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ORIGINAL PAPER

Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma

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Abstract
Objective To evaluate the associations between diet and non-Hodgkin lymphoma (NHL) according to t(14;18) status, one of the most common chromosomal abnormalities in NHL, as t(14;18)-positive NHL represents a genetically more homogeneous group than NHL overall.
Methods We determined the presence of the t(14;18) (q32;q21) by fluorescence in situ hybridization in 172 of 175 tumor blocks from a population-based, case–control study conducted in Nebraska during 1983–1986. Information on the frequency of consumption as an adult of 30 food items was derived from the parent case–control study. Dietary factors in 60 t(14;18)-positive and 87 t(14;18)-negative cases were compared with 1,075 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using polytomous logistic regression.
Results The risk of t(14;18)-positive NHL for the highest *versus* the lowest approximate tertile of intake was elevated for milk (OR = 2.2; 1.0–5.0) and dietary nitrite (OR = 2.8; 1.3–6.1), whereas coffee consumption was inversely associated with risk (OR = 0.4; 0.2–0.7). We also found inverse associations between the intake of fish (OR = 0.5; 0.3–1.0) and carotene (OR = 0.5; 0.2–0.9) and risk of t(14;18)-negative NHL. There was no association between the intake of meats, vegetables, protein, or vitamin C and risk of either t(14;18)-positive or t(14;18)-negative NHL.
Conclusion We observed differences in associations between diet and t(14;18)-defined subgroups of NHL. These findings should be interpreted cautiously because of the small sample.

Keywords Lymphoma · Non-Hodgkin · Chromosomal aberrations · Diet · Risk factors · Epidemiology

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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies with a variety of different molecular characteristics. NHL is presently classified according to the World Health Organization (WHO) classification, which reflects the postulated cell of origin and stage of differentiation [1]. While the WHO classification may be useful for etiologic research, many of the WHO-defined subtypes remain heterogeneous at the genetic and molecular level [2, 3]. Therefore, it is possible that genetic and molecular categorization of these NHL subtypes may have etiologic significance.

Recently, two epidemiologic studies [4–7] investigated risk factors for NHL according to presence or absence of the t(14;18)(q32;q21), one of the most common chromosomal translocations in NHL. The t(14;18) occurs in 70–90% of cases of follicular lymphoma, 20–30% of diffuse large B-cell lymphoma, and 5–10% of other less common NHL subtypes [8–10] and might characterize a more homogenous group than NHL cases as a whole. Both studies [4, 6] found that the association between pesticide exposure and risk of NHL was limited to t(14;18)-positive NHL cases. One study [5] found a positive association between cigarette smoking and risk of t(14;18)-negative NHL but not t(14;18)-positive NHL, among women. A family history of hematopoietic cancer was associated with risk of t(14;18)-negative NHL in one study [7] and with both t(14;18)-positive and t(14;18)-negative NHL in the other study [5]. These findings suggest that molecular classification of NHL according to t(14;18) status may be useful for etiologic research [11].

Certain dietary factors have been linked to the risk of follicular lymphoma and diffuse large B-cell lymphoma [12–16], the two major subtypes that exhibit the t(14;18). There is some evidence that a higher intake of antioxidants was associated with a decrease in the frequency of chromosomal damage in human lymphocytes [17, 18]. Therefore, we investigated the association of diet with risk of subgroups of NHL according to the presence or absence of the t(14;18). We hypothesized that dietary risk factors differ for t(14;18)-positive and t(14;18)-negative subgroups of NHL. We are not aware of any study that evaluated the associations between diet and NHL stratified by t(14;18) status.

Materials and methods

Study population

The current study used existing epidemiologic data from a population-based, case–control study conducted in Nebraska between 1983 and 1986 that included 385 histologically confirmed cases of NHL (males = 201; females = 184) and 1,432 controls (males = 725; females = 707). The study population and methods of the parent case–control study have been reported in detail elsewhere [19, 20]. In that study, telephone interview were conducted directly with the subjects, or with their next-of-kin if the subjects were deceased or incapacitated (40.5% of cases and 43.6% of controls). Participants were asked to provide information on the frequency of consumption as an adult of 30 food items as well as coffee, tea, and the duration of use of vitamin supplements. Responses to the usual frequency of consumption of food and beverage items were given in times/day, week, month, or year.

