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Vitamin Supplement Use and the Risk of Non-Hodgkin's Lymphoma among Women and Men

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The authors examined use of individual supplements of vitamins A, C, and E only and multivitamins in relation to risk of non-Hodgkin's lymphoma in prospective cohorts of 88,410 women in the Nurses' Health Study (1980–1996), with 261 incident cases during 16 years of follow-up, and of 47,336 men in the Health Professionals Follow-Up Study (1986–1996), with 111 incident cases during 10 years of follow-up. Multivitamin use was associated with a higher risk of non-Hodgkin's lymphoma among women but not among men; the multivariate relative risks for long-term duration (10 or more years) were 1.48 (95% confidence interval (CI): 1.01, 2.16) for women and 0.85 (95% CI: 0.45, 1.58) for men. The pooled multivariate relative risk from the two cohorts was 1.18 (95% CI: 0.70, 2.02). Use of individual supplements of vitamins A, C, and E only was not associated with risk among men. An increased risk associated with the use of individual supplements of vitamins A, C, and E only among women appeared to be secondary to the use of multivitamins by the same persons. Because an elevated risk among multivitamin users was not observed consistently in the two cohorts and the pooled data were not significant, the elevated risk among women may be the result of chance. *Am J Epidemiol* 2001;153:1056–63.

ascorbic acid; lymphoma, non-Hodgkin; vitamin A; vitamin E; vitamins

Between 1973 and 1992, the incidence of non-Hodgkin's lymphoma increased by nearly 75 percent, and mortality due to non-Hodgkin's lymphoma increased by 36 percent in the United States, one of the largest increases of any cancer (1). Risk of non-Hodgkin's lymphoma has been related to drugs, pesticides, solvents and other chemicals, hair dyes, smoking, and diet (2) and has been consistently associated with compromised immune status (3–6). Oxidant-antioxidant balance can influence immune function (7). Lower intake of vitamins C and E has adversely affected immune responses in populations with severe or marginal nutritional deficiency (7, 8), and supplemental vitamins C and E in healthy persons have improved responses on delayed-type hypersensitivity skin tests, an indicator of cell-mediated immunity (7, 8). Vitamin A supplementation has long been recognized to increase immune status in undernourished populations (9).

Epidemiologic data relating supplemental vitamins A, C, and E and multivitamins to non-Hodgkin's lymphoma risk are limited. A lack of association with supplemental vitamins C and E was suggested in one prospective study (10), and in a case-control study, use of multivitamins for 9 or more years was associated with a reduced risk of non-Hodgkin's lymphoma among men, although not among women (11). Because a protective effect of supplemental vitamin use would be important, we evaluated these relations in two large prospective cohorts among US women and men.

MATERIALS AND METHODS

Study cohorts

The Nurses' Health Study. 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 cancers and other diseases. In 1980, a 61-food-item semiquantitative food frequency questionnaire was first included to obtain dietary information. In 1984, 1986, and 1990, an expanded food frequency questionnaire was used to update dietary intake. The validity and reliability of the food frequency questionnaires used in the Nurses' Health Study have been described elsewhere (12–14).

Women were excluded from the 1980 baseline population if they did not complete the 1980 dietary questionnaire, completed a 1980 dietary questionnaire with implausible

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Abbreviation: CI, confidence interval.

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total energy intake (outside the range of 500–3,500 kcal per day), left 10 or more 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. Up to May 31, 1996, the follow-up was 98 percent complete as a percentage of potential person-years.

The Health Professionals Follow-Up Study. The Health Professionals Follow-Up Study was established in 1986, when 51,529 US male health professionals aged 40–75 years answered a mailed questionnaire about their medical history and health-related behaviors. The participants consist of dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians. Every 2 years, questionnaires have been sent to cohort members to update information on potential risk factors for cancer and heart disease and to ascertain newly diagnosed cancer and other diseases. In 1986, 1990, and 1994, a detailed food frequency questionnaire was administered to obtain dietary information. The validity and reliability of the food frequency questionnaires used in the Health Professionals Follow-Up Study have been published previously (15).

For the analyses presented here, men were excluded from the 1986 baseline population if they did not complete the 1986 dietary questionnaire, completed a 1986 dietary questionnaire with implausible total energy intake (outside the range of 800–4,200 kcal per day), left 70 or more 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 47,336 men for the analyses. Up to January 31, 1996, the follow-up was 97 percent complete as a percentage of potential person-years.

