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Dietary vitamin D and risk of non-Hodgkin lymphoma: the multiethnic cohort

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The present study explored the association between dietary vitamin D and non-Hodgkin's 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 proportional hazards' models adjusted for possible confounders. Vitamin D intake was not associated with NHL risk in the entire cohort ($P_{trend} = 0{\cdot}72$ for men and $P_{trend} = 0{\cdot}83$ for women), but significantly lowered disease risk in African American women (hazard ratio (HR) = 0·50, 95 % CI: 0·28, 0·90, $P_{trend} = 0{\cdot}03$) and was borderline protective in African American men (HR = 0·68; 95 % CI: 0·39, 1·19; $P_{trend} = 0{\cdot}31$) 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.

Non-Hodgkin lymphoma: Dietary vitamin D: Prospective studies: Ethnicity

The bioactive form of vitamin D ($1,25(OH)_2D$) has been hypothesised to lower non-Hodgkin's lymphoma (NHL) risk through its anti-proliferative and immunomodulatory effects[1,2]. Most previous studies evaluated the effect of direct or indirect measures of sun exposure and a recent pooled analysis has 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 UV radiation[5]. Therefore, we analysed the association between vitamin D from food sources plus multivitamins and NHL risk prospectively in a large US 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 Angeles, were recruited in the multiethnic cohort study of diet and cancer between 1993 and 1996. Participants filled out a mailed baseline questionnaire, including a quantitative FFQ[6]. The quantitative FFQ included food items that were identified from 3-d food records so as to capture 85 % or more of the ethnic-specific intake of main nutrients. A calibration substudy indicated good agreement between the quantitative FFQ and three 24 h recalls[7]. Levels of vitamin D intake from food sources were determined using a customised and ethnic-specific food composition database based on the US Department of Agriculture Nutrient Database and additional laboratory analyses of local foods[6]. In addition to the quantitative FFQ, 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 10 μg vitamin D. We did not inquire about vitamin D as a single supplement, but at the time, single vitamin D supplement use was not common. Dietary vitamin D was computed as vitamin D from foods plus multivitamins.

After exclusions (13 992 not in main ethnic groups, 8264 invalid dietary information and 514 prior NHL cases), 87 078 men and 105 972 women were part of the analysis. The present 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 multiethnic cohort with the tumour 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 outmigration rate was

Abbreviation: NHL, non-Hodgkin's lymphoma.

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reported previously[6]. Follow-up ended at the earliest of the following events: diagnosis of NHL, death or 31 December 2003. NHL was classified into the most common subtypes according to the adaptation of the WHO classification for epidemiologic studies[8,9].

All statistical analyses were performed using the SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC, USA). Dietary vitamin D was energy adjusted, and the association with NHL was estimated as hazard ratios (HR) and 95 % CI using 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)[10]. Due to previously reported associations with NHL, the models were adjusted for age at cohort entry, ethnicity, education, BMI, alcohol use and total energy. 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 with non-cases at baseline (Table 1). Diffuse large B-cell lymphoma 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 leukaemia. The proportion of follicular lymphoma was low across all ethnicities. Mean intake of vitamin D in IU/4184 kJ/d (1000 kcal/d) was highest among Caucasians (215), followed by Japanese Americans (180), African Americans (179), Latinos (152) and Native Hawaiians (146).

Dietary vitamin D was not associated with NHL risk among men ($P_{trend} = 0{\cdot}72$) and women ($P_{trend} = 0{\cdot}83$) overall (Table 2). The interaction between ethnicity and dietary vitamin D was not significant ($P = 0{\cdot}70$). However, after stratification by ethnic group, a significant inverse association was observed among African American women with HR = 0·50 (95 % CI: 0·28, 0·90; $P_{trend} = 0{\cdot}03$) 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; $P_{trend} = 0{\cdot}31$). 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 diffuse large B-cell lymphoma, follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia in women, but not in men (Table 2).

Discussion

In agreement with the present 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,

Table 1. Baseline characteristics (in percentage) of non-Hodgkin's 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 (years)	<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
	Latino	24	24	23	21
Education (years)*	≤12	41	42	52	46
	13–16	47	44	36	41
	>16	12	13	11	12
Alcohol (serving/d)*	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	

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.
* Might not add up to 100 % due to missing values.

