Intakes of Fruits, Vegetables, and Related Nutrients and the Risk of Non-Hodgkin's Lymphoma among Women[1]

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Abstract

Non-Hodgkin's lymphoma is etiologically related to suppressed immune status, and certain nutrients found in fruits and vegetables have been associated with increased immune responses. However, limited information exists on associations between intake of fruits, vegetables, and related nutrients and non-Hodgkin's lymphoma risk. We thus examined these associations among 88,410 women in the Nurses' Health Study cohort who were aged 34–60 years in 1980 and provided dietary information in 1980. During 14 years of follow-up, we documented 199 incident cases of non-Hodgkin's lymphoma. Higher intake of fruits and vegetables was associated with a lower risk of non-Hodgkin's lymphoma (*P* for trend = 0.02); the multivariate relative risk (RR) was 0.62 [95% confidence interval (CI), 0.38–1.02] for women who consumed greater than or equal to six servings per day as compared with those consuming less than three servings per day. When fruits and vegetables were examined separately, intake of vegetables rather than fruits was most clearly associated with a reduced risk (*P* for trend = 0.02 for vegetables; *P* for trend = 0.16 for fruits); compared with those consuming less than one serving per day, the multivariate RRs were 0.62 (95% CI, 0.35–1.07) for women who consumed greater than or equal to three servings per day of vegetables and 0.70 (95% CI, 0.44–1.12) for women who consumed this amount of fruits. Higher intake of cruciferous vegetables was also associated with a decreased risk (*P* for trend = 0.03); the multivariate RR was 0.67 (95% CI, 0.40–1.11) for women who consumed greater than or equal to five servings per week as compared with those consuming less than two servings per week. These associations were slightly attenuated when we additionally adjusted for intake of beef, pork, or lamb as a main dish. Intake of dietary fiber from vegetable sources was related to a reduced risk; the multivariate RR was 0.54 (95% CI, 0.34–0.87) for women in the highest quintile as compared with those in the lowest quintile (*P* for trend = 0.01), and it was slightly attenuated with additional adjustment for saturated and *trans* unsaturated fats. However, we observed no associations between intakes of specific dietary carotenoids, vitamins A, C, E, and folate, and non-Hodgkin's lymphoma risk. Higher intake of vegetables, particularly cruciferous vegetables, may reduce the risk of non-Hodgkin's lymphoma among women.

Introduction

Incidence and mortality rates of non-Hodgkin's lymphoma have greatly increased during the past several decades (1). High risk of non-Hodgkin's lymphoma has been consistently related to compromised immune status (2–5).

Fruits and vegetables are rich sources of carotenoids, vitamins C and E, folate, and dietary fiber, as well as numerous other phytochemicals that may inhibit carcinogenesis (6). Carotenoids and vitamins C and E might protect against carcinogenesis by neutralizing reactive oxygen species generated endogenously or exogenously, thus reducing oxidative DNA damage and mutations (7), and by enhancing immune responses (8). Cells of the immune system in general have higher concentrations of nutrients with antioxidant activities than do other cells (8). Inadequacy of folate results in abnormal DNA methylation and synthesis, chromosome breaks, and disruption of DNA repair (9–11). Normal DNA synthesis may be particularly important in the lymphatic system, which depends on cell proliferation to respond to foreign stimuli. Vitamin A influences growth and differentiation of various hematopoietic progenitor cells (12) and enhances immunity (12, 13).

Only a few studies have examined the associations between intake of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma; the findings have been inconsistent (14–18). Because food composition data have only recently become available for specific carotenoids (19, 20), no study has examined the associations between intakes of specific dietary carotenoids and non-Hodgkin's lymphoma risk, and no published data are available for folate intake. We therefore evaluated these associations in the Nurses' Health Study, a large prospective cohort among United States women.

Materials and Methods

Study Cohort. The Nurses' Health Study was established in 1976 when 121,700 female registered nurses aged 30–55 years living in 11 states completed a mailed questionnaire on risk factors for cancer and other diseases. Every 2 years, questionnaires have been sent to cohort members to update information on potential risk factors and to identify newly diagnosed can-

Received 9/1/99; revised 1/28/00; accepted 2/28/00.
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[1] Supported in part by research Grant CA 40356 from the NIH.
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cers and other diseases. In 1980, a 61-food-item semiquantitative food frequency questionnaire was included to obtain dietary information. In 1984, the food frequency questionnaire was expanded to 116 items, and similar questionnaires were used to update dietary intake of women in 1986 and 1990. Through May 31, 1994, the follow-up rate was 98% complete as a percentage of potential person-years.

Women were excluded from the 1980 baseline population if they did not complete the 1980 dietary questionnaire ($n = 23,238$), had implausible total energy intake (<500 or >3500 kcal/day), left ≥ 10 food items blank ($n = 5994$), had a previous diagnosis of cancer (other than nonmelanoma skin cancer; $n = 3629$), or had missing information on height ($n = 99$) or cigarette smoking ($n = 330$). These exclusions left a total of 88,410 women for the analyses. The Human Research Committee at the Brigham and Women's Hospital approved the study.