For the current study, 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. Other specimens were not available due to the length of time since case diagnosis, which exceeded the average time most hospitals and laboratories keep their blocks (approximately 10–15 years). All procedures were performed in accordance with a protocol approved by human investigation committees at Northwestern University and the University of Nebraska Medical Center. 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 selection bias was unlikely because the availability of tumor blocks did not differ by exposures of interest, and it is unlikely that t(14;18) status is related to tumor block availability.

Ascertainment of the t(14;18)(q32;q21)

As previously described in detail [4, 5], tissue microarrays were prepared from archival paraffin-embedded tissue. Four representative 0.6 mm cores were obtained from each case and inserted in a grid pattern into a recipient paraffin block using a tissue arrayer (Beecher Instruments, Silver Spring, MD). The fluorescence in situ hybridization (FISH) studies were performed on 4 μm 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 18s present in cells (Abbott-Vysis Inc., Downers Grove, IL). The FISH probes are approved by the U.S. FDA as analyte specific reagents. The tissue sections were pretreated using VP2000® (Abbott-Vysis Inc.) following the manufacturer's standard protocol for paraffin-embedded tissue sections. The probe mixture was placed on the tissue sections, coverslipped, and sealed. Co-denaturation of probes and target DNA at 75°C for 5 min was followed by overnight hybridization at

37°C using an automated hybridization chamber (HYBrite®, Abbott-Vysis, Inc.) The slides were then washed with standard post hybridization washes and the nuclei were counterstained with 4,6-diamidino-2-phenylindole. Analysis was performed on an Olympus BX51 microscope equipped with appropriate filters, and images were captured with CytoVision® image capture software (Applied Imaging, Santa Clara, CA).

Blind replicates of 5% of the specimens were analyzed for quality control. In addition, classical cytogenetic analysis was performed in 5% of the samples. 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 the number of chromosome 18s. The agreement between the two readers was 100%.

Data analysis

Related food items were combined into food groups according to their dietary similarities. Processed meats included bacon, sausage, processed ham, and hot dogs. All meats included beef, chicken, turkey, pork, fish, and processed meats. Dark-green vegetables included broccoli, green beans, spinach, kale, collard, and turnip greens. High-nitrate vegetables included beets, celery, lettuce, spinach, endive, radishes, rhubarb, turnip greens, kale, collard, and cabbage. All vegetables included dark-green vegetables, high-nitrate vegetables, carrots, cauliflower, onions, potatoes, beans, and dried peas. Citrus fruits included oranges, grapefruit, and citrus fruit juice. Breads included all breads, pasta dishes, and pizza. Cereals included hot and cold breakfast cereals.

Intake of nutrients (i.e., animal protein, vegetable protein, vitamin C, and pro-vitamin A carotenoids, nitrate, and nitrite) was calculated by multiplying the reported frequency of consumption (converted to times/day) for the individual food items by their nutrient content and the gender-specific portion sizes derived from the second National Health and Nutrition Evaluation Survey II [21]. The nitrate and nitrite content of the various food items was determined from the literature [22, 23]. For subjects who took a multivitamin or vitamin C supplement once a week for 3 years or more, we assumed that multivitamins contributed 60 mg/day of vitamin C and that vitamin C supplements contributed 250 mg/day. Total vitamin C intake was calculated by summing the vitamin C intake from foods with the estimated intake from vitamin supplements [20]. Intake of vitamin E was not calculated because of the lack of information about foods which contribute substantially to intake of this nutrient.

Dietary intake was grouped into approximate tertiles of consumption for food groups and foods (times/week), and nutrients (grams or milligrams/day), based on the frequency of consumption among controls. When the shape of the distribution was skewed or showed distinct modes, categorization of intake of some food items resulted in cutpoints that were not tertiles. The final analysis included 147 cases (t(14;18)-positive cases = 60 and t(14;18)-negative cases = 87) and 1,075 controls who had a satisfactory dietary history defined by no greater than 20% "missing or don't know" responses to the food item questions.

