Dietary Factors and Risk of Non-Hodgkin Lymphoma in Men and Women

Ellen T. Chang,[1] Karin Ekström Smedby,[1] Shumin M. Zhang,[5] Henrik Hjalgrim,[6] Mads Melbye,[6] Åke Öst,[4] Bengt Glimelius,[2,7] Alicja Wolk,[3] and Hans-Olov Adami[3]

Departments of [1]Medical Epidemiology and Biostatistics and [2]Oncology and Pathology; [3]Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Karolinska Institutet; [4]Department of Pathology and Cytology, Medilab, Stockholm, Sweden; [5]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [6]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; [7]Department of Oncology, Radiology and Clinical Immunology, University of Uppsala, Uppsala, Sweden

Abstract

Background: **The incidence of non-Hodgkin lymphoma (NHL) has increased worldwide in recent decades. Diet could influence NHL risk by modulating the immune system, although evidence is limited. We did a population-based case-control study to determine whether differences in diet were associated with NHL risk.**
Methods: **A total of 597 NHL cases and 467 population controls in Sweden completed a semiquantitative food frequency questionnaire evaluating their dietary habits 2 years before the interview. Unconditional logistic regression was used to estimate the odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for associations between food intake and risk of NHL.**
Results: **High consumption of dairy products and fried red meat was associated with increased risk of NHL. The OR of NHL for individuals in the highest quartile compared with the lowest quartile of dairy intake was 1.5 (95% CI, 1.1-2.2; P_{trend} = 0.003). The OR for the highest versus lowest quartile of fried red meat intake was 1.5 (95% CI, 1.0-2.1; P_{trend} = 0.02). In contrast, high consumption of fruits and vegetables was associated with reduced risk of NHL, particularly follicular lymphoma, among women but not men. Compared with the lowest quartile of vegetable intake, the OR of follicular lymphoma among women in the highest quartile of vegetable intake was 0.3 (95% CI, 0.1-0.7; P_{trend} = 0.002).**
Conclusions: **The positive associations of NHL risk with dairy products and fried red meat and the inverse association with fruits and vegetables suggest that diet affects NHL risk and could explain the increase of some histopathogic subtypes.** (Cancer Epidemiol Biomarkers Prev 2005;14(2):512–20)

Introduction

The incidence of non-Hodgkin lymphoma (NHL), a heterogeneous group of malignancies of the lymphoid tissue (1), has risen rapidly in recent decades, with an annual increase of 2% to 4% in most developed countries and growing incidence rates in developing countries as well (2, 3). The reasons for the increase are largely unknown, even after accounting for changes in diagnostic methods and criteria, HIV/AIDS and other immunosuppressive conditions, family history of NHL, drug use, infectious agents, including oncogenic viruses, and occupational exposures such as pesticides and solvents (4-7).

Because dietary habits in Western countries have changed dramatically over time, the potential influence of diet on NHL risk is of primary interest, particularly because diet is known to modulate the immune system (8). Diet may also affect cancer risk through changes in energy balance, levels of dietary carcinogens and anticarcinogens, and/or DNA damage and methylation (9). Fewer than a dozen studies have examined the role of diet in NHL development (10-21), with results suggesting that higher consumption of meat, especially red meat (11, 16-18, 21), dairy products (10, 12, 14, 15, 21), liver (10, 15), methylxanthine-containing (e.g., caffeinated) beverages such as coffee and tea (10, 16), butter, oil (10), and eggs (21) were associated with increased risk of NHL. In contrast, increased intake of vegetables (12, 19, 21), fruits (12, 17, 19, 21), whole grains and pasta (10, 15), and fresh fish (22) may reduce NHL risk. However, results from these studies have been inconsistent, possibly due to differences in study population and design, sample size, and/or system of histopathologic classification of NHL cases.

Given the promising but inconclusive data on the relationship between diet and NHL development, we investigated the dietary habits of male and female NHL cases and population controls in Sweden. To account for the heterogeneity of NHL as a disease entity and to determine whether the role of diet varies by histopathology, we also examined the associations between food consumption and major subtypes of NHL.

Materials and Methods

Study Population. The Scandinavian Lymphoma Etiology study is a population-based case-control study of newly diagnosed malignant lymphoma patients and controls in Sweden and Denmark. The study base for the dietary component of the study, which was conducted only in Sweden, included all persons ages between 18 and 74 years living in Stockholm, Uppsala, Gotland, Västra Götaland, Västmanland, Dalarna, and Gävleborg counties between mid-October 2000 and April 15, 2002. These counties cover about half of the population in Sweden. Subjects were required to have sufficient knowledge of the Swedish language to participate. Individuals with a history of organ transplantation or HIV infection, as well as those with a prior hematopoietic malignancy, were excluded.

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Requests for reprints: Ellen Chang, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden. Phone: 46-8-524-86154; Fax: 46-8-31-49-57. E-mail: ellen.chang@meb.ki.se

Cases were all patients with a first, newly diagnosed, and morphologically verified diagnosis of NHL (*International Classification of Diseases, 10th Revision* codes C82-C85, C88.0, C91.3-5, and C91.7), including chronic lymphocytic leukemia (*International Classification of Diseases, 10th Revision* code C91.1; ref. 23). Cases were identified through a rapid case ascertainment system set up expressly for this study, consisting of a network of contact physicians from all departments where malignant lymphomas are diagnosed and/or treated in Sweden. Continuous collaboration with the six regional cancer registries in Sweden, with an estimated coverage of close to 100%, ensured complete reporting through the network (24).

Controls were randomly sampled from the Swedish population in the eligible counties using computerized population registers that are updated continuously. A subset of controls was sampled every 6 months during the study period and frequency matched to the expected distribution of the NHL cases on sex and age (in 10-year intervals).

Among the Swedish residents in the above counties, 811 cases of malignant lymphoma were identified between October 25, 2000 and April 15, 2002. Of this total, 686 cases (85%) consented to participate in the study. In the same geographic area and time frame, 718 eligible individuals identified from the population registers were asked to participate as controls; of these potential controls, 576 (80%) participated.

Among the study participants who initially consented to enroll in the study, all cases and controls residing in the specified counties were asked to complete a written diet questionnaire. Of these, 613 cases (89%; 76% of all identified cases) and 492 controls (85%; 69% of all potential controls) returned the questionnaire; subsequently, 23% of cases and 28% of controls were contacted by telephone to resolve ambiguous or missing answers. Among the controls, 12 (2%) were ruled out as ineligible. Individuals who left more than half of the food frequency questionnaire blank (16 cases, 3%; 13 controls, 3%) were excluded from the analyses, leaving 597 cases and 467 controls.

All study participants granted informed consent at the time of enrollment in the study. This investigation was approved in Sweden by the Institutional Review Board (also called the Research Ethical Committee) and the National Data Inspection Board.