Dietary Assessment. The 1980 food frequency questionnaire with 61 items of foods was used for our major analyses. For each food in the questionnaires, a commonly used unit or portion size (*e.g.,* one orange or one-half cup of broccoli) 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.

For analyses of intake of fruits and vegetables in relation to non-Hodgkin's lymphoma risk, frequencies in the 1980 food frequency questionnaire were summed overall fruits (six items) consisting of fresh apples or pears; oranges; orange or grapefruit juice; peaches, apricots, or plums; bananas; and other fruits; and vegetables (11 items) consisting of string beans; broccoli; cabbage, cauliflower, or Brussels sprouts; carrots; corn; spinach or other greens; peas or lima beans; winter squash; sweet potatoes; dried beans or lentils; and tomatoes or tomato juice. In the 1980 dietary questionnaire, cabbage, cauliflower, or Brussels sprouts was asked in one item; this was added to broccoli intake to comprise cruciferous vegetables. Spinach or other greens was asked in one item to represent green leafy vegetables. Yellow/orange vegetables consisted of carrots, sweet potatoes, and winter squash, and citrus fruits consisted of oranges, orange, or grapefruit juice. These groupings of fruits and vegetables have been used in other epidemiological studies to assess the association between intake of fruits and vegetables and cancer risk and to represent, to some extent, certain phytochemicals rich in these foods that may inhibit carcinogenesis and affect cancer risk. For example, cruciferous vegetables are high in glucosinolates, yellow/orange vegetables are high in carotenoids, green leafy vegetables are high in lutein, and citrus fruits are high in vitamin C.

The validity and reliability of the food frequency questionnaires used in the Nurses' Health Study have been described elsewhere (21–23). A reproducibility and validity study indicated that fruits and vegetables on the 1980 food frequency questionnaire reasonably reflect long-term dietary intake (21, 22). The Pearson correlation coefficients between estimates from the 1980 dietary questionnaire and from the four 1-week dietary records over 1 year ranged from 0.28 (peaches) to 0.80 (orange or grape juice) for fruits, 0.08 (spinach or other greens) to 0.49 (broccoli) for vegetables, 0.24 (sweet potatoes) to 0.31 (carrots) for yellow/orange vegetables, and 0.59 (oranges) to 0.80 (orange or grapefruit juice) for citrus fruits.

Nutrient intakes calculated from the 1980 food frequency questionnaire were reasonably correlated with those recorded by 173 Boston women who kept diet diaries for four 1-week periods over 1 year (21, 22). The Pearson correlation coefficients between estimates from the 1980 dietary questionnaire and from the four 1-week dietary records for vitamins A and C from food and supplements were 0.49 and 0.75, and for vitamins A and C from foods, the Pearson correlation coefficients were 0.36 and 0.66 (21). Vitamin E intake was positively correlated with its plasma concentrations in two studies [$r = 0.34$ (24); $r = 0.51$ (25)]. The estimates of specific dietary carotenoids from the 1986 food frequency questionnaire were significantly correlated with their respective plasma concentrations; among non-smoking women, the Pearson correlation coefficients were 0.48 for α-carotene, 0.27 for β-carotene and lutein/zeaxanthin, 0.32 for β-cryptoxanthin, and 0.21 for lycopene (26). Using the 1980 dietary questionnaire, correlations with erythrocyte folate level in 1987 were 0.55 for folate from food and supplements and 0.38 for folate from foods (27) in a sample of 188 participants. In this sample, the mean erythrocyte folate concentrations (ng/ml $\pm$ SE) for increasing quintiles of total folate intake were 301 $\pm$ 15, 341 $\pm$ 10, 355 $\pm$ 11, 355 $\pm$ 11, and 406 $\pm$ 21 (27). All were within the normal range (>150 ng/ml).

Ascertainment of Non-Hodgkin's Lymphoma Cases. Women who reported the diagnosis of lymphoma on each biennial questionnaire from 1982 to 1994 (or their next of kin if they had died) were asked for permission to obtain their hospital records and pathology reports. Physicians without knowledge of dietary intake of participants reviewed hospital records and pathology reports to document non-Hodgkin's lymphoma (International Classification of Diseases code, 202). Deaths in the cohort were identified by reports from family members, the postal service, and a search of the National Death Index (28); we estimated that 98% of all deaths were identified. During 14 years and 1,169,326 person-years of follow-up, 199 cases of non-Hodgkin's lymphoma were documented and confirmed with medical records.

Statistical Analysis. We calculated person-years of observation for each participant from the date of returning the 1980 questionnaire to the date of diagnosis of non-Hodgkin's lymphoma, death, or May 31, 1994, whichever came first. For nutrient analyses, women were categorized by quintiles of the 1980 dietary intakes of specific carotenoids, vitamins A, C, and E, folate, and dietary fiber with adjustment for total energy by the residual method (29). For each category of nutrient intake, we calculated the incidence rate by dividing the number of non-Hodgkin's lymphoma cases by the number of person-years of follow-up.

