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Plasma 25-hydroxyvitamin D concentration and lymphoma risk: results of the European Prospective Investigation into Cancer and Nutrition[1–3]

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ABSTRACT

Background: The relation between vitamin D status and lymphoma risk is inconclusive.

Objective: We examined the association between prediagnostic plasma 25-hydroxyvitamin D [25(OH)D] and lymphoid cancer risk.

Design: We conducted a study nested within the European Prospective Investigation into Cancer and Nutrition cohort of 1127 lymphoma cases and 1127 matched controls with a mean follow-up time of 7.1 y. Conditional logistic regression was used to estimate multivariable-adjusted incidence rate ratios of lymphoma risk in relation to plasma 25(OH)D. Season-standardized and season-specific 25(OH)D quartiles were used. We also analyzed 25(OH)D as a continuous variable and used predefined cutoffs.

Results: No statistically significant association between plasma 25(OH)D and overall lymphoid cancer risk was observed. A positive association for B-cell non-Hodgkin lymphoma was noted only in those with a diagnosis made during the first 2 y of follow-up (*P*-heterogeneity = 0.03), which suggests the possibility of reverse causality. Further analysis restricted to participants with ≥2 y of follow-up time showed a significant association between 25(OH)D and chronic lymphocytic leukemia (CLL) (n = 161): adjusted incidence rate ratios were 0.40 (95% CI: 0.18, 0.90; *P*-trend = 0.05) and 0.31 (95% CI: 0.13, 0.76; *P*-trend = 0.03) for the top compared with the bottom season-standardized and season-specific quartiles, respectively. Data on dietary vitamin D intake provided further support for the observed association (incidence rate ratio: 0.33; 95% CI = 0.12, 0.89; *P*-trend = 0.006).

Conclusions: Our findings do not support a protective role of high 25(OH)D concentration in lymphoid cancers overall. However, they suggest that higher concentrations of 25(OH)D are associated with a reduced risk of CLL.

INTRODUCTION

Lymphomas are estimated to account for ∼3–4% of cancers worldwide. In Europe, they are among the 10 most frequent malignancies (1). They constitute a heterogeneous group of cancers that predominantly arise from B-cell lymphocytes (2). Knowledge of the etiology of most lymphoma subtypes remains scarce. Immune dysregulation is widely believed to play a major role in lymphomagenesis (3). There is also a well-established association between infectious agents and specific lymphoma subtypes. Infectious agents can directly infect and transform lymphocytes, induce immunosuppression, or cause chronic antigen stimulation, which in turn may lead to the development of lymphoid tissue malignancies (4).

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Initially, exposure to UV light was suggested as a risk factor for lymphoma, particularly non-Hodgkin lymphoma (NHL)[4] (5–7). Later on, and contrary to previous results, several case-control studies (8–11), but not all (12), documented a decrease in NHL risk with increasing self-reported lifetime sun exposure. A pooled analysis of 10 case-control studies of the InterLymph consortium indicated an inverse association of NHL risk with recreational sun exposure in a dose-dependent manner (13).

One plausible mechanism for the observed association between sunlight exposure and lymphoma risk is UVB-induced vitamin D production (14). Vitamin D_3 generated from the skin or delivered from dietary sources is converted to 25-hydroxyvitamin D [25(OH)D], which is the major circulating form and the best indicator of vitamin D status (15). Consequently, 25(OH)D is converted to 1,25-dihydroxyvitamin D—the biologically active form with reported antiproliferative and prodifferentiative effects on lymphocytes (16) and immunosuppressive influence on T helper 1– and T helper 17–mediated responses (17).

Thus far, only 2 prospective studies, 1 including a consortial effort, have investigated serum concentrations of 25(OH)D in association with lymphoma risk (18, 19). Neither study showed a significant association with NHL. The aim of the current study was to investigate the association between prediagnostic plasma 25(OH)D and lymphoma risk in European populations. For this purpose, we used the resources of a large multicenter cohort study—the European Prospective Investigation into Cancer and Nutrition (EPIC). We report here the results of an analysis performed on 1127 lymphoma cases and matched controls from 9 countries from northern to southern Europe.

SUBJECTS AND METHODS

Study population and data collection

EPIC is a prospective cohort study aimed at investigating the relations between nutritional, lifestyle, and environmental factors and the risk of cancer and other chronic diseases. The detailed study description and data-collection process have been reported elsewhere (20). Briefly, the cohort consists of more than half a million participants from 23 centers in 10 European countries (Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom), mainly aged 35–65 y at recruitment. Enrollment into the study took place between 1992 and 2000.

Detailed information on diet and lifestyle was obtained by using standardized questionnaires and interviews. Validated country-specific questionnaires were used to assess diet over the 12 mo before recruitment. Anthropometric measurements were performed and blood samples were collected at baseline—before disease diagnosis.

All participants gave written informed consent to take part in the study. The research was approved by the local ethics committees in the participating countries and by the Internal Review Board of the International Agency for Research on Cancer (Lyon, France).

Case assessment and control selection

In most countries, incident lymphoma cases were identified via population-based cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). In Germany and Greece, data were collected through active follow-up.

Cases with lymphoid cancers were originally classified according to the second revision of the International Classification of Diseases for Oncology (ICD-O-2), but were subsequently reclassified according to the WHO classification of hematopoietic and lymphoid tissue cancers, third edition (21), by using a program available on the US National Cancer Institute Surveillance, Epidemiology and End Results website (http://seer.cancer.gov/) and the expertise of pathologists. If the ICD-O-2 codes could not be exactly translated to ICD-O-3, a patient was categorized as "lymphoma, not otherwise specified."

Of the total EPIC population at baseline (n = 521,457), participants with prevalent cancer at any site (except nonmelanoma skin cancer) were excluded (n = 27,089). Participants in the French cohort (n = 68,050) were excluded from the study because of incomplete coding for lymphoid neoplasms. The final analyses included 1127 lymphoma cases: Hodgkin lymphoma

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[4]Abbreviations used: B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FL, follicular lymphoma; ICD-O, International Classification of Diseases for Oncology; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; 25(OH)D, 25-hydroxyvitamin D.

