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Sunlight exposure, vitamin D, and risk of non-Hodgkin lymphoma in the Nurses' Health Study

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Abstract

Purpose—Case-control studies suggest increased sun exposure reduces non-Hodgkin lymphoma (NHL) risk. Evidence from prospective cohort studies, however, is limited and inconsistent. We evaluated the association between ambient ultraviolet radiation (UV) exposure and NHL in a nationwide cohort of women, the Nurses' Health Study (NHS).

Methods—Between 1976 and 2006, we identified 1064 incident NHL cases among 115,482 women in the prospective NHS. Exposures assessed included average annual UV-B flux based on residence at various times during life, vitamin D intake, and predicted plasma 25-hydroxyvitamin D levels. We estimated incidence rate ratios (RRs) and 95% confidence intervals (CIs) for risk of all NHL and histologic subtypes using Cox proportional hazards models.

Results—NHL risk was increased for women residing in areas of high ambient UV radiation (UV-B flux >113 R-B count × 10^{-4}) compared to those with lower exposure (<113), with positive linear trends at all time points. The multivariable-adjusted RR for high UV area at age 15 was 1.21 (95% CI: 1.00, 1.47; p-trend <0.01). There was no evidence of statistical heterogeneity by subtype, although power was limited for subtype analyses. We observed no association between vitamin D measures and risk of NHL overall or by subtype.

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Conflict of interest
The authors declare that they have no conflicts of interest.

Conclusions—Our findings do not support the hypothesis of a protective effect of UV radiation exposure on NHL risk. We found no association between vitamin D and NHL risk.

Keywords

non-Hodgkin lymphoma; sunlight; ultraviolet radiation; vitamin D; epidemiology

Introduction

Several recently published case-control studies, including a pooled analysis from the InterLymph Consortium, have reported evidence of an inverse association between self-reported personal sun exposure and risk of non-Hodgkin lymphoma (NHL) [1–8]. The apparent protective effect of sun exposure on NHL risk implicates a possible role of vitamin D in the development of NHL, since ultraviolet (UV) radiation triggers production of potentially anti-carcinogenic endogenous vitamin D in the skin [9,10]. Vitamin D from the skin enters the circulation and is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), the major circulating form, which reenters the circulation and is converted to its active form, 1,25-dihydroxyvitamin D [10]. 1,25-dihydroxyvitamin D promotes differentiation and inhibits proliferation of lymphoma cells [11] and contributes to normal B-cell homeostasis [12] *in vitro*, which may contribute to possible anti-cancer effects; however, epidemiologic evidence for an association between vitamin D and NHL remains limited [13,14] and results from a recent large pooled analysis of measured 25(OH)D were null [15].

Very few prospective cohort studies have examined personal sun exposure and risk of NHL, with mixed results [16,17]. Using data from the Nurses' Health Study (NHS), a large prospective cohort of U.S. women, we evaluated the roles of ambient UV radiation exposure, total and dietary vitamin D intake, and predicted plasma 25(OH)D levels on risk of NHL and its most common subtypes.

Methods

Study population

The NHS is an ongoing cohort study established in 1976, when 121,700 female registered nurses aged 30–55 years living in 11 U.S. states completed a self-administered questionnaire on risk factors for cancer and other diseases. Every 2 years, questionnaires are sent to cohort members to update information on potential risk factors and to identify newly diagnosed cancers and other diseases. Vital status is ascertained through next-of-kin and the National Death Index; both methods have identified an estimated 98 percent of deaths in the cohort [18]. For this analysis, women diagnosed with cancer (except non-melanoma skin cancer) before baseline in 1976 were excluded. The study population was restricted to whites. The analytic cohort for analyses of ambient UV exposure included 115,482 women representing 3,049,041 person-years of follow-up from 1976–2006.