RR[3] was calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. The Mantel-Haenszel method (30) was used to calculate age-adjusted RR with the use of 5-year age categories. Using the pooled logistic regression method with 2-year time increments (31, 32), we simultaneously adjusted for age (5-year categories), total energy (quintiles), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, present smoking of 1–14 cigarettes and ≥ 15 cigarettes/day), and height (<62 inches, ≥ 62 to <64 inches, ≥ 64 to <66 inches, ≥ 66 to <68 inches, or ≥ 68 inches). These variables were either risk factors for non-Hodgkin's lymphoma in this population (age and height; Ref. 33) or they were mostly controlled for in other studies of non-Hodgkin's lymphoma (smoking status and geographic region) or in the studies of diet

[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

and diseases (total energy) to reduce measurement errors attributable to general over or under reporting of food items. In these models, age and smoking status were updated biennially, and total energy was calculated from the 1980 dietary questionnaire.

Because the 1984 food frequency questionnaire contained additional detail on foods contributing to specific carotenoids, particularly to intakes of lycopene and lutein/zeaxanthin, we conducted an additional analysis for specific carotenoids using the 1984 dietary questionnaire completed by 81,757 women as the baseline. In a separate analysis, we also modeled non-Hodgkin's lymphoma incidence in relation to the cumulative average of nutrient intake from all available dietary questionnaires up to the start of each 2-year follow-up interval (34). For example, the incidence of non-Hodgkin's lymphoma during the 1980–1984 period was related to the dietary information from the 1980 questionnaire, and the incidence of non-Hodgkin's lymphoma during the 1984–1986 time period was related to the average intake from the 1980 and 1984 questionnaires. For all RRs, we calculated 95% CIs. A test for trend was conducted by using the median values for each quintile of nutrient intake as a continuous variable for nutrient analysis or by using the frequency responses in servings per day or per week for food analysis. All *P*s were two-tailed.

Results

Table 1 presents the associations between total intake of fruits and vegetables, intake of fruits and vegetables separately, and their groupings (cruciferous, green leafy, and yellow/orange vegetables, and citrus fruits) and the risk of non-Hodgkin's lymphoma. Higher total intake of fruits and vegetables was significantly related to a lower risk of non-Hodgkin's lymphoma; the multivariate RR was 0.62 (95% CI, 0.38–1.02) for women who consumed greater than or equal to six servings per day as compared with women consuming less than three servings per day (*P* for trend = 0.02). Similar inverse associations were seen for both follicular type of non-Hodgkin's lymphoma and diffuse type of non-Hodgkin's lymphoma; the multivariate RRs for women who consumed greater than or equal to six servings per day of fruits and vegetables as compared with women consuming less than three servings per day were 0.64 (95% CI, 0.26–1.58) for follicular lymphoma and 0.51 (95% CI, 0.21–1.23) for diffuse lymphoma. When intakes of fruits and vegetables were examined separately, the multivariate RRs were 0.70 (95% CI, 0.44–1.12) for women who consumed greater than or equal to three servings per day of fruits (*P* for trend = 0.16) and 0.62 (95% CI, 0.35–1.07) for women who consumed this amount of vegetables (*P* for trend = 0.02) as compared with those consuming less than one serving per day. Intake of cruciferous vegetables of greater or equal to five servings per week was associated with a 33% lower risk of non-Hodgkin's lymphoma as compared with intake of less than two servings per week (*P* for trend = 0.03). These associations were slightly attenuated after further adjustment for beef, pork, or lamb as a main dish (Table 1), which was associated with an increased risk of non-Hodgkin's lymphoma in this population (33). When we included intakes of cruciferous vegetables and of noncruciferous vegetables simultaneously in the multivariate model including beef, pork, or lamb as a main dish, the RRs were somewhat attenuated for intake of cruciferous vegetables [RR, 0.73 (95% CI, 0.43–1.24) for greater or equal to five servings per week *versus* less than two servings per week]. We observed no associations between intakes of green leafy vegetables, yellow/orange vegetables, or citrus fruits and the risk of non-Hodgkin's lymphoma.

To address the potential bias that women may change their diet because of clinical symptoms of non-Hodgkin's lymphoma before they are diagnosed, we excluded incident cases occurring during the first 4 years of follow-up; the associations became stronger. The comparable multivariate RRs for intake of fruits and vegetables were 1.00 (referent), 0.92, 0.66, 0.65, and 0.51 (95% CI, 0.30–0.89; *P* for trend = 0.006); for intake of vegetables, the RRs were 1.00 (referent), 1.05, 0.78, and 0.61 (95% CI, 0.34–1.12; *P* for trend = 0.04); and for intake of cruciferous vegetables, the RRs were 1.00 (referent), 0.68, and 0.58 (95% CI, 0.33–1.04; *P* for trend = 0.01). All associations became slightly weaker when we additionally adjusted for beef, pork, or lamb as a main dish.