(n = 52); B-cell lymphoma (n = 949), a category that includes B-cell NHL (B-NHL; n = 699) and multiple myeloma (MM) (n = 250); T-cell non-Hodgkin lymphoma (n = 39); and lymphoma not otherwise specified (n = 87). The B-cell lymphoma subtypes included diffuse large B-cell lymphoma (DLBCL) (n = 132), follicular lymphoma (FL) (n = 122), chronic lymphocytic leukemia (CLL) (n = 203), and MM.

For each incident case, one control subject was identified by incidence density sampling (22) from all cohort members alive and without a cancer diagnosis (except for nonmelanoma skin cancer) at the time of diagnosis of the index case. Matching criteria were study center, sex, length of follow-up, and age (±3 mo), time (±1 h), and date (±1 mo) of blood collection.

Laboratory assays

Citrated plasma samples were analyzed with the fully automated IDS-iSYS 25(OH)D (Immunodiagnostic Systems Ltd)—a method that is 100% specific for both vitamin D_2 and vitamin D_3. For manual quantification of 25(OH)D in EDTA-treated samples, we used the OCTEIA 25(OH)D enzyme immunoassay (Immunodiagnostic Systems Ltd). The kit is 100% specific for vitamin D_3 and ≥75% specific for vitamin D_2 (23). A total of 255 lymphoma cases and controls from Sweden (EDTA samples) were measured with the manual assay because the automated method at the time was not available for our use. To monitor the difference in 25(OH)D concentrations between the 2 assays, we measured 25 samples from the Vitamin D External Quality Assurance Scheme Patient Library as well as 3 levels of internal quality-control sets. Moreover, results from the 2 methods were further compared with the nominal gold standard HPLC liquid chromatography–tandem mass spectrometry (24).

Spearman's correlation coefficients between 25(OH)D concentrations in samples determined with HPLC liquid chromatography–tandem mass spectrometry and the automated and the manual assay were ρ = 0.97 (P = <0.0001) and ρ = 0.96 (P = <0.0001) respectively. The Spearman's correlation coefficient between 25(OH)D values from the automated and the manual assays was ρ = 0.98 (P = <0.0001). Recovery of both assays was evaluated by spiking a high with a low concentrated serum sample in different ratios. Recoveries ranged between 91.2% and 106.8% (at 15.2–131.8 nmol/L).

Intra- and interassay CVs were 2.2% and 15.7% (at 52.7 nmol/L) and 3.2% and 9.5% (at 118.3 nmol/L), respectively, for the automated assay. The manual assay measurement of a quality-control sample showed an intraassay CV of 8.2% and an interassay CV of 12.4% (at 52.7 nmol/L). Each case-control set was measured in the same analytic batch. For all measurements, laboratory personnel were blinded to the case-control status of the samples.

Statistical analysis

Differences between cases and matched controls in the continuous baseline characteristics were tested by paired t test. Differences for categorical variables between cases and controls were evaluated by conditional logistic regression. Any missing values on investigated confounding factors were assigned to a separate category to keep all of the observations in the analysis. The percentage of missing values in each category can be found in **Table 1**.

The association between plasma 25(OH)D concentrations and lymphoid cancers was estimated by incidence rate ratios and corresponding 95% CIs with conditional logistic regression. In this nested case-control study with controls selected by incidence density sampling, the OR from conditional logistic regression provides an estimate of the incidence rate ratio (25). Plasma 25(OH)D concentration was modeled both as a categorical and a log-transformed continuous variable.

TABLE 1
Baseline characteristics of lymphoma cancer cases and matched controls in the European Prospective Investigation into Cancer and Nutrition[1]

Characteristic	Cases (n = 1127)	Controls (n = 1127)	P[2]
Women [n (%)]	543 (48.2)	543 (48.2)	
Men [n (%)]	584 (51.8)	584 (51.8)	
Educational level [n (%)]			
None	42 (3.7)	40 (3.5)	
Primary school	373 (33.1)	408 (36.2)	
Technical/professional school	303 (26.9)	300 (26.6)	
Secondary school	156 (13.8)	132 (11.7)	
University	204 (18.1)	204 (18.1)	
Missing information	49 (4.3)	43 (3.8)	0.45
Physical activity [n (%)]			
Inactive	245 (21.7)	249 (22.1)	
Moderately inactive	325 (28.8)	317 (28.1)	
Moderately active	211 (18.7)	219 (19.4)	
Active	216 (19.2)	218 (19.3)	
Missing information	130 (11.5)	124 (11.0)	0.74
Smoking status [n (%)]			
Life-long nonsmoker	457 (40.6)	487 (43.2)	
Current smoker	216 (19.2)	220 (19.5)	
Ex-smoker	378 (33.5)	345 (30.6)	
Missing information	76 (6.7)	75 (6.7)	0.44
Alcohol consumption [n (%)]			
0 g/d	148 (13.1)	126 (11.2)	
<5 g/d	317 (28.1)	329 (29.2)	
5–14 g/d	295 (26.2)	339 (30.1)	
15–29 g/d	188 (16.7)	156 (13.8)	
≥30 g/d	174 (15.4)	171 (15.2)	
Missing information	5 (0.4)	6 (0.5)	0.12
BMI [n (%)][3]			
Tertile 1	378 (33.5)	375 (33.3)	
Tertile 2	353 (31.3)	384 (34.1)	
Tertile 3	396 (35.1)	368 (32.7)	0.29
Season of blood draw [n (%)][4]			
Spring	321 (28.5)	318 (28.2)	
Summer	199 (17.7)	193 (17.1)	
Autumn	352 (31.2)	358 (31.2)	
Winter	255 (22.6)	258 (22.9)	
Age at recruitment	56.8 ± 8.1[5]	56.8 ± 8.2	0.55
Plasma 25-hydroxyvitamin D (nmol/L)	59.2 ± 26.1	59.9 ± 26.8	0.48
Calcium intake (mg/d)[6]	1023.6 ± 419.8	1001.5 ± 420.6	0.20
Dietary vitamin D intake (μg/d)[6]	4.7 ± 3.6	4.6 ± 3.2	0.73
Energy intake (kcal/d)[6]	2175.1 ± 720.6	2143.9 ± 661.1	0.31

[1] Percentages may not add up to 100 because of rounding.
[2] Values for differences in means between cases and controls in continuous baseline covariates were tested by paired t test; conditional logistic regression was used for categorical variables.
[3] BMI (in kg/m^2): tertile 1, <22.4; tertile 2, 22.4–27.5; tertile 3, >27.5.
[4] Spring: March, April, May; summer: June, July, August; autumn: September, October, November; winter: December, January, February.
[5] Mean ± SD (all such values).
[6] Estimates based on dietary data.

