Short Communication

Dietary Factors and Risk of Non-Hodgkin Lymphoma by Histologic Subtype: A Case-Control Analysis

Mark P. Purdue,[1,2] Diego G. Bassani,[1,4] Neil S. Klar,[1,2] Margaret Sloan,[1] Nancy Kreiger,[1,2,3] and The Canadian Cancer Registries Epidemiology Research Group

[1]Division of Preventive Oncology, Cancer Care Ontario, Toronto, Ontario, Canada; Departments of [2]Public Health Sciences and [3]Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; and [4]Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

Abstract

There is speculation that etiologic heterogeneity exists among tumors classified as non-Hodgkin lymphoma (NHL), although it is not known whether diet-related associations vary between tumor subgroups. We analyzed data on 1,642 NHL cases and 5,039 controls aged 20 to 74 years from a population-based case-control study conducted in eight Canadian provinces to explore associations between dietary factors and NHL by histologic subtype. Dietary information was collected using a 69-item food frequency questionnaire. Tumors were categorized into histologic subtypes using the contents of pathology reports from the original histopathologic review of diagnostic material. Odds ratios (OR) relating consumption of dietary factors (divided into three categories) to each NHL subtype (diffuse, follicular, small lymphocytic, high grade, peripheral T cell, and unspecified lymphomas) were calculated using polytomous logistic regression. We found an increased risk of NHL with high (versus low) intake of processed meat (OR, 1.49), cheese (OR, 1.38), eggs (OR, 1.49), and dessert foods (OR, 1.24). Positive associations with NHL were also found for high consumption of total fat (OR, 1.28), saturated fat (OR, 1.29), and monounsaturated fat (OR, 1.27). Associations for consumption of some vegetables and fats were found to differ between lymphoma subtypes. Given the large number of diet/subtype comparisons done, however, the possibility that this heterogeneity arose by chance cannot be ruled out. In conclusion, these findings generally do not support the existence of etiologic heterogeneity between histologic subtypes of NHL in their associations with components of dietary intake. (Cancer Epidemiol Biomarkers Prev 2004;13(10):1665–76)

Introduction

Non-Hodgkin lymphoma (NHL) is a classification for all lymphoid tumors that do not contain Reed-Sternberg cells (characteristic of Hodgkin's disease; ref. 1). The etiology of NHL is not well understood, although decreased immune function has consistently been found to be an important risk factor and is likely an important mechanism through which the effects of other risk factors are mediated (2-6). Other putative risk factors include infectious diseases (7-10), agricultural and pesticide exposures (11-14), nitrates in drinking water (15, 16), and alcohol consumption (17, 18).

There is limited evidence supporting some aspects of diet as risk factors for NHL. Experimental evidence from animal studies suggests that greater fat and protein intake can alter immune function and increase the risk of lymphomas (19-21). Nine epidemiologic studies have investigated the relationship between dietary factors and NHL (17, 22-29). Risk factors suggested from these studies include increased consumption of animal protein, milk, liver, meat, and fat and decreased consumption of fruits, vegetables, and whole grain foods. However, there is considerable inconsistency across the studies in the findings for these dietary components.

Tumors classified as NHL represent several distinct morphologic and histologic entities with different prognoses and responses to treatment; it has been speculated that disease etiology may also vary between these tumors (30, 31). Analyses of incident NHL tumors recorded in the Surveillance, Epidemiology and End Results registry suggest that NHL subtypes have distinct sex, age,

Received 12/11/03; revised 3/29/04; accepted 5/4/04.

Grant support: Canadian Program of Research in Environmental Etiology of Cancer predoctoral training award (M.P. Purdue).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: The Canadian Cancer Registries Epidemiology Research Group comprises a principal investigator from each of the Provincial Cancer Registries: Bertha Paulse, M.Sc., B.N., Newfoundland Cancer Foundation; Ron Dewar, M.Sc., Nova Scotia Cancer Registry; Dagny Dryer, M.D., Prince Edward Island Cancer Registry; Nancy Kreiger, Ph.D., Cancer Care Ontario; Erich Kliewer, Ph.D., CancerCare Manitoba; Diane Robson, B.A., Saskatchewan Cancer Foundation; Shirley Fincham, Ph.D., Division of Epidemiology, Prevention and Screening, Alberta Cancer Board; and Nhu Le, Ph.D., British Columbia Cancer Agency. The group also includes Drs. Yang Mao and Kenneth Johnson from the Environmental Risk Assessment and Case Surveillance Division, Cancer Bureau, Center for Chronic Disease Prevention and Control, Health Canada.

Requests for reprints: Mark P. Purdue, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 8121, MSC 7240, Bethesda, MD 20892-7240. Phone: 301-451-5036; Fax: 301-402-1819. E-mail: purduem@mail.nih.gov

race, geographic, and temporal patterns (32, 33). However, eight of the nine studies that investigated diet and NHL did not conduct subtype-specific analysis, probably due to insufficient power.

The National Enhanced Cancer Surveillance System (NECSS) of Canada is one of the largest studies of NHL conducted to date, with information on past diet and other exposures from 1,642 affected individuals (34). We examined these data to explore the associations between dietary factors and NHL by histologic subtype as defined using the Working Formulation (WF) classification system (35).

Materials and Methods

Selection of Cases and Controls. The NECSS was conducted in a collaborative effort between Health Canada and the Provincial Cancer Registries to increase understanding about the environmental causes of cancer. As part of the NECSS, a population-based case-control study of 18 different cancer types was carried out. Individuals diagnosed with histologically confirmed NHL [*International Classification of Diseases for Oncology* (ICDO), Second Edition (Morphology Code) 9590-9595, 9670-9723; *International Classification of Diseases*, Ninth Edition 162, 2002, 202; refs. 36, 37] in one of the eight provinces (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan) between January 1994 and August 1997 (January 1995-August 1997 for Ontario) and aged 20 to 74 years were eligible for the case series. Cases of chronic lymphocytic leukemia were not included in the study. No information on HIV status was collected. Eligible cases (n = 2,648) were identified from pathology reports collected by provincial cancer registries. Physicians denied permission to contact 7% of cases, and an additional 10% of cases died before they could be contacted. We received completed questionnaires from 1,642 subjects (76% of women and 75% of men who were sent questionnaires; 62% of all cases ascertained). Proxy interviews were excluded from this analysis.

Frequency matching was used in the selection of population controls to achieve a similar age and sex distribution to that of all cancer cases. Control selection varied by province, with provincial health insurance records used as a sampling frame for most provinces and with property assessment files (Ontario) or random digit dialing (Alberta and Newfoundland) used in others. In Alberta, a random sample of provincial telephone numbers, including unlisted numbers, was generated. Each randomly selected telephone number was called up to eight times on a pattern structured around call attempts during the day, evenings, and on Saturday. Of the numbers called, 4% were not in service or were businesses, there was a communication barrier in 4%, and no one could be reached for 11%. Of those households contacted, 91% agreed to a census of residents, and 90% of eligible individuals agreed to be sent a questionnaire. In Newfoundland, a random sample of listed and unlisted telephone numbers was also obtained. Exact contact and eligibility rates are unavailable from this province; study personnel estimated that 85% of telephone numbers were reached.

In total, questionnaires were mailed to 8,060 individuals selected as potential controls in the eight provinces. For 7% of individuals, the mailed questionnaire was returned because of a wrong or old address, and no updated address could be found through publicly available sources. In total, 5,039 controls completed and returned the questionnaire (70% of women and 65% of men; 63% of all ascertained controls).