Assessment of use of individual supplements of vitamins A, C, and E only and multivitamins

In the Nurses' Health Study, we first asked questions about the use of specific vitamins and brands and types of multivitamins as well as the dose and duration of use in 1980. In each 2-year follow-up cycle, we asked current users about their daily dosage of vitamins A, C, and E supplements and the number of multivitamins taken weekly. A comprehensive database on multivitamin preparations that provides the dose of vitamins A, C, and E in each preparation has been developed and updated biennially. Women who reported use of vitamin supplements but did not report the dose or duration were assigned the median value among the users.

In the Health Professionals Follow-Up Study, we asked about current and past use of vitamin supplements in 1986. Current users of vitamins A, C, and E were asked about their daily dosage (<8,000, 8,000–12,000, 13,000–22,000, and ≥23,000 IU for vitamin A; <400, 400–700, 750–1,250, and ≥1,300 mg for vitamin C; <100, 100–250, 300–500, and ≥600 IU for vitamin E) and duration of use (0–1, 2–4, 5–9, and ≥10 years). We also asked about the weekly number of multivitamins taken (≤2, 3–5, 6–9, and ≥10 per week). Information on multivitamins and specific vitamin supplement use was updated every 2 years. Men who reported use of vitamin supplements but did not report the dose or duration were assigned the median value among the users.

Ascertainment of non-Hodgkin's lymphoma cases

We identified incident cases of non-Hodgkin's lymphoma (*International Classification of Diseases*, Eighth Revision, code 202) from self-report of participants on each biennial questionnaire from 1980 to 1996 for the Nurses' Health Study and from 1986 to 1996 for the Health Professionals Follow-Up Study. Deaths in the cohort were identified by reports from family members, the postal service, and a search of the National Death Index (16); approximately 98 percent of all deaths were identified. Participants who reported non-Hodgkin's lymphoma (or their next of kin if they had died) were asked for permission to obtain hospital records and pathology reports. Physicians without knowledge of the dietary intake of the participants reviewed the records. A total of 261 incident cases of non-Hodgkin's lymphoma were documented during 16 years of follow-up in the Nurses' Health Study, and 111 incident cases of non-Hodgkin's lymphoma were documented during 10 years of follow-up in the Health Professionals Follow-Up Study. All cases were confirmed by medical records.

The average age at diagnosis of non-Hodgkin's lymphoma cases was 60 years for women in the Nurses' Health Study and 65 years for men in the Health Professionals Follow-Up Study. According to the Working Formulation (17), non-Hodgkin's lymphoma cases in the Nurses' Health Study were composed of 9.3 percent small lymphocytic cell, 19.9 percent follicular small cleaved cell, 11.5 percent follicular mixed cell, 6.2 percent follicular large cell, 5.8 percent diffuse small cleaved cell, 6.2 percent diffuse mixed cell, 22.1 percent diffuse large cell, 6.6 percent immunoblastic large cell, and 12.3 percent others or unknown. Non-Hodgkin's lymphoma cases in the Health Professionals Follow-Up Study were composed of 13.7 percent small lymphocytic cell, 12.2 percent follicular small cleaved cell, 5.0 percent follicular mixed cell, 5.8 percent follicular large cell, 14.4 percent diffuse small cleaved cell, 8.6 percent diffuse mixed cell, 14.4 percent diffuse large cell, 2.2 percent immunoblastic large cell, and 23.7 percent others or unknown.

Statistical analysis

We calculated person-months of observation for each participant from the date of returning the baseline dietary questionnaire to the date of diagnosis of non-Hodgkin's lymphoma, death, or end of follow-up, whichever came first. The end of follow-up was May 31, 1996, for the Nurses' Health Study and January 31, 1996, for the Health Professionals Follow-Up Study.

Incidence rates of non-Hodgkin's lymphoma within categories of vitamin supplements were calculated by dividing the number of non-Hodgkin's lymphoma cases by the number of person-years of follow-up. Relative risks were calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. Age-adjusted rela-

TABLE 1. Age-standardized characteristics* by use of vitamin supplements among 88,410 women in the Nurses' Health Study (1980–1996) and 47,336 men in the Health Professionals Follow-Up Study (1986–1996)

