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Original Contribution

Nutrient Intake and Risk of Non-Hodgkin's Lymphoma

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The mechanisms through which diet may influence the development of non-Hodgkin's lymphoma (NHL) are unclear but can be better understood by examining associations between nutrient consumption and NHL risk. Between 2000 and 2002, 591 NHL cases and 460 population-based controls in Sweden completed a semiquantitative food frequency questionnaire. Unconditional logistic regression was performed to estimate odds ratios and 95% confidence intervals for associations with nutrient intake; all statistical tests were two sided. Dietary intake of most macronutrients was not associated with risk of NHL or its common subtypes. Consumption of omega-3 or marine fatty acids was associated with decreased risk of NHL and chronic lymphocytic lymphoma, and dietary fiber was associated with lower risk of all subtypes examined. When the highest and the lowest quartiles of marine fat intake were compared, the odds ratio for NHL risk was 0.6 (95% confidence interval: 0.4, 0.9), $p_{trend} = 0.03$; for dietary fiber intake, the corresponding odds ratio was 0.5 (95% confidence interval: 0.3, 0.7), $p_{trend} < 0.001$. Dietary consumption of beta-carotene or alpha-tocopherol was associated with lower NHL risk, whereas intake of calcium or retinol was associated with increased NHL risk. Nutrients that affect inflammation, vitamin D activity, oxidative DNA damage, or DNA methylation may be associated with risk of NHL.

case-control studies; diet; fatty acids; lymphoma, non-Hodgkin; nutrition; vitamin D

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma.

Because nutrient intake influences immune system function (1, 2), exploring its potential effects is of particular interest in etiologic studies of non-Hodgkin's lymphoma (NHL). However, previous epidemiologic studies of associations between nutrient consumption and risk of NHL are inconclusive (3–14). We recently reported that high consumption of dairy products or fried red meat was associated with increased risk of NHL and several subtypes in men and women, whereas fruit and vegetable intake was inversely associated with risk of NHL in women (15). Building on these results, we next aimed to examine associations with a broad range of macro- and micronutrients to gain a better biologic understanding of how diet may affect NHL development.

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Few findings have been replicated among previous dietary studies of NHL. Three studies detected a positive association between consumption of animal protein and/or fat, or saturated fat, and NHL risk (3, 6, 10), but three others did not (4, 8, 13). An inverse association was observed between beta- or total carotene intake and risk of NHL in two studies (4, 7) but not in most others (6, 9, 10, 13, 14). In contrast, two investigations found a positive association of retinol intake with NHL risk (7, 10), whereas another pair did not (9, 13). Finally, an inverse association has been observed between consumption of dietary fiber and NHL risk (9, 10), but two studies failed to detect an association (6, 13). Otherwise, reported associations have generally been null.

Importantly, most prior studies—with some exceptions (4, 10, 12–14)—grouped all NHL cases together, without examining whether associations differ by histopathologic subtype. Given that NHLs are a diverse set of malignancies (16), it is likely that etiologic associations vary by subtype. Therefore, in an effort to clarify the mechanisms by which diet may affect development of NHL subtypes, we extended our prior analysis of food items by identifying specific nutrients that may influence lymphomagenesis.

MATERIALS AND METHODS

Study population

The Scandinavian Lymphoma Etiology (SCALE) study is a population-based case-control study of newly diagnosed malignant-lymphoma patients and controls in Sweden and Denmark (17). The dietary study included residents (aged 18–74 years) of seven Swedish counties between October 2000 and April 2002; about half of Sweden's population resides in the counties. Eligible subjects were those without a history of organ transplantation, human immunodeficiency virus infection, or prior hematopoietic malignancy, and they were required to have sufficient knowledge of the Swedish language to participate.

Cases were all patients with a first, incident, and morphologically verified diagnosis of NHL, including chronic lymphocytic leukemia (*International Classification of Diseases and Related Health Problems*, Tenth Revision, codes C82–85, C88.0, C91.1, C91.3–5, C91.7) (18). Cases were identified through a rapid case ascertainment system organized for this study (17), with backup from the nationwide cancer registry (19). Case specimens were histopathologically evaluated by a senior hematopathologist or cytologist and were classified according to the World Health Organization system (16) (described by Ekström Smedby et al. (17)).

Controls were randomly identified from the Swedish population (aged 18–74 years) in the eligible counties by using computerized, continuously updated registers of the total population. A subset of controls was sampled without replacement every 6 months during the study period and was frequency matched to the expected 10-year age group and sex distribution of the cases.

Among the residents in the eligible counties, 811 NHL cases were identified between October 25, 2000, and April 15, 2002; of these patients, 686 (85 percent) consented to participate in the founding case-control study interview. Of 718 potential controls identified during the same time period, 576 (80 percent) participated. All interview participants were subsequently asked to complete a written diet questionnaire. Among the cases, 614 (90 percent of participants; 76 percent of all identified cases) completed the diet questionnaire, and, among the controls, 492 (85 percent of participants; 69 percent of all potential controls) did so. To resolve ambiguous or missing answers, we recontacted 23 percent of cases and 28 percent of controls by telephone. Individuals were excluded if they were later discovered to be living in an ineligible county (14 controls); had omitted more than half of the main questions in the food frequency questionnaire (19 cases, 16 controls); or reported an average daily caloric intake judged to be too low (<800 kcal if male or <600 kcal if female, based on lower median intake among women) or too high (>5,000 kcal if male or >4,000 kcal if female) (four cases, two controls). After these exclusions, 591 cases and 460 controls remained for the analysis.

