	40	1.0	(ref)
Quartile 2	0.06	115	67	0.9	0.6–1.3		32	0.7	0.3–1.2	35	1.2	0.7–2.1

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		median (mg/1,000kcal)	NHL Overall				NHL in Men			NHL in Women		
			Controls	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Quartile 3		0.1	114	110	1.4	0.9–2.1	63	1.0	0.6–1.8	47	1.9	1.1–3.5
Quartile 4		0.21	115	83	1.0	0.6–1.5	56	0.8	0.4–1.4	27	1.2	0.7–2.4
p-value for trend					0.9			0.3			0.2	
Nitrate + Nitrite from Processed Meat Sources												
Quartile 1		0.14	115	72	1.0	(ref)	32	1.0	(ref)	40	1.0	(ref)
Quartile 2		0.42	114	73	1.0	0.6–1.5	37	0.7	0.4–1.4	36	1.2	0.7–2.2
Quartile 3		0.78	115	104	1.3	0.9–2.0	61	1.0	0.6–1.9	43	1.7	0.9–3.0
Quartile 4		1.51	115	86	1.0	0.7–1.6	56	0.7	0.4–1.4	30	1.4	0.7–2.7
p-value for trend					0.9			0.4			0.2	

Models adjusted for sex (overall model), age (categorical), body mass index (categorical), education, family history of cancer, vitamin C, and total daily caloric intake (continuous).

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) according to tertiles of nitrate or nitrite intake and NHL subtype in Nebraska

	median (mg/1,000kcal)	DLBCL		FL	
		Controls	Cases	OR	95% CI
Nitrate					
Tertile 1	42.6	153	37	1.0	(ref)
Tertile 2	87.4	153	24	0.6	0.3–1.1
Tertile 3	132.7	153	26	0.7	0.4–1.4
p-value for trend				0.9	0.7
Nitrite					
Tertile 1	0.8	153	28	1.0	(ref)
Tertile 2	1.2	153	29	1.0	0.6–1.8
Tertile 3	1.8	153	30	1.1	0.6–1.9
p-value for trend				0.2	0.7
Nitrite from Plant Sources					
Tertile 1	0.4	153	33	1.0	(ref)
Tertile 2	0.7	153	28	0.9	0.5–1.6
Tertile 3	0.1	153	26	0.9	0.5–1.7
p-value for trend				0.7	0.8
Nitrite from Animal Sources					
Tertile 1	0.3	153	24	1.0	(ref)
Tertile 2	0.5	153	22	0.9	0.5–1.7
Tertile 3	0.8	153	41	1.5	0.8–2.7
p-value for trend				0.2	0.9
Nitrite from Processed Meat Sources					
Tertile 1	0	153	24	1.0	(ref)
Tertile 2	0.1	153	31	1.1	0.6–2.0
Tertile 3	0.4	153	32	1.0	0.5–1.8
p-value for trend				0.6	0.3
Nitrate + Nitrite from Processed Meat Sources					
Tertile 1	0.3	153	25	1.0	(ref)
				35	1.0

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	median (mg/1,000kcal)	DLBCL				FL			
		Controls		Cases	OR	95% CI	Cases	OR	95% CI
Tertile 2	1.1	153	26	0.9	0.5–1.7	42	1.1	0.7–1.9	
Tertile 3	2.7	153	36	1.1	0.6–2.0	29	0.7	0.4–1.3	
p-value for trend				0.5			0.4		

Models adjusted for sex (overall model), age (categorical), body mass index (categorical), education, family history of cancer, and total daily caloric intake (continuous).

Diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL).

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) according to tertiles of nitrate or nitrite intake and NHL t(14;18) status in Nebraska

		Controls		Cases	OR	95% CI	Cases	OR	95% CI
Nitrate									
Tertile 1	42.6	153	21	1.0	(ref)	42	1.0	(ref)	
Tertile 2	87.4	153	12	0.6	0.3–1.2	29	0.6	0.4–1.1	
Tertile 3	132.7	153	19	0.9	0.4–2.0	33	0.8	0.5–1.5	
p-value for trend				0.9			0.7		
Nitrite									
Tertile 1	0.8	153	14	1.0	(ref)	33	1.0	(ref)	
Tertile 2	1.2	153	16	1.2	0.5–2.5	34	1.1	0.6–1.8	
Tertile 3	1.8	153	22	1.6	0.8–3.3	37	1.2	0.7–2.0	
p-value for trend				0.2			0.2		
Nitrite from Plant Sources									
Tertile 1	0.4	153	13	1.0	(ref)	33	1.0	(ref)	
Tertile 2	0.7	153	23	1.8	0.9–3.8	32	1.0	0.6–1.8	
Tertile 3	0.1	153	16	1.3	0.6–3.0	39	1.4	0.8–2.4	
p-value for trend				0.2			0.1		
Nitrite from Animal Sources									
Tertile 1	0.3	153	14	1.0	(ref)	35	1.0	(ref)	
Tertile 2	0.5	153	22	1.5	0.8–3.1	29	0.9	0.5–1.5	
Tertile 3	0.8	153	16	1.1	0.5–2.4	40	1.0	0.6–1.8	
p-value for trend				0.8			1.0		
Nitrite from Processed Meat Sources									
Tertile 1	0	153	12	1.0	(ref)	25	1.0	(ref)	
Tertile 2	0.1	153	23	1.4	0.7–2.8	50	1.9	1.1–3.4	
Tertile 3	0.4	153	13	0.7	0.3–1.7	28	0.9	0.5–1.7	
p-value for trend				0.4			0.3		
Nitrate + Nitrite from Processed Meat Sources									
Tertile 1	0.3	153	14	1.0	(ref)	27	1.0	(ref)	

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	median (mg/1,000kcal)	t(14;18) Positive				t(14;18) Negative			
		Controls	Cases	OR	95% CI	Cases	OR	95% CI	
Tertile 2	1.1	153	21	1.2	0.6–2.3	46	1.6	1.0–2.8	
Tertile 3	2.7	153	14	0.8	0.3–1.6	30	0.9	0.5–1.7	
p-value for trend				0.4			0.4		

* Models adjusted for sex, age (categorical), body mass index (categorical), education, family history of cancer, vitamin C, and total daily caloric intake (continuous).