Dietary fat intake and risk of non-Hodgkin lymphoma in 2 large prospective cohorts

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ABSTRACT

Background: Dietary fat intake may contribute to non-Hodgkin lymphoma (NHL) pathogenesis by influencing carcinogen exposure or through immune modulation.

Objective: We aimed to evaluate NHL risk associated with total and specific dietary fat intake.

Design: We evaluated associations within the Nurses' Health Study (NHS) (n = 88,598) and the Health Professionals Follow-Up Study (HPFS) (n = 47,531) using repeated validated dietary assessments. We confirmed 1802 incident NHL diagnoses through 2010. Using multivariable Cox proportional hazards models, we estimated hazard ratios (HRs) for all NHL and common subtypes associated with a 1-SD increase in cumulative mean intakes of total, animal, saturated, *trans,* and vegetable fats and marine fatty acids. We pooled sex-specific HRs using random-effects meta-analysis.

Results: Over 24–30 y of follow-up, neither total nor specific dietary fats were significantly associated with NHL risk overall. Higher total, animal, and saturated fat intakes were positively associated with the risk of the chronic lymphocytic leukemia/small lymphocytic lymphoma subtype among women only (253 cases; P-trend $\leq$ 0.05), driven by strong associations during 1980–1994. From baseline through 1994, among women and men combined, total fat intake was borderline-significantly positively associated with NHL overall (pooled HR per SD: 1.13; 95% CI: 0.99, 1.29) and was significantly associated with diffuse large B cell lymphoma (pooled HR per SD: 1.47; 95% CI: 1.06, 2.05), with similar trends for animal and saturated fat intake. For women only, *trans* fat was significantly positively associated with all NHL. In contrast, during 1994–2010, there was little evidence for associations of dietary fat intake with NHL overall or by subtype.

Conclusion: Previous observations of an increased risk of NHL associated with intakes of total, animal, saturated, and *trans* fat with 14 y of follow-up did not persist with longer follow-up. *Am J Clin Nutr* 2017;106:650–6.

Keywords: non-Hodgkin lymphoma, diet, fat, nutrition, epidemiology

INTRODUCTION

Dietary factors may contribute to the pathogenesis of non-Hodgkin lymphoma (NHL) by influencing exposure to carcinogens or by inducing metabolic and hormonal imbalances that influence lymphocyte growth and survival. Consumption of *trans* fatty acids (FAs) or ω-3 (n–3) FAs may impact cancer risk (in opposing directions) by influencing the composition of cellular phospholipid membranes (1–3), which in turn could affect cell susceptibility to oxidative stress and membrane or membrane-bound receptor function. FAs may also influence NHL risk by modulating inflammation, a condition characterized by secretion of numerous B cell–stimulatory cytokines. In a prior analysis of data from the Nurses' Health Study (NHS) (1980–1994), we reported an elevated risk of NHL among women reporting higher intakes of *trans* fats, with an RR of 2.4 (95% CI: 1.3, 4.6; P-trend = 0.01) for the highest quintile of exposure compared with the lowest quintile (4). Intake of ω-3 FAs, which have anti-inflammatory and proapoptotic properties, was inversely associated with NHL in another population (5). To date, the epidemiologic evidence for associations of dietary factors and NHL has been inconsistent (6–8). Although some previous studies reported positive associations of animal and saturated fat with NHL (4, 9–13) and inverse associations of ω-3 FAs or fish with NHL (5, 14–16), others did not (5, 16–21). Furthermore, many studies were subject to methodologic limitations, such as the potential for recall bias in case-control study designs and/or dietary assessments conducted at a single point in time.

In light of the mixed evidence from prior studies, we evaluated associations of total and specific dietary fat intake with the risk of incident NHL over 24–30 y of follow-up within the NHS and the Health Professionals Follow-Up Study (HPFS). These analyses

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Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Abbreviations used: ALA, α-linolenic acid; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FA, fatty acid; FFQ, food-frequency questionnaire; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

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update our previous study in the NHS, which included only 199 cases and 14 y of follow-up (4), and extend our findings to men. Furthermore, we assessed the consistency of associations over time and investigated possible heterogeneity in associations of dietary fat intake with common histologic subtypes of NHL for the first time in these cohorts.