In 1980, a 61-item semi-quantitative food frequency questionnaire (FFQ) was sent to NHS participants to obtain dietary information. Similar, expanded questionnaires were sent approximately every 4 years. For the analyses of dietary vitamin D intake, women were excluded from the 1980 baseline population if they did not complete the 1980 FFQ, reported implausible total energy intake (<500 or >3500 kcal/day), left ≥ 10 items blank, or had a previous diagnosis of cancer (except non-melanoma skin cancer) before 1980. These additional exclusions left 88,220 women with available dietary data representing 1,988,853 person-years of follow-up from 1980–2006.

This study was approved by the Institutional Review Board of Brigham and Women's Hospital and all participants provided written informed consent at initial enrollment.

Case ascertainment

Cases included new diagnoses of NHL, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). In the NHS cohort, women (or their next-of-kin) who reported a new diagnosis of NHL on any biennial questionnaire from 1976 to 2006 were asked for permission to obtain related medical records and pathology reports. Study investigators blinded to exposure information reviewed available medical records and pathology reports to confirm NHL (ICD-8 codes 200, 202 and 204.1). Histologic subtype was determined according to the World Health Organization classification of lymphomas [19]. Specifically, diagnoses were made on the basis of morphology and immunophenotype information available in medical records and pathology reports. Immunophenotype information was not required for diagnoses of CLL/SLL or follicular lymphoma, which can be reliably diagnosed by morphology alone [19]. After exclusions, there were 1064 incident diagnoses of NHL as of June 2006; of these, 270 were CLL/SLL, 140 were diffuse large B-cell lymphoma (DLBCL), and 194 were follicular lymphoma. The remaining cases included 130 patients with uncommon or unspecified B-cell histology, 36 patients with T-cell lymphoma, and 294 patients who were determined to have NHL on the basis of morphology alone but lacked adequate phenotyping to assign the tumor to the B- or T-cell lineage. Overall, there were 808 NHL cases with 1980 nutrient data and diagnosed from 1980–2006.

Exposure assessment

Average annual UV-B flux, a composite measure of mean UV-B radiation level based on latitude, altitude, and cloud cover [20], was estimated for subjects at birth, age 15 years, age 30 years, at baseline in 1976, and every 2 years since 1986 according to state of residence. State of residence at birth, age 15, and age 30 was asked on the 1992 questionnaire; therefore this information is known only for women who were alive and responded to the 1992 questionnaire. Throughout cohort follow-up, current residence is known from mailing addresses of participants. UV-B flux is measured in Robertson-Berger (R-B) units [21]. Although not a direct measure of personal sun exposure, UV-B flux is associated with melanoma risk [22], suggesting that it is a reasonable proxy. Moreover, it is an objective exposure metric that does not rely on personal recall of time spent outdoors. Beginning in 1980, vitamin D intake from food and supplements was assessed using semi-quantitative FFQs [23]. Dietary vitamin D and other nutrients were calculated according to the nutrient content of foods, derived from the U.S. Department of Agriculture, food manufacturers, and other published sources. The validity and reliability of FFQs used in the NHS have been described elsewhere [24,23].

Because UV-B radiation is the major source of vitamin D for most individuals, dietary vitamin D may not be an accurate indicator of plasma 25(OH)D levels [25,10]. Using a subsample of 2079 NHS participants with available plasma 25(OH)D measurements, we fit a linear regression model to predict measured 25(OH)D based on known determinants of vitamin D status [26]. The model r^2 was 0.33. Based on the regression coefficients for each variable in the prediction model, we then calculated a predicted 25(OH)D score for each member of our analytic cohort at each questionnaire cycle beginning in 1986, using personal data on predictors. We validated the prediction model in an independent sample of women from the NHS and found that predicted 25(OH)D scores tracked with measured 25(OH)D levels (unpublished data).

Statistical analyses

Person-time of follow-up was calculated for each participant from the return date of the baseline questionnaire (i.e., 1976 for the analysis of UV-B flux, 1980 for the analysis of vitamin D intake, or 1986 for the analysis of predicted 25(OH)D) to the date of lymphoma diagnosis, death, or the end of follow-up (June 2006), whichever occurred first. Women who reported cancer or who died were excluded from subsequent follow-up. Cox proportional hazards models, stratifying by 2-year questionnaire period and treating age in months as the time scale, were used to estimate incidence rate ratios (RRs) and 95 percent confidence intervals (CIs).

