

Dietary Fat and Protein in Relation to Risk of Non-Hodgkin's Lymphoma Among Women

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Background: Non-Hodgkin's lymphoma occurs more frequently in individuals with suppressed immune status, and some types of dietary fat and protein have been associated with decreased immune responses. In this study, we examined the intake of specific types of dietary fat and protein in relation to the risk of non-Hodgkin's lymphoma. **Methods:** We documented 199 incident cases of non-Hodgkin's lymphoma in a cohort of 88 410 women, who were enrolled in the Nurses' Health Study and were aged 34–60 years in 1980, during 14 years of follow-up. Relative risks of the disease and 95% confidence intervals (95% CIs) were calculated. All *P* values are two-sided and were considered to be statistically significant for *P* < .05. **Results:** Intake of saturated fat was associated with an increase in risk that was not statistically significant; the multivariate relative risk for the highest versus the lowest quintiles of intake was 1.4 (95% CI = 0.7–3.0; *P* for trend = .42). Intake of beef, pork, or lamb as a main dish was associated with a statistically significantly increased risk of non-Hodgkin's lymphoma; the multivariate relative risk for consumption of these meats at least once per day as compared with less than once per week was 2.2 (95% CI = 1.1–4.4; *P* for trend = .002). Higher intake of *trans* unsaturated fat was also statistically significantly associated with an increased risk of the disease; the multivariate relative risk for the highest versus the lowest quintiles was 2.4 (95% CI = 1.3–4.6; *P* for trend = .01). Higher intake of red meat cooked by broiling or barbecuing—but not by roasting, pan-frying, or boiling or stewing—was associated with an increase in risk that was not statistically significant. **Conclusions:** Greater dietary intake of certain meats and fats was associated with a higher

risk of non-Hodgkin's lymphoma. These relationships and their potential mechanisms deserve further examination. [J Natl Cancer Inst 1999;91:1751–8]

Higher risk of non-Hodgkin's lymphoma has been reported consistently in immunocompromised patients (1–4). An increase in dietary fat, particularly of *n*-6 polyunsaturated fatty acids, suppresses immune status in several animal models (5), but this has not been seen in humans fed polyunsaturated fat at levels of from 3% to 13% of energy (6,7). A decrease in total fat intake (to 25% of energy, mainly due to a reduction in saturated fat) improved the immune status of healthy women (6), and long-term ingestion of large amounts of dietary protein has increased immune tolerance (8). We thus hypothesized that higher dietary intakes of fat and protein would increase the risk of non-Hodgkin's lymphoma.

In a large cohort of postmenopausal women, the risk of non-Hodgkin's lymphoma increased with higher intakes of animal fat, saturated and monounsaturated fats but not with polyunsaturated fat (9). In that study, the association with intake of *trans* unsaturated fat was not reported (9). Few studies (9–14) have examined dietary protein and foods contributing to dietary fat and protein in relation to non-Hodgkin's lymphoma risk, and the findings have been inconsistent. We, therefore, evaluated these relationships in the Nurses' Health Study, a large prospective cohort of U.S. women.

METHODS

Study Cohort

In 1976, a total of 121 700 female registered nurses, aged 30–55 years living in 11 states of the United States, completed a mailed questionnaire about their medical history and health-related behaviors. Every 2 years, questionnaires have been sent to cohort members to update information on potential risk factors and to ascertain newly diagnosed cancers and other diseases. In 1980, a 61-food-item, semiquantitative food-frequency questionnaire was included to obtain dietary information (15). In 1984, the food-frequency questionnaire was expanded to 116 items (16). Similar questionnaires were used to update dietary intakes in 1986 and 1990. Through May 31, 1994, the follow-up was 95% complete as a percentage of potential person-years.

For the analyses presented here, women were excluded from the 1980 baseline population if they completed a 1980 dietary questionnaire with implausible total energy intake (i.e., <500 or >3500 kcal/day), left more than 10 food items blank, had a previous diagnosis of cancer (other than nonmelanoma

skin cancer), or had missing information on height and cigarette smoking. These exclusions left a total of 88 410 women for the analyses. The study was approved by the Human Research Committee at the Brigham and Women's Hospital.