METHODS

Study populations

The NHS is an ongoing cohort study established in 1976, when 121,700 female registered nurses aged 30–55 y completed a self-administered questionnaire on risk factors for cancer and other diseases. Every 2 y, questionnaires are sent to cohort members to update information on potential risk factors and to identify newly diagnosed conditions. The HPFS cohort includes 51,529 men who were aged 40–75 y at baseline in 1986. Similar to the NHS, HPFS participants are followed with biennial questionnaires. Semiquantitative food-frequency questionnaires (FFQs) have been included every 2–4 y since 1980 for the NHS and every 4 y since 1986 for the HPFS (see below). Vital status is ascertained through next of kin and the National Death Index. For this analysis, men and women diagnosed with cancer (except nonmelanoma skin cancer) before dietary baseline (1980 for women; 1986 for men) were excluded. We also excluded men and women with a BMI (in kg/m^2) <15 or >45 at baseline, as well as individuals with missing or implausible FFQ responses. The analytic cohort included 47,531 men and 88,598 women.

This study was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. Informed consent was implied by return of the baseline questionnaire.

Case ascertainment

Cases included new diagnoses of NHL, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). We asked men and women who reported a new diagnosis of NHL on any biennial questionnaire through 2010 (or their next of kin who reported death owing to NHL) for permission to obtain related medical records and pathology reports. In the absence of medical records, we relied on information from state cancer registries. We previously demonstrated the completeness of reporting of lymphoid malignancies in the NHS (22). Study investigators blinded to exposure information reviewed available medical records and pathology reports to confirm NHL (International Classification of Diseases, 8th revision, codes 200, 202 and 204.1). Ninety percent of cases in the NHS and 95% of cases in the HPFS were confirmed by medical record (or cancer registry) review. Histologic subtype was determined according to the WHO classification of lymphomas (23). Specifically, diagnoses were made on the basis of morphology and immunophenotype information available in medical records and pathology reports. Immunophenotype information was not required for diagnoses of CLL/SLL or follicular lymphoma (FL), which can be reliably diagnosed by morphology alone (23). There were 1802 incident diagnoses of NHL (710 men and 1092 women) over the course of follow-up; of these, 494 were CLL/SLL (241 men and 253 women), 236 were diffuse large B cell lymphoma (DLBCL) (62 men and 174 women), and 262 were FL (79 men and 183 women). The remaining cases included 278 patients with uncommon or unspecified B cell histology, 69 patients with T cell lymphoma, and 463 patients who were determined to have NHL on the basis of morphology alone but lacked adequate phenotyping to assign the tumor to the B or T cell lineage.

Exposure assessment

Total and specific fat intake from food was assessed using semiquantitative FFQs (24). In the HPFS, diet was first assessed in 1986 and was updated every 4 y. In the NHS, diet was first assessed in 1980 and was updated every 2–4 y. On each FFQ, study participants responded to questions about usual consumption of specific foods; 9 response categories ranged from never or <1 serving/mo to ≥ 6 servings/d. Except for the 1980 and 1984 NHS FFQs, which included 61 and 116 items, respectively, all other FFQs in the NHS and HPFS queried 131 specific food items. Dietary fat intake was calculated according to the nutrient content of foods, derived from the USDA, food manufacturers, and other published sources, based on the frequency of consumption of specified portion sizes. In non-FFQ years, we used the nutrient intake value from the most recent FFQ. The validity and reliability of FFQs used in the HPFS and NHS were described elsewhere (24–27). Nutrients were adjusted for total energy (assessed on the same FFQ) using the residual method (28) and were considered continuous measures. To represent mean long-term exposure, we calculated cumulative mean intakes of energy-adjusted total and specific dietary fats, including animal, saturated, *trans,* and vegetable fats, α-linolenic acid (ALA; 18:3n–3), marine ω-3 FAs (sum of EPA [20:5n–3], docosapentaenoic acid [22:5n–3], DHA [22:6n–3]), and ω-6 FAs. Cumulative mean intakes were calculated as the mean of all available information from baseline up to the beginning of each 2-y follow-up cycle (29).