Data Collection. Mailed questionnaires were used to collect information from subjects on suspected risk factors for cancer, with telephone follow-up for clarification of the answers as needed. Information on dietary habits 2 years before interview was collected using a 69-item food frequency questionnaire. Subjects were asked to indicate the frequency with which they consumed a specified portion size of each food; the nine possible answers ranged from <1 serving per month to ≥6 servings per day. The dietary questionnaire was adapted from two previously validated instruments: the reduced Block questionnaire (38) and the questionnaire used in the Nurses' Health Study (39). The NCESS questionnaire is less comprehensive than these other instruments, because the study focused quite broadly on environmental causes of cancer rather than focusing specifically on nutrition.

The questionnaire also collected information on subjects' residential and occupational histories and on other possible risk factors, including education, income, ethnicity, height, weight, physical activity, smoking, and exposure to specific occupational carcinogens.

Data Analysis. The topographical and morphologic characteristics of all tumors were classified according to the ICDO-2 (36) based on the contents of pathology reports associated with the original histopathologic review of diagnostic material. Ontario cases had been classified according to the ICDO-1 system; these cases were recoded to ICDO-2 using the IARCtools software application (40). The ICDO-2 coding for Ontario cases was confirmed by a re-review of pathology reports. All tumors were grouped by histologic subtype based on ICDO-2 coding using the method developed by Groves et al. (33). This method, modeled after the WF classification system (35), categorizes tumors into six morphologic categories: small lymphocytic, follicular, diffuse, high grade, peripheral T cell, and not otherwise specified.

Information from the food frequency questionnaire was summarized into several foods or food groups: milk, cheese, fruit, vegetables, potatoes, legumes/nuts, breads/cereals, meat, fish, eggs, and sweets (Appendix 1). Subgroups were also defined as follows: yellow/orange, cruciferous, leafy, or other vegetable; whole grain, or nonwhole grain bread/cereal; and poultry, nonprocessed beef/pork/lamb, or processed beef/pork/lamb. Estimates of total weekly intake of animal protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and total energy were calculated from nutrient estimates assigned to each dietary item using Canadian nutrient data (41). All dietary variables were categorized with tertile cut points based on the distribution in the controls.

Data analysis was done using Stata (42). The associations between food groups and NHL risk were estimated using odds ratios (OR) and 95% confidence intervals (95% CI) calculated from maximum likelihood

estimates using binary logistic regression. OR and 95% CI relating dietary components and histologic subgroups of NHL were calculated using polytomous logistic regression. Likelihood ratio tests assessing the presence of OR heterogeneity across disease subgroups compared the likelihoods of unconstrained polytomous models against those of models constrained to have identical ORs across disease subgroups.

ORs were estimated in two ways: adjusting for age and sex only and adjusting for age, sex, total energy intake, and suspected confounding factors. For analysis of food groups, energy intake was modeled as a continuous variable. Analyses of macronutrient intake employed the multivariate nutrient density method to adjust for energy intake (43). Nondietary variables (education, income adequacy, body mass index, smoking, alcohol consumption, and exposure to herbicides/pesticides) were considered to be confounders if their inclusion resulted in ≥10% change in the magnitude of ORs relating dietary variables to all NHL. Based on this criterion, only income adequacy (an index of household income adjusted for household size) and alcohol consumption were identified as confounders. In addition to estimating ORs for dietary variables individually, a single multivariable model was fit adjusting for intake of different food groups, total protein and total fat simultaneously, in addition to age, sex, income adequacy, energy intake (modeled using the multivariate nutrient density method), and alcohol consumption.

Results

Data from 1,642 NHL cases and 5,039 controls were available for analysis. Diffuse lymphomas were the most common histologic subtype identified among cases (n = 536, 33% of all cases) followed by follicular (n = 442, 27%), not otherwise specified (n = 341, 21%), small lymphocytic (n = 174, 11%), high grade (n = 80, 5%), and peripheral T cell (n = 69, 4%) subtypes. Overall, NHL cases were slightly more likely to be male, with a male/female ratio of 1.2:1, although the ratio varied across subtypes (Table 1). High-grade lymphomas had the highest ratio of males to females (1.6:1); in contrast, a slight majority of follicular lymphoma cases were female (0.9:1). Clear differences in the age distribution of subtypes were apparent. Small lymphocytic lymphomas were generally diagnosed at an older age than other subtypes, with only 6% of these cases aged <40 years and 61% aged ≥60 years. High-grade and peripheral T-cell lymphomas were comparatively more common among young subjects (20% and 19% aged <40 years, respectively); at least half of the cases from these subtypes, along with those of follicular lymphomas, were aged <60 years at diagnosis. No clear differences across subtypes in the distributions of income adequacy and alcohol consumption were apparent.

ORs describing the association between individual dietary components and risk of any type of NHL are summarized in Table 2; all reported associations are relative to the lowest level of intake. Overall measures of fruit and vegetable consumption were not found to be associated with NHL risk. When vegetables were categorized by type, no association with NHL risk was found for intake of yellow/orange, cruciferous, or leafy vegetables. However, a weak positive association with NHL risk was observed for high consumption of ''other'' vegetables (OR, 1.22; 95% CI, 1.02-1.45). Consumption of potatoes, legumes and nuts, and breads and cereals were not associated with NHL. A weak association was found for high consumption of dessert foods (OR, 1.24; 95% CI, 1.04-1.49).

Risk estimates for animal products are summarized in Table 3. High total meat consumption was found to

Table 1. Percentage distribution of NHL cases and controls by sex, age, income adequacy, and alcohol consumption

Characteristics	Controls (n = 5,039)	NHL (n = 1,642)	NHL histologic subtype						
			Small lymphocytic (n = 174)	Follicular (n = 442)	Diffuse (n = 536)	High grade (n = 80)	Peripheral T cell (n = 69)	Not otherwise specified (n = 341)	P*
Sex									
Male	50.6	52.7	56.3	46.8	54.3	61.3	53.6	53.7	0.07
Female	49.5	47.3	43.7	53.2	45.7	38.8	46.3	46.3	
Age (y)									
20-39	13.6	11.3	5.7	12.9	11.2	20.0	19.1	8.5	<0.001
40-59	34.0	38.3	33.3	47.9	33.4	30.0	39.7	37.5	
60-74	52.4	50.5	61.0	39.1	55.4	50.0	41.2	53.9	
Income adequacy†									
Low income	22.1	23.1	23.1	19.3	28.5	21.1	27.1	20.3	0.34
Low middle income	23.0	18.8	20.8	20.5	16.9	15.8	16.7	19.2	
Upper middle income	33.5	31.3	30.8	29.3	32.3	33.3	31.3	32.2	
High income	21.4	26.8	25.4	31.0	22.3	29.8	25.0	28.4	
Alcohol consumption (servings/wk)									
0	22.1	23.2	23.1	19.3	28.5	21.1	27.1	20.3	0.05
0.01-1.47	23.0	18.7	20.8	20.5	16.9	15.8	16.7	19.2	
1.48-7.00	33.6	31.3	30.8	29.3	32.3	33.3	31.3	32.2	
>7.00	21.4	26.8	25.4	31.0	22.3	29.8	25.0	28.4	

*Correspond to Pearson χ^2 test of independence across NHL subtypes.
†An index of household income adjusted for household size.