All study participants granted informed consent at the time of enrollment. The study protocol was approved by all regional ethics committees in Sweden.

Interview and dietary assessment

All study participants completed a comprehensive telephone interview evaluating known and suspected risk factors for malignant lymphoma. Following completion of the interview, participants were mailed a self-administered written diet questionnaire. The validated, semiquantitative food frequency questionnaire (described by Chang et al. (15)) evaluated average dietary intake of 137 foods, beverages, additives, and supplements 2 years before the interview, with the assumption that recent diet is highly correlated with diet in the more distant past (20).

Average daily consumption of nutrients, nutrient groups, and total calories was calculated by using standard portion sizes and nutrient composition values from the current version of the Swedish National Food Administration database (21, 22). Although use of vitamins, minerals, or other dietary supplements was evaluated in the diet questionnaire, supplemental micronutrient intake was not calculated because values were unavailable in the database. In addition to the nutrient values provided by the National Food Association, we calculated average daily consumption of omega-3 fatty acids by combining intake of eicosapentaenoic, docosahexaenoic, and alpha-linolenic acids. Marine fatty acids, a subgroup of omega-3 fats, were calculated as eicosapentaenoic and docosahexaenoic acids, and we calculated intake of omega-6 fatty acids by summing linoleic, arachidonic, and docosapentaenoic acids intake. The ratios of omega-6 to omega-3 and omega-6 to marine fatty acids consumption were additionally examined since a high ratio may promote inflammation and the risk of related chronic diseases (23, 24). We also calculated consumption of animal or vegetable fatty acids based on food sources of fat.

Statistical analysis

We used unconditional logistic regression, adjusting for 5-year age group, sex, total energy intake, and other potential

TABLE 1. Odds ratios and 95% confidence intervals for associations between dietary intake of total energy, fats, or dietary fiber and risk of non-Hodgkin's lymphoma and histopathologic subtypes in Sweden, 2000–2002*

Daily nutrient intake	Median	Non-Hodgkin's lymphoma			Diffuse large B-cell lymphoma			Chronic lymphocytic leukemia			Follicular lymphoma			T-cell lymphoma		
		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
Total energy (kcal)																
≤1,690	1,483	130	1.0		31	1.0		33	1.0		26	1.0		8	1.0	
>1,690–2,080	1,889	148	1.2	0.8, 1.7	39	1.3	0.7, 2.2	40	1.5	0.9, 2.6	28	1.2	0.6, 2.2	6	0.8	0.3, 2.2
>2,080–2,470	2,263	161	1.2	0.9, 1.8	36	1.2	0.7, 2.0	46	1.5	0.9, 2.6	35	1.4	0.8, 2.6	11	0.7	0.2, 2.4
>2,470	2,810	152	1.2	0.9, 1.8	41	1.3	0.8, 2.3	29	0.9	0.5, 1.7	19	0.8	0.4, 1.5	16	0.4	0.1, 1.6
p_{trend}				0.27			0.42			0.80			0.63			0.08
Total fat (g/1,000 kcal)																
≤31.5	28.5	130	1.0		36	1.0		36	1.0		22	1.0		8	1.0	
>31.5–35.3	33.5	158	1.2	0.8, 1.7	38	1.0	0.6, 1.7	36	0.8	0.5, 1.5	28	1.2	0.6, 2.2	17	1.6	1.0, 6.3
>35.3–38.8	36.9	154	1.2	0.8, 1.7	35	0.9	0.6, 1.6	40	1.1	0.6, 1.9	36	1.6	0.9, 3.0	9	1.0	0.4, 2.9
>38.8	41.1	149	1.1	0.7, 1.5	38	1.0	0.6, 1.8	36	0.8	0.5, 1.5	22	1.0	0.5, 1.9	7	0.8	0.3, 2.5
p_{trend}				0.72			0.99			0.70			0.74			0.45
Saturated fatty acids (g/1,000 kcal)¶																
≤13.0	11.4	129	1.0		29	1.0		36	1.0		24	1.0		12	1.0	
>13.0–15.0	14.0	155	1.2	0.8, 1.7	43	1.8	0.9, 3.4	38	0.9	0.5, 1.7	26	0.9	0.4, 1.9	11	0.8	0.3, 2.2
>15.0–17.0	15.9	146	1.2	0.7, 1.8	35	1.6	0.8, 3.4	36	1.0	0.5, 2.0	32	1.1	0.5, 2.5	11	0.7	0.2, 2.4
>17.0	18.6	161	1.3	0.8, 2.3	40	1.8	0.8, 4.1	38	1.2	0.5, 2.6	26	0.9	0.4, 2.2	7	0.4	0.1, 1.6
p_{trend}				0.31			0.23			0.63			0.83			0.21
Polyunsaturated fatty acids (g/1,000 kcal)¶																
≤4.1	3.7	144	1.0		42	1.0		31	1.0		26	1.0		11	1.0	
>4.1–4.7	4.4	173	1.0	0.7, 1.5	43	1.0	0.6, 1.7	45	1.0	0.6, 1.9	32	1.0	0.5, 1.8	14	1.4	0.5, 3.7
>4.7–5.2	4.9	124	0.7	0.5, 1.1	29	0.6	0.3, 1.2	35	0.8	0.4, 1.5	26	0.7	0.4, 1.5	5	0.6	0.2, 2.0
>5.2	5.7	150	0.9	0.6, 1.4	33	0.7	0.4, 1.4	37	0.9	0.4, 1.7	24	0.6	0.3, 1.3	11	1.3	0.4, 4.1
p_{trend}				0.44			0.27			0.59			0.15			0.88
Omega-3 fatty acids (g/1,000 kcal)¶																
≤0.7	0.6	149	1.0		41	1.0		33	1.0		32	1.0		15	1.0	
>0.7– 0.8	0.8	158	0.9	0.6, 1.4	41	0.9	0.5, 1.7	44	0.9	0.5, 1.7	24	0.7	0.4, 1.4	7	0.5	0.2, 1.3
>0.8–1.0	0.9	149	0.9	0.6, 1.3	36	0.8	0.4, 1.6	40	0.7	0.4, 1.3	29	0.9	0.4, 1.8	11	0.8	0.3, 2.4
>1.0	1.2	135	0.8	0.5, 1.2	29	0.7	0.3, 1.3	31	0.5	0.2, 1.0	23	0.7	0.3, 1.6	8	0.6	0.2, 2.2
p_{trend}				0.20			0.21			0.03			0.52			0.66
Marine fatty acids (g/1,000 kcal)¶																
≤0.1	0.1	150	1.0		38	1.0		32	1.0		30	1.0		13	1.0	
>0.1–0.2	0.2	146	0.8	0.6, 1.2	43	1.0	0.6, 1.8	36	0.9	0.5, 1.6	23	0.7	0.4, 1.4	12	0.8	0.3, 2.1
>0.2–0.3	0.3	182	1.0	0.7, 1.5	36	0.9	0.5, 1.5	51	1.2	0.5, 2.0	36	1.2	0.6, 2.2	10	0.8	0.3, 2.2
>0.3	0.4	113	0.6	0.4, 0.9	30	0.8	0.4, 1.4	29	0.6	0.3, 1.2	19	0.6	0.3, 1.1	6	0.5	0.2, 1.5
p_{trend}				0.03			0.30			0.15			0.15			0.22
Omega-6 fatty acids (g/1,000 kcal)¶																
≤3.1	2.8	152	1.0		41	1.0		30	1.0		31	1.0		11	1.0	
>3.1–3.5	3.3	156	1.0	0.7, 1.4	40	0.9	0.5, 1.7	39	1.2	0.6, 2.3	28	0.7	0.4, 1.4	12	1.3	0.5, 3.7
>3.5–3.9	3.7	153	1.0	0.6, 1.5	36	0.9	0.5, 1.8	46	1.7	0.8, 3.3	30	0.7	0.3, 1.5	8	1.0	0.3, 3.7
>3.9	4.3	130	0.9	0.5, 1.4	30	0.9	0.4, 1.9	33	1.5	0.7, 3.2	19	0.4	0.2, 1.0	10	1.3	0.3, 4.9
p_{trend}				0.63			0.81			0.27			0.05			0.79