Data Collection and Dietary Assessment. Study participants first completed a telephone interview, including questions on current height and usual weight, family background, smoking habits, medical history, family medical history, education, occupation, and other possible risk factors for NHL. Following completion of the interview, participants were sent a self-administered written diet questionnaire. The semiquantitative food frequency questionnaire evaluated average intake of 137 items 2 years before the interview, ensuring that cases reported predisease diet. Individuals were asked how often, on average, they had consumed certain foods, beverages, additives, and supplements. For 71 food items that are consumed with widely varying frequency, such as specific types of grains, meat, vegetables, fruits, and snacks, respondents were asked to report their average intake by choosing one of eight possible responses, ranging from ''zero times per month'' to ''three or more times per day.'' For 23 food items that are usually consumed on a more regular basis, including milk, other beverages, cheese, and bread, respondents were asked to write the number of servings (specific commonly used portion sizes or units) they consumed on average per day and/or week. For eight food items that are generally less frequently consumed, such as fried or grilled meat, respondents were asked to write the average number of times they ate the food each month or year. For 35 additives and supplements, respondents marked ''yes'' to indicate whether they consumed the item. Additional questions assessed food preparation habits (e.g., degree of frying or grilling), alcohol drinking status (never, former, or current) and volume of intake (in centiliters), and vegetarian/vegan status. Missing answers to write-in and yes/no questions were assumed to be zero or no, respectively; missing answers to multiple-choice answers were assumed to be zero if the respondent left the majority of responses blank (i.e., if the option for ''zero'' was always left unchecked) and missing if otherwise (i.e., if the option for ''zero'' was usually checked).

In the analyses, individual food items were combined into major food groups as follows. Dairy products included milk, soured milk/yogurt, cheese, cottage cheese/curd, ice cream, crème fraiche, cream, and pancakes (comprised largely of milk, in Sweden). Red meat included mincemeat/hamburger, pork, beef/veal, sausage, sandwich meat, fried sausage/beef/pork chop, and grilled sausage/beef/pork chop. White meat included chicken/other poultry, fried chicken, roasted chicken, and grilled chicken. Seafood included herring/mackerel, salmon/whitefish, cod/fish fingers, shellfish, fried fish, and grilled fish. Grains included crispbread, white bread, wholegrain bread, oatmeal, other porridge, cereal/muesli, pasta, pancakes, pizza, rice, wheat bran/oat bran, and flaxseed. Fruits included oranges/citrus fruit, orange/grapefruit juice, apples/pears, bananas, berries, other fruit, lingonberry jam, other jam/marmalade, and fruit cream/soup. Citrus fruits included oranges/citrus fruit and orange/grapefruit juice. Vegetables included carrots, beets, lettuce, cabbage, cauliflower, broccoli/brussels sprouts, tomatoes/tomato juice, peppers, spinach, green peas, onions/leeks, garlic, mixed vegetables, pea soup/lentils, and soy products. Cruciferous vegetables included cabbage and broccoli/brussels sprouts. Green leafy vegetables included lettuce and spinach. Green vegetables included lettuce, cabbage, cauliflower, broccoli/brussels sprouts, spinach, peas, and mixed vegetables. Red or orange vegetables included carrots, beets, tomatoes, and ketchup.

The validity of food intake estimates in a nearly identical version of this food frequency questionnaire was previously evaluated in a group of 203 Swedish women ages 30 to 74 years. During four separate weeks 3 to 4 months apart, each participant weighed and recorded all foods consumed. The Pearson correlation coefficients between the estimates derived from the questionnaire and the weighed food records, generally ranged between $r = 0.2$ and $r = 0.6$ (e.g., $r = 0.5$-0.6 for dairy products, $r = 0.2$ for pork, $r = 0.4$ for beef, $r = 0.3$ for chicken, $r = 0.2$-0.4 for fish, $r = 0.4$ for apples, $r = 0.6$ for oranges, $r = 0.2$ for broccoli, $r = 0.4$ for cabbage, $r = 0.5$ for tea, and $r = 0.5$ for coffee; $P \leq 0.05$ for all correlations).[8] Correlations are expected to be very similar among men (25, 26). However, it is unclear whether weighed food records or food frequency questionnaires are a more accurate measure of average food intake over time, nor whether correlation between these metrics is expected to be high or low. Furthermore, individuals willing to weigh and record all foods consumed for a week may not be representative of other study populations.

Histopathologic Classification. In Sweden, all cases were histopathologically evaluated by a senior hematopathologist or cytologist and uniformly classified according to the WHO classification of hematopoietic and lymphoid tumors (1). The original tumor slides were retrieved and reviewed for all but 1% of the cases. In these remaining cases, the results of the primary morphologic and immunohistochemical investigation were evaluated by the study hematopathologists or

[8] A. Wolk, unpublished data.

Table 1. Frequencies of food intake and ORs and 95% CIs for associations between food intake and risk of NHL

Food group (servings per day)	Median servings per day in quartile	Controls (n = 467)	Cases (n = 597)	OR* (95% CI)
Dairy (milk, yogurt, soured milk, cheese, cottage cheese, ice cream, crème fraiche, cream, and pancakes)				
0.0-3.3	2.4	117	129	1.0
>3.3-4.9	4.1	115	119	0.9 (0.6-1.3)
>4.9-6.6	5.7	118	153	1.2 (0.8-1.7)
>6.6	8.5	117	196	1.5 (1.1-2.2)
				P_{trend} = 0.003
Red meat (pork, beef, sausage, sandwich meat, fried red meat, and grilled red meat)				
0.0-0.8	0.6	116	153	1.0
>0.8-1.1	1.0	117	114	0.8 (0.5-1.1)
>1.1-1.6	1.3	116	147	1.0 (0.7-1.4)
>1.6	2.0	118	183	1.2 (0.8-1.7)
				P_{trend} = 0.13
White meat (chicken/poultry, fried chicken, roasted chicken, and grilled chicken)				
0.0-0.1	0.1	116	194	1.0
>0.1-0.2	0.2	120	162	0.8 (0.6-1.2)
>0.2-0.4	0.3	113	112	0.6 (0.4-0.9)
>0.4	0.5	118	129	0.8 (0.5-1.1)
				P_{trend} = 0.08
Seafood (herring/mackerel, salmon/whitefish/char, cod/fishfingers, shellfish, fried fish, and grilled fish)				
0.0-0.3	0.2	115	128	1.0
>0.3-0.4	0.4	119	190	1.3 (0.9-1.9)
>0.4-0.6	0.5	117	146	1.0 (0.7-1.4)
>0.6	0.7	116	133	0.9 (0.6-1.3)
				P_{trend} = 0.21
Grains (crispbread, bread slices, oatmeal, porridge, cereal/muesli, pasta, pancakes, pizza, rice, wheat bran/oat bran, and flaxseed)				
0.0-3.9	2.9	116	153	1.0
>3.9-5.1	4.6	115	126	0.8 (0.6-1.2)
>5.1-6.7	5.8	119	143	0.9 (0.6-1.2)
>6.7	8.2	117	175	1.1 (0.7-1.5)
				P_{trend} = 0.63
Tea				
0.0	0.0	215	271	1.0
>0.0-0.1	0.1	32	33	1.0 (0.6-1.6)
>0.1-1.0	1.0	130	183	1.2 (0.9-1.6)
>1.0	2.0	90	110	1.0 (0.7-1.5)
				P_{trend} = 0.60
Coffee				
0.0-1.0	0.3	117	112	1.0
>1.0-2.9	2.0	97	129	1.3 (0.9-1.9)
>2.9-4.0	3.0	165	232	1.3 (0.9-1.8)
>4.0	5.0	88	124	1.4 (0.9-2.1)
				P_{trend} = 0.11
Juice or soda				
0.0	0.0	230	298	1.0
>0.0-0.6	0.3	115	142	1.1 (0.8-1.5)
>0.6	1.0	122	157	1.1 (0.8-1.6)
				P_{trend} = 0.40

*OR adjusted for age (5-year categories) and sex.

cytologist.[9] Information on anatomic location of the malignancy was not available.