Table 2. ORs and 95% CIs relating NHL risk and intake of selected dietary factors

Dietary item (servings/wk)	Cases [*n* (%)]	Controls [*n* (%)]	OR_1* (95% CI)	OR_2† (95% CI)
Fruit				
0-6.47	489 (32.2)	1,573 (33.9)	1.00	1.00
6.48-12.94	507 (33.3)	1,487 (32.1)	1.10 (0.96-1.28)	1.06 (0.89-1.27)
>12.94	525 (34.5)	1,577 (34.0)	1.09 (0.94-1.25)	1.06 (0.89-1.27)
Total vegetables				
0-7.47	490 (32.0)	1,458 (31.0)	1.00	1.00
7.48-13.47	530 (34.6)	1,559 (33.2)	1.01 (0.88-1.17)	1.04 (0.88-1.23)
>13.47	512 (33.4)	1,680 (35.8)	0.92 (0.79-1.06)	0.93 (0.78-1.12)
Yellow/orange vegetables				
0-3	534 (33.4)	1,642 (33.6)	1.00	1.00
3.1-6	720 (45.1)	1,989 (40.8)	1.11 (0.98-1.27)	1.14 (0.96-1.36)
>6	343 (21.5)	1,250 (25.6)	0.85 (0.73-0.99)	0.91 (0.76-1.08)
Cruciferous vegetables				
0-1	576 (36.2)	1,806 (37.2)	1.00	1.00
1.1-3	489 (30.8)	1,444 (29.7)	1.11 (0.95-1.29)	1.13 (0.94-1.36)
>3	525 (33.0)	1,611 (33.1)	1.04 (0.88-1.22)	0.95 (0.78-1.17)
Leafy vegetables				
0-0.4	461 (28.9)	1,448 (29.7)	1.00	1.00
0.5-1	733 (46.0)	2,224 (45.7)	1.05 (0.91-1.20)	0.85 (0.71-1.03)
>1	400 (25.1)	1,200 (24.6)	1.06 (0.91-1.24)	1.01 (0.86-1.18)
Other vegetables				
0-1	262 (16.3)	928 (18.7)	1.00	1.00
1.1-3	420 (26.1)	1,292 (26.1)	1.16 (0.97-1.38)	1.14 (0.96-1.35)
>3	929 (57.7)	2,735 (55.2)	1.22 (1.03-1.41)	1.22 (1.02-1.45)
Potatoes				
0-2.9	292 (17.8)	1,184 (23.5)	1.00	1.00
3-5.4	527 (32.1)	2,140 (42.5)	1.06 (0.90-1.24)	1.05 (0.86-1.28)
≥5.5	823 (50.1)	1,715 (34.0)	1.14 (0.98-1.33)	1.12 (0.92-1.36)
Legumes and nuts				
0-0.9	382 (23.3)	1,313 (26.1)	1.00	1.00
1-3	609 (37.1)	1,854 (36.8)	1.13 (0.98-1.31)	1.08 (0.90-1.29)
>3	651 (39.7)	1,872 (37.1)	1.19 (1.03-1.38)	1.09 (0.90-1.30)
Breads and cereals, whole grain				
0-5.4	459 (28.0)	1,614 (32.0)	1.00	1.00
5.5-13.9	584 (35.6)	1,697 (33.7)	1.21 (1.05-1.40)	1.14 (0.96-1.36)
>13.9	599 (36.5)	1,728 (34.3)	1.21 (1.05-1.40)	1.16 (0.98-1.39)
Breads and cereals, nonwhole grain				
0-4.5	567 (34.5)	1,602 (31.8)	1.00	1.00
4.6-10.9	497 (30.3)	1,674 (33.2)	0.85 (0.74-0.98)	0.77 (0.64-0.91)
>10.9	578 (35.2)	1,763 (35.0)	0.93 (0.81-1.06)	0.86 (0.72-1.02)
Dessert food				
0-3.3	430 (27.8)	1,528 (32.3)	1.00	1.00
3.4-8.9	516 (33.4)	1,591 (33.6)	1.15 (0.99-1.33)	1.13 (0.95-1.35)
>8.9	599 (38.8)	1,616 (34.1)	1.30 (1.13-1.50)	1.24 (1.04-1.49)

NOTE: Numbers of cases and controls do not sum to total number of study subjects due to missing data.
*ORs adjusted for age and sex.
†ORs adjusted for age, sex, income adequacy, alcohol consumption, and total energy (continuous).

be associated with a significantly higher risk of NHL (OR, 1.35; 95% CI, 1.12-1.62). Within groups of meat consumption, an association with NHL risk was observed only for high intake of processed beef, pork, or lamb (OR, 1.49; 95% CI, 1.24-1.80). Levels of consumption of fresh beef/pork/lamb, chicken, and fish did not differ between cases and controls. NHL risk was significantly increased among those reporting high consumption of cheese (OR, 1.38; 95% CI, 1.06-1.53) and eggs (OR, 1.49; 95% CI, 1.25-1.78); no relationship with milk consumption was apparent.

Estimates of total animal protein and fat intake were calculated from individual dietary items and compared between cases and controls (Table 4). With adjustment for age and sex only, a positive association between total animal protein intake and NHL was apparent (OR, 1.31; 95% CI, 1.14-1.52). However, when energy intake and other possible confounders were controlled for in the analysis, no relationship with animal protein consumption was observed. High consumption of total fat was positively associated with NHL (OR, 1.28; 95% CI, 1.08-1.52). When consumption of different types of fat was examined, NHL risk was positively associated with high intake of saturated fat (OR, 1.29; 95% CI, 1.09-1.53) and monounsaturated fat (OR, 1.27; 95% CI, 1.07-1.51); no relationship with polyunsaturated fat was apparent. High total energy intake showed a relatively strong association with NHL risk (OR, 1.44; 95% CI, 1.21-1.72).

Estimated ORs describing associations with individual dietary components by histologic subtype are summarized in Table 5. The associations with some dietary factors were found to differ significantly across histologic subtypes. High intakes of total vegetables and cruciferous vegetables were associated with an elevated risk of small lymphocytic lymphoma (OR, 2.58 and 2.61, respectively), with no relationship apparent for other

Table 3. ORs and 95% CIs relating NHL risk and intake of animal products

Dietary item (servings/wk)	Case [*n* (%)]	Controls [*n* (%)]	OR_1* (95% CI)	OR_2† (95% CI)
Total meat				
0-6.94	213 (27.7)	772 (32.6)	1.00	1.00
6.95-11.38	506 (35.1)	1,589 (33.4)	1.24 (1.07-1.44)	1.30 (1.09-1.54)
>11.38	748 (37.2)	2,107 (34.0)	1.28 (1.10-1.49)	1.35 (1.12-1.62)
Chicken				
0-0.9	350 (21.3)	1,035 (20.5)	1.00	1.00
1-2.9	645 (39.3)	2,005 (39.8)	0.96 (0.83-1.12)	0.93 (0.77-1.12)
≥3	647 (39.4)	1,999 (39.7)	0.98 (0.84-1.14)	0.86 (0.71-1.04)
Beef/pork/lamb, fresh				
0-1.9	406 (26.5)	1,352 (28.8)	1.00	1.00
2-3.9	525 (34.2)	1,566 (33.4)	1.11 (0.96-1.29)	1.14 (0.95-1.36)
≥4	604 (39.4)	1,772 (37.8)	1.14 (0.98-1.31)	1.11 (0.93-1.33)
Beef/pork/lamb, processed				
0-1.3	389 (24.9)	1,374 (29.0)	1.00	1.00
1.4-3.9	548 (35.1)	1,719 (36.3)	1.14 (0.98-1.32)	1.19 (0.99-1.43)
≥4	623 (39.9)	1,645 (34.7)	1.36 (1.17-1.59)	1.49 (1.24-1.80)
Fish, fresh				
0-0.5	230 (14.3)	748 (15.1)	1.00	1.00
0.6-0.9	559 (34.7)	1,587 (32.1)	1.13 (0.95-1.35)	1.04 (0.84-1.29)
>0.9	821 (51.0)	2,612 (52.8)	1.00 (0.85-1.18)	1.00 (0.81-1.24)
Eggs				
0-0.9	327 (20.2)	1,268 (25.7)	1.00	1.00
1-2.9	353 (21.8)	1,239 (25.1)	1.10 (0.93-1.31)	1.06 (0.87-1.31)
>2.9	939 (58.0)	2,434 (49.3)	1.49 (1.29-1.72)	1.49 (1.25-1.78)
Milk				
0-6.9	468 (28.7)	1,529 (30.7)	1.00	1.00
7-10.9	289 (17.7)	974 (19.5)	0.97 (0.82-1.15)	1.00 (0.81-1.22)
>10.9	874 (53.6)	1,482 (49.8)	1.15 (1.01-1.31)	1.12 (0.95-1.31)
Cheese				
0-0.9	308 (19.1)	1,107 (22.4)	1.00	1.00
1-2.9	316 (19.6)	919 (18.6)	1.25 (1.04-1.49)	1.29 (1.04-1.62)
>2.9	992 (61.4)	1,912 (59.0)	1.24 (1.07-1.43)	1.38 (1.06-1.53)

NOTE: Numbers of cases and controls do not sum to total number of study subjects due to missing data.
*ORs adjusted for age and sex.
†ORs adjusted for age, sex, income adequacy, alcohol consumption, and total energy (continuous).