Animal fatty acids (g/1,000 kcal)¶																
≤17.7	15.5	140	1.0		34	1.0		38	1.0		22	1.0		15	1.0	
>17.7–20.5	19.3	131	1.0	0.7, 1.4	37	1.1	0.6, 1.9	33	0.9	0.5, 1.5	23	1.0	0.5, 2.0	11	0.8	0.3, 1.8
>20.5–23.9	22.0	154	1.1	0.8, 1.5	38	1.1	0.6, 1.9	40	1.1	0.6, 1.9	30	1.3	0.7, 2.4	8	0.5	0.2, 1.4
>23.9	26.6	166	1.2	0.8, 1.8	38	1.1	0.6, 1.9	37	1.0	0.6, 1.8	33	1.5	0.8, 2.9	7	0.6	0.2, 1.5
p_{trend}				0.23			0.83			0.82			0.16			0.17
Vegetable fatty acids (g/1,000 kcal)¶																
≤11.3	9.7	132	1.0		28	1.0		32	1.0		27	1.0		6	1.0	
>11.3–13.4	12.4	146	1.1	0.8, 1.6	43	1.6	0.9, 2.8	33	1.1	0.6, 1.9	32	1.1	0.6, 2.0	8	1.2	0.4, 3.8
>13.4–16.4	14.8	182	1.4	1.0, 2.1	49	1.8	1.0, 3.2	44	1.5	0.9, 2.6	28	0.9	0.5, 1.8	14	2.0	0.7, 5.9
>16.4	18.5	131	1.0	0.7, 1.5	27	1.0	0.5, 1.8	39	1.3	0.7, 2.2	21	0.7	0.4, 1.4	13	1.8	0.6, 5.3
p_{trend}				0.72			0.91			0.33			0.32			0.22
Dietary fiber (g/1,000 kcal)																
≤8.8	7.5	186	1.0		54	1.0		43	1.0		33	1.0		12	1.0	
>8.8–10.7	9.8	163	0.8	0.5, 1.1	29	0.5	0.3, 0.8	40	0.7	0.4, 1.3	32	0.9	0.5, 1.6	15	1.4	0.6, 3.3
>10.7–12.6	11.4	126	0.6	0.4, 0.8	35	0.6	0.3, 0.9	38	0.7	0.4, 1.1	18	0.4	0.2, 0.8	11	1.2	0.5, 3.1
>12.6	14.4	116	0.5	0.3, 0.7	29	0.5	0.3, 0.8	27	0.4	0.2, 0.8	25	0.5	0.3, 1.0	3	0.4	0.1, 1.6
p_{trend}				<0.001			0.01			0.004			0.02			0.28

* No. of controls per quartile = 115.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age (in 5-year categories), sex, and total energy intake (logarithm).
§ Additionally adjusted for body mass index (in quartiles).
¶ Additionally adjusted for intake of other types of fat.

confounders, to estimate odds ratios and corresponding 95 percent confidence intervals for associations between nutrient intake and risk of NHL. Nutrient intakes and intake ratios were categorized into quartiles based on the distribution in the control population. The lowest quartile of intake was the reference group for all comparisons. For ease of interpretation, consumption of fish was categorized into less than 1.5, 1.5 to less than 3.0, or 3.0 or more servings per day based on the distribution among controls. To adjust for total energy intake, daily caloric consumption was modeled on the logarithmic scale. Associations with intake of specific types of fat (e.g., omega-3 fatty acids) were adjusted for other fat types (e.g., saturated, monounsaturated, and omega-6 fatty acids).