Average annual UV-B flux (in R-B counts × 10^{-4}) was categorized as low (<113; reference), medium (113), or high (>113). Because UV-B flux takes into account altitude and cloud cover in addition to latitude, estimates vary by state within geographic regions of the U.S. [20]. Although over the course of follow-up nurses are represented in all 50 states, because they were originally recruited from 11 states, more than one-third of the person-time in our study population included residence in states with average annual UV-B flux values of 113 (e.g., Ohio, Pennsylvania, New Jersey), which made this value a natural "medium" cut-off for analysis. Over the course of follow-up, UV-B flux estimates ranged from 93–196 for all participants. To test for linear trend, we modeled UV-B flux as a continuous variable. We also examined whether the relation between UV-B flux and the RR of NHL was non-linear using restricted cubic splines [27]. Tests for non-linearity were performed using the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. We analyzed risk of NHL according to UV-B flux estimates at birth, age 15 years, age 30 years, in 1976, and in 1986. In addition, we used updated UV-B flux estimates for each questionnaire cycle with available measurements beginning in 1986 as a proxy for long-term average ambient UV exposure.

Cumulatively updated averages of total vitamin D intake from food and supplements and from food alone beginning in 1980 were categorized in quintiles to examine risk of NHL associated with vitamin D. Tests for linear trend across quintiles were performed using the median value for each quintile of vitamin D intake as a continuous variable in age-adjusted and multivariable models. We examined whether the relation between vitamin D and the RR of NHL was non-linear with restricted cubic splines. We performed separate analyses of vitamin D intake from food alone among women who reported no current multivitamin use. Baseline (i.e., 1986) and biennially updated predicted 25(OH)D scores were considered as categorical (in quintiles) or continuous variables for analysis of NHL risk.

To control for potential confounding, we used multivariable models that included height as a continuous variable and indicator variables for categories of smoking status (never, past, or current), and body mass index (BMI) (<21, 21–22.9, 23–24.9, 25–29.9, or 30+ kg/m^2). Models for dietary vitamin D intake and predicted 25(OH)D were additionally adjusted for current multivitamin supplement use (yes/no) and intake of retinol and calcium (quintiles). Height, smoking status, and BMI were included in all multivariable analyses because of evidence of an association with NHL in previous studies [28–30]. Confounding by other factors was assessed based on whether addition of covariates to the model substantially changed RR estimates [31]. Other covariates, including alcohol consumption, physical activity, personal sun exposure and sun sensitivity characteristics (e.g., hair color, susceptibility to burn, or ability to tan), and dietary intake of saturated fat, animal protein, fruits, and vegetables did not appreciably affect RR estimates, and therefore were not included in the final models. Smoking, BMI, and multivitamin use were treated as time-varying and were updated biennially in all analyses; cumulatively updated averages of nutrients were used in analyses incorporating updated vitamin D. Nutrients were adjusted for

total energy intake by using the residuals of the regression of each nutrient on total caloric intake and by including total calories (quintiles) in these models [32].

To explore possible effect modification of any vitamin D-NHL association observed by UV exposure, we analyzed the association of vitamin D intake within strata defined by categories of UV-B flux. We also considered potential effect modification by BMI. Statistical interaction was assessed by the likelihood ratio test comparing a model with interaction terms for joint exposure categories with a main-effects-only model.

The main analyses included all NHL cases; we also performed separate analyses for the most common NHL subtypes in the NHS [i.e., CLL/SLL, DLBCL, and follicular lymphoma]. We used a contrast test, which followed an approximate χ^2 distribution, to test whether associations for major NHL histologic subtypes differed [33]. Individuals missing primary exposure variables were excluded from relevant analyses. The missing indicator method was used to account for missing values for categorical covariates; the median height was assigned to 148 women with missing data on height. All statistical tests were two-sided and *P*-values <0.05 were considered significant.