Semiquantitative Food-Frequency Questionnaire

The validity and reliability of the food-frequency questionnaires used in the Nurses' Health Study have been described elsewhere (15–18). For each food, a commonly used unit or portion size (i.e., one egg or one slice of bread) was specified, and women were asked how often on average over the previous year they had consumed that amount of each food. There were nine possible responses, ranging from "never" to "six or more times per day." Nutrient intake was computed by multiplying the frequency response by the nutrient content of the specified portion sizes. We also asked questions on the types of fats or oil used in the preparation of foods and at the table. Values for the specific types of fat and protein in the foods were obtained from the Harvard University Food Composition Database (updated on November 22, 1993), which is derived from U.S. Department of Agriculture sources (19) and supplemented with information from manufacturers. Total *trans* isomers of unsaturated fat were based on values analyzed by Enig et al. (20) and by Slover et al. (21). We included all *trans* isomers of 18-carbon unsaturated fatty acids. The polyunsaturated fat reported in this study was the *n*-6 polyunsaturated linoleic acid (comprising 81% of total polyunsaturated fat in this population). To calculate the total red meat intake, we summed the frequencies for six categories—beef, pork, or lamb as a main dish; beef, pork, or lamb as a sandwich or mixed dish; hamburgers;

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hot dogs; processed meats; and bacon—and took into account the gram weights of servings.

Nutrient intakes calculated from the 1980 food-frequency questionnaire were found reasonably correlated with those recorded by 173 Boston women who kept diet diaries for four 1-week periods for more than 1 year (15,16). The Pearson correlation coefficients between energy-adjusted nutrient estimates from the 1980 food-frequency questionnaire and from the four 1-week dietary records were .47 for total protein, .53 for total fat, .59 for saturated fat, .48 for polyunsaturated fat, and .61 for cholesterol (15). The Pearson correlation coefficient between the calculated dietary intake of *trans* unsaturated fatty acids and the proportion of *trans* unsaturated fatty acids in adipose tissue was .51 (22). The Pearson correlation coefficients between the dietary records and the 1980 food-frequency questionnaire were .38 for meat and .71 for margarine (17). For meat products, fish, and eggs, the Pearson correlation coefficients between the dietary records and the 1980 food-frequency questionnaire ranged from .26 for hamburgers to .68 for eggs; for dairy products, the values ranged from .49 for hard cheese to .79 for skim milk and for butter; for sweet and baked foods, the values ranged from .27 for rice or pasta to .67 for peanut butter (17).

Because heterocyclic amines (HCAs) generated during the cooking of meats may be of etiologic significance for non-Hodgkin's lymphoma (23–25), we examined the method of cooking and the degree of doneness, which have been reported to be related to HCA levels (26,27). In the 1980 food-frequency questionnaire, women were also asked what percentage of the time they ate their meat cooked well-done. In the 1986 food-frequency questionnaire, we asked participants how often they ate beef, pork, or lamb as roasted, pan-fried, broiled, barbecued, and boiled or stewed; there were six possible responses for each form of cooking ranging from “never” to “five or more times per week.”

Ascertainment of Non-Hodgkin's Lymphoma Cases

Incident cases of non-Hodgkin's lymphoma (International Classification of Diseases, 8th Revision, code No. 202) were identified by self-report on each biennial questionnaire from 1982 through 1994. Deaths in the cohort were identified by reports from family members, the postal service, and a search of the National Death Index; we estimated that 98% of all deaths were identified (28). Women who reported lymphomas (or their next of kin, if the subject had died) were asked for permission to obtain hospital records and pathology reports. Physicians who had no knowledge of the dietary intake of the participants reviewed the records. During 14 years (representing 1 169 326 person-years) of follow-up, 199 cases of non-Hodgkin's lymphoma were documented.

Statistical Analysis

Person-years of observation for each participant were calculated from the date of returning the 1980 questionnaire to the date of diagnosis of non-Hodgkin's lymphoma, death, or June 1, 1994, whichever came first. For nutrient analyses, women were categorized by quintile of the 1980 baseline dietary intake of specific types of fat and protein,

after adjustment for total energy by the multivariate nutrient density method (18). In the multivariate nutrient density method, nutrient intake was expressed as a percentage of total energy intake, and total energy was simultaneously included in the model (18).

For each category of nutrient intake, we calculated the incidence rate by dividing the number of non-Hodgkin's lymphoma case patients by the number of person-years of follow-up. Relative risk (RR) was calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. Age-adjusted RRs were calculated with the use of 5-year age categories by the Mantel-Haenszel method (29). In multivariate analyses by use of pooled logistic regression with 2-year time increments (30,31), we simultaneously adjusted for age (5-year categories), smoking status (never, past, or current smoking of one to 14 cigarettes per day or ≥ 15 cigarettes per day), geographic region (Northeast, Midwest, South, or California), length of follow-up, total energy intake (quintiles),

and height in inches (<62 , ≥ 62 to <64 , ≥ 64 to <66 , ≥ 66 to <68 , or ≥ 68). These variables were risk factors for non-Hodgkin's lymphoma either in this population (age and height) or in other populations (smoking status and geographic region). We controlled for total energy to reduce measurement error due to general overreporting or underreporting of food items (18). For analyses of types of fat and protein, we adjusted as well for consumption of other types of fat, protein, and alcohol; in such models, the effect of each macronutrient can be considered as a substitution for carbohydrate (18). We controlled for fruit and vegetable intake, since this was inversely associated with risk of non-Hodgkin's lymphoma in this population. In these models, age and smoking status were updated biennially, and total energy intake was calculated from the 1980 food-frequency questionnaire. We also related body mass index, defined as the weight in kilograms divided by the square of the height in meters, to non-Hodgkin's lymphoma risk. We did not include body mass index