Characteristics	Vitamin A supplements			Vitamin C supplements			Vitamin E supplements			Multivitamins		
	Never	Past	Current	Never	Past	Current	Never	Past	Current	Never	Past	Current
						Women						
Use of supplements† (%)	91	5	4	67	8	25	74	10	16	44	19	37
Mean												
Age† (years)	53	56	54	53	55	54	53	56	55	52	55	54
Height (cm)	164	164	164	164	164	164	164	164	164	164	164	164
Total energy‡ (kcal/day)	1,565	1,580	1,577	1,562	1,578	1,575	1,567	1,565	1,562	1,550	1,578	1,580
Saturated fat‡ (% energy)	16	15	15	16	16	15	16	15	15	16	16	15
Trans unsaturated fat‡ (% energy)	2.3	2.0	2.0	2.3	2.2	2.1	2.3	2.1	2.1	2.3	2.2	2.2
Fruits and vegetables‡ (servings/day)	4.1	4.5	4.6	4.0	4.2	4.4	4.0	4.3	4.4	4.0	4.1	4.3
%												
Current smokers† (%)	22	17	19	23	19	19	23	18	18	25	19	19
Residence, South (%)	10	11	12	11	11	10	11	11	10	11	10	11
Current use of supplements												
Vitamin A† (%)				1	1	14	1	3	21	1	4	7
Vitamin C† (%)	21	51	88				14	31	73	11	21	44
Vitamin E† (%)	12	34	79	5	10	46				6	13	29
Multivitamins† (%)	35	56	68	27	38	65	29	43	69			
						Men						
Use of supplements† (%)	81	13	6	44	27	29	65	17	18	34	29	37
Mean												
Age† (years)	57	58	59	58	57	58	57	58	60	57	57	58
Height (cm)	178	178	178	178	178	178	178	178	178	178	178	178
Total energy‡ (kcal/day)	1,984	1,989	2,006	1,985	1,984	1,990	1,988	1,981	1,985	1,987	1,975	1,994
Saturated fat‡ (% energy)	11	11	10	11	11	11	11	11	10	11	11	11
Trans unsaturated fat‡ (% energy)	1.3	1.2	1.1	1.3	1.2	1.2	1.3	1.2	1.1	1.3	1.2	1.2
Fruits and vegetables‡ (servings/day)	5.8	6.3	6.8	5.6	6.0	6.4	5.7	6.2	6.5	5.7	5.9	6.1
%												
Current smokers† (%)	9	8	9	10	8	8	10	8	8	10	9	8
Residence, South (%)	27	29	28	27	29	26	27	29	27	26	28	27
Current use of supplements												
Vitamin A† (%)				1	1	18	1	2	27	1	3	12
Vitamin C† (%)	23	38	93				15	26	81	11	18	54
Vitamin E† (%)	12	25	87	4	7	51				5	10	37
Multivitamins† (%)	33	42	78	22	27	69	27	34	76			

* All factors except age are directly standardized.
† Updated every 2 years.
‡ 1980 information in the Nurses' Health Study for women and 1986 information in the Health Professionals Follow-Up Study for men.

tive risks were calculated with the use of 5-year age categories by the Mantel-Haenszel method (18). In multivariate analysis using pooled logistic regression with 2-year time increments (19, 20), we simultaneously adjusted for age (5-year categories), smoking status, geographic region, length of follow-up, total energy intake, body height, saturated fat, *trans* unsaturated fat, and fruit and vegetable intake. In the Nurses' Health Study, age, height, saturated fat, and *trans* unsaturated fat were positively associated with risk of non-Hodgkin's lymphoma (21), and fruit and vegetable intake was inversely associated with risk. We adjusted for total energy to reduce measurement error due to general overreporting or underreporting of food items and to control for confounding (22). In these models, age and smoking status were updated biennially. For all relative risks, we calculated 95 percent confidence intervals; all p values were two-tailed. Tests for trend were conducted by using the median values for each category of vitamin supplements as a continuous variable. Tests for trend for duration of vitamin supplements were calculated after the exclusion of past users. Log relative risks for use of individual supplements of vitamins C and E only and multivitamin supplements for 10 or more years from the two studies were pooled by the random-effects model developed by DerSimonian and Laird (23). We did not conduct the analysis for use of vitamin A supplements for 10 or more years because we had too few cases to analyze in both cohorts.

RESULTS

Table 1 presents characteristics of populations according to use of vitamins A, C, and E and multivitamin supplements. Among women in the Nurses' Health Study, the average percentages of current users among women were 4 percent for vitamin A supplements, 25 percent for vitamin C supplements, 16 percent for vitamin E supplements, and 37 percent for multivitamins. Among men in the Health Professionals Follow-Up Study, the average percentages of current users were 6 percent for vitamin A supplements, 29 percent for vitamin C supplements, 18 percent for vitamin E supplements, and 37 percent for multivitamins. Participants who took one type of vitamin supplement were more likely to take other supplements. Use of vitamin supplements was slightly inversely associated with current smoking and positively associated with fruit and vegetable intake. We did not observe any other important differences in risk factors for non-Hodgkin's lymphoma across statuses of vitamin supplement use (table 1).

