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Dietary Vitamin D and Risk of Non-Hodgkin Lymphoma: The Multiethnic Cohort

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Abstract

This study explored the association between dietary vitamin D and non-Hodgkin lymphoma (NHL) risk. The Multiethnic Cohort (MEC) includes more than 215,000 Caucasians, African Americans, Native Hawaiians, Japanese Americans, and Latinos, aged 45-75. After 10 years of follow-up, 939 incident NHL cases were identified. Risk was estimated using Cox proportional hazards models adjusted for possible confounders. Vitamin D intake was not associated with NHL risk in the entire cohort (P_{trend}=0.72 for men and P_{trend}=0.83 for women), but significantly lowered disease risk in African American women (HR=0.50, 95% CI: 0.28-0.90, P_{trend}=0.03) and was borderline protective in African American men (HR=0.68; 95% CI: 0.39-1.19; P_{trend}=0.31) when the highest to the lowest tertile was compared. In NHL subtype analyses, a 19%, 36%, and 32% lowered risk, although not significant, was observed for diffuse large B-cell lymphoma, follicular lymphoma, and small lymphocytic lymphoma/chronic lymphocytic leukemia in women, respectively. High dietary intake of vitamin D did not show a protective effect against NHL within the MEC except among African Americans, possibly because vitamin D production due to sun exposure is limited in this population.

Keywords

non-Hodgkin lymphoma; dietary vitamin D; prospective studies; ethnicity

Introduction

The bioactive form of vitamin D (1,25(OH)$_2$D) has been hypothesized to lower non-Hodgkin lymphoma (NHL) risk through its antiproliferative and immunomodulatory effects(1;2). Most previous studies evaluated the effect of direct or indirect measures of sun exposure and a recent pooled analysis found an inverse association with recreational sun exposure and NHL risk (OR=0.76; 95% CI: 0.63-0.91)(3). However, evidence on the effect of dietary vitamin D is limited in general(4) and scarce in non-white ethnic groups with darker skin pigmentation and less efficient synthesis from solar ultraviolet (UV) radiation(5). Therefore, we analyzed the association between vitamin D from food sources plus multivitamins and NHL risk prospectively in a large U.S. cohort of Caucasians, African Americans, Native Hawaiians, Japanese Americans, and Latinos.

Methods

Subjects from five main ethnic groups (Caucasian, African American, Native Hawaiian, Japanese American, and Latino), who were 45-75 years old and resided in Hawaii or Los

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Angeles were recruited in the Multiethnic Cohort (MEC) Study of diet and cancer between 1993 and 1996. Participants filled out a mailed baseline questionnaire, including a quantitative food frequency questionnaire (QFFQ)(6). The QFFQ included food items that were identified from 3-day food records so as to capture 85% or more of the ethnic-specific intake of main nutrients, e.g., fat, dietary fiber, vitamin A, carotenoids, vitamin C, and vitamin D. The QFFQ included approximately 180 food items and showed portion size illustrations to assist participants in estimating the amounts of foods they typically consume. A calibration substudy indicated good agreement between the QFFQ and three 24h recalls(7). Levels of vitamin D intake from food sources were determined using a customized and ethnic-specific food composition database based on the U.S. Department of Agriculture Nutrient Database and additional laboratory analyses of local foods(6). In addition to the QFFQ, the baseline questionnaire queried subjects about the duration, frequency, and amount of multivitamin use. Information on supplements was considered complete (only 2% missing) and 50% of the population indicated multivitamin use. For this analysis only regular supplement use, defined as use for >1 year, was considered, and each tablet was estimated to contain 400 IU of vitamin D, a composite of levels in the two brands of multivitamins most frequently reported in the dietary recalls for the calibration study(8). The QFFQ did not inquire about vitamin D as a single supplement as its use was not common at the time. Dietary vitamin D was computed as vitamin D from foods plus multivitamins.

After exclusions (13,992 not in main ethnic groups, 8,264 invalid dietary information, and 514 prior NHL cases), 87,078 men and 105,972 women were part of the analysis. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Boards at the University of Hawaii and at the University of Southern California. Written informed consent was obtained from all subjects.