Statistical Analyses. Intake of all food groups and items was converted to number of servings per day, then categorized a priori into quartiles based on the distribution in the control population. The lowest quartile of intake was the reference group for all comparisons. If the distribution of a food group or item was too limited or skewed to allow categorization into quartiles (as for tea, coffee, and juice/soda), the most balanced divisions of the distribution were used, with the lowest category as the reference group. Quartiles were not redefined separately for men and women in order to allow direct comparison of estimates between the sexes.

Unconditional logistic regression was done to estimate the odds ratios (OR) for NHL, and the corresponding 95% confidence intervals (95% CI), associated with average daily intake of food groups and items, adjusting for age (5-year categories) and sex. Other potential confounders were considered based on prior knowledge of risk factors for NHL, as well as change-in-estimate criteria (27) and likelihood ratio tests comparing models with and without adjustment for additional covariates. When considered as a possible confounder, alcohol intake was grouped according to grams of ethanol consumed per day (0.0-4.9, 5.0-9.9, 10.0-19.9, or ≥20.0). Smoking status was classified as never, former, or current.

Tests for linear trend were conducted using the median values for quartiles of food intake. Stratified analyses were done by sex and by NHL subtype, including diffuse large B-cell lymphoma, chronic lymphocytic leukemia, follicular lymphoma, and T-cell lymphoma (the four most common subtypes in the study population). Heterogeneity of estimates between males and females was evaluated using a likelihood ratio test for the significance of an interaction term between the exposure and sex. All statistical tests were two sided. Analyses were done with the SAS System software, release 8.2 (SAS Institute, Inc., Cary, NC, 1999-2001).

Results

The mean age of the 597 cases was 60 years (SD = 11 years), with a median of 62 years. Among the 467 controls, the mean age was 56 years (SD = 13 years), with a median of 59 years (P < 0.0001 for difference in means between cases and controls). The mean body mass index among cases was 25.5 kg/m^2 (SD = 3.8), with a median of 24.9 kg/m^2. The controls had the same mean body mass index as the cases (SD = 3.6) and a median of 24.8 kg/m^2 (P = 0.31). Cases did not differ from controls by smoking status (cases: 45% never, 40% former, 15% current; controls: 49% never, 35% former, 16% current; P = 0.31 for difference in proportions between cases and controls), alcohol drinking status (cases: 6% never, 5% former, 89% current; controls: 7% never, 4% former, 89% current; P = 0.92), or years of education (cases: 32%, ≤9 years; 44%, 10-12 years; 24%, ≥13 years and controls: 28%, ≤9 years; 46%, 10-12 years; 27%, ≥13 years; P = 0.29).

Dairy Products. Table 1 presents the associations between intake of major food groups and risk of NHL. Higher intake of dairy products was significantly associated with increased risk of NHL, adjusted for age and sex. Additional adjustment for other variables, including smoking status, body mass index, height, alcohol intake, education level, history of rheumatoid arthritis, history of blood transfusion, history of skin cancer, and occupational exposure to pesticides, had minimal effect on this and all other associations (<5% change in the estimated OR for virtually all comparisons). The association between dairy product consumption did not vary between men and women. For men, the ORs and 95% CIs copmparing the second, third, and fourth quartiles to the first were 1.1 (95% CI, 0.7-1.8), 1.2 (95% CI, 0.8-1.9), and 1.5 (95% CI, 1.0-2.3), respectively. For women, the corresponding ORs and 95% CIs were 0.7 (95% CI, 0.4-1.2), 1.1 (95% CI, 0.6-1.9), and 1.6 (95% CI, 0.9-2.9), respectively (P = 0.39 for test of heterogeneity by sex).

When subtypes of NHL were examined separately, increased consumption of dairy products was positively

[9] K. Ekström Smedby, H. Hjalgrim, M. Melby, et al. Ultraviolet light exposure and risk of malignant lymphomas. J Natl Cancer Inst 2005;97:In Press.

Table 2. Frequencies of prepared meat intake and ORs and 95% CIs for associations between prepared meat intake and risk of NHL

Food group (servings per day)	Median servings per day in quartile	Controls (n = 467)	Cases (n = 597)	OR* (95% CI)
Fried meat (fried beef, pork, sausage, chicken, and fish)				
0.0-0.2	0.1	139	154	1.0
>0.2-0.3	0.3	106	129	1.1 (0.8-1.6)
>0.3-0.5	0.4	95	112	1.1 (0.8-1.6)
>0.5	0.7	127	202	1.5 (1.0-2.0)
				P_{trend} = 0.02
Fried red meat (fried beef, pork, and sausage)				
0.0-0.07	0.0	115	121	1.0
>0.07-0.1	0.1	104	118	1.1 (0.7-1.5)
>0.1-0.3	0.2	107	142	1.3 (0.9-1.8)
>0.3	0.4	141	216	1.5 (1.0-2.1)
				P_{trend} = 0.02
Well-fried meat (fried beef, pork, sausage, chicken, and fish; degree of frying: well or very well done)				
0.0-0.2	0.0	10	9	1.0
>0.2-0.3	0.3	14	11	1.1 (0.3-4.1)
>0.3-0.7	0.5	10	15	2.2 (0.6-9.1)
>0.7	0.9	10	10	1.4 (0.3-5.6)
				P_{trend} = 0.52
Grilled meat (grilled beef, pork, sausage, chicken, and fish)				
0.0-0.02	0.01	112	182	1.0
>0.02-0.04	0.03	127	143	0.8 (0.5-1.1)
>0.04-0.08	0.05	104	140	0.9 (0.7-1.3)
>0.08	0.11	124	132	0.8 (0.5-1.1)
				P_{trend} = 0.23
Grilled red meat (grilled beef, pork, and sausage)				
0.0-0.01	0.00	117	180	1.0
>0.01-0.02	0.01	95	153	1.1 (0.8-1.6)
>0.02-0.04	0.03	133	127	0.7 (0.5-1.0)
>0.04	0.05	122	137	0.8 (0.6-1.2)
				P_{trend} = 0.21
Well-grilled meat (grilled beef, pork, sausage, chicken, and fish; degree of grilling: well or very well done)				
>0.0-0.03	0.02	9	11	1.0
>0.03-0.07	0.04	18	31	1.5 (0.5-5.0)
>0.07-0.1	0.09	11	11	1.0 (0.3-4.1)
>0.1	0.17	14	10	0.5 (0.1-2.1)
				P_{trend} = 0.08
Degree of frying meat				
Light/none	—	56	58	1.0
Moderate	—	363	489	1.3 (0.9-1.9)
Well done	—	40	43	1.1 (0.6-2.0)
Very well done	—	4	2	0.4 (0.1-2.3)
				P_{trend} = 1.00
Degree of grilling meat				
Light/none	—	22	13	1.0
Moderate	—	371	465	2.0 (1.0-4.0)
Well done	—	47	62	2.2 (1.0-4.9)
Very well done	—	5	1	0.3 (0.03-2.5)
				P_{trend} = 0.57

*OR adjusted for age (5-year categories) and sex.

associated with risk of diffuse large B-cell lymphoma (Table 3). There was also a marginally positive association between dairy product intake and risk of chronic lymphocytic leukemia, but no other histopathologic subtype of NHL.

