Research Article

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Pigmentary Characteristics, UV Radiation Exposure, and Risk of Non–Hodgkin Lymphoma: a Prospective Study among Scandinavian Women

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Abstract

Background: UV radiation and pigmentary characteristics may be associated with non–Hodgkin lymphoma (NHL) risk, but few prospective studies exist. We investigated these associations in a Norwegian-Swedish cohort.

Methods: The cohort included women ages 30 to 50 years at enrolment in 1991 to 1992. Host factors, and exposure to sun and artificial tanning devices in life-decades 0 to 50 years were collected by questionnaire. Relative risks (RR) with 95% confidence intervals (CI) were estimated by Poisson regression.

Results: Among 104,953 women with complete follow-up through 2006 (Sweden) and 2007 (Norway), 158 were diagnosed with NHL. Women with brown hair had an increased risk of NHL compared with dark brown–haired/black-haired women (RR, 1.72; 95% CI, 1.08-2.74); decreased risks were found among women with gray, green or mixed (RR, 0.50; 95% CI, 0.32-0.77), or blue (RR, 0.54; 95% CI, 0.35-0.81) eyes compared with those with brown eyes, and among those with high propensity to burn compared with those with low propensity (RR, 0.57; 95% CI, 0.36-0.91). Annual number of sunburns and bathing vacations in any age decade, or ever use of artificial tanning devices were not significantly associated with NHL risk. After exposure at ages 10 to 39 years, RRs for ever versus never exposed were 0.99 (95% CI, 0.65-1.50) for sunburn, 1.00 (95% CI, 0.64-1.54) for bathing vacations, and 0.99 (95% CI, 0.67-1.46) for artificial tanning device use.

Conclusion: Whereas several pigmentary characteristics were associated with NHL risk, our results do not support an association between UV radiation and NHL.

Impact: Studies of UV radiation and NHL are warranted for etiologic understanding and public health recommendations. *Cancer Epidemiol Biomarkers Prev; 19(6); 1569–76. ©2010 AACR.*

Introduction

Increasing attention has been directed toward possible protective effects of UV radiation chiefly from sun exposure on the development of several cancer forms, including non–Hodgkin lymphoma (NHL; refs. 1-4). The first two large case-control studies of sun exposure and NHL risk reported protective effects, especially in relation to recreational sun exposure (5, 6). However, in more recent case-control studies, the inverse association was less convincing (7-10), lacking (11), or even the opposite (12). A pooled analysis from the InterLymph Consortium (13) that included some of these studies (5-8, 12) found a protective effect of recreational sun exposure, although there was significant interstudy heterogeneity. An inverse association between use of artificial tanning devices and NHL risk has also been reported in some but not all case-control studies (5, 7, 8, 10-12). A recent review concluded that the available epidemiologic evidence does not confirm that UV radiation exposure is a risk factor of NHL (14).

Pigmentary characteristics are indicators of sensitivity to UV radiation, and increased skin pigmentation reduces UV radiation–related vitamin D synthesis, one mechanism by which sun exposure might protect against NHL (2, 15). A handful of studies have investigated pigmentary characteristics and risk of NHL, but the results are inconsistent (5, 7, 10, 11, 16, 17).

Because most previous studies on pigmentary characteristics, UV radiation exposure, and NHL were of case-control design, prospective studies are needed to further explore the role of host susceptibility, and to confirm or refute the hypothesis of an association between UV radiation and risk of NHL.

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Subjects and Methods

Study population

The Norwegian-Swedish Women's Lifestyle and Health Cohort Study established in 1991 to 1992 has been described in detail previously (18). A nationwide random sample of 100,000 women (born 1943-1957) was drawn from the Norwegian National Population Register, and a random sample of 96,000 women (born 1943-1962) residing in the Uppsala Health Care Region (comprising about one sixth of the Swedish population) was drawn from the Swedish National Population Register. The women received an invitation letter that requested written informed consent, and a comprehensive questionnaire to be completed and returned in a prepaid envelope. The study cohort includes only women who consented. The national Data Inspection Boards and responsible Medical Ethics Committees approved the study.