Statistical analyses

Person-time of follow-up was calculated for each participant from the return date of the baseline questionnaire (i.e., 1986 for the HPFS and 1980 the NHS) to the date of NHL diagnosis, death, or the end of follow-up (January 2010 for the HPFS and June 2010 for the NHS), whichever occurred first. Men and women who reported cancer or who died were excluded from subsequent follow-up. Cox proportional hazards models, stratifying by 2-y questionnaire period and treating age in months as the time scale, were used to estimate cohort-specific HRs and 95% CIs. We examined the possibly nonlinear relation between total fat intake and the HRs of NHL overall (among men and women separately) nonparametrically with restricted cubic splines (30). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. We found no evidence of nonlinearity in associations (P values >0.05). We also tested for violations of the proportional hazards assumption by including an interaction term between total fat and age in multivariable models. There was no violation of proportional hazards (P values >0.05). HRs are presented per cohort-specific SD of each dietary fat.

To control for potential confounding, we fit multivariable models that included total caloric intake (quintiles), height (in

inches), cumulative mean BMI (quintiles), race (white or nonwhite), smoking status (never, past, or current), physical activity (quintiles of metabolic equivalent hours per week), and multivitamin use (yes or no). These covariates were chosen because of evidence of an association with NHL in previous studies (4, 31–34). All covariates were treated as time varying in analyses and were updated every 2 y. Although there was no evidence of confounding by any of these variables in our study sample (compared with age- and calorie-adjusted models), we present results from fully adjusted models for completeness and ease of comparison of our data with the prior literature. There was also no evidence of confounding by alcohol intake (data not shown), which was not included in the final models. Individuals missing primary exposure variables were excluded from relevant analyses. Missing indicator categories were used to account for missing values for categorical covariates (35).

A priori, we examined the associations between dietary fat intake and NHL separately for men and women. With few exceptions as noted below, there was little evidence of between-cohort heterogeneity in associations; therefore, sex-specific results are presented in **Supplemental Tables 1–3**. We used a random-effects meta-analysis approach to derive effect estimates for men and women combined and we tested for heterogeneity by cohort and sex (36, 37). In pooled analyses, HRs are presented per SD of fat intake among women. We conducted analyses for NHL overall and also performed separate analyses for the most common NHL subtypes in these cohorts [i.e., CLL/SLL, DLBCL, and FL, classified for analysis according to guidelines from the International Lymphoma Epidemiology Consortium (38, 39)]. We used a contrast test to test for statistical heterogeneity in associations by histologic subtype (40). Because of smaller sample sizes for NHL subtypes, we conducted the tests for heterogeneity by subtype in combined (i.e., pooled) analyses only. Finally, because of known secular trends in fat intake over time (41), which were also observed in our cohorts, we stratified analyses by calendar time (1980/1986–1994 compared with 1994–2010) to evaluate whether associations differed in these 2 time periods, and we tested for differences in associations by time period using a Z test. In time-stratified analyses of NHL subtypes, models are adjusted for age and total calorie intake only. Analyses were carried out using SAS software (version 9.4; SAS Institute). All statistical tests were 2-sided and P values <0.05 were considered statistically significant.