The odds ratios (ORs) and 95% confidence intervals (CIs) for groups defined by t(14;18) status were derived from multivariate polytomous logistic regression where the dependent variable was treated as a three-level variable (i.e., t(14;18)-positive NHL, t(14;18)-negative NHL, and controls), and the logit estimator always compared t(14;18)-defined NHL groups with controls. This allowed the comparison of ORs for t(14;18)-positive NHL versus t(14;18)-negative NHL. We also re-classified the 175 cases with available tumor blocks according to the new WHO classification for NHL [1]. We conducted logistic regression to estimate risks for follicular lymphoma (ICD-O-3 codes 9690–9691, 9695, 9698) and diffuse large B-cell lymphoma (all types) (ICD-O-3 codes 9675(B), 9678–9680), the two major subtypes that exhibit the t(14;18). There were 53 follicular lymphoma cases (t(14;18)-positive = 34 and t(14;18)-negative = 19) and 54 diffuse large B-cell lymphoma cases (t(14;18)-positive = 19, t(14;18)-negative = 34, and undeterminable = 1). We also conducted analysis using only direct respondents. The patterns of associations are similar regardless of inclusion or exclusion of proxies. Thus, data from proxies were included in the current report. Indicator variables for age (continuous), type of respondent (direct or proxy interview), and sex were included in the final model because controls were frequency matched by these variables to cases in the parent case–control study. Other potential confounders were considered based on prior knowledge of risk factors for NHL, as well as change-in-estimate criteria [24]. Tobacco use was not included in the final model because it did not change the risk estimate by more than 10%. Analyses were conducted using PROC CATMOD of the SAS 9.1 statistical software package (SAS Institute, Cary, NC). The reported *p*-values are two-sided.

Results

Characteristics of the study subjects and possible risk factors for t(14;18)-positive and t(14;18)-negative NHL

cases are shown in Table 1. There was a higher proportion of females among the t(14;18)-negative cases than among the controls. Compared with controls, t(14;18)-positive cases were more likely to be overweight (body mass index 25.0–29.9 kg/m^2) or obese (body mass index $\geq$ 30.0 kg/m^2) and to have never used tobacco products. In comparison with controls, both t(14;18)-positive and t(14;18)-negative cases were more likely to have first degree relatives with hematopoietic cancer.

Table 2 shows the association between intake of animal products and risk of NHL according to t(14;18) status. Milk consumption was significantly associated with a higher risk of t(14;18)-positive NHL, but not t(14;18)-negative NHL. Intake of fish was associated with a lower risk of t(14;18)-negative NHL. There was no association between all meats, processed meats, or eggs and risk of either t(14;18)-positive or t(14;18)-negative NHL. Individual food items within these food groups were also not associated with the risk of either subgroup of NHL (data not shown). Analysis by histologic subtype showed that milk intake was associated with a higher risk of diffuse large B-cell lymphoma (OR = 2.0; 1.1–3.6), but not follicular lymphoma (data not shown). None of the other food groups or individual food items were associated with the risk of either follicular lymphoma or diffuse large B-cell lymphoma (data not shown).

Table 3 shows the associations among other food groups and risk of t(14;18)-defined subgroups of NHL. We found no association among the intake of all vegetables, dark-green vegetables, high-nitrate vegetables, citrus fruits, or tea and risk of either t(14;18)-positive or t(14;18)-negative NHL. Intake of cereals was weakly associated with a higher risk of t(14;18)-positive NHL. In contrast, coffee consumption was significantly associated with a lower risk of t(14;18)-positive NHL, but not t(14;18)-negative NHL. When individual food items were evaluated, the risk of t(14;18)-negative NHL was inversely associated with intake of celery (OR = 0.6; 0.3–1.0) and some other vegetables including cauliflower (OR = 0.5; 0.3–0.9) and green beans (OR = 0.6, 0.3–1.0) (data not shown). None of