Results

Baseline characteristics of women according to category of UV-B flux are shown in Table 1. Overall, women residing in areas of different levels of UV-B flux were similar in height, BMI, and physical activity. Women in the highest category of UV-B flux had slightly higher intakes of total vitamin D and were somewhat more likely to be current users of multivitamins, but were less likely to be current smokers.

Table 2 shows associations between average annual UV-B flux assessed at various times during life and NHL risk. For most measures, risk of NHL was slightly increased for women in the highest category of exposure compared to those in the lowest. After adjusting for age, smoking status, BMI, and height, RRs for the top category of UV-B flux ranged from 1.11 (95% CI: 0.95, 1.29) for UV-B flux based on residence in 1976 to 1.21 (95% CI: 1.00, 1.47) for UV-B flux at age 15 years. Positive linear trends were observed for all measures. Effect estimates were somewhat stronger for UV-B flux assessed at birth, age 15 years, and age 30 years than for UV-B flux assessed in 1976, 1986, or updated every two years from 1986. There was no evidence of non-linearity of UV-NHL associations when restricted cubic splines were examined (data not shown).

In multivariable models, we found no evidence of confounding by any covariates considered, including vitamin D intake. Similar results were observed when women with a previous diagnosis of non-melanoma skin cancer were excluded from the analysis and there was no evidence of effect modification by sun sensitivity characteristics (data not shown).

Finally, although statistical power was limited, there was no evidence of heterogeneity in effects by histological subtype of NHL; all *P*-values for heterogeneity were >0.20 (Table 3).

In multivariable models, there was no evidence of a protective effect of higher intakes of vitamin D from food and supplements or from food alone on risk of NHL (Table 4). The multivariable-adjusted RR for the highest quintile of total vitamin D intake versus the lowest was 1.02 (95% CI: 0.71, 1.47; *P*-trend=0.22). Although there was some suggestion of a U-shaped relationship with total vitamin D intake, there was no statistical evidence of non-linearity when restricted cubic splines were examined (data not shown). Findings were similarly null when we restricted this analysis to women who did not currently use multivitamins and further adjustment for UV-B flux did not affect the results (data not

shown). There was no association between predicted 25(OH)D calculated in 1986 or updated biennially and NHL risk (data not shown).

Strong differences in effect estimates for DLBCL, follicular lymphoma, and CLL/SLL were not observed. Regarding total vitamin D intake, results for DLBCL were similar to those for NHL overall, reflecting a possibly U-shaped relationship, whereas associations were generally null for follicular lymphoma and CLL/SLL (*P*-value, test for heterogeneity=0.74). There was no association between vitamin D intake from food or predicted 25(OH)D and risk of DLBCL, follicular lymphoma, or CLL/SLL (*P*-values, test for heterogeneity >0.15).

In stratified analyses, the association between total vitamin D intake or vitamin D intake from food alone and NHL risk did not vary by level of UV-B flux or by BMI (<25 vs. ≥25 kg/m^2) (all *P*-interaction >0.10).

Discussion

In this prospective cohort of 115,482 women with over 3 million person-years of follow-up, we found statistically significant positive associations between UV-B flux assessed at various points in time and NHL risk. Effects appeared somewhat stronger for CLL/SLL and follicular lymphoma whereas no association was observed for DLBCL. We also found no evidence of a protective effect of higher vitamin D status on risk of NHL.

Our findings do not support results from several retrospective case-control studies published between 2004 and 2010, which provided fairly consistent evidence of a 30–40% decreased risk of NHL associated with various measures of self-reported recreational UV exposure (e.g., sunbathing, cumulative sun exposure, history of sunburns, and vacations in sunny climates) [1–8]. One prior retrospective case-control study also reported a non-statistically significant inverse association between lifetime average residential UV-B level and NHL risk [3]. In prospective analyses in the California Teachers Study cohort, Chang et al. [17] reported significant inverse associations between residential ambient UV and NHL risk. Our results are consistent, however, with a 2007 case-control study among women in Connecticut, which reported a 70% increased risk of NHL for the highest tertile of duration of self-reported summer sun exposure compared with the lowest [34] and with a Swedish retrospective cohort study based on latitude of residence [35]. Three recent studies [36,37,16], including one prospective cohort [16], reported no association between self-reported sun exposure behaviors and NHL risk, although a non-significant inverse association was noted for ambient UV in the U.S. Radiologic Technologists cohort [36].