When intake of fruits and vegetables was expressed as the cumulative updated average intake, the associations were attenuated. The multivariate RRs for fruits were 0.82 (<1 serving/day), 1.00 (referent, for 1–1.9 servings/day), 0.86 (2–2.9 servings/day), 0.92 (3–3.9 servings/day), and 0.75 (95% CI, 0.41–1.37, for ≥4 servings/day); for vegetables, the RRs were 1.04 (<1 serving/day), 1.00 (referent, for 1–1.9 servings/day), 0.87 (2–2.9 servings/day), 0.86 (3–3.9 servings/day), and 0.89 (95% CI, 0.57–1.41, for ≥4 servings/day), and for cruciferous vegetables, the RRs were 1.00 (referent, for <2 servings/week), 0.97 (2–4 servings/week), and 0.89 (95% CI, 0.56–1.41, for ≥5 servings/week).

We also examined each individual fruit and vegetable item on the 1980 food frequency questionnaire in relation to risk of non-Hodgkin's lymphoma. Each individual cruciferous vegetable item was inversely associated with a lower risk; the multivariate RRs for a combination of cabbage, cauliflower, and Brussels sprouts were 1.00 (referent, for less than one serving per week), 0.75 (one serving per week), and 0.56 (95% CI, 0.35–0.92, for greater or equal to two servings per week), and for intake of broccoli, they were 1.00 (referent, for less than one serving per week), 0.90 (one serving per week), and 0.78 (95% CI, 0.52–1.18, for greater than or equal to two servings per week). These associations were slightly attenuated when we limited our analyses to women who reported that they did not greatly change their diet during the past 10 years. Intake of corn was also significantly related to a reduced risk; the comparable multivariate RRs were 1.00 (referent), 0.89, and 0.53 (95% CI, 0.31–0.92). Other fruit and vegetable items were not significantly associated with risk of non-Hodgkin's lymphoma.

Intakes of specific dietary carotenoids, including α-carotene, β-carotene, lutein/zeaxanthin, lycopene, and β-cryptoxanthin, were not related to non-Hodgkin's lymphoma risk in both age-adjusted and multivariate-adjusted analyses using the 1980 dietary questionnaire as the baseline (Table 2) or using the 1984 dietary questionnaire as the baseline. After adjustments for age and other potential confounders, including saturated and *trans* unsaturated fats, the multivariate RRs comparing women in the highest quintile with those in the lowest quintile for intakes of specific carotenoids calculated from the 1984 food frequency questionnaire were 1.12 (95% CI, 0.68–1.85) for α-carotene, 1.02 (95% CI, 0.62–1.68) for β-carotene, 0.95 (95% CI, 0.55–1.64) for lutein/zeaxanthin, 0.91 (95% CI, 0.52–1.58) for lycopene, and 1.46 (95% CI, 0.85–2.53) for β-cryptoxanthin. Similarly, intake of folate from food and supplements or from foods was not associated with risk (Table 3). However, intake of total dietary fiber was significantly associated with a lower risk of non-Hodgkin's lymphoma after controlling for age and other nondietary risk factors (Table 3). Compared with women in the lowest quintile of intake, the multivariate RR of non-Hodgkin's lymphoma for total dietary fiber was 0.63 (95% CI, 0.41–0.98) among women in the

Table 1 RRs and 95% CIs for non-Hodgkin's lymphoma by categories of fruits and vegetables in 1980

	Categories of intake (servings/day)					P for trend[c]
	<3	3–3.9	4–4.9	5–5.9	≥6	
Fruits and vegetables						
No. of cases	73	52	31	19	24	
RR						
Age-adjusted	1.00	0.99	0.73	0.64	0.61	0.006
Multivariate-adjusted[a]	1.00	1.02	0.76	0.69	0.62	0.02
95% CI		0.71–1.46	0.50–1.17	0.41–1.16	0.38–1.02	
Multivariate-adjusted[b]	1.00	1.04	0.80	0.74	0.69	0.07
95% CI		0.73–1.50	0.52–1.23	0.44–1.24	0.42–1.15	

	Categories of intake (servings/day)				P for trend[c]
	<1	1–1.9	2–2.9	≥3	
Fruits					
No. of cases	45	68	51	35	
RR					
Age-adjusted	1.00	0.86	0.82	0.65	0.06
Multivariate-adjusted[a]	1.00	0.88	0.87	0.70	0.16
95% CI		0.60–1.29	0.57–1.31	0.44–1.12	
Multivariate-adjusted[b]	1.00	0.91	0.93	0.79	0.39
95% CI		0.62–1.33	0.61–1.41	0.49–1.27	
Vegetables					
No. of cases	35	100	42	22	
RR					
Age-adjusted	1.00	1.03	0.72	0.58	0.008
Multivariate-adjusted[a]	1.00	1.06	0.76	0.62	0.02
95% CI		0.72–1.57	0.48–1.20	0.35–1.07	
Multivariate-adjusted[b]	1.00	1.08	0.77	0.65	0.04
95% CI		0.73–1.60	0.49–1.23	0.37–1.13	