Table 1. Relative risks of non-Hodgkin's lymphoma by age, smoking status, geographic region, height, body mass index, and total energy intake*

Characteristic	No. of case patients	Person-years	Multivariate RR†	95% CI
Age,‡ y				
<50	34	473 384	1.0	Referent
50–54	39	239 398	2.1	1.3–3.3
55–59	47	228 573	2.6	1.6–4.0
60–64	43	153 210	3.2	2.0–5.1
≥ 65	36	74 761	5.4	3.1–9.1
Smoking status‡				
Never	82	510 112	1.0	Referent
Past	78	393 047	1.2	0.8–1.6
Current, 1–14 cigarettes/day	16	82 289	1.3	0.7–2.2
Current, ≥ 15 cigarettes/day	23	183 878	0.9	0.6–1.4
Geographic region of residence§				
Northeast	101	682 974	1.0	Referent
Midwest	41	221 512	1.3	0.9–1.8
South	28	123 349	1.4	0.9–2.2
California	29	141 492	1.2	0.8–1.8
Height, in				
<62	12	116 096	1.0	Referent
≥ 62 to <64	44	285 636	1.5	0.8–2.9
≥ 64 to <66	65	364 426	1.8	1.0–3.4
≥ 66 to <68	51	279 291	1.9	1.0–3.6
≥ 68	27	123 878	2.4	1.2–4.7
Two-sided <i>P</i> for trend			.01	
Body mass index,§ weight in kg/(height in m) ²				
<21.0	36	249 464	1.0	Referent
21.0–22.9	49	284 711	1.1	0.7–1.7
23.0–24.9	45	235 730	1.2	0.8–1.8
25.0–29.9	48	268 573	1.1	0.7–1.6
≥ 30	21	125 246	1.0	0.6–1.8
Two-sided <i>P</i> for trend			.92	
Total energy,§ kcal				
<1139	51	233 646	1.0	Referent
1139–1392	42	233 283	0.8	0.6–1.3
1393–1634	30	234 280	0.6	0.4–0.9
1635–1954	40	234 619	0.8	0.5–1.2
≥ 1955	36	233 498	0.7	0.5–1.1
Two-sided <i>P</i> for trend			.14	

*RR = relative risk; CI = confidence interval.

†Variables were mutually adjusted for each other with additionally controlling for length of follow-up (seven periods).

‡Updated every 2 years.

§1980 information.

Table 2. Relative risks (RRs) of non-Hodgkin's lymphoma by quintiles of specific types of dietary fat, cholesterol, and dietary protein in 1980 among 88 410 women