After adjustment for age and other potential risk factors for non-Hodgkin's lymphoma, women who took vitamin A supplements, 400 mg or more of vitamin C supplements, less than or equal to 250 IU of vitamin E supplements, and six or more multivitamins per week experienced significantly higher risks of non-Hodgkin's lymphoma than did nonusers (table 2). The positive associations for individual

TABLE 2. Relative risks and 95% confidence intervals for non-Hodgkin's lymphoma by dose of vitamin supplements* in a cohort of 88,410 women, Nurses' Health Study, 1980–1996

Supplements	RR†	RR	95% CI†	RR	95% CI	RR	95% CI	p for trend
Vitamin A (IU/day)	Never users		<8,000		≥8,000			
No. of cases	233		9		29			
Age-adjusted RR	1.00	2.55	1.31, 4.97	1.40	0.95, 2.06			0.04
Multivariate RR‡	1.00	2.72	1.40, 5.32	1.49	1.01, 2.21			0.02
Multivariate RR§	1.00	1.89	0.93, 3.84	1.16	0.75, 1.80			0.43
Vitamin C (mg/day)	Never users		<400		400–700		≥750	
No. of cases	145		12		73		31	
Age-adjusted RR	1.00	1.43	0.80, 2.58	1.49	1.12, 1.97	1.59	1.08, 2.34	0.002
Multivariate RR‡	1.00	1.56	0.87, 2.83	1.48	1.11, 1.97	1.66	1.12, 2.46	0.001
Multivariate RR§	1.00	1.22	0.66, 2.28	1.29	0.94, 1.78	1.29	0.83, 2.02	0.14
Vitamin E (IU/day)	Never users		≤250		≥300			
No. of cases	165		18		78			
Age-adjusted RR	1.00	2.04	1.25, 3.32	1.25	0.96, 1.64			0.10
Multivariate RR‡	1.00	2.20	1.35, 3.59	1.25	0.95, 1.65			0.10
Multivariate RR§	1.00	1.52	0.88, 2.61	0.94	0.68, 1.30			0.58
Multivitamins (no./week)	Never users		≤5		6–9		≥10	
No. of cases	82		25		139		15	
Age-adjusted RR	1.00	1.26	0.80, 1.98	1.45	1.09, 1.92	3.17	1.82, 5.50	0.0005
Multivariate RR‡	1.00	1.26	0.80, 1.97	1.39	1.05, 1.83	3.36	1.93, 5.86	0.0008
Multivariate RR§	1.00	1.10	0.69, 1.75	1.25	0.93, 1.68	2.60	1.44, 4.72	0.02

* Updated every 2 years.

† RR, relative risk; CI, confidence interval.

‡ Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (eight periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, current smoking of 1–14 or ≥15 cigarettes/day), height (<62, ≥62 to <64, ≥64 to <66, ≥66 to <68, or ≥68 inches (1 inch = 2.54 cm)), saturated fat (quintiles), *trans* unsaturated fat (quintiles), and consumption of fruits and vegetables (<3, 3–3.9, 4–4.9, 5–5.9, or ≥6 servings/day).

§ Additional adjustment for other vitamin supplements in the table.

supplements of vitamins A, C, and E only were greatly attenuated after mutually controlling for other vitamin supplements. The positive association among women between multivitamin use and the risk of non-Hodgkin's lymphoma remained even after controlling for other vitamin supplements (p for trend = 0.02); the multivariate relative risks were 1.25 (95 percent confidence interval (CI): 0.93, 1.68) for women taking 6–9 multivitamins per week and 2.60 (95 percent CI: 1.44, 4.72) for women taking 10 or more multivitamins per week compared with never users (table 2).

Women who were short-term users (0–4 years) rather than long-term users (≥5 years) of vitamin A supplements had a higher risk of non-Hodgkin's lymphoma even after further adjustments for other vitamin supplements; the multivariate relative risk for use of vitamin A supplements for 0–4 years was 1.99 (95 percent CI: 1.11, 3.58) (table 3). After adjustments for age and other potential risk factors, long-term use of individual supplements of vitamins C and E only also was associated with a higher risk of non-Hodgkin's lymphoma. However, these positive associations were again greatly attenuated after further controlling for other vitamin supplements. Women who used multivitamins for 10 or more years had a significantly higher risk of non-Hodgkin's lymphoma even after further adjustments for individual supplements of vitamins A, C, and E only; the multivariate relative risk was 1.48 (95 percent CI: 1.01, 2.16) (table 3). A positive association for women taking multivitamins for 10 or more years remained after we further adjusted for parity (multivariate relative risk = 1.48, 95 percent CI: 1.01, 2.16) or after we excluded users of individual supplements of vitamins A, C, and E only from the analyses (multivariate relative risk = 1.62, 95 percent CI: 0.88, 2.97). We conducted further analyses to examine associations by dose and duration of multivitamin use; the multivariate relative risk for women who took 6 or more multivitamins per week for 10 or more years was 1.60 (95 percent CI: 1.08, 2.38) compared with never users.