Incident NHL cases were ascertained through annual linkages of the MEC with the tumor registries of Hawaii and Los Angeles. Deaths from cancer and other causes were identified from the state death certificate files and the National Death Index. A low out-migration rate was reported previously(6). Follow-up ended at the earliest of the following events: diagnosis of NHL, death, or December 31, 2003. NHL was classified into the most common subtypes according to the adaptation of the World Health Organization classification for epidemiologic studies(9;10).

All statistical analyses were performed using the SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC). Dietary vitamin D was energy-adjusted and the association with NHL was estimated as hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression that compared vitamin D tertiles with age as the underlying time metric and with stratification by follow-up time (≤2 years, 2-5 years, and >5 years)(11). Due to previously reported associations with NHL, the models were adjusted for age at cohort entry, ethnicity, education, body mass index (BMI), alcohol use, and total energy. Exposure to vitamin D was adjusted for total energy to account for over- and underreporting of total energy as energy-adjustment increased the correlation between the QFFQ and the 24-hour recalls in the calibration study(7). We tested for linear trend using an ordinal variable with median values for each tertile. Stratified analyses by ethnicity and NHL subgroups were performed.

Results

After a median follow-up of 10 years, 939 (514 men and 425 women) incident NHL cases were identified. NHL cases were more likely to be older and Caucasian compared to non-cases at baseline (Table 1). Diffuse large B-cell lymphoma (DLBCL) was the most common NHL subgroup among Native Hawaiians (34%), Japanese Americans (37%), and Latinos (45%), while 32% of Caucasians and 28% of African Americans were affected by small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). The proportion of follicular lymphoma (FL) was low across all ethnicities. Mean intake of dietary vitamin D was similar in men and women (336 vs. 339 IU/1,000), but differed by ethnicity; it was highest among Caucasians (391 IU/1,000) followed by Japanese Americans (331 IU/1,000), Native Hawaiians (328 IU/1,000), Latinos (313 IU/1,000), and African Americans (309 IU/1,000).

Dietary vitamin D was not associated with NHL risk among men (P_{trend}=0.72) and women (P_{trend}=0.83) overall (Table 2). The interaction between ethnicity and dietary vitamin D was not significant (p=0.70). However, after stratification by ethnic groups, a significant inverse association was observed among African American women with HR=0.50 (95% CI: 0.28-0.90; P_{trend}=0.03) comparing the highest tertile to the lowest. A lowered NHL risk, although non-significant, was also observed among African American men (HR=0.68; 95% CI: 0.39-1.19; P_{trend}=0.31). Native Hawaiian women and men experienced a non-significant 38% and 14% lowered risk, respectively. On the other hand, non-statistically significant increased risks were seen in Latino men and women and Caucasian women. Stratification by NHL subtypes revealed a non-significant inverse association between dietary vitamin D and DLBCL, FL, and SLL/CLL in women, but not in men (Table 2).

Discussion

In agreement with our hypothesis that vitamin D intake may be more protective against NHL in non-Caucasians, we found an association between vitamin D from foods plus multivitamins and lower NHL risk in African Americans, and to a lesser degree among Native Hawaiians. The few previous studies on dietary vitamin D among primarily Caucasians did not find an association(4;12-14) except for one case-control study that reported an inverse association with an OR=0.6 (95% CI: 0.4-0.9)(15). The major source of vitamin D in humans is ultraviolet B (UV-B) light, which accounts for more than 90% of vitamin D requirement, rather than food items(5;16). This might explain the lack of an overall association in our study. However, increased pigmentation, as in African Americans and Native Hawaiians, can reduce cutaneous vitamin D production through sun exposure by up to 99.9% due to filtering of UV-B and, therefore, dietary intake of vitamin D might be much more relevant for these ethnic groups (5;17). The slightly elevated risk observed in Latinos, despite their darker skin pigmentation, is hard to explain and might be due to chance.