Pigmentary characteristics and UV radiation exposure

The questionnaire at inclusion recorded natural hair color (dark brown/black, brown, blond/yellow, or red), eye color (brown, gray/green, or blue), number of asymmetric nevi >5 mm on the legs from toes to groin (0, 1, 2-3, 4-6, 7-12, 13-24, or ≥25 nevi; color brochure with pictures of three examples of asymmetric nevi enclosed), skin reaction to heavy (acute) sun exposure at the beginning of the summer (turns brown without first becoming red, turns red, turns red with pain, or turns red with pain and blisters), and skin reaction to repeated and long-lasting (chronic) sun exposure (turns deep brown, brown, or light brown, or never turns brown).

For each life-decade until inclusion in the study (<10, 10-19, 20-29, 30-39, and 40-49 y of age), the participant was asked to report the number of times per year she had been burned by the sun so severely that it resulted in pain or blisters and subsequent peeling (never, <1, 2-3, 4-5, or ≥6 times/y), the average number of weeks per year spent on bathing vacations in southern latitudes or within Norway or Sweden (never, 1, 2-3, 4-6, or ≥7 wk/y), and the average use of an artificial tanning device [i.e., sunbed or a sunlamp that emits artificial UV radiation (never, rarely, 1, 2, 3-4 times/mo, or >1 time/wk)]. UV radiation exposure before age 10 years was only recorded for Norwegian women. UV radiation exposure has been associated with melanoma risk in an earlier analysis of this cohort (18). The questionnaire also recorded highest educational level achieved, current height and weight, current and past contraceptive use, reproductive history, prevalent diseases, and other lifestyle habits.

Follow-up and end points

Start of follow-up was defined as the date of receipt of the returned questionnaire, and end of follow-up was December 31, 2006 for Swedish women and December 31, 2007 for Norwegian women. Cancer cases were identified by linkage to the national cancer registries in the two countries. All NHL cases registered in the Norwegian and Swedish cancer registries during follow-up were included. We did not include multiple myeloma, or acute or chronic lymphocytic leukemia because UV radiation was not associated with chronic lymphocytic leukemia in several previous studies (5, 13), and multiple myeloma has not been studied in this regard. Linkage to Statistics Norway and Statistics Sweden gave information on death and emigration. The individually unique national registration number assigned to all residents of Norway and Sweden ensured the linkages. Person-years were calculated from the start of follow-up to the date of diagnosis of primary cancer, the date of emigration or death, or the end of follow-up, whichever occurred first.

Completed questionnaires were returned by 57,584 (57.6%) of the Norwegian women and 49,259 (51.3%) of the Swedish women (18). A total of 106,826 women were available for the analysis. We excluded 1 woman with inadequate information on vital status, 11 women who had emigrated, 3 women who had died before the start of follow-up, 1,663 women diagnosed with cancer before the start of follow-up, and 195 women who did not adequately answer the questions about exposure to sun and artificial tanning devices or personal characteristics (sun sensitivity of skin, hair color, eye color, and number of asymmetric nevi). Thus, 104,953 women were included in the analyses.