Although observations of inverse associations between recreational UV exposure and NHL risk in published case-control studies have been generally consistent, these studies may collectively suffer from several important methodological limitations. First, exposure assessment in most studies relied on personal recall of historical sun exposures, which could lead to exposure misclassification that may be differential between cases and controls. Second, because NHL patients were interviewed after diagnosis, they may have inaccurately reported their past sun exposure as being similar to their post-diagnosis exposure. If cases reduced their sun exposure after NHL onset (e.g., as a result of treatment or illness), then an apparent inverse association between sun exposure may have resulted from reverse causality. Finally, participation rates among controls were fairly low (between 50 and 70%) for many studies. If controls who participated were healthier than non-participants and were therefore more likely to spend time outdoors, then the effect estimates could have been biased downward. Our study used an objective measure of ambient UV radiation exposure that was assessed prospectively and is therefore not subject to potential biases associated with retrospective recall of sun exposure.

The biological mechanism underlying a possible protective effect of sunlight exposure on NHL is hypothesized to act through pathways involving vitamin D. Vitamin D may be involved in regulation of the immune system as vitamin D receptors are expressed on B and T cells [25]. In addition, vitamin D has anti-proliferative and pro-differentiation properties [11], and can induce apoptosis and inhibit angiogenesis [10]. Epidemiologic evidence suggests that vitamin D is protective against a number of cancers, including prostate, breast, colorectal, and oropharyngeal cancers [38–41], but prior evidence for a link between vitamin D and NHL risk is weak [13,14]. We found no association with measures of vitamin D status, confirming recent studies which have found no link between vitamin D intake [3,5,42,43] or prospectively measured plasma 25(OH)D [44,45,15] and risk of NHL. A lack of strong epidemiologic evidence for an inverse association between vitamin D and NHL from this study and others suggests that vitamin D status may not protect against development of NHL. Alternatively, a protective effect of UV exposure on NHL risk could be mediated through vitamin D-independent pathways, such as through enhanced activity of regulatory T cells [46,47].

Because the bulk of epidemiologic literature on NHL suggests a possible protective effect of UV exposure, our findings of significant positive associations between ambient UV radiation and NHL risk were unexpected. In addition to similar results from one prior case-control study [34], there are several lines of evidence suggesting that UV exposure could increase NHL risk. In particular, observations that risk is increased among melanoma or non-melanoma skin cancer patients and that these cancers display similar geographic and temporal patterns of incidence initially prompted researchers to hypothesize that exposure to sunlight might be a common cause of skin cancer and NHL [48,49]. Increased risk of NHL has also been associated with fair skin, susceptibility to burn, and poor ability to tan [50,37]. Because light pigmentation allows more UV penetration of the skin, these findings are consistent with the theory that sunlight could be a risk factor for NHL. In our analyses, however, neither sun sensitivity characteristics (e.g., hair color, susceptibility to burn, or ability to tan) nor prior diagnosis of skin cancer predicted risk of NHL nor did these factors appear to confound the effects of ambient UV-B exposure. Finally, although our findings warrant replication, it is biologically plausible that UV exposure could increase NHL risk since immunosuppression, a strong risk factor for NHL, is an established systemic response to UV exposure [47].