Table 1 Description of non-Hodgkin lymphoma cases by t(14;18) status and controls

	t(14;18)-positive cases		t(14;18)-negative cases		Controls	
	No.[a]	%	No.[a]	%	No.[a]	%
Overall	60		87		1,075	
Sex						
Male	32	53.3	34	39.1	543	50.5
Female	28	46.7	53	60.9	532	49.5
		$p = 0.7$[b]		$p = 0.04$		
Respondent status						
Self	37	61.5	50	57.5	678	63.1
Proxy	23	38.5	37	42.5	397	36.9
		$p = 0.8$		$p = 0.3$		
Tobacco product use						
Never	35	58.3	42	48.3	505	47.0
Ever	25	41.7	45	51.7	569	53.0
		$p = 0.09$		$p = 0.8$		
Hair dye use						
Never	45	75.0	54	62.1	756	70.4
Yes	15	25.0	33	37.9	318	29.6
		$p = 0.4$		$p = 0.1$		
Family history of cancer						
No	30	51.7	48	56.5	689	64.5
Non-hematopoietic cancer	22	37.9	26	30.6	318	29.8
Hematopoietic cancer	6	10.3	11	12.9	61	5.7
		$p = 0.1$		$p = 0.02$		
Body mass index[c]						
$\leq$24.9	22	37.3	51	59.3	565	53.3
25.0–29.9	26	44.1	23	26.7	393	37.1
$\geq$30.0	11	18.6	12	14.0	102	9.6
		$p = 0.02$		$p = 0.1$		

[a] Numbers may not sum to overall total due to missing data

[b] Chi-square p-value compares differences in proportion between controls and subsets of NHL defined by t(14;18) status

[c] Body mass index defined as weight (kg)/height (m)^2

Table 2 Associations between intake of animal products and risk of non-Hodgkin lymphoma according to t(14;18) status

Food groups, (times/week)[a]	Controls[b]	t(14;18)-positive versus controls			t(14;18)-negative versus controls			*p*-difference[d]
		Cases[b]	OR[c]	95% CI	Cases[b]	OR[c]	95% CI	
Milk								
<7	216	11	1.0	Referent	18	1.0	Referent	
7	649	30	1.0	(0.5, 2.2)	49	0.9	(0.5, 1.7)	0.9
>7	210	19	2.2	(1.0, 5.0)	20	1.3	(0.7, 2.6)	0.3
Processed meats								
<2	391	19	1.0	Referent	34	1.0	Referent	
2–4	324	16	1.0	(0.5, 2.0)	25	1.0	(0.6, 1.7)	0.9
>4	360	25	1.4	(0.7, 2.7)	28	0.9	(0.5, 1.6)	0.3
All meats								
<10	352	16	1.0	Referent	35	1.0	Referent	
10–13	360	22	1.2	(0.6, 2.3)	22	0.7	(0.4, 1.2)	0.2
>13	363	22	1.2	(0.6, 2.4)	30	0.8	(0.5, 1.4)	0.4
Fish								
<0.5	363	21	1.0	Referent	36	1.0	Referent	
0.5–1	396	25	1.1	(0.6, 2.0)	34	0.9	(0.5, 1.5)	0.6
>1	316	14	0.7	(0.4, 1.5)	17	0.5	(0.3, 1.0)	0.5
Eggs								
<2	427	20	1.0	Referent	35	1.0	Referent	
2–4	323	22	1.4	(0.7, 2.7)	28	1.1	(0.7, 1.9)	0.6
>4	325	18	1.2	(0.6, 2.3)	24	0.9	(0.5, 1.7)	0.6

[a] Food groups: processed meats included bacon, sausage, processed ham, and hot dogs; all meats included beef, chicken, turkey, pork, processed meats, and fish

[b] Numbers may not sum to overall total due to missing data

[c] Odd ratios (ORs) and confidence intervals (CIs), adjusted for age (continuous), sex, type of respondent (direct or proxy interview), family history of cancer (yes, no), and body mass index (continuous)

[d] *p*-values for difference were computed from polytomous logistic regression by testing the difference of regression coefficients of the exposures of interest corresponding to t(14;18)-positive versus controls and t(14;18)-negative versus controls

these vegetables was associated with risk of t(14;18)-positive NHL. Analysis by histologic subtype showed no association between any food groups and risk of either follicular lymphoma or diffuse large B-cell lymphoma (data not shown).