In contrast, multivitamin use was not associated with risk of non-Hodgkin's lymphoma among men; the multivariate relative risks were 1.17 (95 percent CI: 0.74, 1.85) for men taking six or more multivitamins per week (table 4) and 0.85 (95 percent CI: 0.45, 1.58) for men taking multivitamins for 10 or more years (table 5). We also observed no significant association between the use of individual supplements of vitamins A, C, and E only and the risk of non-Hodgkin's lymphoma among men (tables 4 and 5).

In the pooled multivariate analyses for long-term users (≥10 years), controlling for age, other potential risk factors for non-Hodgkin's lymphoma, and other vitamin supplements, the relative risks were 1.28 (95 percent CI: 0.85, 1.93) for vitamin C supplements, 1.26 (95 percent CI: 0.73, 2.18) for vitamin E supplements, and 1.18 (95 percent CI: 0.70, 2.02) for multivitamins. The tests for heterogeneity for vitamin C supplements (p value for heterogeneity = 0.76), vitamin E supplements (p value for heterogeneity = 0.25), and multivitamins (p value for heterogeneity = 0.14) between the two cohorts were not significant, suggesting

TABLE 3. Relative risks and 95% confidence intervals for non-Hodgkin's lymphoma by duration of vitamin supplements* in a cohort of 88,410 women, Nurses' Health Study, 1980–1996

Supplements	Never users (RR†)	Past users		Current users						p for trend‡
				0–4 years		5–9 years		≥10 years		
		RR	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI	
Vitamin A supplements										
No. of cases	223		19		14		5			
Age-adjusted RR	1.00	1.38	0.87, 2.20	2.44	1.42, 4.18		1.07	0.44, 2.60		0.28
Multivariate RR§	1.00	1.44	0.90, 2.33	2.58	1.50, 4.44		1.20	0.49, 2.92		0.17
Multivariate RR¶	1.00	1.21	0.72, 2.01	1.99	1.11, 3.58		0.93	0.36, 2.39		0.32
Vitamin C supplements										
No. of cases	145		24		36		24		32	
Age-adjusted RR	1.00	1.36	0.88, 2.09	1.54	1.07, 2.22	1.51	0.98, 2.32	1.60	1.09, 2.36	0.006
Multivariate RR§	1.00	1.27	0.82, 1.97	1.61	1.11, 2.33	1.58	1.02, 2.43	1.66	1.12, 2.45	0.002
Multivariate RR¶	1.00	1.16	0.73, 1.84	1.35	0.90, 2.02	1.37	0.84, 2.22	1.33	0.81, 2.17	0.41
Vitamin E supplements										
No. of cases	165		36		24		15		21	
Age-adjusted RR	1.00	1.26	0.88, 1.81	1.51	0.98, 2.31	1.21	0.71, 2.05	1.44	0.91, 2.28	0.10
Multivariate RR§	1.00	1.22	0.84, 1.75	1.57	1.02, 2.42	1.27	0.75, 2.17	1.53	0.96, 2.43	0.05
Multivariate RR¶	1.00	1.01	0.68, 1.50	1.10	0.68, 1.78	0.90	0.50, 1.62	1.01	0.57, 1.80	0.99
Multivitamins										
No. of cases	82		60		31		28		60	
Age-adjusted RR	1.00	1.44	1.03, 2.03	1.44	0.95, 2.17	1.23	0.80, 1.90	1.83	1.28, 2.60	0.004
Multivariate RR§	1.00	1.29	0.92, 1.82	1.51	1.00, 2.29	1.20	0.78, 1.85	1.76	1.25, 2.49	0.003
Multivariate RR¶	1.00	1.19	0.84, 1.70	1.35	0.88, 2.06	1.05	0.67, 1.64	1.48	1.01, 2.16	0.13

* Updated every 2 years.
† RR, relative risk; CI, confidence interval.
‡ Tests for trend were calculated after exclusion of past users.
§ Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (eight periods), geographic region (Northeast, Midwest, South, California), cigarette smoking (never, past, current smoking of 1–14 or ≥15 cigarettes/day), height (<62, ≥62 to <64, ≥64 to <66, ≥66 to <68, or ≥68 inches (1 inch = 2.54 cm)), saturated fat (quintiles), *trans* unsaturated fat (quintiles), and consumption of fruits and vegetables (<3, 3–3.9, 4–4.9, 5–5.9, or ≥6 servings/day).
¶ Additional adjustment for other vitamin supplements in the table.