Possible confounders were evaluated based on prior subject knowledge, changes in estimates of association, and likelihood ratio tests of nested models. Characteristics previously associated with at least one subtype of NHL in this study population include ultraviolet radiation exposure (17), body mass index (25), alcohol consumption (26), smoking status (27), antibiotic use (28), and history of autoimmune disease (29). Measures of ultraviolet radiation exposure included frequency of sunbathing 5–10 years ago or at age 20 years (0, ≤1, 2 to 3, or ≥4 times/week) and frequency of sunburns 5–10 years ago or at age 20 years (0, <1, 1, or ≥2 times/year). Body mass index was calculated as height (in meters) divided by normal weight (in kilograms) squared; both body mass index and alcohol consumption (in grams of ethanol/day) were categorized into quartiles based on the distribution among controls. Smoking status was classified as never, former, or current smoking of cigarettes daily for at least 1 year. Lifetime antibiotic use was categorized as 0, 1 to 2, 3 to 5, 6 to 10, or 11 or more times. History of an autoimmune disease (rheumatoid arthritis, systemic lupus erythomatosus, primary Sjögren's syndrome, or celiac disease) at least 1 year earlier was classified as ever or never.

Dietary intake of macronutrients was adjusted for total energy intake by using the multivariate nutrient density model (20), in which nutrient consumption is divided by total energy intake, and total energy is simultaneously included as a separate variable in the statistical model. Consumption of micronutrients was energy adjusted by including total energy intake independently in the model. All analyses of nutrient intake were repeated by using the residual method (20), which adjusts nutrient consumption for energy intake by taking the residual from a linear least-squares regression model in which nutrient intake is the dependent variable and total energy is the independent variable, then adding the residual to the expected nutrient intake for a given mean energy intake. Because there were no substantial differences in the results based on the two methods, the results of only the nutrient density analysis are reported for simplicity of interpretation.

Tests for trend in NHL risk with increasing nutrient intake were performed by using the median of each quartile coded as an ordinal variable. Heterogeneity of estimates between strata of participants was evaluated with a likelihood ratio test for the significance of an interaction term between nutrient intake and the stratifying factor. Stratified analyses were not conducted for T-cell lymphoma because of the limited

number of cases. Total energy intake by cases versus controls was compared by using a Wilcoxon rank-sum test. Differences in odds ratios among case subgroups were compared with polytomous logistic regression, controlling for the same variables as described above. All statistical tests were two sided. Analyses were performed by using SAS System software, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Median daily total energy intake was 2,117 kcal among NHL cases and 2,080 kcal among controls ($p = 0.32$ for difference). There was no association between total energy intake and risk of NHL or any histologic subtype examined (table 1).

Intake of macronutrients and dietary fiber

Dietary consumption of total, saturated, polyunsaturated, animal, or vegetable fat was not associated with risk of overall NHL or its most common subtypes, controlling for age, sex, total energy intake, and consumption of other types of fat (table 1). Associations with risk of diffuse large B-cell lymphoma (DLBCL) were additionally adjusted for body mass index because of confounding. High intake of saturated fat was associated with a nonsignificantly increased risk of DLBCL, with no apparent dose-response association. Risk of NHL or its major subtypes was not associated with intake of palmitic or stearic acids, the main sources of saturated fatty acids, or with intake of total monounsaturated fat or its main sources—oleic, elaidic, and palmitoleic acids (data not shown). Further adjustment of these and all other associations for additional potential confounders (listed in the Materials and Methods section) had negligible effects (data not shown).

High dietary intake of marine fatty acids was associated with statistically significantly lower NHL risk, whereas high omega-3 fat intake was associated with significantly lower risk of chronic lymphocytic leukemia (table 1). Risk of DLBCL, follicular lymphoma, or T-cell lymphoma was also nonsignificantly lower among individuals in the highest compared with the lowest quartile of omega-3 or marine fatty acids intake. We previously examined associations of NHL risk with consumption of all seafood (15) but not fish or fatty fish (e.g., salmon, mackerel, and herring), which were associated with significantly lower risk of NHL, DLBCL, and chronic lymphocytic leukemia and with nonsignificantly reduced risk of follicular lymphoma (table 2).