	Categories of intake (servings/unit time)					P for trend[c]
	<2/wk	2–4/wk	5–6/wk	1/day	≥2/day	
Cruciferous vegetables						
No. of cases	119	63	17			
RR						
Age-adjusted	1.00	0.70	0.66			0.02
Multivariate-adjusted[a]	1.00	0.71	0.67			0.03
95% CI		0.52–0.96	0.40–1.11			
Multivariate-adjusted[b]	1.00	0.72	0.69			0.04
95% CI		0.53–0.98	0.41–1.15			
Green leafy vegetables						
No. of cases	121	40	10	28		
RR						
Age-adjusted	1.00	0.98	0.64	1.13		0.92
Multivariate-adjusted[a]	1.00	1.01	0.67	1.18		0.87
95% CI		0.71–1.45	0.35–1.28	0.78–1.79		
Multivariate-adjusted[b]	1.00	1.02	0.67	1.19		0.86
95% CI		0.71–1.46	0.35–1.28	0.78–1.80		
Yellow/orange vegetables						
No. of cases	125	52	22			
RR						
Age-adjusted	1.00	0.65	0.94			0.17
Multivariate-adjusted[a]	1.00	0.67	0.98			0.27
95% CI		0.48–0.93	0.62–1.56			
Multivariate-adjusted[b]	1.00	0.69	1.04			0.39
95% CI		0.50–0.96	0.65–1.65			
Citrus fruits						
No. of cases	40	37	19	81	22	
RR						
Age-adjusted	1.00	1.06	0.82	1.18	0.80	0.39
Multivariate-adjusted[a]	1.00	1.08	0.86	1.27	0.87	0.66
95% CI		0.69–1.70	0.49–1.48	0.86–1.86	0.51–1.49	
Multivariate-adjusted[b]	1.00	1.11	0.90	1.34	0.97	0.98
95% CI		0.71–1.74	0.52–1.55	0.91–1.97	0.57–1.66	

[a] The multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, present smoking of 1–14 cigarettes and ≥15 cigarettes/day), and height (<62 inches, ≥62 to <64 inches, ≥64 to <66 inches, ≥66 to <68 inches, or ≥68 inches).
[b] Additional controlling for beef, pork or lamb as a main dish (less than one serving per week, one serving per week, two to four servings per week, five to six servings per week, and greater or equal to one serving per day).
[c] *P*s are two-sided (Wald's test).

Table 2 RRs and 95% CIs for non-Hodgkin's lymphoma by the quintile group for intake of specific dietary carotenoids in 1980

	Quintile of nutrient intake[a]					Q_5 95% CI[d]	*P* for trend[e]
	1	2	3	4	5		
α-Carotene							
No. of cases	38	44	31	52	34		
Intake (μg/day)	192	313	441	648	1561		
RR							
Age-adjusted	1.00	1.12	0.79	1.26	0.83	0.52–1.31	0.34
Multivariate-adjusted[b]	1.00	1.08	0.78	1.20	0.80	0.50–1.28	0.34
Multivariate-adjusted[c]	1.00	1.10	0.81	1.26	0.90	0.56–1.45	0.69
β-Carotene							
No. of cases	42	44	36	28	49		
Intake (μg/day)	1358	2236	3351	5280	8535		
RR							
Age-adjusted	1.00	1.01	0.82	0.61	1.04	0.69–1.57	0.93
Multivariate-adjusted[b]	1.00	1.02	0.81	0.64	1.05	0.70–1.60	0.99
Multivariate-adjusted[c]	1.00	1.06	0.87	0.70	1.26	0.82–1.93	0.42
Lutein/zeaxanthin							
No. of cases	43	39	39	37	41		
Intake (μg/day)	1172	2064	2815	6047	11,695		
RR							
Age-adjusted	1.00	0.91	0.89	0.86	0.90	0.59–1.38	0.75
Multivariate-adjusted[b]	1.00	0.90	0.85	0.88	0.91	0.59–1.40	0.86
Multivariate-adjusted[c]	1.00	0.94	0.92	0.96	1.05	0.68–1.62	0.67
Lycopene							
No. of cases	35	42	48	36	38		
Intake (μg/day)	837	1841	3997	6518	11,680		
RR							
Age-adjusted	1.00	1.17	1.30	0.94	1.00	0.63–1.59	0.38
Multivariate-adjusted[b]	1.00	1.10	1.31	0.93	0.88	0.55–1.42	0.27
Multivariate-adjusted[c]	1.00	1.12	1.35	0.96	0.98	0.61–1.59	0.57
β-Cryptoxanthin							
No. of cases	30	42	44	48	35		
Intake (μg/day)	20	49	80	125	219		
RR							
Age-adjusted	1.00	1.36	1.34	1.42	0.97	0.60–1.58	0.52
Multivariate-adjusted[b]	1.00	1.39	1.36	1.48	0.99	0.60–1.62	0.54
Multivariate-adjusted[c]	1.00	1.46	1.50	1.73	1.30	0.77–2.17	0.54