We used 2 approaches to account for seasonal variation in 25(OH)D concentration: season-standardized and season-specific quartiles, and the lowest category was chosen as a referent. In the first approach the residuals of 25(OH)D concentrations against week of blood draw were calculated by using the local polynomial regression method (PROC LOESS, SAS 9.2; SAS Institute). Season-standardized 25(OH)D values were calculated by adding the residuals from the regression model to the overall population mean. Use of regression residuals enabled us to use standardized quartiles of plasma 25(OH)D in the conditional logistic regression analysis, regardless of the season of blood collection (26, 27). In the second approach, season-specific quartiles using the 4-category season variable for plasma 25(OH)D were created. The cutoffs were calculated so that each stratum of season among controls was equally represented. The season variable was categorized as follows: spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February).

We also examined the association between lymphoma risk and predefined cutoffs for 25(OH)D. The concentration of 25(OH)D was divided into 5 categories (<25, 25 to <50, 50 to <75, 75 to <100, and ≥100 nmol/L) by using cutoffs of vitamin D deficiency/insufficiency (28, 29). For the stratified analysis, 3 categories (<50, 50 to <75, and ≥75 nmol/L) of plasma 25(OH)D concentrations were evaluated. A central concentration of 50 to <75 nmol/L served as the reference category for both the main and the stratified analyses.

To evaluate the crude association between plasma 25(OH)D concentrations and risk of lymphoid cancers, univariate analyses based on the matching factors were performed. In multivariate analyses, the effect of potential confounders—including smoking status (current, past, or never), alcohol consumption (nonconsumers or 1–4, 5–14, 15–29, or ≥30 g/d), education level (as a proxy variable for socioeconomic status; none/primary, technical/professional, secondary, university, or missing), BMI (tertiles), physical activity (inactive, moderately inactive, moderately active, active, or missing), dietary calcium intake (mg/d; continuous), and total energy intake (kcal/d; continuous)—was evaluated by including these variables in the model. The choice of confounding factors was based on whether addition of the covariate to the model changed the crude incidence rate ratio estimates by ≥10% and/or whether they have been shown to be risk factors for lymphoma.

Stratified analyses were conducted by sex, lymphoma subtypes (B-NHL, MM, and B-NHL subtypes DLBCL, FL, and CLL), age at diagnosis (≤60 or >60 y), season of blood draw (summer, winter, autumn, or spring), season of diagnosis (summer, winter, autumn, or spring), and latitude (southern Europe, below 46°N: Italy, Spain, and Greece; central Europe, between 46 and 54°N: United Kingdom, Germany, and the Netherlands; northern Europe, above 54°N: Sweden, Norway, and Denmark). Hodgkin lymphoma and T-cell non-Hodgkin lymphoma cases were too few to perform subtypes analyses. The likelihood ratio chi-square test was used to assess heterogeneity in the association between 25(OH)D concentration and all main variables. Reported *P* values were derived from 2-sided tests, and those <0.05 were considered statistically significant.

Dietary intake of vitamin D was analyzed as an exposure of interest by using quartile cutoffs based on the variable distribution among controls. In the sensitivity analysis, all models were run with the exclusion of cases that developed lymphoma within the first 2 y of follow-up to exclude reverse causation. An

TABLE 2
Incidence rate ratios and 95% CIs for the association between circulating 25-hydroxyvitamin D and risk of lymphoma: results obtained by using season-standardized quartiles, season-specific quartiles, and a continuous measure of 25-hydroxyvitamin D

	25-Hydroxyvitamin D					
Quartile	Mean ± SD	Median	No. of cases[1]	No. of controls[1]	Rate ratio (95% CI)[2]	Adjusted rate ratio (95% CI)[3]
	nmol/μL	*nmol/μL*				
Season-standardized cutoffs[4]						
1	34.7 ± 4.5	33.2	295	281	1.00	1.00
2	48.9 ± 10.5	47.1	261	282	0.88 (0.69, 1.12)	0.87 (0.68, 1.11)
3	62.3 ± 10.2	61.3	284	282	0.96 (0.75, 1.22)	0.99 (0.77, 1.28)
4	93.5 ± 25.3	88.3	287	282	0.97 (0.75, 1.25)	1.05 (0.81, 1.37)
P-trend					0.97	0.52
Season-specific cutoffs[5]						
1	32.9 ± 9.2	32.6	288	280	1.00	1.00
2	49.3 ± 8.3	49.2	260	283	0.89 (0.70, 1.14)	0.89 (0.69, 1.14)
3	63.1 ± 9.2	63.4	306	280	1.06 (0.83, 1.36)	1.08 (0.84, 1.40)
4	93.7 ± 25.1	88.4	273	284	0.93 (0.72, 1.22)	1.00 (0.76, 1.32)
P-trend					0.93	0.66
Continuous model			1127	1127	0.91 (0.73, 1.14)	0.97 (0.77, 1.22)
P-trend					0.43	0.80

[1] Numbers before adjustment.

[2] Determined by conditional logistic regression. Model based on matching variables.

[3] Determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

[4] Cutoffs were as follows (by quartile): Q1, ≤43.1; Q2, >43.1–56.4; Q3, >56.4–71.6; and Q4, >71.6 nmol/L.

[5] Cutoffs were as follows (by quartile): Q1, ≤33.9; Q2, >33.9 to ≤47.5; Q3, >47.5 to ≤62.2; and Q4, >62.2 nmol/L for spring. Q1, ≤51.2; Q2, >51.2 to ≤63.3; Q3, >63.3 to ≤81.6; and Q4, >81.6 nmol/L for summer. Q1, ≤48.6; Q2, >48.6 to ≤63.2; Q3, >63.2 to ≤82.4; and Q4, >82.4 nmol/L for autumn. Q1, ≤37.7; Q2, >37.7 to ≤49.4; Q3, >49.4 to ≤65.8; and Q4, >65.8 nmol/L for spring.