	Quintile of nutrient intake					Quintile 5, 95% CI*	Two-sided <i>P</i> for trend
	1	2	3	4	5		
Total fat							
No. of case patients	32	38	43	46	40		
Intake, % energy†	28.7	34.9	39.1	43.1	48.7		
Age-adjusted RR	1.0	1.3	1.5	1.6	1.4	0.9–2.2	.10
Multivariate RR‡	1.0	1.3	1.5	1.7	1.4	0.9–2.3	.07
Multivariate RR§	1.0	1.2	1.4	1.4	1.2	0.7–2.0	.44
Animal fat							
No. of case patients	34	32	46	43	44		
Intake, % energy†	18.6	24.5	28.9	33.4	40.1		
Age-adjusted RR	1.0	1.0	1.5	1.4	1.4	0.9–2.2	.07
Multivariate RR‡	1.0	1.0	1.5	1.4	1.4	0.9–2.2	.06
Multivariate RR§ + adjustment for vegetable fat	1.0	0.9	1.3	1.2	1.2	0.7–2.1	.30
Vegetable fat							
No. of case patients	38	43	42	41	35		
Intake, % energy†	4.0	6.7	9.0	11.7	16.2		
Age-adjusted RR	1.0	1.2	1.2	1.2	1.0	0.6–1.5	.81
Multivariate RR‡	1.0	1.2	1.2	1.2	1.0	0.6–1.6	.90
Multivariate RR§ + adjustment for animal fat	1.0	1.2	1.2	1.2	1.0	0.6–1.7	.89
Saturated fat							
No. of case patients	30	36	50	36	47		
Intake, % energy†	11.0	13.7	15.6	17.4	20.1		
Age-adjusted RR	1.0	1.3	1.8	1.3	1.7	1.1–2.7	.03
Multivariate RR‡	1.0	1.3	1.9	1.4	1.8	1.1–2.9	.02
Multivariate RR§ + adjustments for monounsaturated, polyunsaturated, and <i>trans</i> unsaturated fats	1.0	1.1	1.5	1.1	1.4	0.7–3.0	.42
Monounsaturated fat							
No. of case patients	31	34	47	42	45		
Intake, % energy†	11.1	13.9	15.9	17.9	20.9		
Age-adjusted RR	1.0	1.2	1.7	1.5	1.6	1.0–2.6	.03
Multivariate RR‡	1.0	1.2	1.7	1.6	1.7	1.1–2.7	.02
Multivariate RR§ + adjustments for saturated, polyunsaturated, and <i>trans</i> unsaturated fats	1.0	0.9	1.1	0.9	0.8	0.4–1.9	.63
n-6 polyunsaturated fat							
No. of case patients	39	42	43	31	44		
Intake, % energy†	2.5	3.4	4.1	4.8	6.2		
Age-adjusted RR	1.0	1.1	1.2	0.9	1.3	0.9–2.0	.38
Multivariate RR‡	1.0	1.1	1.2	0.9	1.3	0.8–2.0	.49
Multivariate RR§ + adjustments for saturated, monounsaturated, and <i>trans</i> unsaturated fats	1.0	1.0	0.9	0.6	0.8	0.5–1.4	.30
<i>Trans</i> unsaturated fat							
No. of case patients	28	37	46	34	54		
Intake, % energy†	1.3	1.8	2.2	2.6	3.2		
Age-adjusted RR	1.0	1.4	1.8	1.4	2.2	1.4–3.4	.003
Multivariate RR‡	1.0	1.4	1.8	1.4	2.2	1.4–3.5	.002
Multivariate RR§ + adjustments for saturated, monounsaturated, and polyunsaturated fats	1.0	1.3	1.8	1.4	2.4	1.3–4.6	.01
Fish omega-3 fatty acids							
No. of case patients	33	40	46	39	41		
Intake, % energy†	0.02	0.03	0.04	0.05	0.10		
Age-adjusted RR	1.0	1.2	1.3	1.1	1.1	0.7–1.7	.90
Multivariate RR‡	1.0	1.2	1.3	1.0	1.0	0.7–1.7	.71
Multivariate RR‡ + adjustments for saturated and <i>trans</i> unsaturated fats and fruit and vegetable intake	1.0	1.2	1.4	1.2	1.4	0.8–2.2	.42
Cholesterol							
No. of case patients	36	37	45	39	42		
Intake, mg/1000 kcal/day†	133.8	172.3	201.8	234.6	296.9		
Age-adjusted RR	1.0	1.1	1.3	1.1	1.2	0.8–1.9	.49
Multivariate RR‡	1.0	1.1	1.3	1.1	1.1	0.7–1.7	.75
Multivariate RR§ + adjustments for saturated, monounsaturated, polyunsaturated, and <i>trans</i> unsaturated fats	1.0	0.9	1.1	0.9	1.0	0.6–1.6	.92
Total protein							
No. of case patients	31	48	37	41	42		
Intake, % energy†	14.7	17.1	18.8	20.6	24.0		
Age-adjusted RR	1.0	1.5	1.1	1.2	1.2	0.8–1.9	.77
Multivariate RR‡	1.0	1.5	1.1	1.2	1.2	0.7–1.8	.99

(Table continues)

Table 2 (continued). Relative risks (RRs) of non-Hodgkin's lymphoma by quintiles of specific types of dietary fat, cholesterol, and dietary protein in 1980 among 88 410 women

	Quintile of nutrient intake					Quintile 5, 95% CI*	Two-sided P for trend
	1	2	3	4	5		
Multivariate RR [‡] + adjustments for saturated, monounsaturated, polyunsaturated, and <i>trans</i> unsaturated fats, alcohol, and fruit and vegetable intake	1.0	1.4	1.1	1.2	1.3	0.8–2.1	.69
Animal protein							
No. of case patients	29	50	34	45	41		
Intake, % energy [†]	10.7	13.3	15.2	17.2	20.6		
Age-adjusted RR	1.0	1.7	1.1	1.5	1.3	0.8–2.1	.54
Multivariate RR [‡]	1.0	1.7	1.1	1.5	1.3	0.8–2.0	.71
Multivariate RR [‡] + adjustments for saturated, monounsaturated, polyunsaturated, and <i>trans</i> unsaturated fats, vegetable protein, alcohol, and fruit and vegetable intake	1.0	1.6	1.0	1.4	1.2	0.7–2.1	.86
Vegetable protein							
No. of case patients	47	33	47	40	32		
Intake, % energy [†]	2.4	3.0	3.5	4.1	5.0		
Age-adjusted RR	1.0	0.7	1.0	0.8	0.6	0.4–1.0	.09
Multivariate RR [‡]	1.0	0.7	1.0	0.8	0.6	0.4–0.9	.06
Multivariate RR [‡] + adjustments for saturated, monounsaturated, polyunsaturated, and <i>trans</i> unsaturated fats, animal protein, alcohol, and fruit and vegetable intake	1.0	0.7	1.0	0.9	0.7	0.4–1.3	.49