[a] Values for intake are medians for each quintile.
[b] The multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, present smoking of 1–14 cigarettes and ≥15 cigarettes/day), and height (<62 inches, ≥62 to <64 inches, ≥64 to <66 inches, ≥66 to <68 inches, or ≥68 inches).
[c] Additional adjustment for quintiles of saturated and *trans* unsaturated fats.
[d] Q_5 95% CI = 95% CIs for quintile 5 RRs.
[e] *P*s are two-sided (Wald's test).

highest quintile of intake (*P* for trend = 0.05; Table 3). The comparable multivariate RR was 0.54 (95% CI, 0.34–0.87) for fiber from vegetables (*P* for trend = 0.01). These associations were somewhat attenuated after further controlling for saturated and *trans* unsaturated fats (Table 3). We adjusted for saturated and *trans* unsaturated fats because beef, pork, or lamb as a main dish is one of the major contributors to these nutrients, and they were associated with a higher risk in this population (33). Intakes of dietary fiber from fruits, cereals, and legumes were not associated with risk of non-Hodgkin's lymphoma; the multivariate RRs comparing women in the highest quintile with those in the lowest quintile were 0.96 (95% CI, 0.58–1.60) for fruit fiber, 1.02 (95% CI, 0.65–1.59) for cereal fiber, and 0.90 (95% CI, 0.57–1.44) for legume fiber.

We also observed no significant associations between intakes of preformed vitamin A from food and supplements or from foods, and total vitamins A, C, and E from food and supplements or from foods and risk of non-Hodgkin's lymphoma (*P* for trend > 0.05; Table 4).

Discussion

In this large cohort of women, higher intakes of vegetables, particularly cruciferous vegetables, and dietary fiber from vegetables were related to a lower risk of non-Hodgkin's lymphoma after controlling for age and other potential risk factors. Intakes of specific dietary carotenoids, vitamins A, C and E, folate, and dietary fiber from fruit, cereal, or legume sources were not significantly associated with risk of non-Hodgkin's lymphoma.

In this study, we collected the data on diet and other risk factors prospectively; thus, a biased measurement is unlikely to explain these findings. The high follow-up rates also minimize the concern that differential loss-to-follow-up could influence these findings. Although the estimates of dietary intakes derived from the food frequency questionnaires used in this study have been shown to reasonably reflect long-term intakes of study subjects (21–23, 27), some misclassification of individual long-term diet is inevitable, which would tend to weaken any true associations and could partly explain the weak associations for some food groupings.

Table 3 RRs and 95% CIs for non-Hodgkin's lymphoma by the quintile group for intake of dietary fiber and folate in 1980

	Quintile of nutrient intake[a]					Q_5 95% CI[d]	*P* for trend[e]
	1	2	3	4	5		
Total dietary fiber							
No. of cases	49	35	43	35	37		
Intake (g/day)	9.8	13.1	15.9	19.1	24.9		
RR							
Age-adjusted	1.00	0.69	0.82	0.62	0.63	0.41–0.96	0.04
Multivariate-adjusted[b]	1.00	0.69	0.82	0.64	0.63	0.41–0.98	0.05
Multivariate-adjusted[c]	1.00	0.70	0.86	0.71	0.82	0.51–1.33	0.52
Fruit fiber							
No. of cases	37	49	36	43	34		
Intake (g/day)	1.0	2.3	3.6	5.3	8.5		
RR							
Age-adjusted	1.00	1.26	0.86	0.99	0.76	0.47–1.22	0.07
Multivariate-adjusted[b]	1.00	1.25	0.88	1.00	0.73	0.45–1.17	0.07
Multivariate-adjusted[c]	1.00	1.29	0.95	1.15	0.96	0.58–1.60	0.65
Vegetable fiber							
No. of cases	46	45	37	43	28		
Intake (g/day)	2.2	3.3	4.3	5.6	8.3		
RR							
Age-adjusted	1.00	0.95	0.77	0.86	0.53	0.33–0.86	0.009
Multivariate-adjusted[b]	1.00	0.95	0.76	0.86	0.54	0.34–0.87	0.01
Multivariate-adjusted[c]	1.00	0.97	0.79	0.92	0.63	0.39–1.03	0.07
Folate from food and supplements							
No. of cases	41	44	29	39	46		
Intake (μg/day)	158	217	277	392	698		
RR							
Age-adjusted	1.00	0.99	0.63	0.81	0.97	0.64–1.48	0.71
Multivariate-adjusted[b]	1.00	1.02	0.65	0.86	1.01	0.66–1.54	0.70
Multivariate-adjusted[c]	1.00	1.09	0.75	1.09	1.23	0.79–1.92	0.20
Folate, food only							
No. of cases	39	52	36	29	43		
Intake (μg/day)	151	200	240	289	379		
RR							
Age-adjusted	1.00	1.26	0.82	0.66	0.92	0.59–1.43	0.17
Multivariate-adjusted[b]	1.00	1.28	0.84	0.66	0.93	0.60–1.44	0.21
Multivariate-adjusted[c]	1.00	1.36	0.95	0.79	1.28	0.79–2.07	0.80