TABLE 3
Incidence rate ratios and 95% CIs for the association between circulating 25-hydroxyvitamin D and risk of lymphoma: results obtained by using predefined cutoffs

	Predefined cutoffs (nmol/L)					
	<25	25 to <50	50 to <75	75 to <100	≥100	*P*-trend
No. of cases[1]	70	378	404	195	80	
No. of controls[1]	57	389	429	161	91	
Rate ratio (95% CI)[2]	1.32 (0.89, 1.98)	1.04 (0.84, 1.28)	1.00 (referent)	1.29 (1.00, 1.65)	0.93 (0.65, 1.32)	0.94
Adjusted rate ratio (95% CI)[3]	1.36 (0.89, 2.06)	1.00 (0.80, 1.24)	1.00 (referent)	1.33 (1.02, 1.72)	1.01 (0.70, 1.45)	0.62

[1] Numbers before adjustment.
[2] Determined by conditional logistic regression. Model based on matching variables.
[3] Determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

analysis with the exclusion of data from Sweden was also conducted. All statistical analyses were carried out by using SAS 9.2 (SAS Institute).

RESULTS

The final sample comprised 1127 cases and 1127 controls with a mean follow-up time of 7.1 y (range: 2 d to 13.7 y). Included in the main analysis were 923 case-control pairs (81.9%) with a follow-up time of ≥2 y. We observed no significant differences between cases and controls with respect to any of the baseline characteristics. The mean age at blood collection was 56.8 y. The mean plasma concentrations of 25(OH)D in cases and controls were 59.2 and 59.9 nmol/L, respectively (Table 1).

Adjusted geometric mean concentrations of 25(OH)D, as expected, varied by month of blood collection. The highest values were observed in the summer months and the lowest in winter and early spring (*see* Supplemental Figure 1 under "Supplemental data" in the online issue). Among controls, age-adjusted geometric mean concentrations based on season-standardized 25(OH)D values and stratified by sex varied significantly between countries ($P < 0.0001$). The highest mean concentrations were noted in Nordic countries as compared with southern European countries (*see* Supplemental Figure 2 under "Supplemental data" in the online issue).

Overall, no statistically significant association was found between plasma 25(OH)D and lymphoid cancers, with or without adjustment for covariates (**Table 2**). Adjusted incidence rate ratios were 1.05 (95% CI: 0.81, 1.37) for the highest compared with the lowest season-standardized quartiles and 1.00 (95% CI: 0.76, 1.32) for season-specific quartiles. Analyses using natural log-transformed 25(OH)D as a continuous variable (Table 2) and as a priori defined cutoffs (**Table 3**) similarly showed no association between plasma 25(OH)D and overall lymphoma risk.

To address the possibility of reverse causality, we conducted a sensitivity analysis separating the cohort by the length of the follow-up period (≥2 or <2 y) (**Table 4**; *see* Supplemental Table 1 under "Supplemental data" in the online issue). No evidence of heterogeneity was found between the 2 groups regarding the association between plasma 25(OH)D and lymphoma considered overall (*P*-heterogeneity = 0.43 and 0.12 for season-standardized quartiles and by a priori defined cutoff analyses, respectively). However, in analyses limited to B-NHL only, significant heterogeneity (*P*-heterogeneity = 0.03) was identified between the 2 follow-up groups when season-standardized quartiles were used. The positive association between B-NHL lymphoma risk and increasing plasma 25(OH)D concentrations was seen only for cases diagnosed during the first 2 y of follow-up. Among those, the adjusted incidence rate ratio was 4.29 (95% CI: 1.55, 11.88) for the top compared with the bottom

TABLE 4
Incidence rate ratios and 95% CIs for the association between circulating 25-hydroxyvitamin D and risk of all lymphoma and B-NHL only: results obtained by using season-standardized quartiles and stratified by diagnosis during the first 2 y of follow-up[1]

	Quartiles based on season of blood collection (nmol/L)									
	≤43.1		>43.1–56.4		>56.4–71.6		>71.6			
	No. cases /controls	RR (95% CI)[2]	No. cases /controls	RR (95% CI)[2]	No. cases /controls	RR (95% CI)[2]	No. cases /controls	RR (95% CI)[2]	*P*-trend	*P*-heterogeneity
All lymphoma										
≥2 y follow-up	245/227	Reference	206/226	0.83 (0.63, 1.09)	236/228	0.96 (0.72, 1.28)	226/232	0.93 (0.69, 1.25)	0.84	0.43
<2 y follow-up	46/51	Reference	51/55	0.96 (0.53, 1.77)	45/52	1.02 (0.55, 1.89)	61/45	1.39 (0.75, 2.56)	0.27	
B-NHL										
≥2 y follow-up	158/153	Reference	123/143	0.82 (0.57, 1.17)	142/123	1.15 (0.79, 1.67)	148/152	0.97 (0.67, 1.41)	0.77	0.03
<2 y follow-up	21/32	Reference	32/34	1.75 (0.74, 4.13)	26/33	1.38 (0.54, 3.54)	42/22	4.29 (1.55, 11.88)	0.009	

[1] B-NHL, B-cell non-Hodgkin lymphoma.
[2] Data are incidence rate ratios (RRs) determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

TABLE 5
Incidence rate ratios and 95% CIs for the association between season-standardized circulating 25(OH)D and B-NHL: results from stratified analyses before and after exclusion of cases diagnosed during the first 2 y of follow-up[1]