Dietary intake of omega-6 fatty acids was not significantly associated with risk of NHL or any subtype examined except for follicular lymphoma, which was inversely associated. Furthermore, there were no statistically significant associations between the ratio of omega-6 to marine or to omega-3 fatty acids and risk of NHL or its subtypes (data not shown). Likewise, intake of cholesterol, protein, carbohydrates, or saccharides was not associated with risk of NHL or any subtype examined (data not shown). Consumption of dietary fiber was associated with significantly lower risk of NHL and all major subtypes except T-cell lymphoma

TABLE 2. Odds ratios and 95% confidence intervals for associations between consumption of fish and risk of non-Hodgkin's lymphoma and histopathologic subtypes in Sweden, 2000–2002

Type of fish (servings/day)	Median	Controls (no.)	Non-Hodgkin's lymphoma			Diffuse large B-cell lymphoma			Chronic lymphocytic leukemia			Follicular lymphoma			T-cell lymphoma		
			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
All fish (salmon, mackerel, herring, cod, fish fingers)																	
<1.5	0.9	237	331	1.0		91	1.0		81	1.0		53	1.0		24	1.0	
1.5–<3.0	2.4	144	176	0.8	0.6, 1.0	34	0.6	0.4, 0.9	43	0.7	0.5, 1.2	44	1.2	0.7, 1.9	13	1.1	0.5, 2.3
≥3.0	3.5	79	84	0.6	0.4, 0.9	22	0.6	0.4, 1.1	24	0.6	0.3, 1.1	11	0.5	0.2, 1.0	4	0.6	0.2, 2.0
p_{trend}					0.01			0.02			0.06			0.30			0.61
Fatty fish (salmon, mackerel, herring)																	
<1.5	0.9	337	449	1.0		113	1.0		113	1.0		85	1.0		34	1.0	
1.5–<3.0	2.0	88	110	0.8	0.6, 1.2	29	0.9	0.6, 1.5	24	0.6	0.4, 1.1	19	0.7	0.4, 1.3	5	0.7	0.3, 2.0
≥3.0	3.0	35	32	0.5	0.3, 0.9	5	0.3	0.1, 0.9	11	0.6	0.3, 1.2	4	0.4	0.1, 1.1	2	0.7	0.1, 3.2
p_{trend}					0.02			0.06			0.05			0.05			0.47
Fish oil supplements																	
None		424	559	1.0		141	1.0		139	1.0		103	1.0		39	1.0	
Any		36	32	0.6	0.4, 1.1	6	0.5	0.2, 1.2	9	0.7	0.3, 1.6	5	0.6	0.2, 1.5	2	0.7	0.2, 2.9

* OR, odds ratio; CI, confidence interval.
† Adjusted for age (in 5-year categories), sex, and total energy intake (logarithm).
‡ Additionally adjusted for body mass index (in quartiles).

(table 1). The inverse associations of dietary fiber intake and marine or omega-3 fatty acids intake with NHL or chronic lymphocytic leukemia risk, respectively, persisted after mutual adjustment (data not shown).

Intake of micronutrients

Intake of beta-carotene was associated with lower risk of overall NHL, DLBCL, follicular lymphoma, or T-cell lymphoma, whereas retinol was associated with higher risk of overall NHL, DLBCL, or T-cell lymphoma, although no significant dose-response trends were observed (table 3). Dietary consumption of vitamin C was associated with marginally lower risk of NHL but no individual subtypes examined. In contrast, vitamin E (data not shown) and its major form, alpha-tocopherol, were associated with significantly lower risk of NHL, chronic lymphocytic leukemia, or follicular lymphoma and with nonsignificantly lower risk of DBLCL.

High dietary intake of vitamin D was not associated with risk of total NHL or any common subtypes other than T-cell lymphoma. Dietary calcium intake was associated with statistically significantly elevated risks of NHL, DLBCL, and chronic lymphocytic leukemia. In contrast, dietary phosphorus intake was associated with significantly lower risks of these three outcomes and with nonsignificantly lower risk of T-cell lymphoma. Associations with intake of vitamin D, retinol, calcium, and phosphorus were mutually adjusted since the latter three micronutrients are negative regulators of biologically available levels of active vitamin D (30, 31).

Most of the B vitamins, including thiamine, riboflavin, vitamin B_6, and vitamin B_{12}, were not associated with NHL or its major subtypes (data not shown). However, high folate consumption was associated with significantly decreased NHL risk and with nonsignificantly decreased DLBCL risk (table 3), and high dietary intake of niacin was associated with lower risk of overall NHL (odds ratio for highest vs. lowest quartile of intake = 0.6, 95 percent confidence interval: 0.5, 1.0; $p_{trend} = 0.03$). Dietary consumption of iron was associated with decreased risks of NHL and all three B-cell subtypes. Of the other minerals examined, zinc, selenium, and potassium were not associated with risk of overall NHL or any subtype examined, while magnesium was significantly associated with lower risk of chronic lymphocytic leukemia (odds ratio for highest vs. lowest quartile = 0.4, 95 percent confidence interval: 0.2, 1.0; $p_{trend} = 0.05$) but no other subtypes (data not shown).

To avoid misclassification of micronutrient intake as a result of not accounting for dietary supplement use, we repeated all analyses of vitamins and minerals for participants who reported not using dietary supplements 2 years previously (53 percent of cases, 59 percent of controls). The estimated odds ratios in this group did not differ substantially from those in the overall study population (data not shown).

Heterogeneity of associations between participant subgroups

We detected no meaningful differences between men and women in the associations of nutrient intake with risk of NHL (data not shown). Similarly, we found that associations with dietary intake of retinol, vitamin D, calcium, or phosphorus did not vary by frequency of sunbathing 5–10 years ago ($\leq$1 time/week vs. $\geq$2 times/week), nor did the association between folate intake and risk of NHL or its most common subtypes differ by daily alcohol consumption (dichotomized at the median among controls) (data not shown). Associations with intake of dietary fiber ($p_{homogeneity} = 0.01$), calcium ($p_{homogeneity} = 0.01$), alpha-tocopherol ($p_{homogeneity} = 0.07$), and iron ($p_{homogeneity} = 0.08$) differed among the four NHL subtypes examined.