Table 4. ORs and 95% CIs relating NHL risk and intake of fat and animal protein

Macronutrient (g/10,000 kJ)	Cases [*n* (%)]	Controls [*n* (%)]	OR_1* (95% CI)	OR_2† (95% CI)
Total animal protein				
0-53.0	468 (30.7)	1,508 (33.0)	1.00	1.00
53.1-70.2	542 (35.6)	1,508 (33.0)	1.15 (0.99-1.34)	1.18 (1.00-1.40)
>70.2	514 (33.7)	1,553 (34.0)	1.31 (1.14-1.52)	1.08 (0.91-1.28)
Total fat				
0-60.8	432 (28.4)	1,507 (33.0)	1.00	1.00
60.9-75.6	509 (33.4)	1,509 (33.0)	1.28 (1.10-1.49)	1.14 (0.95-1.35)
>75.6	583 (38.3)	1,553 (34.0)	1.49 (1.29-1.73)	1.28 (1.08-1.52)
Saturated fat				
0-20.1	417 (27.4)	1,507 (33.0)	1.00	1.00
20.2-26.0	529 (34.7)	1,509 (33.0)	1.29 (1.11-1.49)	1.19 (1.01-1.42)
>26.0	578 (37.9)	1,553 (34.0)	1.52 (1.31-1.76)	1.29 (1.09-1.53)
Monounsaturated fat				
0-23.4	438 (28.7)	1,508 (33.0)	1.00	1.00
23.5-30.0	527 (34.6)	1,509 (33.0)	1.32 (1.14-1.54)	1.16 (0.98-1.38)
>30.0	559 (36.7)	1,552 (34.0)	1.47 (1.27-1.71)	1.27 (1.07-1.51)
Polyunsaturated fat				
0-8.3	456 (29.9)	1,508 (33.0)	1.00	1.00
8.4-11.3	557 (36.7)	1,507 (33.0)	1.15 (0.99-1.34)	1.12 (0.95-1.33)
>11.3	511 (33.5)	1,554 (34.0)	1.32 (1.14-1.53)	1.07 (0.91-1.28)
Total energy (kJ)				
0-409,078	412 (27.4)	1,508 (33.0)	1.00	1.00
409,079-54,416	500 (33.3)	1,508 (33.0)	1.21 (1.04-1.40)	1.21‡ (1.01-1.44)
>54,416	591 (39.3)	1,553 (34.0)	1.38 (1.20-1.60)	1.44‡ (1.21-1.72)

NOTE: Numbers of cases and controls do not sum to total number of study subjects due to missing data.
*ORs adjusted for age and sex.
†ORs adjusted for age, sex, income adequacy, and alcohol consumption, and total energy (multivariate nutrient density).
‡ORs adjusted for age, sex, income adequacy, and alcohol consumption.

Table 5. ORs relating associations with dietary factors for histologic subtypes of NHL

Dietary component (servings/wk)	NHL (n = 1,642)	NHL histologic subtype						
		Small lymphocytic (n = 174)	Follicular (n = 442)	Diffuse (n = 536)	High grade (n = 80)	Peripheral T cell (n = 69)	Not otherwise specified (n = 341)	P for heterogeneity
Total fruit								
0-6.47								
6.48-12.94	1.06	0.92	1.08	1.11	1.07	0.66	1.16	
>12.94	1.06	1.10	1.09	1.03	1.39	0.87	1.10	0.97
Total vegetables								
0-7.47								
7.48-13.47	1.04	1.60	1.07	0.89	0.95	0.91	1.11	
>13.47	0.93	2.58*	0.73	0.81	0.96	0.57	0.97	0.01
Yellow/orange vegetables								
0-3								
3.1-6	1.14	1.36	1.39*	0.80	1.20	1.38	1.30	
>6	0.91	1.36	0.83	0.70*	1.38	0.52	1.21	0.01
Cruciferous vegetables								
0-1								
1.1-3	1.13	1.82	1.01	1.08	0.78	1.54	1.33	
>3	0.95	2.61*	0.89	0.78	0.60	0.80	1.01	0.02
Leafy vegetables								
0-0.4								
0.5-1	0.85	0.60	0.80	0.74	0.83	0.83	1.28	
>1	1.01	1.25	0.95	0.85	1.13	0.99	1.26	0.26
Other vegetables								
0-1								
1.1-3	1.14	0.89	1.05	1.17	1.31	1.63	1.19	
>3	1.22*	1.68*	0.91	1.25	1.90	1.64	1.17	0.19
Potatoes								
0-2.9								
3-5.4	1.05	1.25	1.28	0.96	0.66	0.87	0.94	
>5.4	1.12	1.63	1.34	0.98	0.93	1.09	0.99	0.77
Legumes and nuts								
0-0.9								
1-3	1.08	1.56	1.06	1.01	0.96	1.27	1.02	
>3	1.09	1.36	1.21	0.99	1.01	1.65	0.95	0.86
Breads and cereals, whole grain								
0-5.4								
5.5-13.9	1.14	1.17	1.06	1.07	2.07	1.39	1.16	
>13.9	1.16	1.52	1.07	1.02	1.41	0.98	1.34	0.61
Breads and cereal, nonwhole grain								
0-4.5								
4.6-10.9	0.77*	1.02	0.83	0.82	0.56	1.01	0.61	
>10.9	0.86	0.89	1.09	0.86	0.51	1.19	0.69	0.41
Dessert food								
0-3.3								
3.4-8.9	1.13	1.12	1.31	1.01	0.95	1.99	1.06	
>8.9	1.24*	0.97	1.27	1.39*	0.82	1.35	1.28	0.44
Total meat								
0-6.94								
6.95-11.38	1.30*	2.12*	1.30	1.13	0.95	1.38	1.35*	
>11.38	1.35*	1.91*	1.33	1.28*	0.80	1.99	1.40	0.62
Fish, fresh								
0-0.5								
0.6-0.9	1.04	1.16	1.12	1.13	1.27	3.49	0.69	
>0.9	1.00	1.06	1.04	1.04	1.28	3.25	0.77	0.56
Eggs								
0-0.9								
1-2.9	1.06	0.88	1.09	1.13	0.59	1.65	1.09	
>2.9	1.49*	1.23	1.44*	1.51*	1.79	2.08	1.63*	0.84
Milk								
0-6.9								
7-10.9	0.97	0.73	0.96	1.11	1.57	1.93	0.92	
>10.9	1.14	0.70	1.02	1.24	1.82	1.57	1.22	0.34
Cheese								
0-0.9								
1-2.9	1.30*	1.53	1.38	1.26	1.93	1.01	1.10	
>2.9	1.30*	1.45	1.35	1.13	2.71	0.67	1.36*	0.52

(Continued on the following page)

Table 5. ORs relating associations with dietary factors for histologic subtypes of NHL (Cont'd)