			Quartiles of 25(OH)D concentration (nmol/L)							
				43.1–56.4		>56.4–71.6		>71.6		
Stratification factor	No. of cases	No. of controls	≤43.1	RR[2]	95% CI[2]	RR[2]	95% CI[2]	RR[2]	95% CI[2]	*P*-trend	*P*-heterogeneity
Full cohort											
B-NHL[3]	692	692	Ref	0.91	(0.66, 1.25)	1.18	(0.84, 1.64)	1.23	(0.88, 1.72)	0.12	
DLBCL	130	130	Ref	1.94	(0.74, 5.11)	1.01	(0.37, 2.75)	2.09	(0.83, 5.30)	0.23	
FL	119	119	Ref	0.80	(0.30, 2.12)	0.94	(0.33, 2.72)	2.30	(0.78, 6.78)	0.07	
CLL	202	202	Ref	0.75	(0.41, 1.38)	1.18	(0.62, 2.26)	0.82	(0.42, 1.61)	0.86	0.12
MM/plasmacytoma	249	249	Ref	0.91	(0.50, 1.64)	0.99	(0.56, 1.75)	0.99	(0.53, 1.84)	0.95	
<2-y follow-up excluded											
B-NHL[3]	571	571	Ref	0.82	(0.57, 1.17)	1.15	(0.79, 1.67)	0.97	(0.67, 1.41)	0.77	
DLBCL	107	107	Ref	1.97	(0.66, 5.88)	1.02	(0.33, 3.14)	1.75	(0.61, 5.06)	0.49	
FL	103	103	Ref	1.17	(0.38, 3.54)	1.36	(0.38, 4.91)	2.97	(0.87, 10.17)	0.06	
CLL	161	161	Ref	0.74	(0.36, 1.51)	0.87	(0.42, 1.81)	0.40	(0.18, 0.90)	0.05	0.08
MM/plasmacytoma	198	198	Ref	0.89	(0.45, 1.76)	1.00	(0.51, 1.95)	1.19	(0.55, 2.56)	0.65	
Sex											
Full cohort											
Women	351	351	Ref	0.72	(0.45, 1.13)	1.09	(0.68, 1.77)	1.07	(0.66, 1.74)	0.47	
Men	341	341	Ref	0.95	(0.58, 1.55)	1.06	(0.64, 1.76)	1.14	(0.68, 1.91)	0.55	0.64
<2-y follow-up excluded											
Women	289	289	Ref	0.95	(0.55, 1.64)	1.11	(0.64, 1.92)	0.99	(0.56, 1.75)	0.91	
Men	282	282	Ref	0.61	(0.36, 1.02)	1.10	(0.63, 1.91)	0.80	(0.46, 1.37)	0.77	0.52
Age[4]											
Full cohort											
≤60 y	452	452	Ref	0.96	(0.64, 1.45)	1.65	(1.09, 2.52)	1.50	(0.98, 2.30)	0.02	
>60 y	230	230	Ref	0.61	(0.34, 1.09)	0.47	(0.24, 0.91)	0.62	(0.32, 1.19)	0.15	0.005
<2-y follow-up excluded											
≤60 y	381	381	Ref	0.90	(0.57, 1.41)	1.55	(0.97, 2.48)	1.12	(0.70, 1.80)	0.27	
>60 y	182	182	Ref	0.49	(0.25, 0.99)	0.44	(0.21, 0.93)	0.50	(0.24, 1.06)	0.08	0.03
Season of blood draw[4,5]											
Full cohort											
Spring	168	168	Ref	0.57	(0.26, 1.27)	0.83	(0.38, 1.80)	0.79	(0.36, 1.73)	0.92	
Summer	105	105	Ref	0.40	(0.14, 1.17)	3.21	(1.15, 9.01)	4.61	(1.36, 15.63)	0.003	
Autumn	170	170	Ref	1.29	(0.67, 2.49)	0.95	(0.45, 2.04)	1.18	(0.60, 2.31)	0.75	
Winter	124	124	Ref	1.49	(0.64, 3.50)	1.43	(0.51, 3.96)	1.90	(0.75, 4.84)	0.21	0.35
<2-y follow-up excluded											
Spring	137	137	Ref	0.49	(0.18, 1.33)	0.59	(0.24, 1.49)	0.63	(0.25, 1.59)	0.58	
Summer	87	87	Ref	0.17	(0.04, 0.73)	2.51	(0.68, 9.29)	4.87	(0.98, 24.16)	0.02	
Autumn	142	142	Ref	1.31	(0.60, 2.88)	1.07	(0.45, 2.57)	0.82	(0.39, 1.75)	0.56	
Winter	105	105	Ref	2.39	(0.82, 7.00)	1.16	(0.35, 3.83)	1.81	(0.61, 5.37)	0.49	0.29

(Continued)

TABLE 5 (*Continued*)

Stratification factor	No. of cases	No. of controls	Quartiles of 25(OH)D concentration (nmol/L)								
			≤43.1	43.1–56.4		>56.4–71.6		>71.6		*P*-trend	*P*-heterogeneity
				RR[2]	95% CI[2]	RR[2]	95% CI[2]	RR[2]	95% CI[2]		
Latitude[6]											
Full cohort											
South	165	165	Ref	1.22	(0.63, 2.38)	1.56	(0.77, 3.18)	1.54	(0.64, 3.73)	0.21	
Central	225	225	Ref	0.88	(0.51, 1.53)	0.75	(0.41, 1.39)	1.01	(0.55, 1.86)	0.88	
North	302	302	Ref	0.76	(0.43, 1.36)	1.16	(0.66, 2.03)	1.10	(0.63, 1.90)	0.37	0.61
<2-y follow-up excluded											
South	138	138	Ref	0.91	(0.42, 1.98)	1.16	(0.52, 2.58)	1.19	(0.44, 3.21)	0.67	
Central	189	189	Ref	0.71	(0.38, 1.33)	0.80	(0.40, 1.60)	0.80	(0.40, 1.60)	0.55	
North	244	244	Ref	0.82	(0.42, 1.59)	1.28	(0.68, 2.42)	0.89	(0.48, 1.65)	0.93	0.84

[1] B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; Ref, reference; 25(OH)D, 25-hydroxyvitamin D.

[2] Data are incidence rate ratios (RRs) determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

[3] B-NHL includes DLBCL, FL, and CLL.

[4] Discrepancy in total number of case-controls results from incomplete matching.

[5] Spring: March, April, May; summer: June, July, August; autumn: September, October, November; winter: December, January, February.

[6] Southern Europe (below 46°N): Italy, Spain, Greece; central Europe (between 46 and 54°N): United Kingdom, Germany, Netherlands; northern Europe (above 54°N): Sweden, Norway, Denmark.

season-standardized quartile (*P*-trend = 0.009). The corresponding value for those with a diagnosis made ≥2 y after baseline was 0.97 (95% CI: 0.67, 1.41; *P*-trend = 0.77) (Table 4). A similar pattern of results was observed in the model based on predefined cutoffs (*see* Supplemental Table 1 under "Supplemental data" in the online issue).