TABLE 4. Relative risks and 95% confidence intervals for non-Hodgkin's lymphoma by dose of vitamin supplements* in a cohort of 47,336 men, Health Professionals Follow-Up Study, 1986–1996

Supplements	RR†	RR	95% CI†	RR	95% CI	RR	95% CI	*p* for trend
Vitamin A (IU/day)	Never users		<8,000		≥8,000			
No. of cases	94		3		14			
Age-adjusted RR	1.00	0.79	0.25, 2.48	0.70	0.40, 1.22			0.19
Multivariate RR‡	1.00	0.83	0.26, 2.63	0.72	0.41, 1.27			0.25
Multivariate RR§	1.00	0.73	0.22, 2.45	0.69	0.37, 1.30			0.25
Vitamin C (mg/day)	Never users		<400		400–700		≥750	
No. of cases	52		6		39		14	
Age-adjusted RR	1.00	1.36	0.58, 3.16	0.84	0.56, 1.27	1.02	0.56, 1.85	0.66
Multivariate RR‡	1.00	1.52	0.65, 3.56	0.85	0.56, 1.29	1.17	0.64, 2.13	0.89
Multivariate RR§	1.00	1.69	0.69, 4.18	0.88	0.54, 1.43	1.27	0.64, 2.53	0.94
Vitamin E (IU/day)	Never users		≤250		≥300			
No. of cases	71		4		36			
Age-adjusted RR	1.00	0.69	0.25, 1.90	0.94	0.63, 1.41			0.77
Multivariate RR‡	1.00	0.73	0.26, 2.00	0.96	0.64, 1.44			0.84
Multivariate RR§	1.00	0.68	0.23, 1.98	1.02	0.62, 1.68			0.89
Multivitamins (no./week)	Never users		≤5		≥6			
No. of cases	35		11		65			
Age-adjusted RR	1.00	1.14	0.58, 2.25	1.08	0.72, 1.63			0.72
Multivariate RR‡	1.00	1.16	0.59, 2.29	1.09	0.72, 1.65			0.72
Multivariate RR§	1.00	1.22	0.60, 2.47	1.17	0.74, 1.85			0.54

* Updated every 2 years.
† RR, relative risk; CI, confidence interval.
‡ Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (five periods), geographic region (Northeast, Midwest, South, West), cigarette smoking (never, past, current smoking of 1–14 or ≥15 cigarettes/day), height (<68, ≥68 to <70, ≥70 to <72, ≥72 to <74, or ≥74 inches (1 inch = 2.54 cm)), saturated fat (quintiles), *trans* unsaturated fat (quintiles), and consumption of fruits and vegetables (<4, 4–4.9, 5–5.9, 6–6.9, 7–7.9, or ≥8 servings/day).
§ Additional adjustment for other vitamin supplements in the table.

that the pooled relative risk is an appropriate summary of the data.

To address the potential bias that women might have taken vitamin supplements due to clinical symptoms of non-Hodgkin's lymphoma before they were diagnosed, we used the repeated questionnaires to examine vitamin supplement use in relation to diagnoses of non-Hodgkin's lymphoma 2–4 years later and found that these associations did not change appreciably. The multivariate relative risks for frequencies of multivitamin use among women were 1.00 (referent, never users), 1.34 (95 percent CI: 0.85, 2.10) for less than or equal to five per week, 1.42 (95 percent CI: 1.05, 1.92) for 6–9 per week, and 2.38 (95 percent CI: 1.24, 4.55) for 10 or more per week (p for trend = 0.007). The multivariate relative risks for duration of multivitamin use among women were 1.00 (referent, never users), 1.38 (95 percent CI: 0.95, 1.99) for past users, 1.17 (95 percent CI: 0.74, 1.85) for 0–4 years, 1.57 (95 percent CI: 1.04, 2.37) for 5–9 years, and 1.68 (95 percent CI: 1.13, 2.50) for 10 or more years (p for trend = 0.004).

DISCUSSION

In the Nurses' Health Study, regular use of multivitamins for 10 or more years among women was significantly related to a higher risk of non-Hodgkin's lymphoma. We did not observe such an association among men in the Health Professionals Follow-Up Study. Supplements of vitamins A, C, and E only were not independently associated with the risk.