Recent evidence has suggested possible etiologic heterogeneity among different NHL subtypes [51]. We found stronger effects of ambient UV exposure for CLL/SLL, although statistical power was limited to detect differences by subtype. Zhang et al. also reported stronger associations of summer sun exposure with risk of CLL/SLL [34]. In contrast, while Adami et al. reported a positive association between decreasing latitude and risk of NHL overall, they found no association with risk of CLL/SLL [35]. There was no association between UV radiation and overall NHL risk in a prospective Scandinavian cohort; however, diagnoses of CLL/SLL were not included [16]. The distribution of major histologic subtypes in the NHS differs somewhat from that typically observed in the U.S, with relatively more confirmed cases of CLL/SLL and fewer confirmed cases of DLBCL. One possible explanation for this finding is that nurses may be more likely to be diagnosed with CLL/SLL (a largely asymptomatic condition) than women in the general population, possibly because of higher levels of overall health vigilance and access to care, as we have previously reported [52]. In addition, we relied on information in medical records and pathology reports to classify subtypes. Therefore, the observed distribution might also reflect underlying challenges of assigning histologic subtype for diagnoses made prior to the introduction of the World Health Organization classification in 2001, especially for diagnoses in the 1970s and 1980s when immunophenotyping was not routinely performed. In particular, many DLBCL diagnoses in the NHS cohort may be misclassified as being of unknown histology.

Underascertainment of DLBCL, while likely reducing statistical power, is not expected to bias our results.

Our study has two important limitations. First, exposure misclassification is a possibility. In particular, UV-B flux estimates based on state of residence may not accurately capture women's actual exposure to sunlight. Given the prospective study design, however, any misclassification is likely to have been non-differential with respect to disease, leading to attenuation of effect estimates. While more local estimates of ambient UV radiation would be ideal, UV-B flux, which takes into account altitude and cloud cover as well as latitude, is expected to be an improvement over geographic region of residence as a proxy for sunlight exposure and may be less prone to misclassification than self-reported hours spent in sunlight [22]. In the NHS, UV-B flux was positively associated with non-melanoma skin cancer risk (A. Qureshi, personal communication), demonstrating that it is a reasonable proxy for sun exposure. Second, although we considered potential confounding by suspected risk factors for NHL, confounding by unmeasured risk factors, such as sunscreen or tanning product use, viral or bacterial infections, or unidentified environmental exposures, cannot be ruled out.

It is difficult to reconcile our findings with those of Chang et al. [17], who reported that residential ambient UV was significantly inversely related to NHL risk in the only other prospective analysis of this association to date. There are several notable differences between these two studies. First, the association could be modified by generational differences in sun exposure behaviors. The NHS began in 1976 whereas the California Teachers Study (CTS) began in 1995–1996 and secular changes in UV exposure behaviors over time have been reported [53]. In fact, in the NHS, the strongest associations with NHL risk were observed for UV exposure estimates in early life (i.e., at birth, age 15, and age 30), periods of life and calendar years not assessed in the CTS. Second, the different occupations represented by these two populations could account for the discrepant results. In 1988, 60% of NHS participants reported at least one year of rotating night shift work [54], which could affect their personal sun exposure behavior. Third, the CTS included women who lived in California only, all of whom would have been classified into our highest category of UV-B flux. NHS participants reside in all 50 U.S. states, allowing us to evaluate a wider range of UV-B exposures. Finally, there may be important differences in lifestyle behaviors, particularly with regard to personal sun exposure behaviors, between California residents and other people who live in areas of higher ambient UV, and these behaviors may in turn influence NHL risk.

Despite some limitations, our study also has several important strengths, including its prospective design, large sample size, estimates of ambient UV exposure for various time points across the lifespan, and availability of detailed information on covariates. Our finding of a statistically significantly increased risk of NHL associated with residence in areas of high UV-B radiation was unexpected and raises doubt about earlier reports of a possible protective effect of sunlight exposure on development of this cancer, especially because, like others, we found no evidence that vitamin D status protects against NHL. Further investigation into the possible association between UV exposure and NHL is warranted, including replication of these findings in other large prospective cohort studies.