Dietary component (servings/wk)	NHL (n = 1,642)	NHL histologic subtype						
		Small lymphocytic (n = 174)	Follicular (n = 442)	Diffuse (n = 536)	High grade (n = 80)	Peripheral T cell (n = 69)	Not otherwise specified (n = 341)	P for heterogeneity
Total animal protein† (g/10,000 kJ)								
0-53.0								
53.1-70.2	1.18	1.02	1.19	1.03	2.84*	1.63	1.28	
>70.2	1.08	0.69	0.98	1.12	1.89	1.78	1.18	0.18
Total fat† (g/10,000 kJ)								
0-60.8								
60.9-75.6	1.14	0.97	1.27	1.59*	0.63	0.75	0.80	
>75.6	1.28*	0.72	1.29	1.76*	1.32	1.01	1.13	0.01
Saturated fat† (g/10,000 kJ)								
0-20.1								
20.2-26.0	1.19*	1.15	1.16	1.47	1.01	1.59	0.95	
>26.0	1.29*	0.85	1.27	1.88*	1.32	0.84	0.98	0.05
Monounsaturated fat† (g/10,000 kJ)								
0-23.4								
23.5-30.0	1.16	0.92	1.08	1.59*	1.44	1.42	0.86	
>30.0	1.27*	0.87	1.22	1.62*	1.47	1.69	1.09	0.27
Polyunsaturated fat† (g/10,000 kJ)								
0-8.3								
8.4-11.3	1.12	1.20	0.96	1.22	1.12	2.37	1.04	
>11.3	1.07	0.87	1.05	1.13	1.48	1.90	0.97	0.60

NOTE: Unless otherwise specified, ORs adjusted for age, sex, income adequacy, alcohol consumption, and total energy (continuous).
*95% CI does not include 1.
†ORs adjusted for age, sex, income adequacy, alcohol consumption, and total energy (multivariate nutrient density).

subtypes. High consumption of yellow/orange vegetables was only associated with a reduced risk of diffuse and peripheral T-cell lymphomas (OR, 0.70 and 0.52, respectively). In addition, high intake of total and saturated fats showed particularly strong associations with diffuse lymphomas (OR, 1.76 and 1.88, respectively).

A multivariable analysis was done to simultaneously estimate the independent associations between dietary groups and risk of NHL, both overall and by histologic subtype (Table 6). Overall consumption of vegetables, potatoes, bread and cereal, and legumes and nuts were not associated with NHL risk. Positive associations were observed for high consumption of total fruit (OR, 1.23; 95% CI, 1.00-1.51), dessert food (OR, 1.22; 95% CI, 0.99-1.51), and total fat (OR, 1.37; 95% CI, 1.09-1.73). Associations with total vegetable consumption significantly differed across NHL subtypes.

A reanalysis of the data stratifying by sex suggested that the estimated associations with NHL risk did not differ between men and women (data not shown).

Discussion

This analysis of NECSS data was done to explore whether relationships with dietary components differed for specific NHL subtypes. We found an increased risk of NHL accompanying high intake of processed meat, cheese, eggs, dessert foods, saturated fat, and monounsaturated fat. No differences between cases and controls were observed for other dietary factors. The study findings generally did not differ between lymphoma subtypes.

An increased risk of NHL was found for high consumption of processed meat, saturated fat, and monounsaturated fat. No association with protein intake was found on adjustment for energy intake and other possible confounders. There is experimental evidence from animal studies that high intake of protein and fat can induce chronic hyperstimulation of the immune system and the development of lymphomas (19-21, 44). The observed association with processed meats may also involve the effect of nitrites, preservatives found in processed meats that are precursors to *N*-nitroso compounds, known carcinogens in animals (45). Other carcinogens, polycyclic aromatic hydrocarbons, are produced when fish or meat is fried or grilled; there is experimental evidence that high levels of ingested polycyclic aromatic hydrocarbon can induce immunotoxicity and lymphomas in mice (46).

Whereas evidence from animal studies supports an etiologic role for protein, fat, and meat intake, findings from epidemiologic studies of humans are inconsistent. A link between protein intake and NHL is supported by an early ecologic study that reported a positive correlation between per capita protein intake and lymphoma mortality (47). Associations with NHL were inconsistently observed across different types of meat in three hospital-based case-control studies from Italy (17, 22) and Uruguay (27); no analyses involving total protein and fat consumption were done. A population-based case-control study conducted in Nebraska by Ward et al. (25) found no association with consumption of animal products or with intake of animal or vegetable protein (fat was not assessed). However, the evidence from these studies is limited by their retrospective design and lack of adjustment for energy intake. Two published cohort analyses (26, 28) likely offer better insight into the relationship between NHL risk and intake of protein and fat. An analysis by Chiu et al. (26) of data from the Iowa Women's Health Study found an increased risk

Table 6. ORs and 95% CIs relating associations with dietary factors for histologic subtypes of NHL, adjusted for all other factors

Dietary components	NHL	NHL histologic subtype					
		Small lymphocytic	Follicular	Diffuse	High grade	Peripheral T cell	Not otherwise specified
Total fruit (servings/10,000 kJ)							
0-1.3	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.4-2.6	1.10 (0.91-1.33)	0.84 (0.48-1.46)	1.17 (0.85-1.61)	1.06 (0.78-1.45)	1.52 (0.68-3.37)	0.75 (0.32-1.77)	1.18 (0.81-1.70)
>2.6	1.23 (1.00-1.51)	0.78 (0.44-1.41)	1.35 (0.96-1.90)	1.26 (0.91-1.75)	2.06 (0.89-4.76)	1.14 (0.47-2.72)	1.16 (0.77-1.73)
Total vegetable* (servings/10,000 kJ)							
0-1.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.7-2.8	1.06 (0.88-1.29)	1.97 (1.03-3.79)	0.97 (0.71-1.32)	0.98 (0.72-1.35)	1.04 (0.48-2.26)	0.74 (0.33-1.65)	1.22 (0.83-1.78)
>2.8	0.85 (0.68-1.07)	2.35 (1.17-4.74)	0.54 (0.37-0.80)	0.91 (0.63-1.31)	0.83 (0.33-2.05)	0.36 (0.13-1.02)	1.12 (0.72-1.73)
Potatoes (servings/10,000 kJ)							
0-0.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.9-1.4	0.96 (0.79-1.18)	1.08 (0.56-2.06)	1.44 (1.01-2.06)	0.74 (0.53-1.02)	0.93 (0.41-2.09)	1.51 (0.57-3.99)	0.75 (0.52-1.10)
>1.4	0.96 (0.76-1.22)	0.93 (0.46-1.87)	1.43 (0.95-2.16)	0.78 (0.54-1.12)	1.10 (0.43-2.78)	1.98 (0.67-5.88)	0.70 (0.45-1.09)
Legumes and nuts (servings/10,000 kJ)							
0-0.2	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.3-0.6	1.01 (0.83-1.22)	1.79 (0.94-3.40)	0.94 (0.67-1.32)	0.97 (0.71-1.33)	0.83 (0.38-1.83)	1.29 (0.47-3.49)	0.94 (0.64-1.38)
>0.6	1.00 (0.82-1.23)	1.30 (0.66-2.57)	1.14 (0.81-1.60)	0.83 (0.60-1.16)	0.96 (0.43-2.17)	2.04 (0.77-5.41)	0.92 (0.62-1.37)
Total bread and cereal (servings/10,000 kJ)							
0-0.7	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.8-1.0	0.99 (0.82-1.20)	1.06 (0.59-1.91)	0.96 (0.70-1.32)	1.14 (0.84-1.56)	0.48 (0.22-1.06)	1.07 (0.46-2.45)	0.95 (0.64-1.39)
>1.0	1.11 (0.90-1.37)	1.25 (0.69-2.30)	1.01 (0.72-1.42)	1.08 (0.77-1.52)	0.73 (0.34-1.59)	1.02 (0.41-2.51)	1.40 (0.94-2.08)
Dessert food (servings/10,000 kJ)							
0-0.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.9-1.8	1.06 (0.87-1.29)	1.20 (0.68-2.12)	1.12 (0.81-1.56)	0.95 (0.69-1.33)	0.89 (0.42-1.90)	1.62 (0.66-3.98)	1.03 (0.70-1.52)
>1.8	1.22 (0.99-1.51)	1.11 (0.59-2.09)	1.17 (0.82-1.68)	1.26 (0.90-1.78)	0.76 (0.34-1.87)	1.38 (0.51-3.73)	1.35 (0.89-2.04)
Total animal protein (g/10,000 kJ)							
0-53.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
53.1-70.2	1.14 (0.95-1.38)	0.82 (0.49-1.37)	1.14 (0.84-1.56)	0.95 (0.70-1.29)	2.86 (1.24-6.61)	1.94 (0.81-4.72)	1.33 (0.92-1.92)
>70.2	1.06 (0.87-1.30)	0.60 (0.32-1.09)	1.03 (0.73-1.44)	0.96 (0.69-1.32)	1.81 (0.70-4.63)	1.79 (0.69-4.62)	1.36 (0.92-2.02)
Total fat (g/10,000 kJ)							
0-60.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00
60.9-75.6	1.17 (0.95-1.44)	1.25 (0.71-2.22)	1.13 (0.80-1.60)	1.77 (1.24-2.53)	0.68 (0.29-1.59)	0.79 (0.30-2.07)	0.78 (0.52-1.18)
>75.6	1.37 (1.09-1.73)	1.07 (0.54-2.12)	1.16 (0.79-1.72)	2.01 (1.36-2.98)	1.25 (0.51-3.03)	0.95 (0.34-2.65)	1.24 (0.80-1.92)