Individual dairy products that were positively associated with NHL risk included milk (OR for highest versus lowest quartile of intake, 1.6; 95% CI, 1.1-2.5; P_{trend} = 0.002) and cheese (OR, 1.4; 95% CI, 1.0-2.0; P_{trend} = 0.05). Eggs, which were not included among the dairy products, were not associated with NHL risk (OR, 0.8; 95% CI, 0.3-2.0) nor with any NHL subtype.

Table 3. ORs and 95% CIs for associations between food intake and risk of NHL histopathologic subtypes

Food group (servings per day)	Diffuse large B-cell lymphoma (n = 128 cases), OR* (95% CI)	Chronic lymphocytic leukemia (n = 147), OR* (95% CI)	Follicular lymphoma cases (n = 105 cases), OR* (95% CI)	T-cell lymphoma (n = 40 cases), OR* (95% CI)
Dairy products				
0.0-3.3	1.0	1.0	1.0	1.0
>3.3-4.9	0.8 (0.4-1.6)	1.1 (0.6-1.9)	0.9 (0.5-1.7)	0.5 (0.2-1.7)
>4.9-6.6	1.2 (0.7-2.2)	1.1 (0.7-2.0)	0.9 (0.5-1.7)	1.2 (0.5-2.9)
>6.6	2.0 (1.2-3.5)	1.5 (0.9-2.6)	1.2 (0.6-2.2)	1.2 (0.5-2.9)
P_{trend}	0.002	0.11	0.50	0.48
Red meat				
0.0-0.8	1.0	1.0	1.0	1.0
>0.8-1.1	0.6 (0.4-1.2)	1.5 (0.9-2.7)	0.6 (0.3-1.3)	0.4 (0.1-1.1)
>1.1-1.6	0.8 (0.5-1.5)	1.3 (0.8-2.3)	1.3 (0.7-2.4)	0.4 (0.1-1.2)
>1.6	1.1 (0.6-1.9)	1.1 (0.6-2.0)	1.3 (0.7-2.4)	1.2 (0.5-2.7)
P_{trend}	0.50	0.87	0.17	0.37
Fried meat				
0.0-0.2	1.0	1.0	1.0	1.0
>0.2-0.3	0.7 (0.4-1.4)	1.3 (0.8-2.2)	1.0 (0.5-1.9)	1.3 (0.5-3.6)
>0.3-0.5	1.5 (0.9-2.6)	1.1 (0.6-2.0)	0.7 (0.3-1.4)	0.8 (0.2-2.5)
>0.5	1.4 (0.8-2.4)	1.3 (0.8-2.2)	1.5 (0.9-2.7)	2.3 (1.0-5.7)
P_{trend}	0.11	0.42	0.10	0.04
Fried red meat				
0.0-0.07	1.0	1.0	1.0	1.0
>0.07-0.1	0.8 (0.4-1.5)	1.2 (0.6-2.1)	1.3 (0.6-2.6)	0.9 (0.3-2.8)
>0.1-0.3	1.3 (0.7-2.3)	1.4 (0.8-2.5)	1.6 (0.8-3.2)	0.9 (0.3-2.5)
>0.3	1.6 (1.0-2.8)	1.3 (0.8-2.3)	1.7 (0.9-3.3)	1.6 (0.6-4.0)
P_{trend}	0.02	0.33	0.10	0.21
Grilled meat				
0.0-0.02	1.0	1.0	1.0	1.0
>0.02-0.04	0.7 (0.4-1.2)	0.9 (0.5-1.5)	1.0 (0.6-1.8)	1.5 (0.4-5.3)
>0.04-0.08	1.2 (0.7-2.1)	0.9 (0.5-1.5)	0.8 (0.4-1.6)	2.9 (0.9-9.7)
>0.08	0.6 (0.3-1.0)	0.8 (0.5-1.4)	0.8 (0.4-1.6)	3.1 (1.0-10.1)
P_{trend}	0.13	0.55	0.49	0.04
Grilled red meat				
0.0-0.01	1.0	1.0	1.0	1.0
>0.01-0.02	0.9 (0.5-1.5)	1.5 (0.9-2.5)	0.9 (0.5-1.8)	6.8 (1.4-31.6)
>0.02-0.04	0.5 (0.3-0.8)	0.9 (0.5-1.5)	0.9 (0.5-1.7)	4.7 (1.0-22.1)
>0.04	0.6 (0.3-1.1)	0.9 (0.5-1.6)	0.9 (0.5-1.7)	5.1 (1.1-24.3)
P_{trend}	0.06	0.30	0.75	0.25
Grains				
0.0-3.9	1.0	1.0	1.0	1.0
>3.9-5.1	0.8 (0.4-1.4)	1.1 (0.6-2.0)	0.6 (0.3-1.1)	0.8 (0.3-2.2)
>5.1-6.7	0.8 (0.4-1.3)	1.1 (0.6-1.9)	1.0 (0.5-1.7)	0.7 (0.3-2.0)
>6.7	0.8 (0.5-1.4)	0.9 (0.5-1.6)	0.9 (0.5-1.7)	1.6 (0.7-3.9)
P_{trend}	0.53	0.65	0.86	0.23
Tea				
0.0	1.0	1.0	1.0	1.0
>0.0-0.1	0.6 (0.2-1.6)	0.9 (0.3-2.2)	0.8 (0.3-2.3)	1.1 (0.3-4.3)
>0.1-1.0	0.7 (0.5-1.2)	1.2 (0.8-1.9)	1.4 (0.9-2.4)	2.0 (0.9-4.3)
>1.0	0.8 (0.5-1.4)	1.1 (0.7-1.9)	1.0 (0.5-1.8)	1.0 (0.4-2.9)
P_{trend}	0.48	0.47	0.69	0.57
Coffee				
0.0-1.0	1.0	1.0	1.0	1.0
>1.0-2.9	1.6 (0.8-3.2)	1.5 (0.8-2.8)	0.9 (0.4-1.8)	0.6 (0.2-1.9)
>2.9-4.0	1.6 (0.9-2.9)	1.5 (0.9-2.5)	1.0 (0.6-1.9)	0.8 (0.3-2.0)
>4.0	1.9 (1.0-3.6)	1.1 (0.6-2.2)	1.0 (0.5-2.1)	0.9 (0.3-2.5)
P_{trend}	0.09	0.66	0.84	0.91
Juice or soda				
0.0	1.0	1.0	1.0	1.0
>0.0-0.6	1.5 (0.9-2.4)	1.1 (0.7-1.8)	0.9 (0.5-1.6)	0.6 (0.3-1.5)
>0.6	1.2 (0.7-2.1)	0.9 (0.5-1.5)	1.4 (0.8-2.4)	0.6 (0.3-1.5)
P_{trend}	0.47	0.66	0.17	0.33

*OR adjusted for age (5-year categories) and sex, comparing cases with 467 controls.