Table 4 shows the associations between nutrients and risk of NHL according to t(14;18) status. There was no association between the intake of protein, irrespective of the sources, and risk of either t(14;18)-positive or t(14;18)-negative NHL. A higher intake of nitrite was significantly associated with a higher risk of t(14;18)-positive NHL. Intake of vegetable nitrate was weakly associated with a lower risk of t(14;18)-negative NHL. We further adjusted for intake of vitamin C because vitamin C inhibits the formation of carcinogenic N-nitroso compounds. The point estimates were not substantially changed with additional adjustment for intake of vitamin C (data not shown). Finally, we found an inverse association between the intake of carotene and risk of t(14;18)-negative NHL, but not t(14;18)-positive NHL. In the analysis by histologic subtypes, intake of carotene was associated with a lower risk of diffuse large B-cell lymphoma (OR = 0.6; 0.4–0.9), but not follicular lymphoma (data not shown). Vitamin C intake was associated with a lower risk of both follicular lymphoma (OR = 0.4; 0.2–0.8) and diffuse large B-cell lymphoma (OR = 0.6; 0.4–1.0) (data not shown). None of the other nutrients were associated with the risk of either follicular lymphoma or diffuse large B-cell lymphoma (data not shown).

Discussion

In this population-based, case–control study, we defined subsets of NHL according to the t(14;18) status and found that intake of dietary nitrite and milk was significantly associated with a higher risk of t(14;18)-positive NHL, but not t(14;18)-negative NHL. Intake of fish and carotene was inversely associated with the risk of t(14;18)-negative NHL. We also found a significant inverse association

Table 3 Associations between intake of various food groups and risk of non-Hodgkin lymphoma according to t(14;18) status

Food groups, (times/week)[a]	Controls[b]	t(14;18)-positive versus controls			t(14;18)-negative versus controls			*p*-difference[d]
		Cases[b]	OR[c]	95% CI	Cases[b]	OR[c]	95% CI	
All vegetables								
<15	356	17	1.0	Referent	35	1.0	Referent	
15–22	359	18	1.0	(0.5, 1.9)	26	0.8	(0.4, 1.3)	0.6
>22	360	25	1.3	(0.7, 2.4)	26	0.7	(0.4, 1.3)	0.2
Dark green vegetables								
<2	357	23	1.0	Referent	31	1.0	Referent	
2–3	332	14	0.9	(0.4, 1.7)	32	1.1	(0.6, 1.9)	0.6
>3	386	23	1.0	(0.5, 1.8)	24	1.2	(0.7, 2.1)	0.6
High nitrate vegetables								
<5	357	17	1.0	Referent	26	1.0	Referent	
5–9	355	17	1.0	(0.5, 2.0)	32	1.2	(0.7, 2.1)	0.6
>9	363	26	1.3	(0.6, 2.4)	29	1.1	(0.6, 1.9)	0.7
Citrus fruits								
<5	317	16	1.0	Referent	29	1.0	Referent	
5–9	380	28	1.6	(0.8, 3.0)	29	0.8	(0.5, 1.5)	0.1
>9	378	16	0.9	(0.4, 1.8)	29	0.8	(0.5, 1.4)	0.9
Breads								
<7	173	8	1.0	Referent	15	1.0	Referent	
7–13	535	26	2.0	(1.1, 3.7)	38	1.3	(0.7, 2.3)	0.2
>13	367	26	0.8	(0.3, 1.9)	34	1.1	(0.6, 2.2)	0.5
Cereals								
<2	334	14	1.0	Referent	28	1.0	Referent	
2–7	329	20	1.4	(0.7, 3.0)	28	1.1	(0.6, 1.9)	0.6
>7	412	26	1.6	(0.8, 3.2)	31	0.9	(0.5, 1.6)	0.2
Coffee								
<9	290	24	1.0	Referent	27	1.0	Referent	
9–28	329	19	0.6	(0.3, 1.2)	29	0.9	(0.5, 1.7)	0.4
>28	423	12	0.4	(0.2, 0.7)	28	0.8	(0.4, 1.4)	0.09
Tea								
0	360	17	1.0	Referent	30	1.0	Referent	
1–14	272	11	0.8	(0.4, 1.8)	26	1.2	(0.7, 2.2)	0.4
>14	386	25	1.4	(0.7, 2.7)	26	0.8	(0.5, 1.5)	0.2