NOTE: ORs adjusted simultaneously for age, sex, income adequacy, alcohol consumption, total energy (multivariate nutrient density), and all other food groups.
*Statistically significant test of heterogeneity in ORs across subtypes ($P = 0.02$).

accompanying high consumption of red meat (particularly hamburgers), animal protein, and saturated and monounsaturated fats. In an analysis of the Nurses' Health Study, Zhang et al. (28) reported an increased risk with high intake of beef, pork, or lamb and saturated and *trans*-unsaturated fats; however, no association with protein intake was found. The results of studies that have investigated the etiologic importance of fat consumption have been generally consistent in identifying an association with fat intake. By contrast, the epidemiologic evidence investigating protein intake and NHL remains unclear.

We found NHL risk to be positively associated with high intake of cheese and eggs but not milk. None of the other studies that analyzed consumption of cheese and eggs reported any association with NHL risk (17, 22, 25, 26). The levels of consumption of these foods did not appreciably differ between those studies and ours. It is possible that our observed associations arose due to chance. High consumption of milk was associated with an increased risk of lymphatic cancers in a Norwegian cohort study (23), and a similar association with NHL risk was reported in the two Italian case-control studies (17, 22). Three other studies conducted in Uruguay and the United States found no association (25-27).

In our analysis, high consumption of dessert foods was weakly associated with elevated NHL risk. Zhang et al. (28) also identified positive associations with consumption of different dessert foods; desserts were not examined in the other studies. The investigators speculated that the increased risk may be attributable to the high levels of *trans*-unsaturated fat present in these foods. Dessert foods are also high in simple sugars, the consumption of which triggers insulin secretion. High insulin levels have been linked to an increased risk of cancers of the breast, colon, prostate, and lung (48). No such relationship with NHL has been reported; however, individuals diagnosed with diabetes have been found in some studies to have an increased risk of NHL (49-51).

Consumption of fruit and most types of vegetables was generally not found to be associated with NHL risk in our data. Six previous NHL studies have investigated fruit and vegetable consumption (17, 24-27, 29). High fruit intake was found to be associated with a low risk of NHL by Ward et al. (25) and Chiu et al. (26); no relationship was found in the other four studies. Evidence suggesting a protective effect from high consumption of at least some types of vegetables consumption has emerged from three studies (17, 25, 29), whereas other studies have reported no association (26) or weak evidence of a positive association with NHL risk (24, 27). There was no consistency in findings across the three cohort studies that investigated fruits, vegetables, and NHL risk (24, 26, 29). Although overall vegetable intake was not found to be a risk factor in our study, high consumption of items categorized as ''other vegetables'' (i.e., other than cruciferous, leafy, or yellow/orange vegetables) was positively associated with NHL. Vegetables naturally contain the suspected carcinogen nitrate (52). However, it is unlikely that nitrate intake underlies these associations, as nitrate-rich vegetables included in our questionnaire (cabbage, spinach, and other greens) were categorized as cruciferous or leafy vegetables and were not associated with NHL risk.

No difference in consumption of fresh fish was found between cases and controls. Investigators conducting a separate case-control analysis of NHL and fish consumption using the NECSS data reported a weak, nonsignificant inverse association with NHL risk accompanying consumption of $\geq$4 servings of fish per week (OR, 0.88; 95% CI, 0.71-1.10; ref. 53). This slightly different finding is likely due to differences between analyses in the choice of cut points for fish consumption, model covariates, and subject inclusion criteria. The findings from past epidemiologic studies of NHL do not suggest an association with fish intake (17, 26, 54).

The findings from the published studies relating diet to NHL risk are limited to varying degrees by a variety of methodologic issues, including a retrospective study design, use of hospital controls, accuracy in measuring past or current diet, and an absence of adjustment for energy intake. The results from the two methodologically strongest studies (Iowa Women's Study and Nurses' Health Study) are fairly consistent in reporting increased risk from red meat and fat intake but are contradictory with respect to the effects of protein, fruit, and vegetable intake (26, 28, 29). In addition, epidemiologic studies of diet (except ecologic analyses) are often limited in their ability to detect dietary effects because of the narrow range of dietary intake reported within study populations, such that only large associations are apparent (55). This issue may have contributed to the inconsistency observed across studies investigating diet and NHL. Such limitations may be particularly acute in our analysis, given our decision to categorize intake levels into only three groups to minimize problems of sparse cell counts in the analysis of disease subtypes. On the other hand, this problem may be offset to some extent by the large sample size of the NECSS, which provided this analysis with reasonable statistical power to detect weak associations.

It is possible that measurement error in the assessment of past diet may have affected the study findings. We believe such measurement error is most likely to be nondifferential in nature, given that diet is not a widely accepted risk factor for NHL and that the project was presented to subjects as a study of health and the environment. The usual effect of such error is to bias observed associations toward the null, which may partly explain the relatively weak dietary associations observed in this study. However, we cannot rule out the possibility that the dietary assessments of some cases were influenced by recent changes in their eating patterns due to the effects of the disease or its treatment. Such nondifferential measurement error could introduce bias toward or away from the null.

We believe it is unlikely that the observed study findings can be explained by confounding. OR estimates were adjusted for alcohol consumption and income adequacy, as these variables were found to influence the magnitude of some variable estimates. Occupational exposure to pesticides and herbicides has been previously identified as a risk factor for NHL but did not seem to confound the dietary associations with NHL in this study. Given that some past studies had been restricted to women (26, 28, 29) and that two studies found evidence of differential risk between sexes (25, 27), it is possible that the combined analyses done in this project may have obscured sex-specific differences. However, a reanalysis stratified by sex suggested no such differences.