TABLE 1
Baseline characteristics of the study samples[1]

Characteristic	NHS, 1980 (n = 88,598)	HPFS, 1986 (n = 47,531)
Age, y	46.7 ± 7.2	54.3 ± 9.8
Height, inches	64.5 ± 2.4	70.2 ± 2.6
BMI, kg/m^2	24.1 ± 4.1	25.5 ± 3.1
Nonwhite race, %	2	3
Smoking history, %		
Never smoker	44	45
Past smoker	28	41
Current smoker	29	10
Fat intake, g/d		
Total fat	69.7 ± 13.9	71.3 ± 14.1
Animal fat	52.2 ± 15.1	41.2 ± 12.6
Saturated fat	28.0 ± 6.4	24.4 ± 6.2
trans Fat	4.0 ± 1.3	2.8 ± 1.1
Vegetable fat	17.5 ± 9.0	30.1 ± 10.0
ALA	1.1 ± 0.28	1.1 ± 0.31
Marine ω-3 PUFAs	0.21 ± 0.16	0.34 ± 0.28
ω-6 PUFAs	6.3 ± 2.5	11.6 ± 3.0
Total calories, kcal/d	1566 ± 502	1985 ± 619
NHL diagnosis	1092	710
DLBCL	174	62
FL	183	79
CLL/SLL	253	241
Other B or T cell lymphomas	232	115
Unclassified	250	213

[1] Values are means ± SDs or n unless otherwise indicated. ALA, α-linolenic acid; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

RESULTS

Because of cohort enrollment criteria, on average, women were younger than men (mean age: 47 y and 54 y, respectively) at baseline (**Table 1**). Women were also more likely to be current smokers at baseline. In both cohorts, few participants were nonwhite (2–3%). Men and women had similar intakes of total fat at baseline; men generally had higher intakes of total calories and of vegetable fats and PUFAs, whereas women had higher intakes of animal and saturated fats at baseline (Table 1).

Over the full 24–30 y of follow-up, neither total nor specific dietary fats were significantly associated with NHL risk overall or with DLBCL (**Table 2**). However, higher intakes of total, animal, and saturated fat were significantly positively associated with an increased risk of the CLL/SLL subtype among women only (253 cases; P-trend ≤ 0.05): for each SD of intake, the risk of CLL/SLL increased by 27–30% (Supplemental Table 1). Non-significant associations were observed among men as well (Supplemental Table 1), but there was no evidence of heterogeneity by sex. In pooled analyses combining men and women, there was evidence of significant heterogeneity by subtype for animal fat, with associations observed only for CLL/SLL (P-heterogeneity = 0.03; Table 2). Vegetable fats, especially ALAs and ω-6 FAs, were associated with an increased risk of FL only: among men and women combined, the per-SD HRs for ALA and ω-6 FAs were 1.12 (95% CI: 1.04, 1.20; P-heterogeneity by subtype < 0.01) and 1.16 (95% CI: 1.03, 1.30; P-heterogeneity by subtype = 0.11), respectively.

Findings from analyses stratified by time period suggested important differences in associations of total fat, animal fat, and *trans* fats with overall NHL and of total fat with DLBCL in pooled analyses (P-heterogeneity < 0.05). The aforementioned associations for total, saturated, and animal fats and CLL/SLL risk among women over the full follow-up period were driven primarily by strong associations during the earlier half of follow-up (i.e., 1980–1994), for which we observed HRs ranging from 1.27 to 1.35 (Supplemental Table 2); however, only the association for total fat reached statistical significance (HR: 1.35; 95% CI: 1.02, 1.77). The corresponding associations were in the same direction, but were greatly attenuated, during the latter half of follow-up (i.e., 1994–2010) (Supplemental Table 3). Among women and men combined, from baseline through 1994, we also found positive associations of total fat intake with NHL overall (HR per SD: 1.13; 95% CI: 0.99, 1.29) and DLBCL in particular

TABLE 2
Associations of dietary fat intake with risk of NHL in pooled analyses for women in the NHS (1980–2010) and men in the HPFS (1986–2010)[1]