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Table 1

Baseline characteristics of the study population, by category of UV-B flux in 1976 (n=115,482).*

	UV-B flux category†		
	Low (n=44,835)	**Medium (n=44,076)**	**High (n=26,571)**
Age	42.4	42.4	44.0
Height (inches)	64.5	64.4	64.7
BMI (kg/m^2)	23.8	24.0	23.4
Smoking history			
Never	39.5%	45.0%	46.8%
Past	25.0%	21.3%	23.5%
Current	35.2%	33.5%	29.3%
Vitamin D intake (IU/d) in 1980§	329.5	323.5	342.7
Physical activity (METs/wk) in 1986	13.3	12.7	13.4
Multivitamin use in 1980			
Non-user	53.0%	50.3%	46.3%
Current user	24.1%	26.3%	28.3%

*All variables (except age) are standardized to the age distribution of the population in 1976. Means or percentages are shown.

†Low, <113 R-B count × 10^{-4}; Medium, 113 R-B count × 10^{-4}; High, >113 R-B count × 10^{-4}

§energy-adjusted; N=27,262 without available 1980 dietary information.

IU/d, international units/day; METs/wk, metabolic equivalents/week.

Table 2

RRs & 95% CIs for NHL in relation to average annual UV-B flux* in the Nurses' Health Study, 1976–2006.

	Cases	Person-years	Multivariable-adjusted RR§	95% CI	*P*-trend
UV-B flux at birth					<0.01
Low	285	917,405	1.0 (ref)		
Medium	325	873,972	1.21	1.03, 1.42	
High	160	412,309	1.18	0.97, 1.43	
UV-B flux at age 15					<0.01
Low	289	918,488	1.0 (ref)		
Medium	324	894,950	1.17	1.00, 1.38	
High	167	409,953	1.21	1.00, 1.47	
UV-B flux at age 30					0.01
Low	288	896,481	1.0 (ref)		
Medium	287	838,733	1.08	0.92, 1.27	
High	212	516,987	1.19	0.99, 1.42	
UV-B flux in 1976					0.02
Low	396	1,186,451	1.0 (ref)		
Medium	389	1,170,507	1.01	0.88, 1.16	
High	279	692,083	1.11	0.95, 1.29	
UV-B flux in 1986†					0.02
Low	317	705,921	1.0 (ref)		
Medium	306	691,927	1.00	0.85, 1.17	
High	283	511,254	1.14	0.97, 1.34	
UV-B flux (simple update from 1986) †					0.10
Low	295	647,921	1.0 (ref)		
Medium	285	638,369	0.98	0.83, 1.16	
High	303	540,972	1.09	0.93, 1.29	
UV-B flux (cumulative updated average from 1986) †					0.02
Low	302	675,468	1.0 (ref)		
Medium	282	649,999	0.98	0.83, 1.15	

	Cases	Person-years	Multivariable-adjusted RR[§]	95% CI	*P*-trend
High	324	586,098	1.10	0.94, 1.29	

RR, rate ratio; CI, confidence interval

[*] UV-B flux reported in units of RB count × 10^{-4} Low, <113; Medium, 113; High, >113

[†] Follow-up begins in 1986 for this analysis.

[§] Adjusted for age (as the time scale), smoking (never, past, current), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, 30+ kg/m^2), and height (continuous inches).

Table 3

RRs & 95% CIs for NHL in relation to average annual UV-B flux* in the Nurses' Health Study, 1976–2006, by NHL subtype.