*95% CI = 95% confidence intervals for RRs for quintile 5.

[†]Values for intake are medians for each quintile of nutrient intake in 1980.

[‡]Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, or California), cigarette smoking (never, past, or current smoking of 1–14 cigarettes per day or ≥ 15 cigarettes per day), and height in inches (< 62 , ≥ 62 to < 64 , ≥ 64 to < 66 , ≥ 66 to < 68 , or ≥ 68).

§Additional adjustments for dietary protein (quintiles), alcohol intake (0 g/day, 0.1–4.9 g/day, 5–14.9 g/day, or ≥ 15 g/day), and fruit and vegetable intake (< 3 servings/day, 3–3.9 servings/day, 4–4.9 servings/day, 5–5.9 servings/day, or ≥ 6 servings/day).

in multivariate analyses of types of fat and protein because it was not a risk factor for non-Hodgkin's lymphoma in this population. In separate analyses that incorporated repeated dietary measurements, the incidence of non-Hodgkin's lymphoma was related to the cumulative average intake from all available dietary questionnaires up to the start of each 2-year follow-up interval or to the most recent intake at the start of each 2-year follow-up interval (32). Indicator variables were used to denote any time period for which a questionnaire was not available. For all RRs, we calculated 95% confidence intervals (CIs). All *P* values were two-tailed and were considered to be statistically significant when $< .05$. Tests for trend were conducted by use of the median values for each quintile of nutrient intake as a continuous variable for nutrient analysis or by use of the frequency responses in servings per day as one variable for food analysis.

RESULTS

Age was strongly associated with an increased risk of non-Hodgkin's lymphoma, and we also observed a strong positive association with height (Table 1). However, smoking status, geographic region, body mass index in 1980, and total energy intake were unrelated to risk (Table 1). When body mass index was updated every 2 years, which represents the most recent status, the association became inverse (RRs for increasing categories = 1.0, 0.8, 0.8, 0.6 and 0.7 [95% CI = 0.4–1.2]; *P* for trend = .11).

After adjustment for age and other potential risk factors, we observed statistically significant positive associations between the 1980 dietary intakes of saturated, monounsaturated, and *trans* unsaturated fats and the risk of non-Hodgkin's lymphoma (*P* for trend $< .05$) (Table 2). The statistically significant association for intake of *trans* unsaturated fat remained after further adjustments for other types of fat, protein, alcohol, and fruit and vegetable intake; the multivariate RR for the highest quintile of intake compared with the lowest quintile of intake was 2.4 (95% CI = 1.3–4.6). The comparable RR after additional adjustment for beef, pork, or lamb as a main dish was 1.8 (95% CI = 1.1–3.0). However, the positive associations for saturated and monounsaturated fats were greatly attenuated after further adjustments for other types of fat, protein, alcohol, and fruit and vegetable intake. We also examined *trans* unsaturated fat from vegetable fat (due to partial hydrogenation of vegetable oils) and from animal fat separately. For increasing quintiles, the multivariate RRs for *trans* unsaturated vegetable fat were 1.0, 1.7, 1.8, 1.8, and 1.9 (95% CI = 1.2–3.1) (*P* for trend = .03) and for *trans* unsaturated animal fat were 1.0, 1.4, 1.3, 1.7, and 1.4 (95% CI =

0.8–2.2) (*P* for trend = .15); the mean intakes as percent of energy for quintiles of *trans* unsaturated vegetable fat were 0.5%, 0.9%, 1.2%, 1.6%, and 2.3% and for *trans* unsaturated animal fat were 0.5%, 0.7%, 0.9%, 1.1%, and 1.3%. Dietary intakes of total fat, animal fat, vegetable fat, n-6 polyunsaturated fat, fish omega-3 fatty acids, cholesterol, total protein, animal protein, and vegetable protein were not statistically significantly related to risk (Table 2).