The suggestive inverse association with FL in women is consistent with a previous study that found a 70% lowered FL risk associated with high dietary vitamin D(15). Unfortunately there is a lack of literature on the effect of dietary vitamin D on NHL subgroups. However, a large pooled analysis of sun exposure and NHL suggested similar inverse associations across all NHL subtypes(3).

Intake of vitamin D in our study population was below the recommended daily intake of 400 IU/day for adults 51-70 years(18) for 66% of participants. However, the mean intakes of 336 and 339 IU/day in men and women were higher than the respective national survey estimates of 227 and 178 IU/day(19). On the other hand, our findings agree with national estimates that described higher intakes among Caucasians than African Americans(20). The calibration study showed acceptable correlation coefficients for most nutrients including vitamin D, but did not capture variability over time. Therefore, the few significant results might be due to chance. However, the QFFQ assessed food intake, thereby capturing seasonal variability.

Other strengths of this study include the use of SEER tumor registries which ensured accurate NHL classification despite the many different institutions involved in diagnosing the cases.

We are confident that the majority of pathologic diagnoses were accurate since all NHL cases occurred after the implementation of the WHO classification(10). Furthermore this study included a multiethnic population with a wide variety of dietary exposures. However, dietary sources of vitamin D are limited to oily fish (e.g., salmon, mackerel, and sardines), fish oils (e.g., cod liver oil), and egg yolk, as well as to fortified food items (e.g., milk, cereals, and orange juice) and the use of dietary supplements(17). Despite the large size of the MEC, this study was still limited in power for stratified analyses by ethnicity and subtypes. Especially because of the multiple comparisons, it is possible that the few significant results could be due to chance.

To our knowledge our study is the first on dietary vitamin D and NHL risk among different ethnic groups. We conclude that the effect of dietary vitamin D on NHL risk might be ethnic-specific and call for more prospective investigations involving non-Caucasian subjects.

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Table 1

Baseline characteristics (in percent) of Non-Hodgkin Lymphoma (NHL) cases and subjects without NHL, the Multiethnic Cohort Study, 1993- 2003.

		Men		Women	
Characteristics		**Cases (n = 514)**	**Non-Cases (n = 86,564)**	**Cases (n = 425)**	**Non-Cases (n = 105,547)**
Age at cohort entry	< 50	5	16	6	17
	50 – 54	9	14	9	15
	55 – 59	10	16	14	16
	60 – 64	20	17	18	17
	65 – 69	25	18	23	17
	70 – 74	24	16	25	15
	75 +	7	3	5	3
Ethnicity	Caucasian	29	25	29	24
	African-American	14	14	20	20
	Native Hawaiian	6	7	6	7
	Japanese-American	27	30	23	27
	Latinos	24	24	23	21
Education (years)*	≤ 12	41	42	52	46
	13-16	47	44	36	41
	> 16	12	13	11	12
Alcohol (serving/day)*	No alcohol	50	52	77	43
	≤ 1	22	21	16	17
	> 1	27	29	8	21
NHL group*	DLBCL	33		34	
	FL	11		21	
	SLL/CLL	24		18	
	Marginal	8		9	
	T-Cell	7		5	
	Other	17		13	

*Might not add up to 100% due to missing values.

Table 2

Association of dietary vitamin D (IU/1,000 kcal/day) with non-Hodgkin lymphoma by ethnicity and NHL subgroup in the Multiethnic Cohort Study, 1993-2003.