Table 4. Frequencies of fruit and vegetable intake and ORs and 95% CIs for associations between fruit and vegetable intake and risk of NHL, stratified by sex

Food group (servings per day)	Median servings per day in quartile	Males			Females			P for test of heterogeneity
		Controls (n = 271)	Cases (n = 356)	OR* (95% CI)	Controls (n = 196)	Cases (n = 241)	OR* (95% CI)	
Fruit (oranges/citrus fruit, orange/grapefruit juice, apples/pears, bananas, berries, other fruit, jam, fruit sauce, and fruit soup)								
0.0-1.2	0.9	92	105	1.0	26	41	1.0	
>1.2-2.0	1.6	81	98	1.0 (0.7-1.6)	34	58	1.0 (0.5-1.9)	
>2.0-3.0	2.4	51	88	1.4 (0.9-2.3)	66	63	0.5 (0.3-1.0)	
>3.0	4.0	47	65	1.0 (0.6-1.7)	70	79	0.6 (0.3-1.1)	0.01
				P_{trend} = 0.65			P_{trend} = 0.08	
Citrus fruit (oranges/citrus fruit, orange/grapefruit juice)								
0.0-0.1	0.1	97	101	1.0	38	58	1.0	
>0.1-0.3	0.3	48	65	1.3 (0.8-2.2)	30	38	0.7 (0.4-1.4)	
>0.3-0.9	0.6	72	93	1.3 (0.8-2.0)	66	68	0.6 (0.4-1.1)	
>0.9	1.2	54	97	1.7 (1.1-2.7)	62	77	0.7 (0.4-1.3)	0.05
				P_{trend} = 0.02			P_{trend} = 0.44	
Vegetables (carrots, beets, lettuce, cabbage, cauliflower, broccoli/brussels sprouts, tomatoes, peppers, spinach, green peas, onions, garlic, mixed vegetables, pea soup, soy products, and ketchup)								
0.0-1.9	1.4	85	119	1.0	32	60	1.0	
>1.9-2.9	2.4	79	94	0.9 (0.6-1.3)	38	75	1.1 (0.6-2.0)	
>2.9-4.0	3.4	63	79	0.9 (0.6-1.4)	53	40	0.4 (0.2-0.8)	
>4.0	5.0	44	64	1.0 (0.6-1.6)	73	66	0.5 (0.3-0.8)	0.01
				P_{trend} = 0.97			P_{trend} = 0.0007	
Fruits and vegetables (all of above)								
0.0-3.5	2.7	93	120	1.0	23	44	1.0	
>3.5-5.1	4.3	80	94	0.9 (0.6-1.3)	37	72	0.9 (0.5-1.8)	
>5.1-7.0	5.9	55	84	1.1 (0.7-1.8)	62	58	0.5 (0.2-0.9)	
>7.0	8.6	43	58	0.9 (0.6-1.5)	74	67	0.4 (0.2-0.8)	0.008
				P_{trend} = 1.00			P_{trend} = 0.001	
Cruciferous vegetables (cabbage, broccoli/brussels sprouts)								
0.0-0.1	0.1	96	120	1.0	40	72	1.0	
>0.1-0.2	0.2	71	95	1.0 (0.7-1.6)	41	56	0.8 (0.4-1.3)	
>0.2-0.5	0.4	54	84	1.2 (0.8-1.9)	55	62	0.6 (0.4-1.1)	
>0.5	0.8	50	57	0.9 (0.6-1.5)	60	51	0.5 (0.3-0.8)	0.17
				P_{trend} = 0.78			P_{trend} = 0.009	
Green leafy vegetables (lettuce and spinach)								
0.0-0.1	0.1	76	115	1.0	40	55	1.0	
>0.1-0.3	0.3	94	98	0.7 (0.5-1.1)	43	73	1.4 (0.8-2.4)	
>0.3-0.6	0.6	52	75	1.0 (0.6-1.6)	45	52	0.8 (0.5-1.5)	
>0.6	0.9	49	68	0.8 (0.5-1.3)	68	61	0.6 (0.4-1.1)	0.04
				P_{trend} = 0.82			P_{trend} = 0.02	
Green vegetables (lettuce, cabbage, cauliflower, broccoli/brussels sprouts, spinach, peas, and mixed vegetables)								
0.0-0.7	0.4	88	126	1.0	28	57	1.0	
>0.7-1.1	0.9	66	83	0.8 (0.5-1.3)	48	71	0.7 (0.4-1.3)	
>1.1-1.6	1.3	68	77	0.8 (0.5-1.2)	52	50	0.5 (0.3-0.9)	
>1.6	2.1	49	70	0.9 (0.6-1.5)	68	63	0.4 (0.2-0.8)	0.16
				P_{trend} = 0.66			P_{trend} = 0.004	
Red/orange vegetables (carrots, beets, tomatoes, and ketchup)								
0.0-0.6	0.4	94	122	1.0	34	69	1.0	
>0.6-0.9	0.7	55	59	0.8 (0.5-1.3)	41	43	0.5 (0.3-0.9)	
>0.9-1.2	1.0	73	83	0.9 (0.6-1.4)	54	58	0.5 (0.3-0.9)	
>1.2	1.6	49	92	1.3 (0.9-2.1)	67	71	0.5 (0.3-0.8)	0.04
				P_{trend} = 0.19			P_{trend} = 0.03	

*OR adjusted for age (5-year categories).

Meat. Although red meat, white meat, and seafood intake were not associated with NHL risk (Table 1), there was a positive association between increased consumption of fried meat, particularly fried red meat, and risk of NHL (Table 2). However, there was no association between degree of frying meat and risk of NHL, and only the suggestion of a positive association with degree of grilling meat. There was no consistent association between consumption of grilled meat and NHL risk. None of the above associations varied between men and women (data not shown).

After stratifying by NHL subtype, we found that increased intake of fried red meat was positively associated with increased risk of diffuse large B-cell lymphoma, and marginally so with risk of follicular lymphoma, with similar ORs between the two histopathologic subtypes (Table 3). Fried meat in general was also somewhat positively associated with these two NHL subtypes, as well as T-cell lymphoma. In addition, consumption of grilled meat, especially grilled red meat, was positively associated with risk of T-cell lymphoma.