When we treated the 1980 nutrients as continuous variables, the multivariate RRs were 2.2 (95% CI = 1.2–3.9) for an increase of 2% in energy obtained from *trans* unsaturated fat compared with the equivalent energy from carbohydrate and 1.2 (95% CI = 0.8–1.7) for an increase of 5% in energy from saturated fat compared with the equivalent energy from carbohydrate. To address the potential bias that women may change their diet because of symptoms of non-Hodgkin's lymphoma, we further excluded incident cases (*n* = 30 cases) occurring during the first 4 years of follow-up; the results did not appreciably change (RR = 2.3 [95% CI = 1.2–4.3] for *trans* unsaturated fat and RR = 1.3 [95% CI = 0.9–2.0] for saturated fat). When nutrients were expressed as the cumulative average intakes, the as-

sociations were greatly attenuated; the multivariate RRs were 1.5 (95% CI = 0.8–3.0) for an increase of 2% in energy obtained from *trans* unsaturated fat and 1.0 (95% CI = 0.6–1.7) for an increase of 5% in energy from saturated fat. When nutrients were expressed as the most recent intakes, the associations were further reduced and became less than 1.0; the multivariate RRs were 0.9 (95% CI = 0.5–1.6) for an increase of 2% in energy obtained from *trans* unsaturated fat and 0.7 (95% CI = 0.4–1.0) for an increase of 5% in energy from saturated fat.

Margarine accounted for 22% of total *trans* unsaturated fat intake; beef, pork, or lamb as a main dish for 16%; and cookies for 12%. Other individual meats, baked foods, and dairy products each accounted for less than 7%. Margarine consumption was weakly and statistically nonsignificantly associated with risk (Table 3). Similar weak associations were seen for both stick margarine (RRs = 1.0, 1.1, 0.7, 1.0, and 1.2 [95% CI = 0.8–1.2]; *P* for trend = .39) and tub margarine (RRs = 1.0, 1.0, 0.8, 0.8, and 1.3 [95% CI = 0.9–2.0]; *P* for trend = .33) and in analyses limited to women who did not

greatly change their margarine intake between 1970 and 1980 (RRs = 1.0, 1.2, 0.8, 1.0, and 1.2 [95% CI = 0.8–1.9]; *P* for trend = .33). A statistically significant increase in the risk of non-Hodgkin's lymphoma was seen with greater intake of beef, pork, or lamb as a main dish; the multivariate RR was 2.2 (95% CI = 1.1–4.4) for consumption at least once per day compared with less than once per week (Table 3) and fell to 2.0 (95% CI = 1.0–4.0) after further adjustment for fruit and vegetable intake and to 1.7 (95% CI = 0.8–3.7) after additional adjustments for saturated and *trans* unsaturated fats. The association was strengthened when we limited analyses to women who reported that they did not greatly change their diet between 1970 and 1980; the comparable multivariate RRs were 1.0 (referent), 1.4, 1.9, 2.4, and 3.2 (95% CI = 1.4–7.3) (*P* for trend = .003). The multivariate RRs for increasing quintiles of total red meat intake were 1.0 (referent), 0.9, 1.3, 1.0, and 1.3 (95% CI = 0.8–2.2) (*P* for trend = .25). Beef, pork, or lamb as a main dish accounted for 68% of the total red meat intake. Intake of homemade pie was also related to an increased risk; the mul-

tivariate RR was 1.6 (95% CI = 1.0–2.6) for women consuming at least one serving per week compared with those consuming less than one serving per month. Higher intake of cake was also statistically significantly associated with a higher risk; the multivariate RR was 2.0 (95% CI = 1.2–3.4) for women consuming at least two servings per week compared with those consuming less than one serving per month. Intakes of cookies and white bread, two other sources of *trans* unsaturated fat, were not statistically significantly related to risk. We did not find statistically significant associations for intakes of beef, pork, or lamb as a mixed dish or sandwich; bacon; hot dogs; processed meats; hamburgers; chicken with skin; chicken without skin; fish; eggs; liver; skim or low-fat milk; whole milk; or other dairy products with the risk of non-Hodgkin's lymphoma (data not shown).