[a] Food groups: all vegetables included high-nitrate vegetables, dark-green vegetables, carrots, cauliflower, onions, potatoes, beans, and dried peas; dark-green vegetables included broccoli, green beans, spinach, kale, collard, and turnip greens; high-nitrate vegetables included beets, celery, lettuce, spinach, endive, radishes, rhubarb, turnip greens, kale, collard, and cabbage; citrus fruits include oranges, grapefruit, and citrus fruit juice; breads included all breads, pasta dishes, and pizza; cereals included hot and cold cereals

[b] Numbers may not sum to overall total due to missing data

[c] Odd ratios (ORs) and confidence intervals (CIs), adjusted for age (continuous), sex, type of respondent (direct or proxy interview), family history of cancer (yes, no), and body mass index (continuous)

[d] *p*-values for difference were computed from polytomous logistic regression by testing the difference of regression coefficients of the exposures of interest corresponding to t(14;18)-positive versus controls and t(14;18)-negative versus controls

between coffee consumption and risk of t(14;18)-positive NHL, but not t(14;18)-negative NHL. Up to our knowledge, this is the first study reporting on diet in relation to NHL risk by t(14;18) status.

Dietary nitrite comes from animal sources (particularly processed meat) and plant sources (mainly baked goods, cereals, and vegetables high in nitrate such as green leafy vegetables and root vegetables). In the current study, 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. When major sources of dietary nitrite and nitrate were evaluated,

Table 4 Associations between various nutrients and risk of non-Hodgkin lymphoma according to t(14;18) status

Nutrient, (mg/day)	Controls[a]	t(14;18)-positive versus controls			t(14;18)-negative versus controls			*p*-difference[c]
		Cases[a]	OR[b]	95% CI	Cases[a]	OR[b]	95% CI	
Protein								
<50	357	18	1.0	Referent	41	1.0	Referent	
50–67	358	21	1.0	(0.5, 2.1)	25	0.6	(0.3, 1.1)	0.3
>67	360	21	1.1	(0.5, 2.6)	21	0.6	(0.3, 1.2)	0.2
Animal protein								
<36	358	19	1.0	Referent	39	1.0	Referent	
36–51	359	21	1.0	(0.5, 2.0)	27	0.7	(0.4, 1.3)	0.5
>51	358	20	1.0	(0.4, 2.3)	21	0.6	(0.3, 1.3)	0.4
Vegetable protein								
<12	357	17	1.0	Referent	40	1.0	Referent	
12–17	358	17	1.0	(0.5, 2.1)	20	0.5	(0.3, 0.9)	0.1
>17	360	26	1.4	(0.7, 3.0)	27	0.8	(0.4, 1.4)	0.2
Nitrite								
<1	357	14	1.0	Referent	39	1.0	Referent	
1	358	15	1.1	(0.5, 2.4)	25	0.7	(0.4, 1.1)	0.3
>1	360	31	2.8	(1.3, 6.1)	23	0.6	(0.3, 1.2)	0.003
Nitrate								
<70	357	17	1.0	Referent	36	1.0	Referent	
70–106	358	19	1.0	(0.5, 1.9)	28	0.8	(0.5, 1.3)	0.7
>106	360	24	1.2	(0.6, 2.4)	23	0.7	(0.4, 1.2)	0.2
Vegetable nitrate								
<65	357	17	1.0	Referent	36	1.0	Referent	
65–101	358	19	1.0	(0.5, 1.9)	29	0.8	(0.5, 1.3)	0.6
>101	360	24	1.2	(0.6, 2.4)	22	0.6	(0.3, 1.1)	0.1
Carotene								
<1459	357	19	1.0	Referent	34	1.0	Referent	
1459–2311	358	22	1.2	(0.6, 2.3)	38	1.1	(0.7, 1.8)	0.8
>2311	360	19	0.9	(0.5, 1.8)	15	0.5	(0.2, 0.9)	0.1
Total vitamin C								
<106	357	18	1.0	Referent	35	1.0	Referent	
106–148	358	24	1.4	(0.7, 2.6)	26	0.7	(0.4, 1.2)	0.1
>148	360	18	1.0	(0.5, 2.0)	26	0.7	(0.4, 1.3)	0.5

[a] Numbers may not sum to overall total due to missing data

[b] Odd ratios (ORs) and confidence intervals (CIs), adjusted for age (continuous), sex, type of respondent (direct or proxy interview), family history of cancer (yes, no), and body mass index (continuous)