DISCUSSION

The results from this nutrient analysis generally accord with, and augment the understanding gained from, our earlier study of foods and NHL (15). The inverse associations of dietary fiber, beta-carotene, vitamins C and E, folate, and iron consumption with NHL risk correspond with the inverse associations we previously observed between NHL risk and intake of fruits and vegetables, especially green leafy or red/orange vegetables. The inverse associations of omega-3 and marine fatty acids and vitamin E/alpha-tocopherol with NHL risk in the current study coincide with the inverse association between total, especially fatty, fish consumption and NHL risk. In addition, the positive associations of calcium and retinol intake with NHL risk tie in with the earlier positive association found between consumption of dairy products and risk of NHL. However, our current findings of inverse associations between niacin, phosphorus, and iron intake and NHL risk do not match our prior observations that dairy product and fried red meat consumption was associated with increased risk of NHL. On the other hand, our new results may differentiate the effects of these nutrients from the effects of other dairy and meat components on NHL.

We did not observe a positive association between saturated or animal fatty acids and NHL risk, as was previously detected in two studies (6, 10) but not in two others (8, 13), although we did detect a statistically nonsignificant association of saturated fat with increased DLBCL risk. Although, to our knowledge, no previous study has examined dietary intake of omega-3 and/or marine fatty acids in relation to NHL risk, one group found a significant inverse association with fish consumption (11) or fish-handling occupations (32), another detected a nonsignificant inverse association with fish protein intake (3), and two reported a significant inverse association with intake of polyunsaturated fatty acids (10, 13), which include the omega-3 fats. However, the inverse association in one of the latter studies was primarily with intake of linoleic acid, an omega-6 fat (13).

The inverse associations between omega-3 or marine fatty acids intake and risk of NHL or chronic lymphocytic leukemia in our study may be attributable to the immunemodulatory effects of dietary fat. Omega-3 fatty acids, especially those derived from fish oils, can dampen inflammation by inhibiting the transcription factors NF-κB and AP-1 or by suppressing the formation of inflammatory prostaglandins and leukotrienes from omega-6 fatty acids (33, 34). Conversely, saturated fats can promote inflammation

TABLE 3. Odds ratios and 95% confidence intervals for associations between dietary intake of micronutrients and risk of non-Hodgkin's lymphoma and histopathologic subtypes in Sweden, 2000–2002*

Daily nutrient intake	Median	Non-Hodgkin's lymphoma			Diffuse large B-cell lymphoma			Chronic lymphocytic leukemia			Follicular lymphoma			T-cell lymphoma		
		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
Beta-carotene (μg)																
≤1,575	1,174	185	1.0		46	1.0		40	1.0		35	1.0		12	1.0	
>1,575–2,287	1,891	125	0.6	0.4, 0.9	34	0.7	0.4, 1.1	29	0.7	0.4, 1.3	16	0.4	0.2, 0.8	13	1.0	0.4, 2.3
>2,287–3,515	2,833	150	0.7	0.5, 1.0	35	0.7	0.4, 1.1	39	0.9	0.5, 1.6	33	0.8	0.4, 1.4	11	0.8	0.3, 2.1
>3,515	4,444	131	0.6	0.4, 0.8	32	0.6	0.3, 1.0	40	0.9	0.5, 1.5	24	0.5	0.3, 1.0	5	0.4	0.1, 1.2
p_{trend}				0.02			0.09			0.87			0.16			0.07
Retinol (μg)¶																
≤519	416	113	1.0		24	1.0		27	1.0		27	1.0		7	1.0	
>519– 836	648	183	1.6	1.1, 2.4	50	2.7	1.5, 5.2	43	1.5	0.8, 2.9	31	1.2	0.6, 2.5	15	3.4	1.0, 11.5
>836–1,233	1,010	137	1.0	0.7, 1.6	31	1.5	0.7, 3.0	36	1.3	0.7, 2.5	22	0.8	0.4, 1.6	9	1.3	0.4, 4.7
>1,233	1,549	158	1.2	0.8, 1.9	42	2.2	1.1, 4.3	42	1.3	0.7, 2.6	28	1.1	0.5, 2.4	10	1.7	0.5, 6.5
p_{trend}				0.83			0.40			0.83			0.91			0.75
Vitamin C (mg)																
≤73	56	165	1.0		37	1.0		38	1.0		29	1.0		11	1.0	
>73–104	87	148	0.8	0.5, 1.1	42	1.0	0.6, 1.8	35	0.9	0.5, 1.6	31	0.9	0.5, 1.7	9	0.6	0.2, 1.7
>104–147	124	137	0.7	0.5, 1.0	31	0.7	0.4, 1.3	30	0.7	0.4, 1.4	22	0.6	0.3, 1.1	13	0.9	0.3, 2.3
>147	185	141	0.7	0.5, 1.0	37	0.9	0.5, 1.6	45	1.1	0.6, 1.9	26	0.6	0.3, 1.2	8	0.6	0.2, 1.9
p_{trend}				0.08			0.51			0.71			0.12			0.60
Alpha-tocopherol (mg)																
≤5.8	5.0	156	1.0		38	1.0		38	1.0		30	1.0		9	1.0	
>5.8–7.1	6.5	142	0.7	0.5, 1.0	34	0.7	0.4, 1.3	35	0.7	0.4, 1.4	23	0.5	0.3, 1.0	12	1.0	0.4, 2.9
>7.1–8.7	7.9	168	0.6	0.4, 1.0	43	0.8	0.4, 1.5	48	0.7	0.4, 1.4	34	0.6	0.3, 1.3	6	0.5	0.1, 1.7
>8.7	9.8	125	0.4	0.2, 0.7	32	0.5	0.2, 1.1	27	0.3	0.1, 0.7	21	0.2	0.1, 0.7	14	0.9	0.2, 3.9
p_{trend}				<0.001			0.11			0.008			0.01			0.84
Vitamin D (μg)¶																
≤4.4	3.7	121	1.0		36	1.0		24	1.0		25	1.0		5	1.0	
>4.4–5.9	5.1	156	1.1	0.8, 1.6	35	0.9	0.5, 1.6	41	1.6	0.8, 3.0	32	1.3	0.7, 2.4	13	2.4	0.7, 7.7
>5.9–7.4	6.6	128	0.9	0.6, 1.3	34	0.7	0.4, 1.4	34	1.1	0.6, 2.2	23	0.9	0.4, 1.8	8	1.5	0.4, 5.7
>7.4	8.8	186	1.3	0.8, 2.1	42	1.0	0.5, 1.9	49	1.7	0.8, 3.4	38	1.1	0.5, 2.4	15	5.0	1.2, 19.9
p_{trend}				0.27			0.93			0.27			0.96			0.03
Calcium (mg)¶																
≤747	599	116	1.0		23	1.0		28	1.0		25	1.0		10	1.0	
>747–1,016	888	172	1.8	1.1, 2.8	48	3.1	1.5, 6.2	50	2.2	1.1, 4.4	34	1.4	0.7, 2.8	8	0.6	0.2, 2.3
>1,016–1,339	1,178	130	1.5	0.8, 2.5	28	2.1	0.8, 5.1	32	1.8	0.8, 4.1	15	0.7	0.3, 1.9	14	0.7	0.1, 3.3
>1,339	1,573	173	2.3	1.2, 4.5	48	4.4	1.5, 12.5	38	2.8	1.0, 7.5	34	1.9	0.6, 5.8	9	0.4	0.1, 2.6
p_{trend}				0.03			0.02			0.10			0.41			0.37
Phosphorus (mg)¶																
≤1,190	1,020	138	1.0		36	1.0		34	1.0		26	1.0		11	1.0	
>1,190–1,483	1,322	143	0.6	0.4, 1.0	33	0.4	0.2, 0.9	41	0.6	0.3, 1.3	32	1.1	0.5, 2.4	4	0.2	0.04, 0.9
>1,483–1,800	1,629	151	0.6	0.3, 1.0	36	0.4	0.2, 1.0	37	0.4	0.2, 1.1	18	0.6	0.2, 1.7	17	0.7	0.1, 4.0