Statistical methods

We used Poisson regression analysis to estimate the association between NHL risk and education, body surface area, nevi, pigmentary characteristics, sunburns, bathing vacations, or use of artificial tanning devices. Education was categorized as ≤9, 10-12, and ≥13 years. Body surface area was calculated as $\text{weight}^{0.425} \cdot \text{height}^{0.725} \cdot 71.84$ (19) and categorized into quartiles (≤1.61, 1.62-1.69, 1.70-1.78, and ≥1.79 m^2). Due to small numbers, we collapsed the upper two categories of hair color and skin reaction to acute and chronic exposure to the sun, whereas asymmetric nevus counts was analyzed in two categories (0, ≥1). We also collapsed higher categories in the analyses of sunburns, bathing vacations, and use of artificial tanning devices during different life-decades. In addition, for sunburns, bathing vacations, and use of artificial tanning devices, we combined the exposure across each of the three decades of life that were recorded for all women (10-19, 20-29, and 30-39 y). All analyses were adjusted for attained age (<50, 50-54, and ≥55 y), and all the multivariate models included geographic region of residence (the southern, middle, and northern regions of Norway, and the Uppsala Health Care Region in Central Sweden; ref. 18). Analyses of sunburns, bathing vacations, and use of artificial tanning devices were also adjusted for pigmentary characteristics of eyes, hair, and skin. Additionally, each age-specific model for use of artificial tanning devices included the age-specific variables for sunburns and sunbathing vacations. Trends across categories of UV radiation exposure were analyzed by assigning equally spaced values (e.g., 1, 2, 3, or 4) to the categories and treating the variable as a continuous variable in the regression analysis. Correlation between covariates was estimated by Spearman's correlation coefficient.

All statistical analyses were conducted in STATA (version 10). Results were computed as incidence rate ratios as estimates of relative risks (RR) with 95% confidence intervals (CI). All *P*-values are two-sided, and a 5% level of significance was used.

Previous case-control studies have been large, and statistically significant odds ratios (OR) of NHL in the highest category of recreational UV radiation exposure ranging from 0.5 to 0.7 have been reported (5, 6, 13). With 160 cases, we had 90%, 67%, and 39% power to detect trends in risk over exposure quartiles, with RRs ranging from 1.0 to 0.5 (or 2.0), 1.0 to 0.6 (or ~1.7), or 1.0 to 0.7 (or ~1.4), respectively (5% level of significance, Poisson regression model, Egret Siz software).

Results

The study cohort of 104,953 women had a mean age at study entry of 40.4 years (range, 30-50 y). A total of 158 cases of NHL were reported to the cancer registries in Norway and Sweden during 1,596,143 person-years of observation. The mean age at diagnosis of NHL was 52 years (range, 34-64 y). In analyses adjusted for age and region of residence, risk of NHL was not significantly associated with level of education (as a proxy for socioeconomic status; $P = 0.56$) or the number of asymmetric nevi (>5 mm) on the legs ($P = 0.26$). Body surface area was significantly associated with NHL in the 2nd and 3rd quartiles; RRs for the 2nd, 3rd and 4th quartiles were 1.81 (95% CI, 1.12-2.91), 1.71 (95% CI, 1.06-2.77), and 1.14 (95% CI, 0.68-1.92), respectively, but no significant trend was found ($P_{trend} = 0.79$).

Pigmentary characteristics

Women with brown hair had a significantly increased risk of NHL compared with women with dark brown/black hair, whereas women with light eye color had a significantly decreased risk compared with women with brown eye color (Table 1). Women with a high propensity to burn after heavy sun exposure at the beginning of the summer (turning red with pain/blisters) also had a significantly decreased risk of NHL compared with women whose skin turned brown after heavy sun exposure. However, skin color after repeated sun exposure was not significantly associated with NHL risk (Table 1). The correlation coefficients between the above variables