No individual type of meat was associated with risk of NHL. Consumption of fried chicken was not significantly associated with elevated NHL risk (OR comparing the highest to lowest quartile of intake, 0.8; 95% CI, 0.6-1.1; P_{trend} = 0.21), nor was consumption of fried fish (OR, 1.3; 95% CI, 0.9-1.9; P_{trend} = 0.18). Types of fried red meat (beef, pork, and sausage) were not assessed separately.

Grains and Pasta. There was no apparent association between consumption of grains and NHL risk, either overall, by sex, or by histopathologic subtype (Tables 1 and 3). No individual grain product was positively or negatively associated with NHL risk.

Beverages. Whereas tea consumption did not vary between cases and controls, coffee consumption was marginally positively associated with NHL risk (Table 1). There was no heterogeneity of the associations with tea or coffee by sex (data not shown). Among specific NHL subtypes, coffee intake was associated with increased risk of diffuse large B-cell lymphoma, comparing the highest to the lowest quartile of intake (Table 3).

There was no association between intake of juice or soda and NHL risk, either overall, by sex, or by NHL subtype.

Table 5. Frequencies of fruit and vegetable intake and ORs and 95% CIs for associations between fruit and vegetable intake and risk of NHL histopathologic subtypes, stratified by sex

Food group (servings per day)	Diffuse large B-cell lymphoma			Chronic lymphocytic leukemia			Follicular lymphoma		
	Males (n = 80 cases), OR* (95% CI)	Females (n = 48 cases), OR* (95% CI)	P for test of heterogeneity by sex	Males (n = 91 cases), OR* (95% CI)	Females (n = 56 cases), OR* (95% CI)	P for test of heterogeneity by sex	Males (n = 48 cases), OR* (95% CI)	Females (n= 57 cases), OR* (95% CI)	P for test of heterogeneity by sex
Fruit									
0.0-1.2	1.0	1.0		1.0	1.0		1.0	1.0	
>1.2-2.0	1.1 (0.5-2.2)	0.7 (0.2-2.0)		1.2 (0.7-2.4)	1.1 (0.4-3.6)		0.9 (0.4-2.1)	0.8 (0.3-2.2)	
>2.0-3.0	2.5 (1.2-5.0)	0.5 (0.2-1.3)		0.9 (0.4-2.0)	0.9 (0.3-2.5)		1.5 (0.6-3.5)	0.3 (0.1-0.7)	
>3.0	1.7 (0.8-3.7)	0.4 (0.2-1.1)	0.02	1.2 (0.6-2.5)	1.2 (0.4-3.2)	0.99	0.5 (0.2-1.6)	0.4 (0.2-1.0)	0.03
P_{trend}	0.06	0.08		0.70	0.74		0.45	0.04	
Citrus fruit									
0.0-0.1	1.0	1.0		1.0	1.0		1.0	1.0	
>0.1-0.3	1.7 (0.8-3.6)	0.7 (0.3-2.0)		1.0 (0.4-2.1)	1.9 (0.6-6.6)		2.1 (0.8-5.4)	0.4 (0.1-1.1)	
>0.3-0.9	1.2 (0.6-2.4)	0.5 (0.2-1.2)		1.4 (0.7-2.7)	1.5 (0.5-4.7)		2.1 (0.9-4.9)	0.3 (0.1-0.7)	
>0.9	2.1 (1.1-4.3)	0.5 (0.2-1.2)	0.05	1.9 (1.0-3.6)	2.4 (0.8-7.3)	0.77	1.4 (0.5-3.7)	0.5 (0.2-1.1)	0.01
P_{trend}	0.05	0.12		0.04	0.14		0.54	0.35	
Vegetables									
0.0-1.9	1.0	1.0		1.0	1.0		1.0	1.0	
>1.9-2.9	0.8 (0.4-1.6)	1.0 (0.4-2.7)		1.2 (0.7-2.4)	1.7 (0.7-4.4)		0.6 (0.3-1.5)	1.0 (0.4-2.3)	
>2.9-4.0	0.7 (0.3-1.4)	0.5 (0.2-1.4)		1.2 (0.6-2.4)	0.6 (0.2-1.6)		0.9 (0.4-2.2)	0.4 (0.2-1.0)	
>4.0	1.0 (0.5-2.1)	0.4 (0.2-1.1)	0.28	1.1 (0.5-2.4)	0.9 (0.4-2.2)	0.31	1.2 (0.5-3.1)	0.3 (0.1-0.7)	0.02
P_{trend}	0.87	0.03		0.76	0.33		0.62	0.001	
Fruits and vegetables									
0.0-3.5	1.0	1.0		1.0	1.0		1.0	1.0	
>3.5-5.1	0.8 (0.4-1.6)	1.1 (0.4-3.0)		1.2 (0.6-2.2)	0.7 (0.2-2.0)		0.9 (0.4-2.1)	0.7 (0.3-1.9)	
>5.1-7.0	1.4 (0.7-2.7)	0.4 (0.1-1.2)		1.3 (0.6-2.6)	0.6 (0.2-1.6)		1.2 (0.5-2.8)	0.4 (0.2-1.1)	
>7.0	1.3 (0.6-2.8)	0.3 (0.1-0.9)	0.01	1.0 (0.5-2.1)	0.7 (0.3-1.7)	0.66	0.8 (0.3-2.4)	0.3 (0.1-0.7)	0.21
P_{trend}	0.27	0.006		0.92	0.55		0.85	0.002	
Cruciferous vegetables									
0.0-0.1	1.0	1.0		1.0	1.0		1.0	1.0	
>0.1-0.2	0.8 (0.4-1.5)	0.7 (0.3-1.8)		1.4 (0.7-2.8)	1.1 (0.4-2.8)		0.6 (0.3-1.4)	0.8 (0.3-1.8)	
>0.2-0.5	1.1 (0.6-2.3)	0.4 (0.1-1.0)		1.6 (0.8-3.2)	1.0 (0.4-2.5)		0.5 (0.2-1.3)	0.5 (0.2-1.1)	
>0.5	0.9 (0.4-1.9)	0.5 (0.2-1.2)	0.35	1.8 (0.9-3.6)	1.0 (0.4-2.4)	0.84	0.6 (0.2-1.6)	0.3 (0.1-0.7)	0.40
P_{trend}	0.95	0.17		0.15	0.87		0.34	0.008	
Green leafy vegetables									
0.0-0.1	1.0	1.0		1.0	1.0		1.0	1.0	
>0.1-0.3	0.7 (0.4-1.5)	1.6 (0.6-4.2)		0.8 (0.4-1.6)	1.5 (0.6-3.9)		0.6 (0.3-1.4)	1.5 (0.6-3.4)	
>0.3-0.6	1.4 (0.7-3.0)	0.9 (0.3-2.6)		1.1 (0.5-2.4)	1.4 (0.5-3.6)		0.7 (0.3-1.8)	0.7 (0.3-1.8)	
>0.6	1.3 (0.6-2.7)	0.8 (0.3-2.2)	0.07	1.3 (0.6-2.6)	1.1 (0.4-2.7)	0.55	0.7 (0.3-1.8)	0.4 (0.1-0.9)	0.13
P_{trend}	0.20	0.30		0.37	0.95		0.54	0.005	
Green vegetables									
0.0-0.7	1.0	1.0		1.0	1.0		1.0	1.0	
>0.7-1.1	0.7 (0.3-1.5)	0.6 (0.2-1.5)		0.8 (0.4-1.5)	1.3 (0.5-3.2)		0.8 (0.3-1.9)	0.7 (0.3-1.5)	
>1.1-1.6	1.0 (0.5-1.9)	0.5 (0.2-1.4)		0.9 (0.5-1.8)	0.5 (0.2-1.4)		0.6 (0.2-1.4)	0.3 (0.1-0.9)	
>1.6	1.0 (0.5-2.0)	0.5 (0.2-1.3)	0.67	1.2 (0.6-2.4)	0.8 (0.3-2.0)	0.27	1.2 (0.5-2.8)	0.3 (0.1-0.7)	0.07
P_{trend}	0.90	0.24		0.57	0.32		0.85	0.003	
Red/orange vegetables									
0.0-0.6	1.0	1.0		1.0	1.0		1.0	1.0	
>0.6-0.9	0.5 (0.2-1.1)	0.3 (0.1-1.0)		0.9 (0.4-1.8)	0.7 (0.3-1.8)		1.0 (0.4-2.5)	0.2 (0.1-0.6)	
>0.9-1.2	0.9 (0.5-1.7)	0.6 (0.3-1.5)		0.7 (0.4-1.5)	0.5 (0.2-1.3)		1.0 (0.5-2.3)	0.4 (0.2-0.8)	
>1.2	1.3 (0.7-2.6)	0.4 (0.2-0.9)	0.15	1.5 (0.8-2.9)	1.0 (0.4-2.3)	0.83	1.1 (0.4-2.8)	0.3 (0.1-0.6)	0.05
P_{trend}	0.27	0.10		0.25	0.74		0.84	0.02	