[c] *p*-values for difference were computed from polytomous logistic regression by testing the difference of regression coefficients of the exposures of interest corresponding to t(14;18)-positive versus controls and t(14;18)-negative versus controls

only intake of cereals was significantly associated with the risk of t(14;18)-positive NHL. Therefore, our findings on dietary nitrite and nitrate are not supportive of the endogenous nitrosation hypothesis and may be due to chance. In a population-based case–control study [25], Ward and colleagues also reported a positive association between dietary nitrite and risk of NHL that was largely due to the intake of bread and cereal as sources of nitrite. The process of frying, roasting, or baking cereal products could produce acrylamide, a chemical that is genotoxic in mouse lymphoma cells [26, 27]. However, the association between acrylamide exposure and the t(14;18) remains to be determined.

We found a significant inverse association between coffee intake and risk of t(14;18)-positive NHL, but not t(14;18)-negative NHL. While coffee consumption has been linked to a lower risk of NHL [20], studies have also reported a positive association [28] or no association [29]. Coffee constituents have been shown to inhibit in vivo genotoxicity [30], as well as protect against DNA and

chromosomal damage in mouse lymphoma cells [31]. A study of eight volunteers found that coffee consumption protected lymphocytes against oxidative DNA-damage [32].

We found a positive association between milk consumption and risk of t(14;18)-positive NHL and, to a lesser extent, t(14;18)-negative NHL. The epidemiologic literature presents an inconsistent picture of the association between milk consumption and risk of NHL overall, ranging from significantly increased risk [13, 14, 20, 33] to no association [34–36]. High intake of milk may induce chronic stimulation of the immune system. In addition, organic pollutants such as polychlorinated biphenyls and dioxins have been found in milk [37, 38], and a study of 144 healthy subjects found a significant association between plasma dioxin levels and the frequency of t(14;18)-positive lymphocytes [39]. In addition, a higher prevalence of the t(14;18) has been reported among individuals occupationally exposed to pesticides [40, 41], and agricultural pesticide use has been associated with a higher risk of t(14;18)-positive NHL [4, 6]. Finally, the association with milk consumption could be due to other factors such as hormones and fats. Unfortunately, we were unable to address this issue due to the lack of data.

In the current study, results of analyses by t(14;18)-defined subgroups of NHL were not entirely consistent with those obtained using histologic subtypes. Since our sample size is not large, these differences may simply be due to chance. Our sample size also does not allow us to compare ORs between t(14;18)-defined subgroups within follicular lymphoma or diffuse large B-cell lymphoma, which might help in evaluating whether using NHL subgroups defined by t(14;18) status is more specific than histologic subtypes for etiologic research. Nevertheless, we found differences in associations of some dietary factors with t(14;18)-positive and t(14;18)-negative NHL, suggesting that molecularly defined subgroups may provide additional information to our understanding of the pathogenesis of NHL.

The major strength of our study is use of the FISH technique which is highly sensitive and specific for chromosomal translocations. FISH is considered the gold standard for detecting specific chromosomal abnormalities in paraffin-embedded tissue. Our study also has potential limitations. First, our findings for individual dietary factors should be interpreted with caution because of small sample sizes and the fact that we evaluated several dietary factors. Second, we were unable to comprehensively evaluate various aspects of the diet due to the fact that the parent case–control study used only an abbreviated dietary questionnaire that was designed mainly to ascertain information on dietary nitrite, nitrate, and vitamin C. We also could not adjust for total energy and other potential dietary confounders such as dietary fats. Third, information on diet was obtained from proxies in about 43% subjects. Although the patterns of associations are similar regardless of inclusion or exclusion of proxies and we adjusted for type of respondents, this remains a concern because proxies may not provide information as accurately as the subjects themselves. Finally, chance findings remain possible because of the large number of foods and nutrients were evaluated.

In summary, we found that the risk of t(14;18)-positive NHL was increased with higher intakes of milk or dietary nitrite, whereas coffee consumption was associated with a lower risk. We also found that intake of vegetable nitrate and carotene was associated with a lower risk of t(14;18)-negative NHL. These findings should be interpreted cautiously because of the small sample. Future epidemiologic studies should explore additional dietary constituents and also investigate other chromosomal abnormalities in addition to the t(14;18).

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