>1,800	2,041	159	0.4	0.2, 0.9	42	0.3	0.1, 1.1	36	0.3	0.1, 0.9	32	0.8	0.2, 3.2	9	0.4	0.04, 4.0
p_{trend}				0.04			0.11			0.04			0.67			0.81
Folate (μg)																
≤213	176	145	1.0		39	1.0		32	1.0		25	1.0		10	1.0	
>213–264	240	151	0.9	0.6, 1.3	37	0.8	0.4, 1.4	40	1.2	0.7, 2.2	34	1.1	0.6, 2.2	10	0.8	0.3, 2.1
>264–329	293	167	0.9	0.6, 1.3	40	0.8	0.4, 1.5	38	1.0	0.5, 1.9	22	0.7	0.3, 1.4	14	1.0	0.3, 2.7
>329	389	128	0.6	0.5, 1.0	31	0.6	0.3, 1.1	38	0.9	0.4, 1.9	27	0.7	0.3, 1.6	7	0.5	0.1, 1.8
p_{trend}				0.03			0.12			0.64			0.25			0.31
Iron (mg)																
≤10.5	9.0	165	1.0		46	1.0		39	1.0		30	1.0		9	1.0	
>10.5–12.9	11.7	134	0.7	0.5, 1.0	32	0.5	0.3, 0.9	32	0.6	0.3, 1.1	31	0.8	0.4, 1.5	8	0.8	0.3, 2.5
>12.9–15.5	14.1	155	0.7	0.5, 1.0	35	0.5	0.3, 0.9	44	0.8	0.4, 1.6	27	0.6	0.3, 1.2	8	0.8	0.2, 2.6
>15.5	17.5	137	0.5	0.3, 0.8	34	0.4	0.2, 0.8	33	0.5	0.2, 1.0	20	0.3	0.1, 0.8	16	1.7	0.5, 6.1
p_{trend}				0.01			0.02			0.09			0.01			0.28

* No. of controls per quartile = 115.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age (in 5-year categories), sex, and total energy intake (logarithm).
§ Additionally adjusted for body mass index (quartiles).
¶ Additionally adjusted for intake of retinol, vitamin D, calcium, and phosphorus.

via the cyclooxygenase and lipoxygenase pathways (10, 33). Chronic inflammation is in turn known to increase the risk of NHL, especially B-cell subtypes (35–38), which may explain the nonsignificantly increased DLBCL risk with high saturated fat intake.

Similarly, dietary fiber—which we and some others (8, 10) found to be inversely associated with NHL risk—may inhibit lymphoma development by suppressing inflammation, as suggested by the inverse association between dietary fiber consumption and serum levels of C-reactive protein, a clinical marker of inflammation (39, 40). Furthermore, short-chain fatty acids produced through intestinal bacterial fermentation of dietary fiber have antioxidant, antimutagenic, and other anticarcinogenic properties (41, 42). Dietary fiber may also decrease NHL risk by modifying the intestinal absorption of other nutrients and chemicals and/or by beneficially influencing the composition and activity of gut microflora (42).