	NHL		DLBCL		FL		CLL/SLL		
Fat type	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*P*-heterogeneity for subtypes
Total fat	1802	1.01 (0.97, 1.07)	236	0.99 (0.85, 1.15)	262	0.96 (0.82, 1.14)	494	1.15 (0.95, 1.38)	0.35
Animal fat	1802	1.03 (0.97, 1.09)	236	0.98 (0.81, 1.19)	262	0.86 (0.72, 1.02)	494	1.17 (1.00, 1.37)	0.03
Saturated fat	1802	1.02 (0.97, 1.08)	236	1.02 (0.80, 1.30)	262	0.89 (0.76, 1.04)	494	1.18 (0.98, 1.42)	0.19
trans Fat	1802	1.00 (0.93, 1.06)	236	1.05 (0.89, 1.23)	262	0.99 (0.86, 1.15)	494	0.99 (0.89, 1.09)	0.82
Vegetable fat	1802	0.99 (0.95, 1.04)	236	1.00 (0.87, 1.16)	262	1.11 (0.95, 1.29)	494	1.01 (0.92, 1.11)	0.57
ω-6 PUFAs	1629	1.01 (0.96, 1.06)	216	1.00 (0.87, 1.15)	240	1.16 (1.03, 1.30)	461	0.99 (0.91, 1.08)	0.11
ALA	1629	1.02 (0.98, 1.07)	216	0.86 (0.74, 1.00)	240	1.12 (1.04, 1.20)	461	1.01 (0.93, 1.10)	<0.01
Marine ω-3 PUFAs	1629	1.01 (0.98, 1.05)	216	1.01 (0.90, 1.13)	240	1.05 (0.91, 1.21)	461	1.00 (0.93, 1.07)	0.80

[1] Cox proportional hazards models, stratifying by 2-y questionnaire period and treating age in months as the time scale, were used to estimate cohort-specific HRs and 95% CIs. Pooled HRs are per SD of intake in grams per day among women. There was no evidence of between-cohort heterogeneity in the random-effects meta-analysis for pooled associations (all *P* values >0.05). All models were adjusted for age (as the time scale), mean BMI (quintiles), total calories (quintiles), height (in continuous inches), smoking (never, past, or current), physical activity (quintiles), race (white or nonwhite), and multivitamin use (yes or no). *P*-heterogeneity is the *P* value from the test for heterogeneity between subtype-specific associations. ALA, α-linolenic acid; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

(HR per SD: 1.47; 95% CI: 1.06, 2.05) (**Table 3**). In addition, higher intakes of animal and saturated fat were significantly associated with a higher risk of NHL overall among women and men combined during this time period, again with elevated risks noted for DLBCL, although associations for DLBCL did not reach statistical significance. Furthermore, there was no evidence of statistical heterogeneity by subtype. For women only, *trans* fat intake was significantly positively associated with all NHL. Finally, for men only, marine ω-3 FAs were associated with a 23% increase in CLL/SLL risk per SD of intake (HR: 1.23; 95% CI: 1.04, 1.45) (Supplemental Table 2).

In contrast with positive associations observed during 1980–1994, there were no significant associations of total, animal, saturated, or *trans* fat intakes with the risk of NHL overall or by subtype among either women or men during 1994–2010 (**Table 4**, Supplemental Table 3). Results suggested that vegetable fats, including ALA and ω-6 FAs, were associated with an increased risk of FL during 1994–2010, particularly among men, for whom risk was significantly increased by 31–39% per SD of intake (Supplemental Table 3). Marine ω-3 FAs were not associated with the risk of NHL or its subtypes during this time period (Table 4).

In general, there was no evidence of between-sex heterogeneity in the random-effects meta-analysis for pooled associations for men and women combined (most *P* values >0.05); sex-specific results are presented in Supplemental Tables 1–3. In time-stratified analyses, a single exception was noted: during 1980/1986–1994, associations of total fat intake with CLL/SLL were significantly stronger among women than men (62 cases and 55 cases, respectively; *P*-heterogeneity = 0.03) (Supplemental Table 2).

DISCUSSION

Among our findings of modest associations with NHL or individual subtypes for intake of some types of fats, we noted appreciable differences in those associations by calendar period.