[a] Values for intake are medians for each quintile.
[b] The multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, present smoking of 1–14 cigarettes and ≥15 cigarettes/day), and height (<62 inches, ≥62 to <64 inches, ≥64 to <66 inches, ≥66 to <68 inches, or ≥68 inches).
[c] Additional adjustment for quintiles of saturated and *trans* unsaturated fats.
[d] Q_5 95% CI = 95% CIs for quintile 5 RRs.
[e] *P*s are two-sided (Wald's test).

One potential source of bias in this study is that women may change their diet because of clinical symptoms, such as significant weight loss, fever, and night sweats, before they are diagnosed with non-Hodgkin's lymphoma. The use of baseline measures of dietary intake rather than the most recent diet helps to reduce this bias, which is supported by our observation that the associations were weaker when we modeled the incidence of non-Hodgkin's lymphoma using the cumulative updated average intake of fruits and vegetables that incorporated recent dietary information. To address this issue further, we excluded non-Hodgkin's lymphoma cases occurring during the first 4 years of follow-up. The results were somewhat stronger, which suggests that the inverse association with fruit and vegetable intake was, if anything, attenuated by recent dietary changes. We cannot exclude the possibility of residual confounding by non-dietary risk factors, but this is unlikely to explain these observed findings because the RRs after controlling for potential non-dietary risk factors for non-Hodgkin's lymphoma were similar to the age-adjusted associations.

The results from previous studies of fruit and vegetable intake in relation to non-Hodgkin's lymphoma risk are mixed. Green vegetable intake was nonsignificantly inversely associated with risk of non-Hodgkin's lymphoma in two hospital-based case-control studies (16, 17), and it was significantly positively associated with risk in another hospital-based case-control study (18). However, these studies did not specify whether cruciferous vegetables were included in the grouping of green vegetables. A population-based case-control study reported an inverse association with intake of dark green vegetables, including broccoli, kale/collard, and turnip greens in men but not in women (15). However, total vegetable intake was not associated with risk of non-Hodgkin's lymphoma either in this study (15) or in a previous cohort study (14). Regarding fruit intake, two studies reported an inverse association, which was not statistically significant (14, 18). Intake of citrus fruits was significantly inversely associated with risk in men but not in women in the population-based case-control study (15). However, no association was seen for fruit intake in other two hospital-based case-control studies (16, 17). Intakes of

Table 4 RRs and 95% CIs for non-Hodgkin's lymphoma according to the quintile group for intake of vitamins A, C, and E in 1980