Despite our previous findings of an inverse association between fruit and vegetable intake and risk of NHL among women but not men (15), we observed inverse associations between intake of several antioxidant micronutrients—including beta-carotene, vitamin C, and alpha-tocopherol, but not selenium—and risk of some NHL subtypes among both men and women. Inverse associations of NHL with dietary intake of vitamin C (4), beta- or total carotenes (4, 7), or other antioxidants (14) have been reported by some studies but not others (6, 9, 10, 13), and three found no association with vitamin E consumption (9, 13, 14). Antioxidants may enhance the immune response by counteracting the potentially immunosuppressive, DNA-damaging, and carcinogenic effects of free radicals and reactive oxygen species (43, 44).

Unlike for the antioxidant vitamins, vitamin D intake was not associated, whereas retinol intake was positively associated, with risk of NHL and its common subtypes. Calcium intake, too, was associated with increased risk of NHL, DLBCL, and chronic lymphocytic leukemia, whereas phosphorus intake was associated with decreased risk of the same three outcomes. These four nutrients may be of particular relevance to the development of NHL because recent studies, including ours, have shown an inverse dose-response relation between ultraviolet radiation exposure and risk of NHL and its main subtypes (17, 45). The inverse association has been attributed to the immunomodulatory, antiproliferative, and antilymphomagenic effects of bioactive vitamin D ($1,25(OH)_2D_3$) (31, 46–48), of which the major source is ultraviolet B. The fact that sunlight, rather than food, is the primary source of vitamin D for most people (49, 50) may explain the lack of an association between dietary vitamin D consumption and NHL risk in our study, although another recent study detected an inverse association with dietary vitamin D intake (13). In contrast, high dietary calcium and high serum phosphate levels lead to feedback inhibition of $1,25(OH)_2D_3$ synthesis (30, 31, 46), which may explain the positive association between calcium consumption and NHL risk observed in our study. It is unknown whether normal dietary levels of phosphorus can suppress $1,25(OH)_2D_3$ synthesis (46), but it is unclear why we found an inverse association with phosphorus intake. Meanwhile, the positive

association between retinol intake and NHL risk in our study and others (7, 10) may be due to the antagonistic effect of retinol on vitamin D activity since retinol competes for the same receptors as $1,25(OH)_2D_3$ (49).

Although we had a priori hypotheses and a convincing biologic model concerning the roles of dietary vitamin D, calcium, and retinol in NHL development, we had no earlier expectations regarding the associations of other micronutrients with NHL risk. Our finding of an inverse association between dietary folate consumption and risk of NHL was preceded by a recent report of an inverse association between dietary folate and risk of diffuse, but not overall, NHL (12), although two studies detected no such association (9, 13). Folate may affect cancer development via its role in normal DNA methylation, which regulates gene transcription (51). Our analyses of other micronutrients were largely exploratory, and the inverse associations of niacin, iron, and magnesium intake with at least some NHL subtypes remain to be confirmed and explained. In addition, the heterogeneity of associations by NHL subtype needs to be explored further in studies investigating etiologic differences among the various histopathologic types of lymphoma.

In general, any of the associations observed in our study may have been due to chance, especially given the many comparisons we performed; several statistically significant findings would be expected because of chance alone. Conversely, we may have failed to detect some true associations because of such reasons as a narrow range of nutrient intake in our study population, misclassification of dietary intake, or insufficient statistical power. Sample-size restrictions also prevented us from examining nutrient associations with less common histopathologic subtypes of NHL and performing robust tests of heterogeneity among subtypes. In addition, our study was limited by the usual restrictions of retrospective nutrient analyses (52). We did not examine dietary patterns earlier in life, changes in diet over time, or cumulative dietary intake. Systematic or random differences in recollection between cases and controls could have affected our results in unpredictable ways. Our method of estimating nutrient intake did not account for intake of dietary supplements, which may be important sources of key nutrients. However, our results were unchanged after we excluded individuals who took dietary supplements. Finally, it is possible that single nutrients are not as relevant to cancer development as nutrients in combination or in whole foods, and that consumption of a nutrient in isolation does not have the same effects as in combination with other nutrients.

In conclusion, our study offers insight into potential mechanisms of lymphoma development or prevention through nutrient-mediated pathways. Our results suggest that intake of nutrients that inhibit the activity of vitamin D or promote inflammation may increase the risk of overall NHL and common B-cell subtypes. In contrast, consumption of nutrients that suppress inflammation, prevent oxidation, or mediate normal DNA methylation may decrease the risk of developing several types of NHL. Thus, the conclusions from our previous analysis of food consumption and risk of NHL (15)—that the international rise in NHL incidence during the mid- to late 20th century (53, 54) could be partly accounted for by a parallel increase in consumption of meat and dairy products and decreased consumption of fresh fruits and vegetables—are substantiated by our current findings. If a causal association exists between nutrients and NHL, dietary modifications may contribute to the reduction of NHL incidence worldwide.

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Errata

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Chang et al. have reported an error in the unit for fish consumption described in their recently published article (1). In the first paragraph of page 1225 and in the first column heading of table 2, the unit should be servings per week and servings/week, respectively.

The authors and the *Journal* regret the error.

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1. Chang ET, Bälter KM, Torrång A, et al. Nutrient intake and risk of non-Hodgkin's lymphoma. Am J Epidemiol 2006; 164:1222–32.

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