TABLE 3
Associations of dietary fat intake with risk of NHL in the NHS and HPFS (1980/1986–1994)[1]

	NHL		DLBCL		FL		CLL/SLL		
Fat type	*n*	HR (95% CI)[2]	*n*	HR (95% CI)[3]	*n*	HR (95% CI)[3]	*n*	HR (95% CI)[3]	*P*-heterogeneity for subtypes
Total fat	458	1.13 (0.99, 1.29)	40	1.47 (1.06, 2.05)	75	0.94 (0.75, 1.16)	117	1.09 (0.75, 1.58)[4]	0.08
Animal fat	458	1.17 (1.06, 1.29)	40	1.43 (0.81, 2.53)	75	0.87 (0.67, 1.11)	117	1.11 (0.87, 1.42)	0.18
Saturated fat	458	1.15 (1.04, 1.26)	40	1.52 (0.88, 2.62)	75	0.89 (0.71, 1.13)	117	1.09 (0.78, 1.52)	0.19
trans Fat	458	1.06 (0.89, 1.26)	40	1.17 (0.87, 1.58)	75	1.12 (0.91, 1.39)	117	0.87 (0.72, 1.05)	0.12
Vegetable fat	458	0.99 (0.88, 1.11)	40	1.18 (0.90, 1.54)	75	1.08 (0.88, 1.32)	117	0.96 (0.81, 1.13)	0.37
ω-6 PUFAs	425	1.06 (0.98, 1.15)	40	1.14 (0.88, 1.47)	72	1.09 (0.80, 1.48)	115	1.02 (0.88, 1.19)	0.77
ALA	425	1.07 (0.99, 1.15)	40	0.90 (0.58, 1.42)	72	1.04 (0.76, 1.41)	115	1.10 (0.94, 1.29)	0.69
marine ω-3 PUFAs	425	1.03 (0.95, 1.10)	40	0.89 (0.66, 1.21)	72	1.05 (0.90, 1.24)	115	1.05 (0.86, 1.29)	0.62

[1] Cox proportional hazards models, stratifying by 2-y questionnaire period and treating age in months as the time scale, were used to estimate cohort-specific HRs and 95% CIs. Pooled HRs are per SD of intake in grams per day among women. ALA, α-linolenic acid; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

[2] Adjusted for age (as the time scale), total calories (quintiles), mean BMI (quintiles), height (in continuous inches), smoking (never, past, or current), physical activity (quintiles), race (white or nonwhite), and multivitamin use (yes or no).

[3] Adjusted for age (as the time scale) and total calories (quintiles).

[4] Between-cohort heterogeneity ($P < 0.05$).

TABLE 4
Associations of dietary fat intake with risk of NHL in the NHS and HPFS (1994–2010)[1]

	NHL		DLBCL		FL		CLL/SLL		
Fat type	*n*	HR (95% CI)[2]	*n*	HR (95% CI)[3]	*n*	HR (95% CI)[3]	*n*	HR (95% CI)[3]	*P*-heterogeneity for subtypes
Total fat	1183	0.98 (0.93, 1.03)	182	0.96 (0.84, 1.10)	170	0.99 (0.86, 1.14)	328	1.08 (0.99, 1.19)	0.38
Animal fat	1183	0.98 (0.91, 1.06)	182	1.06 (0.87, 1.28)	170	0.88 (0.72, 1.07)	328	1.08 (0.95, 1.23)	0.21
Saturated fat	1183	0.98 (0.91, 1.04)	182	0.97 (0.82, 1.16)	170	0.92 (0.77, 1.10)	328	1.13 (1.01, 1.27)	0.11
trans Fat	1183	1.00 (0.94, 1.07)	182	1.00 (0.84, 1.19)	170	0.94 (0.78, 1.14)	328	1.06 (0.95, 1.19)	0.77
Vegetable fat	1183	0.98 (0.93, 1.03)	182	0.91 (0.80, 1.04)	170	1.10 (0.90, 1.35)	328	1.05 (0.96, 1.15)	0.16
ω-6 PUFAs	1183	0.96 (0.91, 1.01)	182	0.91 (0.73, 1.13)	170	1.14 (0.96, 1.37)	328	0.96 (0.88, 1.06)	0.19
ALA	1183	0.99 (0.95, 1.04)	182	0.90 (0.79, 1.04)	170	1.17 (0.99, 1.37)	328	0.97 (0.88, 1.06)	0.05
Marine ω-3 PUFAs	1183	1.00 (0.96, 1.03)	182	0.99 (0.87, 1.12)	170	0.98 (0.79, 1.22)	328	0.95 (0.86, 1.05)	0.87