Risk of non-Hodgkin's lymphoma was slightly lower among women who consumed meat cooked well-done; for increasing quintiles of the percent of instances of consumption as well-done, the multivariate RRs were 1.0 (referent), 0.7,

Table 3. Relative risks (RRs) of non-Hodgkin's lymphoma by intake of foods as major sources of *trans* unsaturated fat in 1980 (unit of consumption given in parentheses)

	Frequency of consumption						Two-sided <i>P</i> for trend	
	<1/mo	1–3/mo	1/wk	2–4/wk	5–6/wk	1/d	≥2/d	
Margarine (teaspoon; 5 mL)								
No. of case patients	41		32		14	42	70	
Multivariate RR*	1.0		1.2		0.9	1.0	1.2	.25
95% CI†	Referent		0.7–1.8		0.5–1.6	0.7–1.5	0.8–1.8	
Beef, pork, or lamb (main dish, 6–8 oz)								
No. of case patients	26		51	82	23	17		
Multivariate RR*	1.0		1.0	1.4	1.7	2.2		.002
95% CI†	Referent		0.6–1.5	0.9–2.2	0.9–3.2	1.1–4.4		
Cookie (1)								
No. of case patients	39	52	27	46	35			
Multivariate RR*	1.0	1.2	1.1	1.5	1.2			.46
95% CI†	Referent	0.8–1.9	0.7–1.8	1.0–2.3	0.7–1.9			
White bread (1 slice)								
No. of case patients	65	14	12	28	25	28	27	
Multivariate RR*	1.0	1.1	0.9	0.9	1.7	1.0	0.9	.65
95% CI†	Referent	0.6–1.9	0.5–1.6	0.6–1.4	1.0–2.6	0.6–1.6	0.5–1.4	
Pie, home-made (1 slice)								
No. of case patients	98	75	26					
Multivariate RR*	1.0	1.1	1.6					.07
95% CI†	Referent	0.8–1.5	1.0–2.6					
Cake (1 slice)								
No. of case patients	51	99	28	21				
Multivariate RR*	1.0	1.6	1.3	2.0				.03
95% CI†	Referent	1.1–2.2	0.8–2.1	1.2–3.4				

*Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, or California), cigarette smoking (never, past, or current smoking of 1–14 cigarettes per day or ≥15 cigarettes per day), and height in inches (<62, ≥62 to <64, ≥64 to <66, ≥66 to <68, or ≥68).

†CI = confidence interval.

1.0, 0.8, and 0.7 (95% CI = 0.5–1.0) (P for trend = .07). Consumption of broiled beef, pork, or lamb at least two to four times per week was associated with a statistically nonsignificant increase in risk (RR = 1.8; 95% CI = 1.0–3.3; P for trend = .09) (Table 4). We also observed a statistically nonsignificant increase in risk with higher intake of barbecued beef, pork, or lamb. However, consumption of beef, pork, or lamb that was roasted, pan-fried, or boiled or stewed was not associated with risk.

DISCUSSION

In this large cohort of women, intake of beef, pork, or lamb as a main dish was most strongly associated with the risk of non-Hodgkin's lymphoma. Higher intakes of *trans* unsaturated fat and, perhaps, saturated fat were associated with an increased risk. Other major types of fat or protein were not independently associated with risk.

The prospective design and high follow-up rates in this study minimize the concern that methodologic biases explain

the findings. The estimates of dietary intakes derived from the dietary questionnaire used in this study reasonably reflect long-term intakes of study subjects (15). However, some misclassification of individual long-term diet still exists, which would tend to weaken any true associations. Because patients with non-Hodgkin's lymphoma are usually diagnosed because of symptoms, such as significant weight loss, fever, and night sweats, dietary change because of these symptoms is a potential source of bias, which is consistent with the different results for body mass index when using the most recent exposure rather than the index in 1980. The use of baseline diet rather than the most recent diet helps to reduce this bias. Residual confounding by nondietary factors cannot be excluded, but it is also unlikely to explain these observed findings because controlling for potential nondietary risk factors for non-Hodgkin's lymphoma had minimal effect on the RRs. Other aspects of foods associated with risk could confound associations with types of fat.

Consistent with the Iowa Women's

Health Study (9), we observed a positive association between saturated fat intake and the risk of non-Hodgkin's lymphoma, albeit not statistically independent of *trans* unsaturated fat, and we found no association with n-6 polyunsaturated fat. Animal protein intake was associated with an increased risk in the Iowa Women's Health Study (9) and in an international correlation study (10). We did not confirm this association in this study, which is consistent with the finding from a case-control study (11).

This study revealed a strong positive association between *trans* unsaturated fat and the risk of non-Hodgkin's lymphoma. Margarine intake, a major source of *trans* unsaturated fat, had a statistically significant positive association with risk in a case-control study (RR = 1.4; P < .05) (13). We found weak and nonsignificant associations with intakes of margarine and cookies and observed no association with white bread. However, we found statistically significant positive associations with intakes of pie and cake, which are often high in *trans* unsaturated fat from partially hydrogenated vegetable oils. Our finding on *trans* unsaturated fat needs to be interpreted with caution. We cannot exclude the possibility that this was due to chance because so many nutrients were examined.