Table 1. RRs and 95% CIs of NHL according to pigmentary characteristics

Characteristic	No. of cases	Age-adjusted	Multivariate*
		RR (95% CI)	RR (95% CI)
Hair color (*n* = 101,633)			
Dark brown, black	23	1.00	1.00
Brown	79	1.85 (1.16-2.93)	1.72 (1.08-2.74)
Blond, yellow/red	54	1.43 (0.88-2.32)	1.23 (0.75-2.01)
		P = 0.02	*P* = 0.03
Eye color (*n* = 101,323)			
Brown	33	1.00	1.00
Gray, green, or mixed	51	0.51 (0.33-0.80)	0.50 (0.32-0.77)
Blue	72	0.55 (0.36-0.82)	0.54 (0.35-0.81)
		P = 0.01	*P* = 0.01
Skin color after heavy sun exposure in the beginning of the summer (*n* = 104,178)			
Brown	50	1.00	1.00
Red	79	0.83 (0.58-1.19)	0.84 (0.59-1.19)
Red with pain/red with pain and blisters	28	0.56 (0.35-0.88)	0.57 (0.36-0.91)
		P = 0.04	*P* = 0.05
Skin color after repeated sun exposure (*n* = 101,923)			
Deep brown	27	1.00	1.00
Brown	100	1.01 (0.66-1.54)	1.02 (0.67-1.56)
Light brown/never brown	30	0.74 (0.44-1.24)	0.71 (0.42-1.20)
		P = 0.29	*P* = 0.20

NOTE: Poisson regression analysis. All statistical tests were two-sided.
*Multivariate models included attained age and region of residence.

were all relatively low (all <0.30, except for acute and chronic skin reaction, 0.44).

Sunburns, bathing vacations, and artificial tanning exposure

There was no significant association between the number of sunburns in any decade of life and risk of NHL, neither in the age-adjusted analysis nor in the analysis adjusted for personal characteristics (Table 2). Similarly, there was no significant association between the number of weeks per year spent on bathing vacations in southern latitudes or within Norway/Sweden in successive decades of life and risk of NHL (Table 3). Use of artificial tanning devices was rare before the age of 20 years in this cohort. Use during ages 20 to 29 years was associated with an ~50% significantly reduced risk of NHL. For such exposure during ages 40 to 49 years, there was also an indication of a decrease in risk, although this was not statistically significant (Table 4). Overall, there was no significant association between use of artificial tanning devices at ages 10 to 39 years and risk of NHL (RR, 0.99; 95% CI, 0.67-1.46 for ever versus never use).

Discussion

In this large prospective cohort of Scandinavian women, we observed that individuals with light-colored eyes compared with those with brown eyes, or those with high propensity to burn compared with those with low propensity had a >40% decreased risk of NHL. Further, individuals with brown hair were at an increased risk compared with those with dark hair. In contrast, we found no consistent evidence of an association between

Table 2. RRs and 95% CIs of NHL according to annual number of sunburns in successive decades of life

Age period and no. of sunburns	No. of cases	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)
<10 y (*n* = 44,932)			
0	45	1.00	1.00
≥1/y	54	0.87 (0.59-1.29)	0.96 (0.63-1.45)
		P = 0.49	*P* = 0.84
10-19 y (*n* = 92,451)			
0	34	1.00	1.00
≤1/y	80	1.01 (0.68-1.51)	1.10 (0.72-1.67)
≥2/y	25	0.84 (0.50-1.42)	1.12 (0.64-1.95)
		P_{trend} = 0.55	P_{trend} = 0.69
20-29 y (*n* = 94,355)			
0	39	1.00	1.00
≤1/y	82	0.76 (0.52-1.12)	0.85 (0.57-1.28)
≥2/y	22	0.69 (0.41-1.16)	0.91 (0.52-1.62)
		P_{trend} = 0.13	P_{trend} = 0.67
30-39 y (*n* = 91,858)			
0	51	1.00	1.00
≤1/y	81	0.88 (0.62-1.25)	0.99 (0.68-1.43)
≥2/y	11	0.66 (0.35-1.27)	0.87 (0.44-1.72)
		P_{trend} = 0.21	P_{trend} = 0.75
40-49 y (*n* = 43,524)			
0	40	1.00	1.00
≥1/y	52	1.00 (0.67-1.52)	1.17 (0.76-1.82)
		P = 0.98	*P* = 0.47
Combined, 10-39 y (*n* = 87,824)			
≤1/y, 10-39 y	104	1.00	1.00
≥2/y, 10-39 y	31	0.80 (0.54-1.20)	0.99 (0.65-1.50)
		P = 0.28	*P* = 0.95

NOTE: Poisson regression analysis. All statistical tests were two-sided. Sunburns at age <10 years were only recorded for the Norwegian women. Analyses of sunburns at ages 40 to 49 years included only women ≥40 years when answering the questionnaire.
*Multivariate models included attained age, region of residence, eye color, hair color, and skin reaction after heavy sun exposure in the beginning of the summer and after repeated sun exposure.