[1] Cox proportional hazards models, stratifying by 2-y questionnaire period and treating age in months as the time scale, were used to estimate cohort-specific HRs and 95% CIs. Pooled HRs are per SD of intake in grams per day among women. There was no evidence of between-cohort heterogeneity (all $P > 0.05$). ALA, α-linolenic acid; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

[2] Adjusted for age (as the time scale), total calories (quintiles), mean BMI (quintiles), height (continuous inches), smoking (never, past, current), physical activity (quintiles), race (white, nonwhite), multivitamin use (yes, no).

[3] Adjusted for age (as the time scale) and total calories (quintiles).

These results suggest that dietary fats may have contributed to increased risks of NHL and specific subtypes of NHL historically but, for the most part, these associations have attenuated in recent years. Our findings of increased risks of NHL overall and of specific NHL subtypes with total, animal, saturated, and *trans* fat intakes during 1980–1994 are generally consistent with an earlier analysis in the NHS cohort during the same time period (4) and agree with findings from several case-control and cohort studies (9–13, 16), as discussed further below. However, for reasons that remain unclear, increases in risk associated with dietary fat have not persisted with longer follow-up. Intake of ALA, the major source of which is vegetables, was positively associated with FL in the most recent time period and overall. Intakes of other types of dietary fats did not appear to influence the risk of NHL or its subtypes in recent years.

Laboratory evidence from animal studies supports the hypothesis that high intakes of fat can lead to development of lymphomas; proposed biological mechanisms of action include inflammatory processes and chronic stimulation of the immune system (2, 3). Dietary fat, particularly ω-6 PUFAs, also has immunosuppressive properties (42). In contrast, ω-3 FAs have anti-inflammatory and proapoptotic properties (1). However, findings from epidemiologic studies have been somewhat inconsistent. Although several studies have reported associations between dietary fats and risk of NHL (4, 5, 9–13, 16, 18, 19, 43), both the specific types of fats and the histologic subtypes of NHL demonstrating the strongest associations have differed. Not including our previous analysis in the NHS (4), 10 case-control and cohort studies evaluated total fat intake in relation to NHL (5, 9–11, 16, 18–21, 43). Of these studies, 5 reported positive associations (9–11, 18, 43) and 5 reported no association (5, 16, 19–21). The most consistent evidence is for animal fat and saturated fat, which several studies have suggested are associated with increased risk of NHL overall (4, 9–13); however, there was no apparent association in one of the largest prospective cohort studies conducted to date, with >10 y of follow-up and 3611 NHL cases (21). To our knowledge, there has not been clear evidence of heterogeneity in associations by histologic subtype of NHL among the studies reporting positive associations. However, in a case-control study with >600 NHL cases, Charbonneau et al. (16) reported positive associations between *trans* FA intake and risk of NHL, which was particularly strong for DLBCL and CLL/SLL, consistent with our observations, particularly for the earlier part of our follow-up period. Another study reported strong positive associations of phytanic acid, a type of SFA, with an increased risk of overall NHL and with CLL/SLL and FL (12).

Some epidemiologic studies suggest that higher intakes of PUFAs, including ω-3 and ω-6 FAs, might be associated with a reduced risk of NHL (5, 10, 16, 19). In a Swedish case-control study, Chang et al. (5) demonstrated that individuals in the highest quartile of marine ω-3 FA intake had a statistically significant 40% lower risk of NHL overall, with reduced risks observed for CLL/SLL, DLBCL, and FL. Similar inverse associations were noted for ω-3 FA intake in another case-control study with 603 cases (16). However, our null results for marine ω-3 FAs are consistent with one other large cohort study, the NIH-AARP Diet and Health Study, which included >3600 NHL cases (21).