If NHL is truly a collection of etiologically distinct lymphoid tumors, then it is possible that the inconsistent evidence in the published literature relating NHL and diet may be due to differences between studies in the distribution of NHL subtypes. The NECSS, with 1,642 cases and 5,039 controls, is one of the largest case-control studies of NHL developed to date and provided an opportunity to explore evidence of etiologic heterogeneity in NHL. Differences in sex and age distributions between subtypes consistent with those identified in previous analyses of Surveillance, Epidemiology and End Results data (32, 33) were apparent in the study data. This analysis generally found no evidence of heterogeneity across disease subtypes with respect to dietary associations. Associations with consumption of some vegetables and fats were found to be significantly different across subtypes. However, given the large number of diet/subtype comparisons made in this analysis, the possibility that these statistically significant findings arose by chance cannot be ruled out. Conversely, some aspects of study design may have limited the ability of this analysis to identify evidence of etiologic heterogeneity. The NECSS was only powered to detect main effects and not to detect heterogeneity in associations across disease subtypes (34); consequently, it is impossible to rule out the existence of such heterogeneity with any certitude.

This analysis may also have been limited in its ability to detect etiologic heterogeneity due to errors in classification of histologic subtype. Disease classification was based on the histopathologic tumor characteristics described in the original pathology reports rather than from review by a single expert pathologist. Given the demonstrated error in classifying NHL cases using the WF criteria (57-63% agreement among expert pathologists; refs. 56, 57) and in assigning ICDO codes to cases (77% agreement among Surveillance, Epidemiology and

End Results Program coders; ref. 58), it is possible that a proportion of cases were assigned an incorrect subtype. Such misclassification, if independent of exposure, would lead to an attenuation of estimated subtype-specific associations. This is of particular concern for high-grade tumors, because the proportion of cases classified as high grade in our study is only half of the corresponding proportion from NHL cases registered in Surveillance, Epidemiology and End Results between 1978 and 1995 (5% versus 10%; ref. 33). These differences suggest that a high proportion of high-grade tumors in our study may have been classified into other categories (most likely not otherwise specified); as a result, the ORs for high-grade tumors should be interpreted with caution. Measurement error in the dietary assessment is likely another important source of OR attenuation. The absence of a difference in the distribution of histologic subtypes between Ontario participants and nonparticipants ($\chi^2 = 6.30$, $df = 5$; $P = 0.28$) suggests that selection bias is unlikely to have affected the subtype-specific results.

It is possible that etiologic heterogeneity may exist between groups of NHL tumors characterized by differences other than their WF classification. A limitation of the WF classification system is that it was not designed to categorize tumors into separate disease entities. Instead, tumors are assigned to subgroups based on their expected clinical outcome. Furthermore, the WF system relies on histologic characteristics of tumors for classification; immunophenotypic and genetic characteristics are not taken into account. Since the creation of the WF in 1982, newer classification systems (the Revised European-American Classification of Lymphoid Neoplasms and the WHO Classification; ref. 59) have been developed that incorporate tumor immunophenotypic and genetic features and are based on a better understanding of lymphoid neoplasia. It would have been preferable to use such classification systems in our study; however, only a minority of tumors had been classified according to these systems and that information had not been collected as part of the NECSS. Ward et al. (25) investigated dietary factors separately by histologic and immunophenotypic type. No differences in dietary associations between different histologic types or between B-cell and T-cell lymphomas were found, although the study was underpowered to detect such heterogeneity.

In conclusion, we found a positive association between NHL risk and higher intake of saturated and monounsaturated fat and particular food items (cheese, eggs, processed meat, and sweet dessert foods). We did not find any clear evidence of heterogeneity between histologic subtypes of NHL in their associations with components of dietary intake. However, given the potential for misclassification in assessing both past dietary intake and histologic subtype, we cannot rule out the existence of such heterogeneity. To effectively investigate the existence of etiologic heterogeneity within NHL subgroups, studies including adequate numbers of cases and a standardized assessment of the histologic, immunophenotypic, and possibly molecular characteristics of tumors are needed. Meta-analyses of data pooled from different studies of NHL may represent an opportunity to conduct such investigations.

Acknowledgments

This project uses data collected through the National Enhanced Cancer Surveillance System, a collaboration of the Cancer Bureau, Center for Chronic Disease Prevention and Control, Health Canada, and Canadian Cancer Registries Epidemiology Research Group.

Appendix 1: List of dietary groups, subgroups, constituents, and weekly serving size as listed on the NECSS food frequency questionnaire

Food group	Food subgroup	Food item (weekly serving size)
Total fruit		Apples or pears (1)
		Oranges (1)
		Bananas (1)
		Cantaloupe (¼ melon)
		Other fruit, fresh or canned (1 piece or ½ cup)
Total vegetables	Yellow/orange vegetables	Tomatoes (1)
		Carrots (1 whole or (½ cup)
	Cruciferous vegetables	Broccoli (½ cup)
		Cabbage, cauliflower, Brussels sprouts (½ cup)
	Leafy vegetables	Spinach or other greens (1 serving)
	Other vegetables	Any other vegetable including green beans, corn, and peas (½ cup)
Potatoes		Potatoes: baked, boiled (1), or mashed (1 cup)
		French fries or fried potatoes (½ cup)
		Sweet potatoes (1 or ½ cup)
Legumes and nuts		Tofu or soybeans (3-4 oz/115 mL)
		Baked beans or lentils (½ cup)
		Peanut butter (1 tbsp)
		Nuts (1 oz/30 g)
Breads and cereals	Whole grain	Bran or granola cereals, shredded wheat (1 cup)
		Other cold cereals (1 cup)
		Cooked cereals (1 cup)
		Dark or whole grain bread (1 slice) or rolls (1)
	Nonwhole grain	White bread (1 slice) or rolls (1)
		Rice (1 cup)
		Macaroni, spaghetti or noodles (1 cup)
Dessert food		Cake (1 slice)
		Cookies (1)
		Doughnuts, pastry (1)
		Pies (1 slice)
		Ice cream (½ cup)
		Chocolate (1 small bar or 1 oz)
Total meat	Poultry	Chicken or turkey (4 oz/115 mL)
	Beef/pork/lamb (nonprocessed)	Beef, pork, or lamb as a main dish (steak, roast, ham; 4 oz/115 mL)

(Continued on following page)

Appendix 1: List of dietary groups, subgroups, constituents, and weekly serving size as listed on the NECSS food frequency questionnaire (Cont'd)

Food group	Food subgroup	Food item (weekly serving size)
		Beef, pork, or lamb as a mixed dish (stew or casserole, pasta dish; 4 oz/115 mL)
		Hamburger (1)
		Sausage (1)
		Liver (4 oz/115 mL)
	Beef/pork/lamb (processed)	Hot dogs (1)
		Luncheon meats (salami, bologna; 1 piece or slice)
		Smoked meat or corned beef (1 piece or slice)
		Bacon (1 slice)
Fresh fish		Fish, fresh, frozen, or canned (4 oz/115 mL)
Eggs		Eggs (1)
Total milk		Whole milk (8 oz/230 mL glass)
		2% milk (8 oz/230 mL glass)
		1% milk (8 oz/230 mL glass)
		Skim milk (8 oz/230 mL glass)
Cheese	Cheese other than cottage cheese (1 slice or 1 oz)	