Because data on vitamin supplements and other risk factors were collected prospectively, a biased measurement is unlikely to explain these findings. The high follow-up rates of these two cohorts minimize the concern that differential loss-to-follow-up could affect our results. Although confounding by unknown variables or other supplements cannot be excluded, this seems unlikely because adjustments for the potential risk factors for non-Hodgkin's lymphoma, such as height, smoking, geographic region, saturated and *trans* unsaturated fats, and total energy had minimal effects on the relative risks. The relative risk for multivitamin use among women also did not change after we additionally adjusted for parity, a variable related to hormones. However, the relative risks for specific vitamin supplements were confounded by use of other vitamin supplements. For example, the positive associations between vitamin C supplements and risk of non-Hodgkin's lymphoma among women became close to null after we controlled for other vitamin supplements. However, the positive association of multivitamin use with risk among women remained after we further adjusted for individual supplements of vitamins A, C, and E only and after we

TABLE 5. Relative risks and 95% confidence intervals for non-Hodgkin's lymphoma by duration of vitamin supplements* in a cohort of 47,336 men, Health Professionals Follow-Up Study, 1986–1996

Supplements	Never users (RR†)	Past users		Current users						*p* for trend‡
				0–4 years		5–9 years		≥10 years		
		RR	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI	
Vitamin A supplements										
No. of cases	94		13				4			
Age-adjusted RR	1.00	0.77	0.43, 1.38			0.56	0.21, 1.52			0.16
Multivariate RR§	1.00	0.78	0.44, 1.40			0.63	0.23, 1.73			0.24
Multivariate RR¶	1.00	0.73	0.38, 1.39			0.47	0.16, 1.38			0.12
Vitamin C supplements										
No. of cases	52		27		6		9		17	
Age-adjusted RR	1.00	0.88	0.55, 1.39	0.69	0.30, 1.61	1.01	0.50, 2.07	1.07	0.62, 1.85	0.77
Multivariate RR§	1.00	0.87	0.54, 1.39	0.77	0.33, 1.79	1.14	0.56, 2.33	1.13	0.64, 1.97	0.60
Multivariate RR¶	1.00	0.92	0.54, 1.56	0.86	0.35, 2.10	1.32	0.59, 2.94	1.16	0.55, 2.46	0.90
Vitamin E supplements										
No. of cases	71		16		4		6		14	
Age-adjusted RR	1.00	0.79	0.46, 1.36	0.56	0.20, 1.53	0.95	0.42, 2.19	1.34	0.76, 2.37	0.37
Multivariate RR§	1.00	0.81	0.47, 1.41	0.53	0.19, 1.48	1.05	0.45, 2.43	1.40	0.78, 2.51	0.27
Multivariate RR¶	1.00	0.92	0.49, 1.72	0.56	0.19, 1.63	1.20	0.47, 3.05	1.80	0.81, 3.97	0.09
Multivitamins										
No. of cases	35		33		13		8		22	
Age-adjusted RR	1.00	1.12	0.70, 1.81	1.87	0.99, 3.54	0.76	0.36, 1.65	0.99	0.58, 1.67	0.49
Multivariate RR§	1.00	1.10	0.68, 1.79	1.89	1.00, 3.59	0.85	0.39, 1.84	0.96	0.56, 1.64	0.48
Multivariate RR¶	1.00	1.20	0.71, 2.01	2.09	1.08, 4.05	0.87	0.39, 1.96	0.85	0.45, 1.58	0.42

* Updated every 2 years.
† RR, relative risk; CI, confidence interval.
‡ Tests for trend for vitamins C and E and for multivitamins were calculated after the exclusion of past users.
§ Multivariate models included age (5-year categories), total energy (quintiles), length of follow-up (five periods), geographic region (Northeast, Midwest, South, West), cigarette smoking (never, past, current smoking of 1–14 or ≥15 cigarettes/day), height (<68, ≥68 to <70, ≥70 to <72, ≥72 to <74, or ≥74 inches (1 inch = 2.54 cm)), saturated fat (quintiles), *trans* unsaturated fat (quintiles), and consumption of fruits and vegetables (<4, 4–4.9, 5–5.9, 6–6.9, 7–7.9, or ≥8 servings/day).
¶ Additional adjustment for other vitamin supplements in the table.

excluded users of these supplements from the analyses. In the United States, individual supplements of vitamins A, C, and E only and multivitamins are the most commonly used vitamin supplements (24). Therefore, our results are unlikely to be confounded by other vitamin supplements. However, we cannot exclude the possibility that these findings might be confounded by mineral supplements.

Clinical symptoms of non-Hodgkin's lymphoma, such as significant weight loss, fever, and night sweats, might have caused some participants to change their diets and to take vitamin supplements if the diagnosis was delayed for a substantial time, which is a potential source of bias. However, the results using the repeated measures of vitamin supplements in relation to incidence of non-Hodgkin's lymphoma 2–4 years later did not change appreciably, which suggests that our findings are unlikely to be explained by recent dietary changes. In addition, if our findings on multivitamins among women were related to recent dietary changes, we would expect the highest risk among women who were short-term users (0–4 years). In contrast, we observed the highest risk among women who were long-term users (≥10 years), which further suggests that our findings are unlikely to be explained by this potential source of bias. Higher risk among women who took vitamin A supplements for a short period of time (0–4 years) might be explained by recent dietary changes because we saw no such an association in women taking vitamin A supplements for a longer period of time.