Table 3. RRs and 95% CIs of NHL according to annual number of weeks per year spent on bathing vacations in southern latitudes or within Norway or Sweden in successive decades of life

Age period and no. of bathing vacations	No. of cases	Age-adjusted	Multivariate*
		RR (95% CI)	RR (95% CI)
<10 y (*n* = 46,287)			
0	71	1.00	1.00
≥1 wk/y	24	1.14 (0.72-1.82)	1.12 (0.70-1.79)
		P = 0.57	P = 0.65
10-19 y (*n* = 90,450)			
0	73	1.00	1.00
1 wk/y	16	0.58 (0.34-1.00)	0.67 (0.38-1.16)
≥2-3 wk/y	44	1.14 (0.78-1.66)	1.24 (0.84-1.82)
		P_{trend} = 0.69	P_{trend} = 0.38
20-29 y (*n* = 92,946)			
0	41	1.00	1.00
1 wk/y	43	1.09 (0.71-1.68)	1.19 (0.77-1.84)
≥2-3 wk/y	61	1.12 (0.75-1.66)	1.16 (0.77-1.73)
		P_{trend} = 0.59	P_{trend} = 0.51
30-39 y (*n* = 90,806)			
0	34	1.00	1.00
1 wk/y	41	1.04 (0.66-1.64)	1.06 (0.67-1.68)
≥2-3 wk/y	68	1.21 (0.80-1.82)	1.17 (0.77-1.77)
		P_{trend} = 0.34	P_{trend} = 0.45
40-49 y (*n* = 43,459)			
0	24	1.00	1.00
1 wk/y	24	1.05 (0.60-1.85)	1.10 (0.62-1.94)
≥2-3 wk/y	42	1.25 (0.76-2.07)	1.26 (0.76-2.11)
		P_{trend} = 0.36	P_{trend} = 0.36
Combined, 10-39 y (*n* = 85,667)			
0, 10-39 y	26	1.00	1.00
≥1/y, 10-39 years	105	0.96 (0.63-1.48)	1.00 (0.64-1.54)
		P = 0.87	P = 0.98

NOTE: Poisson regression analysis. All statistical tests were two-sided. Bathing vacations at age <10 years were only recorded for the Norwegian women. Analyses of bathing vacations at ages 40 to 49 years included only women ≥40 years when answering the questionnaire.

*Multivariate models included attained age, region of residence, hair color, eye color and skin color after heavy sun exposure in the beginning of the summer and after repeated sun exposure.

UV radiation from sun exposure or artificial tanning devices and risk of NHL.

A handful of case-control studies have investigated pigmentary characteristics and risk of NHL with no consistent findings. Light eye color has been associated with both an increased (5) and a decreased risk of NHL (7), as well as with no association (10, 11, 20, 21) compared with dark eye color. Very fair skin was associated with an increased risk, whereas propensity to burn was not significantly associated with NHL in an Australian study (16). Other studies found no association between complexion (7, 21) or skin sensitivity (7, 11, 20) and NHL. Likewise, results for hair color have been mixed (5, 10, 11, 16, 17, 20, 21). As for melanoma, associations with pigmentary characteristics might, however, vary between populations (22, 23). Our study included only women. Consistent effect modification by sex has not been reported for pigmentary characteristics and NHL, although increasing risk with increasing measures of sun sensitivity for women only (10) and association with hair color only significant for men (11) have been reported.