References

1. Banks PM. The pathology of Hodgkin's disease. Semin Oncol 1990; 17:683–95.
2. Hoover RN. Lymphoma risks in populations with altered immunity—a search for mechanism. Cancer Res 1992;52:5477–8s.
3. Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. Lancet 1973;2:55–7.
4. Kinlen LJ, Sheil AG, Peto J, Dol R. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. Br Med J 1979;2:1461–6.
5. Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. Lancet 1991;337:805–9.
6. Rabkin CS, Biggar RJ, Horm JW. Increasing incidence of cancers associated with the human immunodeficiency virus epidemic. Int J Cancer 1991;47:692–6.
7. Cleghorn FR, Manns A, Falk R, et al. Effect of human T-lymphotropic virus type I infection on non-Hodgkin's lymphoma incidence. J Natl Cancer Inst 1995;87:1009–14.
8. Wotherspoon AC. Gastric lymphoma of mucosa-associated lymphoid tissue and *Helicobacter pylori.* Annu Rev Med 1998;49:289–99.
9. Liebowitz D. Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med 1998;338:1413–21.
10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8. Vol. 70. Lyon: IARC; 1997. p. 82–126.
11. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986;256:1141–7.
12. Zahm SH, Weisenburger DD, Babbitt PA, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990;1:349–56.
13. Wigle DT, Semenciw RM, Wilkins K, et al. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J Natl Cancer Inst 1990; 82:575–82.
14. Morrison HI, Semenciw RM, Wilkins K, Mao Y, Wigle DT. Non-Hodgkin's lymphoma and agricultural practices in the prairie provinces of Canada. Scand J Work Environ Health 1994;20:42–7.
15. Ward MH, Mark SD, Cantor KP, Weisenburger DD, Correa-Villasenor A, Zahm SH. Drinking water nitrate and the risk of non-Hodgkin's lymphoma. Epidemiology 1996;7:465–71.
16. Freedman DM, Cantor KP, Ward MH, Helzlsouer KJ. A case-control study of nitrate in drinking water and non-Hodgkin's lymphoma in Minnesota. Arch Environ Health 2000;55:326–9.
17. Tavani A, Pregnolato A, Negri E, et al. Diet and risk of lymphoid neoplasms and soft tissue sarcomas. Nutr Cancer 1997;27:256–60.
18. Chiu BC, Cerhan JR, Gapstur SM, et al. Alcohol consumption and non-Hodgkin lymphoma in a cohort of older women. Br J Cancer 1999;80:1476–82.
19. Ross MH, Bras G. Tumor incidence patterns and nutrition in the rat. J Nutr 1965;87:245–60.
20. Jose DG, Good RA. Quantitative effects of nutritional essential amino acid deficiency upon immune responses to tumors in mice. J Exp Med 1973;137:1–9.
21. Cameron RG, Armstrong D, Clandinin MT, Cinader B. Changes in lymphoma development in female SJL/J mice as a function of the ratio in low polyunsaturated/high polyunsaturated fat diet. Cancer Lett 1986;30:175–80.
22. Franceschi S, Serraino D, Carbone A, Talamini R, La Vecchia C. Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. Nutr Cancer 1989;12:333–41.
23. Ursin G, Bjelke E, Heuch I, Vollset SE. Milk consumption and cancer incidence: a Norwegian prospective study. Br J Cancer 1990;61: 456–9.
24. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F. Vegetable and fruit consumption and cancer risk. Int J Cancer 1991; 48:350–4.
25. Ward MH, Zahm SH, Weisenburger DD, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer Causes Control 1994;5:422–32.
26. Chiu BC, Cerhan JR, Folsom AR, et al. Diet and risk of non-Hodgkin lymphoma in older women. JAMA 1996;275:1315–21.
27. De Stefani E, Fierro L, Barrios E, Ronco A. Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. Leuk Res 1998;22:445–52.
28. Zhang SM, Hunter DJ, Rosner BA, et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. J Natl Cancer Inst 1999;91:1751–8.
29. Zhang SM, Hunter DJ, Rosner BA, et al. Intakes of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma among women. Cancer Epidemiol Biomarkers Prev 2000;9:477–85.
30. Davis S. Nutritional factors and the development of non-Hodgkin's lymphoma: a review of the evidence. Cancer Res 1992;52:5492–5s.
31. Scherr PA, Mueller NE. Non-Hodgkin's lymphomas. In: Schottenfeld DF, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. New York: Oxford; 1996. p. 920–45.
32. Newell GR, Cabanillas FG, Hagemenister FJ, Butler JJ. Incidence of lymphoma in the US classified by the Working Formulation. Cancer 1987;59:857–61.
33. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92: 1240–51.
34. Johnson KC. Status report. National Enhanced Cancer Surveillance System: a federal-provincial collaboration to examine environmental cancer risks. Chronic Dis Can 2000;21:34–5.
35. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982;49:2112–35.
36. WHO. ICD-O International classification of diseases for oncology. Geneva (Switzerland): WHO; 1976.
37. WHO. Manual of the international classification of diseases, injuries and causes of death. 9th revision. Geneva: WHO; 1977.
38. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:64.
39. Willett WC. Nutritional epidemiology. New York: Oxford University Press; 1998.
40. Ferlay J. IARCcrgTools conversion and check programs for cancer registry. Vol. 2.10. Lyon: IARC; 2003.
41. Health and Welfare Canada. Nutrient value of some common foods. Ottawa: Ministry of Supply and Services Canada; 1988.
42. Stata Corporation. Stata statistical software. Vol. 7.0. College Station (TX): Stata Corporation; 1999.

43. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65:1220–8S.
44. El Ayachi N, Begin M, Mercier D, Ellis G, Oth D. Susceptibility of RDM4 lymphoma cells to LAK-mediated lysis is decreased in tumor bearers fed fish oil high fat regimen. Cancer Lett 1990;49: 217–24.
45. Mirvish SS, Weisenburger DD, Salmasi S, Kaplan PA. Carcinogenicity of 2-hydroxy-ethylnitrosourea and 3-nitroso-oxazolikine administered in drinking water to male MRC-Wistar rats: induction of bone, hematopoietic, intestinal and liver tumors. J Natl Cancer Inst 1987;78:387–93.
46. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. Vol. 56. IARC monograph on the evaluation of carcinogenic risks to humans. Lyon: IARC Press; 1993. p. 1–599.
47. Cunningham AS. Lymphomas and animal-protein consumption. Lancet 1976;2:1184–6.
48. LeRoith D, Roberts CTJ. The insulin-like growth factor system and cancer. Cancer Lett 2003;195:127–37.
49. Natazuka T, Manabe Y, Kono M, Muryama T, Matsui T, Chihara K. Association between non-insulin dependent diabetes mellitus and non-Hodgkin's lymphoma. Br Med J 1994;309:1269.
50. Cerhan JR, Wallace RB, Folsom AR, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997;89:816–7.
51. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev 2000;9:59–64.
52. Gangolli SD, van den Brandt PA, Feron VJ, et al. Nitrate, nitrite and *N*-nitroso compounds. Eur J Pharmacol 1994;292:1–38.
53. Fritschi L, Ambrosini G, Kliewer EV, Johnson KC, and the Canadian Cancer Registries Epidemiologic Research Group. Dietary fish intake and risk of leukemia, multiple myeloma and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. In press.
54. Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr 1999;70:85–90.
55. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-control studies: the influence of the distribution of exposure. J Chronic Dis 1985;38:559–68.
56. Dick FR, Van Lier S, Banks P, Frizzera G, Witrak G, Everett G. Comparison of methods of recording subclasses of non-Hodgkin's lymphoma for use in epidemiologic studies. Am J Epidemiol 1985; 122:542.
57. Neiman RS, Cain K, Ben Arieh Y, Harrington D, Mann RB, Wolf BCA. comparison between the Rappaport Classification and Working Formulation in cooperative group trials: the ECOG experience. Hematol Pathol 1992;6:61–70.
58. Dick FR, Van Lier SF, McKeen K, Everett GD, Blair A. Nonconcurrence in abstracted diagnoses of non-Hodgkin's lymphoma. J Natl Cancer Inst 1987;78:675–8.
59. Jaffe E, Harris NL, Diebold J, Muller-Hermelink HK. World Health Organization Classification of lymphomas: a work in progress. Ann Oncol 2004;9:S25–30.