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Table 2. Association of dietary vitamin D (μg/4184 kJ (1000 kcal/d)) with non-Hodgkin's lymphoma (NHL) by ethnicity and NHL subgroup in the multiethnic cohort study, 1993–2003

(Hazard ratios (HR) and 95 % CI)

	Men (*n** 514)				Women (*n** 425)			
Ethnicity	Category	*n**	HR	95 % CI†	Category	*n**	HR	95 % CI†
Overall (*n** 939)	<1·4	155	1·00		<1·6	129	1·00	
	1·4–3·8	173	1·01	0·81, 1·26	1·6–5·0	146	1·00	0·78, 1·27
	>3·8	186	1·04	0·83, 1·29	>5·0	150	0·98	0·77, 1·24
	P_{trend}			0·72	P_{trend}			0·83
Ethnicities								
Caucasian (*n** 270)	<1·4	36	1·00		<1·6	19	1·00	
	1·4–3·8	50	0·94	0·61, 1·46	1·6–5·0	46	1·58	0·92, 2·70
	>3·8	62	0·97	0·63, 1·49	>5·0	57	1·46	0·87, 2·47
	P_{trend}			1·00	P_{trend}			0·48
African American (*n** 156)	<1·4	31	1·00		<1·6	37	1·00	
	1·4–3·8	23	0·67	0·39, 1·16	1·6–5·0	26	0·72	0·43, 1·20
	>3·8	22	0·68	0·39, 1·19	>5·0	17	0·50	0·28, 0·90
	P_{trend}			0·31	P_{trend}			0·03
Native Hawaiian (*n** 59)	<1·4	11	1·00		<1·6	12	1·00	
	1·4–3·8	13	0·92	0·41, 2·07	1·6–5·0	10	0·60	0·25, 1·43
	>3·8	7	0·86	0·33, 2·25	>5·0	6	0·62	0·23, 1·68
	P_{trend}			0·79	P_{trend}			0·47
Japanese American (*n** 242)	<1·4	44	1·00		<1·6	31	1·00	
	1·4–3·8	43	1·07	0·70, 1·64	1·6–5·0	31	1·14	0·69, 1·88
	>3·8	55	1·07	0·72, 1·60	>5·0	38	0·97	0·60, 1·57
	P_{trend}			0·80	P_{trend}			0·73
Latino (*n** 212)	<1·4	33	1·00		<1·6	30	1·00	
	1·4–3·8	44	1·34	0·84, 2·13	1·6–5·0	33	0·97	0·59, 1·61
	>3·8	40	1·47	0·91, 2·37	>5·0	32	1·39	0·84, 2·31
	P_{trend}			0·18	P_{trend}			0·14
NHL subgroups								
DLBCL (*n** 311)	<1·4	56	1·00		<1·6	35	1·00	
	1·4–3·8	58	0·95	0·61, 1·48	1·6–5·0	44	0·73	0·42, 1·26
	>3·8	54	1·26	0·82, 1·93	>5·0	64	0·81	0·49, 1·35
	P_{trend}			0·23	P_{trend}			0·79
FL (*n** 152)	<1·4	16	1·00		<1·6	26	1·00	
	1·4–3·8	20	1·65	0·58, 4·70	1·6–5·0	36	0·73	0·37, 1·43
	>3·8	25	0·75	0·28, 1·96	>5·0	29	0·64	0·29, 1·41
	P_{trend}			0·18	P_{trend}			0·38
SLL/CLL (*n** 198)	<1·4	32	1·00		<1·6	22	1·00	
	1·4–3·8	47	1·05	0·57, 1·93	1·6–5·0	29	0·55	0·24, 1·23
	>3·8	42	1·00	0·56, 1·81	>5·0	26	0·68	0·30, 1·56
	P_{trend}			0·93	P_{trend}			0·90

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.

* Number of NHL cases. May not add up to total (*n* 939) due to missing values.

† Hazards ratios and 95 % CI were adjusted for education (≥12 *v.* <12 years), BMI (overweight (25·0–29·9), obese (≥30·0) *v.* normal (<25·0)), alcohol intake (<1·0, 1·0–1·9, 2·0–2·9, and ≥3 *v.* 0 servings/d), and total energy (log transformed). For the overall category, they were also adjusted for ethnicity (African American, Native Hawaiian, Japanese American, and Latino *v.* Caucasian).

and to a lesser degree among Native Hawaiians. The few previous studies on dietary vitamin D among primarily Caucasians did not find an association[4,11–13], except for one case–control study that reported an inverse association with an OR = 0·6 (95 % CI: 0·4, 0·9)[14]. The major source of vitamin D in human subjects is UV-B light, which accounts for more than 90 % of vitamin D requirement, rather than food items[5,15]. This might explain the lack of an overall association in the present 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[5,16]. 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 follicular lymphoma in women is consistent with a previous study that found a 70 % lowered follicular lymphoma risk associated with high dietary vitamin D[14]. 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].

Strengths of the present study include the use of Surveillance, Epidemiology, and End Results tumour 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 was accurate since all NHL cases occurred after the implementation of the WHO classification[9]. Furthermore, the present study included a multiethnic population with a wide variety

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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[16]. Despite the large size of the multiethnic cohort, the present 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 were due to chance.

To our knowledge, the present 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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