The results for B-NHL stratified by sex, age, season of blood draw, latitude—with and without exclusion of cases diagnosed during the first 2 y of follow-up—are summarized in **Table 5**. No significant association with the overall risk of B-cell lymphoma was observed. Analyses restricted to cases diagnosed ≥2 y after blood donation showed a decreased risk of CLL (incidence rate ratio for the highest compared with the lowest quartile: 0.40; 95% CI: 0.18, 0.90; *P*-trend = 0.05), which was similarly found in the season-specific model (incidence rate ratio for the highest compared with the lowest quartile: 0.31; 95% CI: 0.13, 0.76; *P*-trend = 0.03), but not in the analysis of predefined categories (**Table 6**).

In contrast, an opposite trend, although not statistically significant, was observed for FL (incidence rate ratio for the highest compared with the lowest quartile: 2.97; 95% CI: 0.87, 10.17; *P*-trend = 0.06, *P*-heterogeneity = 0.08) (Table 5); a similar pattern of results was seen in other models (*P*-heterogeneity = 0.02 in both predefined cutoffs and season-specific quartiles models) (Table 6; *see* Supplemental Table 2 under "Supplemental data" in the online issue).

Significant heterogeneity in the trends for B-NHL risk with 25(OH)D by age (*P*-heterogeneity = 0.005) was observed in the whole cohort. We noted an elevated risk of B-NHL for younger individuals (≤60 y; incidence rate ratio for the highest compared with the lowest quartile: 1.50; 95% CI: 0.98, 2.30; *P*-trend = 0.02). For participants older than 60 y, a tendency toward an inverse association was seen (incidence rate ratio for the highest compared with the lowest quartile: 0.62; 95% CI: 0.32, 1.19; *P*-trend = 0.15). This association was still observed, but it was markedly attenuated when only those with a late diagnosis (≥2 y after baseline) were analyzed (*P*-heterogeneity = 0.03). A significant positive relation between B-NHL and 25(OH)D was also shown for individuals whose blood was collected in the summer months (incidence rate ratio: 4.61; 95% CI: 1.36, 15.63; *P*-trend = 0.003), although the *P* value for heterogeneity lacked statistical significance (*P*-heterogeneity = 0.35). This association was less significant in the analysis restricted to cases diagnosed ≥2 y after baseline (incidence rate ratio: 4.87; 95% CI: 0.98, 24.16; *P*-trend = 0.02) (Table 5).

A similar pattern of results was observed when the data were examined by predefined cutoffs, by season-specific quartiles, and in the continuous models (Table 6; *see* Supplemental Table 2 under "Supplemental data" in the online issue, data not shown).

25(OH)D was not associated with the risk of MM in all considered models (Tables 5 and 6; *see* Supplemental Table 2 under "Supplemental data" in the online issue). In the analysis that excluded Sweden, no substantial changes in risk estimates were observed (data not shown). Dietary vitamin D intake showed no association with lymphoma risk overall (data not shown). Complementing the observed association between 25(OH)D concentration and reduced risk of CLL, we observed an inverse relation between dietary vitamin D intake and the risk of CLL in individuals with a diagnosis made ≥2 y after

TABLE 6
Incidence rate ratios and 95% CIs for the association between circulating 25(OH)D and B-NHL: results from stratified analyses based on predefined category cutoffs before and after exclusion of cases diagnosed during the first 2 y of follow-up[1]

	Predefined category cutoffs (nmol/L)											
	Total		<50			50 to <75		≥75				
Stratification factor	No. of cases	No. of controls	No. cases/ controls	RR[2]	95% CI[2]	No. cases/ controls		No. cases/ controls	RR[2]	95% CI[2]	*P*-trend	*P*-heterogeneity
Full cohort												
B-NHL[3]	692	692	266/293	0.85	(0.64, 1.12)	247/254	Ref	179/145	1.36	(1.00, 1.83)	0.007	
DLBCL	130	130	50/50	0.61	(0.26, 1.39)	42/42	Ref	38/28	1.79	(0.76, 4.19)	0.03	
FL	119	119	43/52	1.02	(0.44, 2.37)	37/49	Ref	39/18	3.26	(1.41, 7.56)	0.02	
CLL	202	202	76/85	0.87	(0.51, 1.48)	79/73	Ref	47/44	1.01	(0.56, 1.83)	0.64	0.13
MM/plasmacytoma	249	249	95/88	1.03	(0.61, 1.73)	94/97	Ref	60/64	0.91	(0.52, 1.60)	0.71	
<2-y follow-up excluded												
B-NHL[3]	571	571	226/239	0.89	(0.66, 1.22)	203/204	Ref	148/128	1.17	(0.84, 1.64)	0.16	
DLBCL	107	107	40/46	0.71	(0.28, 1.80)	37/37	Ref	30/24	1.45	(0.56, 3.75)	0.20	
FL	103	103	38/46	0.83	(0.30, 2.31)	31/41	Ref	34/16	3.61	(1.32, 9.88)	0.01	
CLL	161	161	68/65	1.10	(0.59, 2.05)	62/57	Ref	31/39	0.58	(0.28, 1.20)	0.16	0.02
MM/plasmacytoma	198	198	77/65	1.35	(0.72, 2.51)	74/87	Ref	47/46	1.23	(0.64, 2.36)	0.76	
Sex												
Full cohort												
Women	351	351	145/154	0.98	(0.65, 1.47)	116/125	Ref	90/72	1.34	(0.86, 2.09)	0.22	
Men	341	341	121/139	0.78	(0.51, 1.18)	131/129	Ref	89/73	1.27	(0.81, 1.99)	0.06	0.62
<2-y follow-up excluded												
Women	289	289	123/128	0.94	(0.59, 1.50)	97/98	Ref	69/63	1.05	(0.63, 1.74)	0.69	
Men	282	282	103/111	0.83	(0.53, 1.32)	106/106	Ref	73/65	1.12	(0.68, 1.84)	0.30	0.82
Age[4]							Ref					
Full cohort												
≤60 y	452	452	163/203	0.64	(0.45, 0.91)	171/156	Ref	118/93	1.26	(0.86, 1.83)	0.001	
>60 y	230	230	99/89	1.64	(0.96, 2.80)	71/92	Ref	60/49	1.58	(0.89, 2.81)	0.78	0.03
<2-y follow-up excluded												
≤60 y	381	381	144/167	0.73	(0.50, 1.06)	144/131	Ref	93/83	1.09	(0.72, 1.66)	0.07	
>60 y	182	182	79/71	1.62	(0.87, 3.00)	54/69	Ref	49/42	1.44	(0.74, 2.78)	0.67	0.16
Season of blood draw[4,5]							Ref					
Full cohort												
Spring	168	168	95/97	0.88	(0.48, 1.62)	48/54	Ref	25/17	1.26	(0.60, 2.66)	0.35	
Summer	105	105	25/35	0.54	(0.22, 1.27)	41/45	Ref	39/25	2.71	(1.08, 6.81)	0.008	
Autumn	170	170	42/44	1.18	(0.62, 2.25)	66/75	Ref	62/51	1.71	(0.95, 3.07)	0.22	
Winter	124	124	62/65	0.60	(0.28, 1.29)	40/39	Ref	22/20	0.98	(0.41, 2.38)	0.24	0.94
<2-y follow-up excluded												
Spring	137	137	79/78	1.00	(0.49, 2.02)	39/44	Ref	19/15	1.25	(0.53, 2.90)	0.65	
Summer	87	87	22/27	0.85	(0.30, 2.43)	35/40	Ref	30/20	3.56	(1.15, 11.08)	0.06	
Autumn	142	142	38/40	1.09	(0.53, 2.22)	55/57	Ref	49/45	1.19	(0.60, 2.36)	0.82	
Winter	105	105	53/55	0.66	(0.27, 1.58)	34/32	Ref	18/18	0.73	(0.25, 2.13)	0.70	0.83