	Quintile of nutrient intake[a]					Q_5 95% CI[d]	*P* for trend[e]
	1	2	3	4	5		
Preformed vitamin A from food and supplements							
No. of cases	37	39	41	35	47		
Intake (IU/day)	854	1865	2711	5825	10,415		
RR							
Age-adjusted	1.00	0.97	1.01	0.85	1.10	0.72–1.70	0.68
Multivariate-adjusted[b]	1.00	0.99	1.00	0.89	1.08	0.70–1.67	0.74
Multivariate-adjusted[c]	1.00	0.98	1.01	0.93	1.19	0.77–1.85	0.38
Preformed vitamin A, food only							
No. of cases	35	38	31	55	40		
Intake (IU/day)	719	1572	2059	2709	5466		
RR							
Age-adjusted	1.00	1.00	0.82	1.39	0.97	0.62–1.52	0.99
Multivariate-adjusted[b]	1.00	1.07	0.82	1.38	0.99	0.62–1.56	0.96
Multivariate-adjusted[c]	1.00	1.09	0.81	1.39	1.08	0.68–1.71	0.63
Vitamin A from food and supplements							
No. of cases	43	39	32	36	49		
Intake (IU/day)	5131	8044	11,109	14,826	22,418		
RR							
Age-adjusted	1.00	0.84	0.67	0.72	0.95	0.63–1.43	0.94
Multivariate-adjusted[b]	1.00	0.86	0.70	0.74	0.97	0.64–1.47	0.92
Multivariate-adjusted[c]	1.00	0.89	0.75	0.83	1.19	0.78–1.83	0.28
Vitamin A, food only							
No. of cases	44	41	35	32	47		
Intake (IU/day)	4725	6962	9322	12,394	17,912		
RR							
Age-adjusted	1.00	0.86	0.71	0.62	0.86	0.57–1.29	0.51
Multivariate-adjusted[b]	1.00	0.87	0.72	0.65	0.89	0.58–1.34	0.56
Multivariate-adjusted[c]	1.00	0.90	0.77	0.71	1.08	0.70–1.66	0.73
Vitamin C from food and supplements							
No. of cases	34	51	30	34	50		
Intake (mg/day)	70	113	154	228	704		
RR							
Age-adjusted	1.00	1.43	0.81	0.90	1.27	0.82–1.98	0.30
Multivariate-adjusted[b]	1.00	1.47	0.84	0.93	1.30	0.84–2.02	0.31
Multivariate-adjusted[c]	1.00	1.57	0.96	1.17	1.60	1.02–2.51	0.07
Vitamin C, food only							
No. of cases	36	48	44	39	32		
Intake (mg/day)	61	94	121	152	209		
RR							
Age-adjusted	1.00	1.29	1.14	0.98	0.80	0.49–1.29	0.09
Multivariate-adjusted[b]	1.00	1.31	1.15	0.99	0.79	0.49–1.28	0.11
Multivariate-adjusted[c]	1.00	1.38	1.27	1.16	1.06	0.63–1.78	0.85
Vitamin E from food and supplements							
No. of cases	45	31	37	34	52		
Intake (IU/day)	4.1	5.5	7.0	18.4	209.5		
RR							
Age-adjusted	1.00	0.66	0.75	0.72	1.01	0.67–1.52	0.12
Multivariate-adjusted[b]	1.00	0.67	0.76	0.74	1.00	0.66–1.49	0.17
Multivariate-adjusted[c]	1.00	0.65	0.77	0.78	1.08	0.72–1.64	0.06
Vitamin E, food only							
No. of cases	38	39	46	39	37		
Intake (IU/day)	3.9	5.0	5.8	6.7	8.5		
RR							
Age-adjusted	1.00	0.99	1.15	0.93	0.84	0.53–1.34	0.32
Multivariate-adjusted[b]	1.00	0.98	1.13	0.90	0.81	0.51–1.29	0.29
Multivariate-adjusted[c]	1.00	0.96	1.11	0.89	0.89	0.55–1.43	0.53

[a] Values for intake are medians for each quintile.
[b] The multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (seven periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, present smoking of 1–14 cigarettes and ≥15 cigarettes/day), and height (<62 inches, ≥62 to <64 inches, ≥64 to <66 inches, ≥66 to <68 inches, or ≥68 inches).
[c] Additional adjustment for quintiles of saturated and *trans* unsaturated fats.
[d] Q_5 95% CI = 95% CIs for quintile 5 RRs.
[e] *P*s are two-sided (Wald's test).

carotene and vitamins C and E were not associated with risk of non-Hodgkin's lymphoma either in a previous cohort (14) or in other two case-control studies (15, 17). Intakes of specific dietary carotenoids, dietary vitamins C and E, and folate were also not related to non-Hodgkin's lymphoma risk in this study, suggesting that these nutrients are not the factors accounting for the potential beneficial effects of vegetables.

We are unaware of any previous study that has examined the association between cruciferous vegetable intake *per se* and non-Hodgkin's lymphoma risk. The Cruciferae family, vegetables of the *Brassica* genus, includes cabbage, kale, broccoli, cauliflower, Brussels sprouts, collard greens, arugula, kohlrabi, mustard greens, radishes, rutabagas, turnips, and watercress (6, 35, 36). In the 1980 food frequency questionnaire, we included items of broccoli, cabbage, cauliflower, and Brussels sprouts, which are most frequently consumed cruciferous vegetables in this cohort. Cruciferous vegetables are rich sources of glucosinolates and dithiolthiones (6, 36). Dithiolthiones and certain hydrolysis products of glucosinolates, *i.e.*, isothiocyanates and indoles, thiocyanates, have shown to have anticarcinogenic properties (6, 36). They appear to affect Phase 1 and 2 biotransformation enzyme activities and thereby influence several processes related to chemical carcinogenesis, such as the metabolism and DNA binding of carcinogens (6, 36). Fruits and vegetables also contain other phytochemicals, including coumarins, flavonoids, phenols, and protease inhibitors; many of these have been demonstrated to be protective against cancer in animal models and to inhibit cancer cell growth *in vitro* (6).

Dietary fiber from vegetables was inversely associated with risk of non-Hodgkin's lymphoma, but fiber may be merely acting as a marker for vegetable intake because only fiber from vegetable sources was inversely associated with risk. To our best knowledge, no data on dietary fiber from different sources and immune responses are available from human studies.

In summary, data from the Nurses' Health Study suggest that higher intake of vegetables, particularly cruciferous vegetables, may reduce non-Hodgkin's lymphoma risk. Dietary carotenoids, vitamins A, C, E, and folate do not appear to be major factors in the etiology of non-Hodgkin's lymphoma.

Acknowledgments

We are indebted to the participants of the Nurses' Health Study for their continuing outstanding dedication and commitment to the study and to Charlie Fuchs, Barbara Egan, Lisa Li, and Karen Corsano for their assistance.

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