NHL tumors occur more often in individuals who also develop UV radiation–related skin cancers, including basal and squamous cell carcinoma, and malignant melanoma (24, 25). Consequently, it was first assumed that sun exposure was a risk factor also for the development of NHL. However, results of ecologic studies on solar radiation in different geographical regions and NHL have

Table 4. RRs and 95% CIs of NHL according to use of artificial tanning devices in successive decades of life

Age period and use of artificial tanning devices*	No. of cases	Age-adjusted	Multivariate†
		RR (95% CI)	RR (95% CI)
20-29 y (*n* = 86,399)			
Never	117	1.00	1.00
Rarely or ≥1 time/mo	10	0.48 (0.25-0.94)	0.47 (0.24-0.91)
		P = 0.02	P = 0.01
30-39 y (*n* = 85,173)			
Never	67	1.00	1.00
Rarely	45	1.24 (0.84-1.81)	1.11 (0.75-1.64)
≥1 time/mo	18	1.00 (0.59-1.69)	1.03 (0.60-1.76)
		P_{trend} = 0.70	P_{trend} = 0.79
40-49 y (*n* = 39,877)			
Never	39	1.00	1.00
Rarely	23	0.68 (0.41-1.14)	0.61 (0.36-1.04)
≥1 time/mo	16	0.74 (0.41-1.32)	0.74 (0.40-1.36)
		P_{trend} = 0.20	P_{trend} = 0.19
Combined, 10-39 y (*n* = 77,221)			
Never, 10-39 y	59	1.00	1.00
Rarely, 10-39 y	38	1.12 (0.74-1.70)	1.01 (0.66-1.54)
≥1 time/mo in 1-3 decades, 10-39 y	15	0.90 (0.50-1.60)	0.93 (0.52-1.68)
		P_{trend} = 0.91	P_{trend} = 0.86

NOTE: Poisson regression analysis. All statistical tests were two-sided. Analyses of solarium use at ages 40 to 49 years included only women ≥40 years when answering the questionnaire.

*Because there were only two cases that had any solarium exposure before age 20 years, no risk estimates were calculated.

†Multivariate models included attained age, region of residence, eye color, hair color, skin reaction after heavy sun exposure in the beginning of the summer and after repeated sun exposure, and solar exposure (corresponding number of age-specific sunburns and weeks on annual summer vacations).

been mixed (4, 26-31). Two large case-control studies (5, 6) found inverse associations between NHL and measures of personal sun exposure, especially recreational sun exposure, with 20%-to-40% lower risk among the most heavily exposed compared with the least exposed. In contrast, we did not find any significant associations between risk of NHL and sunburns or sunbathing vacations. However, results from case-control studies are conflicting: two studies did not find consistent inverse associations with sun exposure (8, 10), two reported no statistically significant associations with sun exposure (7, 11), one found significant associations restricted to farmers (9), and one study observed an increased risk of NHL among women with a history of frequent sun exposure (12). Heterogeneity between men and women has not been reported for sun exposure in case-control studies including both sexes (5, 7, 9), except in the study by Hughes et al. (6), in which some of the inverse associations seemed to be stronger rather than weaker in women. The pooled analysis of the InterLymph Consortium found that increased recreational sun exposure may protect against NHL, with similar risk estimates for men and women [ORs for highest versus lowest quarters were 0.77 (95% CI, 0.63-0.93) and 0.77 (95% CI, 0.59-1.01), respectively; $P_{heterogeneity}$ = 0.86; ref. 13]. However, the estimated association with total sun exposure was not significant, although it was somewhat stronger for men (OR, 0.82; 95% CI, 0.66-1.02) than women (OR, 0.93; 95% CI, 0.73-1.17; $P_{heterogeneity}$ = 0.60).

Exposure to artificial tanning devices at ages 20 to 29 years was associated with a significantly reduced risk of NHL, but an inverse association was not found overall. Significantly reduced risks associated with frequent use of tanning devices were found in some (5, 8, 10) but not in other case-control studies (7, 11, 12).