(Continued)

TABLE 6 (*Continued*)

Stratification factor	Total		Predefined category cutoffs (nmol/L)								
			<50			50 to <75		≥75			
	No. of cases	No. of controls	No. cases/ controls	RR[2]	95% CI[2]	No. cases/ controls		No. cases/ controls	RR[2]	95% CI[2]	*P*-trend	*P*-heterogeneity
Latitude[6]							Ref					
Full cohort												
South	165	165	85/100	0.77	(0.42, 1.40)	53/51	Ref	27/14	2.53	(0.98, 6.52)	0.03	
Central	225	225	91/97	0.80	(0.48, 1.32)	89/83	Ref	45/45	0.92	(0.51, 1.63)	0.6	
North	302	302	90/96	1.13	(0.71, 1.79)	105/120	Ref	107/86	1.68	(1.08, 2.60)	0.10	0.23
<2-y follow-up excluded												
South	138	138	74/82	0.89	(0.45, 1.76)	41/43	Ref	23/13	2.92	(1.05, 8.13)	0.07	
Central	189	189	80/82	0.79	(0.44, 1.40)	73/66	Ref	36/41	0.69	(0.35, 1.34)	0.84	
North	244	244	72/75	1.09	(0.65, 1.82)	89/95	Ref	83/74	1.34	(0.82, 2.18)	0.45	0.23

[1] B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; Ref, reference; 25(OH)D, 25-hydroxyvitamin D.

[2] Data are incidence rate ratios (RRs) determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

[3] B-NHL includes DLBCL, FL, and CLL.

[4] Discrepancy in total number of case-controls results from incomplete matching.

[5] Spring: March, April, May; summer: June, July, August; autumn: September, October, November; winter: December, January, February.

[6] Southern Europe (below 46°N): Italy, Spain, Greece; central Europe (between and 54°N): United Kingdom, Germany, Netherlands; northern Europe (above 54°N): Sweden, Norway, Denmark.

recruitment (incidence rate ratio: 0.33; 95% CI: 0.12, 0.89; *P*-trend = 0.006) (**Table 7**).

DISCUSSION

In this study, which is the largest prospective investigation based on European populations to date, we observed no association between circulating 25(OH)D concentration and overall risk of lymphoid cancers. Our findings do not support a protective effect of increasing prediagnostic 25(OH)D concentrations on NHL risk. The negative findings are largely consistent with reports from other prospective studies (18, 19). The most recent published data from the Cohort Consortium Vitamin D Pooling Project similarly showed no decrease in lymphoma risk in relation to elevated concentrations of 25(OH)D overall (n = 1353) or with common NHL subtypes (19). Likewise, prediagnostic serum 25(OH)D measured in 270 incident lymphoid cancer cases and matched controls within the Finnish Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort of male smokers showed no relation with the risk of lymphoid cancers (n = 270), NHL (n = 208), or MM (n = 41), although an inverse association in cases diagnosed <7 y from baseline (*P*-trend = 0.01) (18) was reported.

In our analysis, we noted evidence of a differential association between vitamin D and B-NHL lymphoma by length of follow-up. A significant association between 25(OH)D and B-NHL was evident only in the group of individuals with a diagnosis made during the first 2 y of follow-up—a finding that suggests reverse causation. It is plausible that the presence of the growing cancer before the actual diagnosis contributed to dysregulation of vitamin D metabolism (30), as reflected in differential concentrations of vitamin D between earlier and later diagnosed B-NHL cases. Early symptoms may also have led to changes in lifestyle habits, such as intake of supplements, which eventually boosted vitamin D concentrations.

After the exclusion of cases with <2 y of follow-up, we observed a statistically significant inverse association for CLL, regardless of the analysis model applied. Interestingly, recent results from a comparison of the genome-wide binding of the *VDR* with genome-wide association study data sets for common diseases showed a significant enrichment of *VDR* sites within CLL associated regions (31). These findings imply the role of 25(OH)D in the pathogenesis of CLL. Vitamin D deficiency has also been associated with disease progression in CLL (32), and the vitamin D3 analog has been shown to induce apoptosis in primary CLL cells in vitro through a p53-independent mechanism (33). CLL patients in particular are affected by frequent infections and long-term immunodeficiency before cancer diagnosis (34). Moreover, respiratory tract infections and other community-acquired infections, particularly pneumonia, are discussed as triggers of this type of cancer (35, 36). Data have emerged that vitamin D is implicated in the response to microbial infection (37). Vitamin D deficiency was repeatedly shown to be associated with an increased risk of infections (38, 39); along the same line, supplementation proved protective against acute respiratory tract infections (40). An inverse association between rising vitamin D concentrations and CLL risk, as seen when analyzing plasma 25(OH) concentrations and

TABLE 7
Dietary intake of vitamin D and the risk of CLL and other B-NHL subtypes: results from analyses before and after exclusion of cases diagnosed during the first 2 y of follow-up[1]