*OR adjusted for age (5-year categories), comparing male cases with 271 male controls and female cases with 196 female controls.

Table 6. ORs and 95% CIs for mutually adjusted associations between food intake and risk of NHL overall and by sex

Food group (servings per day)	Overall NHL, OR* (95% CI)	Males, OR† (95% CI)	Females, OR† (95% CI)	P for test of heterogeneity
Dairy products				
0.0-3.3	1.0	1.0	1.0	
>3.3-4.9	0.9 (0.6-1.3)	1.0 (0.6-1.7)	0.7 (0.4-1.4)	
>4.9-6.6	1.2 (0.8-1.7)	1.2 (0.7-1.9)	1.1 (0.6-2.0)	
>6.6	1.5 (1.1-2.2)	1.4 (0.9-2.2)	1.9 (1.1-3.6)	0.32
P_{trend}	0.005	0.12	0.007	
Fried red meat				
0.0-0.07	1.0	1.0	1.0	
>0.07-0.1	1.1 (0.7-1.5)	1.2 (0.7-2.0)	0.9 (0.5-1.7)	
>0.1-0.3	1.2 (0.8-1.7)	1.4 (0.8-2.4)	1.0 (0.6-1.7)	
>0.3	1.5 (1.0-2.1)	1.7 (1.0-2.7)	1.2 (0.7-2.2)	0.83
P_{trend}	0.02	0.02	0.01	
Vegetables				
0.0-1.9	1.0	1.0	1.0	
>1.9-2.9	0.9 (0.6-1.3)	0.8 (0.5-1.2)	1.1 (0.6-2.0)	
>2.9-4.0	0.7 (0.5-1.0)	0.8 (0.5-1.3)	0.5 (0.2-0.9)	
>4.0	0.7 (0.5-1.0)	0.9 (0.5-1.5)	0.5 (0.3-0.8)	0.01
P_{trend}	0.02	0.68	0.001	

*OR adjusted for age (5-year categories), comparing male cases with 271 male controls and female cases with 196 female controls.
†OR adjusted for age (5-year categories) and intake of dairy products, fried red meat, coffee, vegetables, and alcohol.

Fruits and Vegetables. Almost all of the associations between fruit and vegetable intake and risk of NHL differed between men and women; therefore, the results are presented separately by sex (Tables 4 and 5). Whereas fruit intake was not associated with NHL risk among men, it was marginally associated with lower NHL risk among women (P = 0.01 for test of heterogeneity by sex). Similarly, vegetable intake was significantly associated with lower NHL risk only among women (P = 0.01 for heterogeneity). Whereas consumption of fruits and vegetables combined, cruciferous vegetables, green leafy vegetables, green vegetables, and red or orange vegetables were all associated with lower risk of NHL among women, none were associated with NHL risk among men.

Inverse associations between fruit or vegetable consumption and risk of NHL were strongest among women with the follicular lymphoma subtype, as well as those with diffuse large B-cell lymphoma (Table 5). Compared with those in the lowest quartile of intake, risk of follicular lymphoma was significantly reduced for women in the highest quartile of intake of fruits, vegetables, fruits and vegetables, cruciferous vegetables, green leafy vegetables, green vegetables, and red or orange vegetables. Point estimates for associations with all categories of fruit or vegetable consumption were also well below 1.0 for women with diffuse large B-cell lymphoma, but not chronic lymphocytic leukemia. There was an insufficient number of women with T-cell lymphoma to examine risk associations by sex.

Significant heterogeneity between men and women existed for several associations with risk of diffuse large B-cell lymphoma and follicular lymphoma. In fact, there was a positive association between citrus fruit intake and risk of diffuse large B-cell lymphoma among men only (P = 0.05 for heterogeneity), although the positive association with risk of chronic lymphocytic leukemia did not vary significantly by sex (P = 0.77 for heterogeneity). Other significant heterogeneity by sex was detected where consumption of fruits or vegetables was inversely associated with lymphoma risk among women but not among men.

Almost all individual vegetables were associated with lower NHL risk among women. These included carrots, beetroots, lettuce, cabbage, cauliflower, peppers, spinach, green peas, garlic, mixed vegetables, and soy products (data not shown). Only green peas (OR, 0.6; 95% CI, 0.3-0.9; P_{trend} = 0.41), mixed vegetables (OR, 0.7; 95% CI, 0.4-1.0; P_{trend} = 0.07), and soy products (OR, 0.7; 95% CI, 0.5-1.0; P_{trend} = 0.03) were associated with decreased risk of NHL among men. Most individual fruits (i.e., oranges and other citrus fruits, apples or pears, bananas, berries, and other fruits) were associated with lower NHL risk among women, whereas no individual fruits were significantly associated with increased or decreased risk of NHL among men (data not shown).

Combined Food Groups. After adjusting simultaneously for intake of dairy products, fried red meat, coffee, and vegetables, as well as age, sex, and alcohol consumption, significant associations remained between overall NHL risk and dairy, fried red meat, and vegetable consumption (Table 6). The latter association varied by sex, being inverse only for women (P = 0.01 for heterogeneity).