Ethnicity	**Men ($N^{\dagger}$ = 514)**			**Women ($N^{\dagger}$ =425)**		
	Category	**$N^{\dagger}$**	**HR (95% CI)‡**	**Category**	**$N^{\dagger}$**	**HR (95% CI)‡**
Overall	< 54	155	1.00	< 62	129	1.00
($N^{\dagger}$ = 939)	54 - 152	173	1.01 (0.81-1.26)	63 – 198	146	1.00 (0.78-1.27)
	≥ 153	186	1.04 (0.83-1.29)	≥ 199	150	0.98 (0.77-1.24)
	P_{trend}		*0.72*	P_{trend}		*0.83*
Ethnicities						
Caucasian	< 54	36	1.00	< 62	19	1.00
($N^{\dagger}$ = 270)	54 - 152	50	0.94 (0.61-1.46)	63 – 198	46	1.58 (0.92-2.70)
	≥ 153	62	0.97 (0.63-1.49)	≥ 199	57	1.46 (0.87-2.47)
	P_{trend}		*1.00*	P_{trend}		*0.48*
African American	< 54	31	1.00	< 62	37	1.00
($N^{\dagger}$ = 156)	54 - 152	23	0.67 (0.39-1.16)	63 – 198	26	0.72 (0.43-1.20)
	≥ 153	22	0.68 (0.39-1.19)	≥ 199	17	**0.50 (0.28-0.90)**
	P_{trend}		*0.31*	P_{trend}		***0.03***
Native Hawaiian	< 54	11	1.00	< 62	12	1.00
($N^{\dagger}$ = 59)	54 - 152	13	0.92 (0.41-2.07)	63 – 198	10	0.60 (0.25-1.43)
	≥ 153	7	0.86 (0.33-2.25)	≥ 199	6	0.62 (0.23-1.68)
	P_{trend}		*0.79*	P_{trend}		*0.47*
Japanese American	< 54	44	1.00	< 62	31	1.00
($N^{\dagger}$ = 242)	54 - 152	43	1.07 (0.70-1.64)	63 – 198	31	1.14 (0.69-1.88)
	≥ 153	55	1.07 (0.72-1.60)	≥ 199	38	0.97 (0.60-1.57)
	P_{trend}		*0.8*	P_{trend}		*0.73*
Latino	< 54	33	1.00	< 62	30	1.00
($N^{\dagger}$ = 212)	54 - 152	44	1.34 (0.84-2.13)	63 – 198	33	0.97 (0.59-1.61)
	≥ 153	40	1.47 (0.91-2.37)	≥ 199	32	1.39 (0.84-2.31)
	P_{trend}		*0.18*	P_{trend}		*0.14*

Ethnicity	Men (N† = 514)			Women (N† =425)		
	Category	N†	HR (95% CI)‡	Category	N†	HR (95% CI)‡
NHL subgroups						
DLBCL	< 54	56	1.00	< 62	35	1.00
(N† = 311)	54 - 152	58	0.95 (0.61-1.48)	63 – 198	44	0.73 (0.42-1.26)
	≥ 153	54	1.26 (0.82-1.93)	≥ 199	64	0.81 (0.49-1.35)
	P_{trend}		*0.23*	P_{trend}		*0.79*
FL	< 54	16	1.00	< 62	26	1.00
(N† = 152)	54 - 152	20	1.65 (0.58-4.70)	63 – 198	36	0.73 (0.37-1.43)
	≥ 153	25	0.75 (0.28-1.96)	≥ 199	29	0.64 (0.29-1.41)
	P_{trend}		*0.18*	P_{trend}		*0.38*
SLL/CLL	< 54	32	1.00	< 62	22	1.00
(N† = 198)	54 - 152	47	1.05 (0.57-1.93)	63 – 198	29	0.55 (0.24-1.23)
	≥ 153	42	1.00 (0.56-1.81)	≥ 199	26	0.68 (0.30-1.56)
	P_{trend}		*0.93*	P_{trend}		*0.90*

† Number of NHL cases. May not add up to total (N = 939) due to missing values.

‡ Hazards ratios (HR) and 95% confidence intervals (CI) were adjusted for education (≥12 *vs.* <12 years), BMI (overweight (25.0-29.9), obese (≥30.0) *vs.* normal (<25.0)), alcohol intake (<1.0, 1.0-1.9, 2.0-2.9, and ≥3 *vs.* 0 servings/day), and total energy (log transformed). For the overall category, they were also adjusted for ethnicity (African American, Native Hawaiian, Japanese American, and Latino *vs.* Caucasian).