	DIFFUSE LARGE B-CELL LYMPHOMA				FOLLICULAR LYMPHOMA				CLL/SLL			
	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend
UV-B flux at birth				0.63				0.22				0.24
Low	50	1.0 (ref)			54	1.0 (ref)			81	1.0 (ref)		
Medium	45	0.95	0.64, 1.43		60	1.14	0.79, 1.64		84	1.12	0.82, 1.52	
High	19	0.77	0.45, 1.31		32	1.16	0.74, 1.80		42	1.11	0.76, 1.62	
UV-B flux at age 15				0.37				0.17				0.09
Low	51	1.0 (ref)			54	1.0 (ref)			81	1.0 (ref)		
Medium	46	0.95	0.63, 1.41		61	1.16	0.80, 1.67		86	1.12	0.83, 1.53	
High	17	0.67	0.38, 1.16		33	1.20	0.78, 1.86		48	1.27	0.88, 1.82	
UV-B flux at age 30				0.93				0.05				0.02
Low	45	1.0 (ref)			52	1.0 (ref)			71	1.0 (ref)		
Medium	44	1.06	0.70, 1.61		55	1.11	0.76, 1.62		78	1.23	0.89, 1.69	
High	24	0.85	0.52, 1.41		41	1.21	0.80, 1.82		68	1.59	1.13, 2.22	
UV-B flux in 1976				0.79				0.03				0.03
Low	53	1.0 (ref)			72	1.0 (ref)			98	1.0 (ref)		
Medium	55	1.09	0.75, 1.59		66	0.91	0.65, 1.26		92	0.99	0.74, 1.32	
High	32	0.97	0.62, 1.50		56	1.19	0.83, 1.69		80	1.31	0.97, 1.76	
UV-B flux in 1986				1.00				0.05				0.09
Low	48	1.0 (ref)			58	1.0 (ref)			77	1.0 (ref)		
Medium	45	1.00	0.66, 1.50		50	0.85	0.58, 1.24		85	1.17	0.86, 1.59	
High	33	0.88	0.56, 1.37		52	1.12	0.77, 1.63		83	1.39	1.02, 1.90	
UV-B flux (simple update from 1986)				0.49				0.08				0.48
Low	45	1.0 (ref)			52	1.0 (ref)			76	1.0 (ref)		
Medium	46	1.07	0.71, 1.62		48	0.89	0.60, 1.32		78	1.08	0.78, 1.48	
High	34	0.79	0.50, 1.23		55	1.10	0.75, 1.61		87	1.23	0.90, 1.68	
UV-B flux (cumulative updated average from 1986)				0.68				0.03				0.15
Low	46	1.0 (ref)			53	1.0 (ref)			77	1.0 (ref)		

	DIFFUSE LARGE B-CELL LYMPHOMA				FOLLICULAR LYMPHOMA				CLL/SLL			
	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend	Cases	Multivariable-adjusted RR†	95% CI	*P*-trend
Medium	42	0.98	0.64, 1.50		47	0.88	0.60, 1.31		75	1.05	0.76, 1.44	
High	38	0.84	0.54, 1.29		60	1.14	0.78, 1.65		94	1.26	0.93, 1.71	

RR, rate ratio; CI, confidence interval; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma

*UV-B flux reported in units of R-B count × 10^{-4}: Low, <113; Medium, 113; High, >113

†Adjusted for age (as the time scale), smoking (never, past, current), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, 30+ kg/m2), and height (continuous inches).

Note: All *P*-values for heterogeneity by subtype >0.20.

Table 4

RRs & 95% CIs for NHL in relation to vitamin D intake in the Nurses' Health Study, 1980–2006.

	Median (IU/day)	Cases	Person-years	Multivariable-adjusted RR†	95% CI	*P*-trend*
Total vitamin D intake (quintiles)						
1	125.8	126	399,650	1.0 (ref)		0.22
2	204.1	139	404,813	0.80	0.62, 1.04	
3	293.7	146	403,745	0.68	0.51, 0.91	
4	415.4	194	397,766	0.87	0.63, 1.18	
5	621.5	203	382,879	1.02	0.71, 1.47	
Dietary vitamin D intake (quintiles)						
1	104.1	125	391,449	1.0 (ref)		0.35
2	150.1	176	402,105	1.16	0.91, 1.46	
3	189.3	162	401,874	0.97	0.76, 1.23	
4	236.3	174	400,457	0.96	0.74, 1.23	
5	319.8	171	392,968	0.96	0.74, 1.25	

RR, rate ratio; CI, confidence interval.

†Adjusted for age (as the time scale), smoking (never, past, current), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, 30+ kg/m^2), height (continuous inches), multivitamin use (current, non-current, missing), retinol, calcium, and total calories (quintiles).

*Trend test based on median of the quintile.