Discussion

The positive association between intake of dairy products and NHL risk in our study is consistent with several previous studies (10, 12, 14, 15, 21), although others have detected no such association (16-18). A positive association between dairy consumption and risk of prostate cancer has been attributed to the effects of dietary calcium and phosphorus, largely found in dairy products, which decrease circulating levels of 1,25$(OH)_2$ vitamin D, a hormone believed to inhibit prostate carcinogenesis (28). Alternatively, dairy intake may increase NHL risk via the immune-suppressive properties of dietary fat (29). The effects of dairy products and their components on lymphoma development need to be clarified before we can plausibly explain the positive association detected in our study and others.

The increased risk of NHL among frequent consumers of fried red meat in our study is somewhat consistent with prior reports of a positive association between red meat intake and NHL development (11, 16-18, 21), although like others (12, 15), we found no association with intake of red or white meat overall, which contradicts some earlier findings. Consumption of cooked meat, especially fried, grilled, or broiled meat, may influence NHL development through the generation of immunotoxic heterocyclic amines (30), which can induce lymphomas in mice (31). However, we found no association between grilled meat consumption and risk of NHL, and other investigations have even found an inverse association between degree of meat cooking and NHL risk (17, 18). This latter result lends support to a counterbalancing hypothesis that undercooking may contribute to NHL risk through the presence of oncogenic viruses, parasites, or other contaminants in lightly cooked meat (17).

Intake of fruits and/or vegetables has been reported to be inversely associated (12, 17, 19, 21) or not associated (16) with NHL, although no other investigations have confined the inverse association to follicular and diffuse large B-cell lymphomas, as in our study. Fruits and vegetables are the primary dietary sources of antioxidants that may protect against cancer by preventing reactive oxygen species from damaging DNA (32). Fruits and vegetables may also have other beneficial effects on immune function, cell communication, cell growth and differentiation, procarcinogen metabolism, DNA methylation, and other biological processes involved in cancer development (33).

The inverse association between fruit and vegetable consumption among women but not men is not easy to explain by known biological differences between the sexes but is unlikely to be due to differential accuracy of reporting between men and women (25, 26). A previous study by Ward et al. (12) found that intake of some fruits and vegetables was inversely associated with NHL risk among men but not women. Some of the variation by sex may be due to the generally lower distribution of fruit and vegetable consumption by men relative to women, resulting in reduced statistical power to detect any association with NHL risk among men. The diminished power also increases the possibility that the results may be due to chance, either in our study, that of Ward et al. (12), or both. Similarly, the positive association between citrus fruit consumption and risk of diffuse large B-cell lymphoma among men and risk of chronic lymphocytic leukemia among men and possibly also women is difficult to explain. Given the large number of tests done in this study, several statistically significant associations would be expected due to chance alone. Without a plausible biological mechanism to explain a positive association between citrus fruit intake and risk of lymphoma, this finding could well be due to chance.

The marginally elevated risk of NHL, particularly diffuse large B-cell lymphoma, in association with increased consumption of coffee, accords with results of some (10, 16), but not all (12, 15, 20), previous studies. Consumption of hot methylxanthine-containing beverages, such as coffee, tea, and maté, may be associated with several aerodigestive tract malignancies (34), although data in association with NHL are inconsistent and lack a solid biological mechanism for lymphomagenesis (16).

Given that the associations between food intake and NHL risk seem to differ by histopathologic subtype, some of the discrepancies among previous results could be due to different proportions of these subtypes in the case populations. Because no other dietary study of NHL has grouped cases according to the current WHO classification scheme, we cannot quantify how different distributions of NHL subtype might explain dissimilar results. However, international surveys have found highly variable subtype distributions in different populations (with the exception of diffuse large B-cell lymphoma, which generally comprises over 30% of NHLs in most populations; ref. 35).

Other explanations for the disparate findings include differences in frequency and range of food intake, available varieties of foods, and methods of food preparation among study populations, as well as differences in study design among population-based case-control, hospital-based case-control, and cohort studies. For example, consumption of milk and fish is generally higher, and bread lower, in Sweden than in the United States (36, 37). In addition, important but unidentified modifiers of the associations between food and NHL risk, including environmental and genetic factors, could vary among populations.

Our study is one of the largest population-based case-control studies of dietary habits and NHL risk to date, uniquely enabling us to examine associations with specific histopathologic subtypes of NHL. Still, our study had several limitations. We lacked an adequate sample size to analyze risk associations with dietary intake for less common histopathologic subtypes of NHL, or to perform meaningful tests of heterogeneity of association among the subtypes. The study also had limited power to examine associations with uncommon food groups and items, such as liver and eggs, and power could also have been reduced due to misclassification of dietary exposures. Selection bias may have existed among both cases and controls, although participation rates were high for both groups. Like all retrospective studies, ours was subject to recall bias (i.e., differential recollection of diet between cases and controls). However, the heterogeneity of results by NHL subtype argues against systematic recall bias among the cases.

We asked participants to report their food consumption 2 years before the completing the questionnaire, to assess dietary exposures before disease onset among cases. Because dietary patterns tend to be reasonably well correlated from year to year (38), we implicitly assumed that reported habits were generally representative of adulthood behavior and did not ask about earlier patterns, which would have been more difficult to recall. However, diet at one point in time may not be representative of lifetime or even adulthood diet for many people, and we were unable to account for timing of food consumption, changes in dietary habits over time, or cumulative dietary intake.

Residual confounding due to imperfect assessment or categorization of dietary intake or due to nondietary risk factors cannot be ruled out. Although the food frequency questionnaire is not a perfect tool for measuring dietary habits, it is the most practical and well-validated method available for a large-scale study. Imprecision of measurement, resulting in exposure misclassification, would have unpredictable effects on the estimated associations. Confounding by other factors is unlikely to explain all of the observed findings because there do not seem to be any strong risk factors for NHL that are also associated with diet. Also, there was almost no change between the estimated ORs adjusted for age and sex alone and those adjusted for additional factors, although dietary exposures may have been somewhat misclassified due to categorization.

In summary, we found that higher intake of dairy products and fried meat, especially red meat, was associated with increased risk of some subtypes of NHL, whereas higher intake of fruits and vegetables was associated with decreased risk of NHL, particularly follicular lymphoma, among women. Two nationwide dietary surveys in Sweden (37, 39) showed that between 1989 and 1997 to 1998, consumption of meat and sausage (among other food items) rose among men and women, although both sexes also consumed more vegetables and less milk, yogurt, and cheese. Based on these findings, it is unclear whether changes in Swedish dietary patterns in the second half of the twentieth century are consistent with a major role for diet in the rising incidence of NHL in this country. Some studies of NHL incidence trends (40, 41) show that diffuse large B-cell lymphoma (the most common subtype, whose risk is most strongly associated with diet in our study) has been the most rapidly increasing histopathologic subtype. Therefore, it is feasible that the spread of the Western diet (high in dairy products and cooked and processed meat, low in fruits and vegetables) could account for a moderate proportion of the worldwide increase in incidence of NHL, and that dietary modifications could help prevent the occurrence of some of the more common subtypes of NHL.

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