In this study, we observed that higher intake of vegetable fats, including ω-6 FAs and ALA, were positively associated with the risk of FL, particularly among men and particularly in the most recent time period. Because vegetable oils are the main sources of both ω-6 FAs and ALA (44), it is not unexpected that associations for ω-6 FAs, ALA, and vegetable fat would be similar. Although prior studies (45–47), including the NHS (48), have suggested that higher intakes of vegetables are inversely associated with NHL risk, the observed positive association for ω-6 FAs is biologically plausible because some ω-6 FAs can promote inflammation (49), which is a hallmark feature of NHL. However, in our study, we are not aware of any evidence that suggests that any effects would be limited to men or would be restricted to FL. In fact, Chang et al. (5) reported an inverse association between ω-6 FAs and the risk of FL (but not overall NHL). In another study, plant-based fat and NHL risk overall were not associated; however, there was evidence for heterogeneity by subtype, with a significant positive association for CLL/SLL only (16). In contrast, a small Italian case-control study reported a significant inverse association (OR: 0.6) for

associations of linoleic acid (a type of ω-6) and NHL (19). To our knowledge, only one prior study investigated associations of linolenic acid with NHL and the investigators found no association (19). Because of the lack of consistency by sex and subtype for the vegetable fats and ALA associations, the possibility of chance in our study cannot be ruled out.

Incidence rates for NHL in the United States have increased dramatically since about the 1950s (50–53). Rates doubled from the 1970s through the mid-1990s (53); for largely unexplained reasons, this increase slowed until about the mid-2000s and seems to have plateaued in recent years for many common subtypes (50, 51). In our study, positive associations for total, animal, saturated, and *trans* fat intake and NHL risk were generally restricted to the earlier time period (1980–1994), consistent with observed secular trends in incidence rates. Because of corresponding secular trends in fat intake, we also note that intakes of these specific fats among study participants were higher during this time period than during the later years (1994–2010). Our findings support the hypothesis that historically higher intakes of saturated and animal fats could have contributed to high incidence rates of NHL during this time period; alternatively, these associations could reflect chance. Our null results for the latter half of follow-up (1994–2010) are in contrast with positive associations reported in other studies with exposure assessment during this time period (9, 10, 16, 18, 43).

One potential limitation of this study is measurement error in fat intake, owing to inaccuracies in self-reports by participants, incorrect estimates of nutrient content of foods, or food sources not queried. However, the FFQ consists of $\sim$130 food items and was designed to include the most common foods consumed at the time of assessment. In addition, repeated measures of foods over time and the use of cumulative mean intake would reduce the influence of measurement error (29, 54). In addition, because diet was assessed prospectively before NHL diagnosis, any misclassification of diet would be nondifferential with respect to disease. Although we adjusted for established and suspected risk factors for NHL, the potential for confounding by unmeasured factors, such as pesticide exposure (55) or a family history of NHL (56), cannot be ruled out. Finally, the majority of participants in the NHS and HPFS are Caucasian; therefore, results might not be generalizable to other racial and ethnic groups.

Strengths of this study include its large sample size, prospective design with repeated and validated dietary assessment, and ability to evaluate possible differences in risk by histologic subtype and calendar period. In conclusion, our findings of differences in associations of dietary fats with NHL by calendar time suggest that certain dietary fats may have contributed to increased risks of NHL and specific subtypes of NHL historically but, for the most part, these associations have attenuated in recent years.

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The authors' responsibilities were as follows—BMB: designed the research with input from KAB; BMB, EG, and KAB: conducted the research; BMB, EG, and FL: provided essential materials; KAB: analyzed the data or performed statistical analysis, and wrote the first draft of the manuscript, which was critically reviewed by all authors; BMB: had primary responsibility for the final content; BAR: provided guidance on statistical analysis; SMZ and FL: provided critical scientific input; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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