Milk consumption has been associated with the risk of non-Hodgkin's lymphoma in two case-control studies and in a cohort study (12–14); however, this was not seen in the Iowa Women's Health Study (9), a case-control study in women (11), or our data. Hamburger intake was associated with an increased risk in the Iowa Women's Health Study (9), but we found no such association. However, women in the Iowa Women's Health Study had higher consumption of hamburgers (36% of them consumed more than one per week as compared with 24% in this study) (9). The present finding of an approximately twofold higher risk of non-Hodgkin's lymphoma among women who consumed a higher amount of beef, pork, or lamb has not been reported before. Because so many foods were examined, we also cannot exclude with confidence the possibility that this positive result was due to chance. However, the greater strength of association among women with consistent long-term consumption suggests that this may be a true causative factor. Although different meat products were most strongly associated with risk in

Table 4. Relative risks (RRs) of non-Hodgkin's lymphoma by method of cooking beef, pork, or lamb in 1986

	Frequency of consumption				Two-sided <i>P</i> for trend
	<1/mo	1–3/mo	1/wk	≥2–4/wk	
Broiled					
No. of case patients	27	37	30	19	
Age-adjusted RR	1.0	1.5	1.6	1.8	.13
Multivariate RR*	1.0	1.5	1.6	1.8	.09
95% CI†	Referent	0.9–2.4	1.0–2.7	1.0–3.3	
Barbecued					
No. of case patients	55	32	25		
Age-adjusted RR	1.0	1.2	1.4		.16
Multivariate RR*	1.0	1.2	1.5		.13
95% CI†	Referent	0.8–1.9	0.9–2.4		
Roasted					
No. of case patients	30	47	37		
Age-adjusted RR	1.0	0.9	0.9		.53
Multivariate RR*	1.0	0.9	0.9		.64
95% CI†	Referent	0.6–1.5	0.5–1.4		
Pan-fried					
No. of case patients	59	29	22		
Age-adjusted RR	1.0	1.4	1.0		.91
Multivariate RR*	1.0	1.4	1.0		.89
95% CI†	Referent	0.9–2.2	0.6–1.7		
Boiled or stewed					
No. of case patients	52	42	17		
Age-adjusted RR	1.0	1.3	0.9		.79
Multivariate RR*	1.0	1.3	1.0		.94
95% CI†	Referent	0.9–2.0	0.5–1.7		

*Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (four periods), geographic region (Northeast, Midwest, South, or California), cigarette smoking (never, past, or current smoking of 1–14 cigarettes per day or ≥15 cigarettes per day), and height in inches (<62, ≥62 to <64, ≥64 to <66, ≥66 to <68, or ≥68).

†CI = confidence interval.

the Nurses' Health Study and in the Iowa Women's Health Study (9), they are consistent in showing that some aspects of red meat consumption may be related to risk of non-Hodgkin's lymphoma.

The formation of HCAs increases with temperature and duration of cooking; meats cooked to a rare or medium-rare state have markedly less mutagen content than well-done meats (26,27,33). However, we found a weak inverse association between a higher frequency of well-done meat consumption and the risk of non-Hodgkin's lymphoma, which is consistent with the finding from the Iowa Women's Health Study comparing women who consumed well-done meats with those who consumed rare or medium-rare meats (9). Food-cooking methods also influence the formation of HCAs; frying, broiling, and barbecuing meats produced substantially more HCAs than did stewing, steaming, and poaching (34). In this study, only intake of beef, pork, or lamb that had been broiled or barbecued was associated with increased risk. However, in this population, chicken was the major source of HCAs (35), yet chicken consumption was unrelated to risk. Thus, our findings do not fully support the hypothesis of HCAs as causative factors for non-Hodgkin's lymphoma. Our questions on meat-cooking method and doneness are not comprehensive and have limitations, which may underestimate the true association of HCAs with non-Hodgkin's lymphoma risk.

We are unaware of other studies that have examined the association between height and the risk of non-Hodgkin's lymphoma. Adult height in part reflects early energy balance (18); its implication on non-Hodgkin's lymphoma deserves further investigation.

In the Nurses' Health Study, higher intakes of beef, pork, or lamb as a main dish, *trans* unsaturated fat, and saturated fat are associated with greater risk of non-Hodgkin's lymphoma. The etiologic importance of these associations remains unclear, and these deserve further investigations in other cohorts.

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NOTES

Supported by Public Health Service grant CA40356 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

We thank the participants of the Nurses' Health Study for their continuing outstanding dedication and commitment to the study and Frank B. Hu, Barbara Egan, Lisa Li, Karen Corsano, Laura Sampson, and Debbie Flynn for their advice and assistance.

Manuscript received February 21, 1999; revised August 4, 1999; accepted August 20, 1999.