An increased risk of non-Hodgkin's lymphoma for women who took multivitamins regularly for 10 or more years in this study is unexpected and needs to be interpreted with caution because we did not observe such an association among men. In the only previous investigation of which we are aware, a case-control study, use of multivitamins for 9 or more years was significantly associated with a 50 percent reduction in risk of non-Hodgkin's lymphoma among men (171 cases and 573 controls), and duration of multivitamin use was not associated with risk among women (144 cases and 532 controls) (11).

Use of individual supplements containing vitamins C and E only was evaluated only in two previous studies; they suggested a null association with risk (10, 11). In a cohort study among older women with 104 incident non-Hodgkin's lymphoma cases, supplemental vitamins C and E did not differ among cases and noncases (10). In a case-control study, duration of vitamin C supplements was not associated with risk of non-Hodgkin's lymphoma, and use of vitamin E supplements was not examined (11). Consistent with these findings, we did not find a significant association of use of individual supplements of vitamins C and E only with risk after controlling for other vitamin supplements. No previous study has evaluated the association between vitamin A supplement use and non-Hodgkin's lymphoma risk.

In summary, we observed an increased risk of non-Hodgkin's lymphoma with regular use of multivitamins for

10 or more years among women but not among men. Because an elevated risk among multivitamin users was not consistently observed in the two cohorts and the pooled data were not significant, the elevated risk among women may be the result of chance. However, this relation should be examined in other prospective studies, but the initiation of studies designed to investigate this hypothesis is not warranted.

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REFERENCES

1. Kosary C, Ries L, Miller B, et al. SEER cancer statistics review, 1973–1992: tables and graphs. Bethesda, MD: National Cancer Institute, 1995.
2. Weisenburger DD. Epidemiology of non-Hodgkin's lymphoma: recent findings regarding an emerging epidemic. Ann Oncol 1994;5(suppl 1):19–24.
3. Filipovich AH, Mathur A, Kamat D, et al. Primary immunodeficiencies: genetic risk factors for lymphoma. Cancer Res 1992;52(suppl):5465s–7s.
4. Kinlen L. Immunosuppressive therapy and acquired immunological disorders. Cancer Res 1992;52(suppl):5474s–6s.
5. Levine AM, Shibata D, Sullivan-Halley J, et al. Epidemiological and biological study of acquired immunodeficiency syndrome-related lymphoma in the county of Los Angeles: preliminary results. Cancer Res 1992;52(suppl):5482s–4s.
6. Rabkin CS, Biggar RJ, Baptiste MS, et al. Cancer incidence trends in women at high risk of human immunodeficiency virus (HIV) infection. Int J Cancer 1993;55:208–12.
7. Meydani SN, Wu D, Santos MS, et al. Antioxidants and immune response in aged persons: overview of present evidence. Am J Clin Nutr 1995;62(suppl):1462s–6s.
8. Kelley DS, Bendich A. Essential nutrients and immunologic functions. Am J Clin Nutr 1996;63:994S–6S.
9. Blomhoff R. Transport and metabolism of vitamin A. Nutr Rev 1994;52:S13–S23.
10. Chiu BC-H, Cerhan JR, Folsom AR, et al. Diet and risk of non-Hodgkin lymphoma in older women. JAMA 1996;275:1315–21.
11. Ward MH, Zahm SH, Weisenburger DD, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer Causes Control 1994;5:422–32.
12. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
13. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–199.
14. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
15. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of a expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
16. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
17. Weisenburger D. Pathological classification of non-Hodgkin's lymphoma for epidemiological studies. Cancer Res 1992;52 (19 suppl):5456s–62s.
18. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia, PA: Lippincott-Raven, 1998.
19. Cupples LA, D'Agostino RB, Anderson K, et al. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med 1988;7:205–22.
20. D'Agostino RB, Lee ML, Belanger AJ, et al. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9:1501–15.
21. Zhang S, Hunter DJ, Rosner BA, et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. J Natl Cancer Inst 1999;91:1751–8.
22. Willett WC. Nutritional epidemiology. Second ed. New York, NY: Oxford University Press, 1998.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
24. Slesinski MJ, Subar AF, Kahle LL. Trends in use of vitamin and mineral supplements in the United States: the 1987 and 1992 National Health Interview Surveys. J Am Diet Assoc 1995;95:921–3.