	Quartiles of dietary vitamin D intake (μg/d)					
	1 (reference) ≤2.5	2 >2.5–3.9	3 >3.9–5.8	4 >5.8	*P*-trend	*P*-heterogeneity
CLL						
No. of cases/controls	67/50	61/53	33/52	41/47		
Rate ratio[2]	1.00	0.76 (0.43, 1.32)	0.41 (0.22, 0.77)	0.50 (0.25, 1.02)	0.011	
Adjusted rate ratio[3]	1.00	0.86 (0.46, 1.59)	0.39 (0.19, 0.078)	0.45 (0.19, 1.04)	0.01	
<2-y follow-up excluded						
No. of cases/controls	55/40	48/40	29/41	29/40		
Rate ratio[2]	1.00	0.71 (0.37, 1.37)	0.41 (0.20, 1.84)	0.36 (0.16, 0.80)	0.004	
Adjusted rate ratio[3]	1.00	0.82 (0.39, 1.73)	0.36 (0.16, 0.83)	0.33 (0.12, 0.89)	0.006	
FL						
No. of cases/controls	30/33	24/25	29/17	20/28		
Rate ratio[2]	1.00	1.03 (0.47, 2.30)	2.03 (0.86, 4.78)	0.71 (0.30, 1.71)	0.95	
Adjusted rate ratio[3]	1.00	1.21 (0.45, 3.25)	2.61 (0.85, 7.96)	0.91 (0.26, 3.21)	0.63	
DLBCL						
No. of cases/controls	33/35	27/30	27/27	20/15		
Rate ratio[2]	1.00	0.95 (0.47, 1.92)	1.05 (0.51, 2.18)	1.42 (0.62, 3.25)	0.44	
Adjusted rate ratio[3]	1.00	1.22 (0.49, 3.05)	1.35 (0.52, 3.51)	1.82 (0.57, 5.84)	0.32	0.04

[1] B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.
[2] Determined by conditional logistic regression. Model based on matching variables.
[3] Determined by conditional logistic regression. Model based on matching variables and adjusted for smoking status, alcohol consumption at recruitment, education, BMI, physical education, and total energy and calcium intakes.

dietary vitamin D intakes, would be in line with an infectious contribution to this lymphoma subtype.

We noted a tendency toward a positive association for FL in contrast with CLL. A test for heterogeneity across lymphoma subtypes, however, lacked statistical significance in the model based on season-standardized 25(OH)D values. A similar pattern of results has been obtained by Lim et al (18). They showed a trend toward decreased risk of CLL and a trend in the opposite direction for FL with increasing concentrations of 25(OH)D, although not statistically significant. Given the limited study power, caution should be taken in the interpretation of these results. Lymphomas are a heterogeneous group of tumors, which makes an analysis of risk for all subtypes combined inconclusive. The distinct etiologies and clinical features of B-NHL subtypes suggest the need to evaluate the potential association between 25(OH)D and the lymphoma subtypes—each one of them individually. Such an investigation, however, is made difficult by the relatively small sample sizes available for analysis. For instance, Polesel et al (41) showed an inverse association between dietary intake of vitamin D and the risk of FL (n = 31), in contradiction with our analysis, whereas Bahar et al documented an increased risk of DLBCL with higher dietary vitamin D in agreement with our data (42).

We observed in all models a significantly positive association between higher 25(OH)D concentrations and B-NHL risk for individuals whose blood was drawn in the summer. We speculate that measurements of the vitamin D concentration in blood collected in summer might best reflect the extremes of vitamin D exposure in the population. The wide range of vitamin D concentrations, as observed here among controls, most likely follows from different interindividual habits of sun exposure and outdoor activity. Whether this result reflects a true elevated risk of B-NHL, other than CLL, associated with very high vitamin D concentrations remains to be seen in future pooled analyses of sufficient statistical power. Power is limited for stratified analysis in the current study; therefore, we cannot safely rule out that some findings have arisen by chance.

Interestingly, the effect of vitamin D concentration on lymphoma risk appears to differ by age. For individuals aged 60 y and younger, a trend in the direction of a positive association between 25(OH)D concentration and B-NHL was noted. Although it was not observed for predefined categories, it seems that—for individuals older than 60 y—a trend in the direction of reduced risk in association with increasing concentrations of 25(OH)D exists. Other data have shown that the elderly require higher concentrations of 25(OH)D than do younger individuals to maintain a similar level of vitamin D metabolism (43, 44). The risk of developing cancer increases as people age and, as a consequence, most studies on the association between vitamin D and tumor development examine individuals aged 60 y and older. Less is known about the effect that vitamin D might exert in younger adults.

We have observed much higher vitamin D concentrations in northern European than in southern European countries—a finding that is in line with the worldwide vitamin D status report (45) One possible explanation is that the mean vitamin D intake in Scandinavia is 200–400IU/d, twice that in other European countries, which is a result of vitamin D fortification of dairy products, higher fatty fish consumption, and greater use of vitamin D supplements (46).

The major strengths of our study were its prospective design and large sample size, which enabled us to cover a wide range of latitudes and to examine associations with NHL subtypes. Another key strength is that we used multiple approaches to adjust

for seasonal variation to minimize its influence. Detailed information on potential confounding variables collected at baseline allowed for the adjustment of major factors implicated either in lymphoma risk or in 25(OH)D status. A single baseline measurement may not accurately reflect personal long-term 25(OH)D status and interseasonal variation. However, correlation coefficients ranging from 0.52 to 0.7 have been reported in samples measured 3–14 y apart and 0.8 when measured 1 y apart (47). Other limitations included the lack of power for stratified and subtype-specific analyses and missing characterization of the study participants regarding genetic factors and biomarkers with known influence on vitamin D metabolism.

In conclusion, findings from the current investigation together with the results from previous prospective studies do not provide support for an inverse relation between plasma 25(OH)D and lymphoma risk. However, our data suggest that higher concentrations of 25(OH)D are associated with a reduced risk of CLL. Age might be a modifying factor in the association between 25(OH)D and B-NHL, which suggests the need to compare the effects of vitamin D supplementation between age groups. It would be worthwhile to integrate genetic variability in vitamin D metabolism genes as well as biomarkers of infection and inflammation in future studies of vitamin D and lymphoma. Moreover, pooled analyses of large data sets are certainly needed to investigate, with sufficient statistical power, the relation between vitamin D concentrations and individual lymphoma subtypes.

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