It is difficult to explain why NHL risk was associated with measures of sun sensitivity but not with sun and artificial tanning exposure in this cohort study. Sun-sensitive women may spend less time in the sun, but in accordance with previous studies (5, 7, 11, 12), we did not find confounding by pigmentation characteristics in the analyses of UV radiation exposure. It has been hypothesized that the UV radiation–NHL association may be mediated by activation of vitamin D (2, 15). Increased skin pigmentation reduces vitamin D synthesis. We found significantly reduced risks of NHL among women with lighter eye colors compared with brown-eyed women and among those with high propensity to burn compared with those with low propensity. A reduced risk was also found among those with poor ability to tan compared with those who become deep brown after repeated sun exposure. We have hypothesized that hair color is the best measure of sun sensitivity in the analysis of melanoma risk in this cohort (18). However, women with brown hair had significantly higher NHL risk than women with dark brown or black hair, whereas a weaker and nonsignificant increased risk was found when comparing women with blond, yellow, or red hair with those with dark brown or black hair. This lack of dose response for hair color and NHL risk weighs against a causal explanation.

Few studies have addressed the vitamin D and NHL association. Vitamin D intake was not associated with risk in four case-control studies (7, 9, 32, 33), whereas one reported a reduced risk of NHL after high intake of vitamin D stronger among women than men (34). In a male cohort, an inverse nonsignificant association was observed with plasma 25-hydroxyvitamin D predicted from multiple determinants of vitamin D, including ambient UV radiation levels and dietary vitamin D intake (35). The majority of participants were White in these studies, and recent analyses of NHL risk in the multiethnic cohort suggested that vitamin D intake might be more relevant for ethnic groups with increased pigmentation (36). A recent nested case-control study within a male Finnish cohort also did not confirm an association between low prediagnostic serum 25-hydroxyvitamin D levels and risk of NHL overall. However, within 7 years of follow-up, high levels of 25-hydroxyvitamin D measured in serum predicted a 60% reduction in risk of NHL, and the association was more pronounced among participants whose blood samples were drawn during less sunny seasons (20). If UV radiation influences risk of NHL through vitamin D, this latter finding may indicate two things: first, that a beneficial effect of vitamin D on risk of NHL is limited in time and does not accumulate infinitely; and second, that the level and/or duration of vitamin D deficiency during winter months is more important than the amount of sun exposure during sunny seasons. If so, self-reports of frequency of sunbathing and burns during summer periods may be less relevant than UV radiation exposure during winter months, such as sun vacations abroad and use of artificial tanning devices. Few published studies that use self-reports of UV radiation have distinguished between seasons of exposure, although one case-control study suggested that high exposure during a given season was less important than total hours of sun exposure (9).

The strengths of our study include the prospective design, detailed exposure information, and complete follow-up through high-quality national registries. Misclassification of exposure, which is inevitable in epidemiologic studies of lifetime UV radiation exposure, would be nondifferential in a cohort study and thus likely to bias effect estimates toward the null. Nevertheless, previous analyses of UV radiation exposure and pigmentary characteristics in this cohort have shown consistent effects on melanoma risk (18). The number of NHL cases in the present study was only slightly lower than in that melanoma analysis (187 cases), but we have considerably fewer cases than in past large case-control studies showing statistically inverse associations between sun exposure and NHL (5, 6, 13). Thus, the statistical power in our study to detect inverse associations of similar size as in previous studies may have been insufficient (see power calculations in Statistical methods). It is noteworthy, however, that we found no evidence of inverse associations between bathing vacations, sunburns, and NHL. Clearly, we could not investigate risk by histologic NHL subtype nor did we have any exposure information during follow-up.

Our prospective data do not support the hypothesis of a causal association between UV radiation exposure and risk of NHL. The reason for the discrepant results between this prospective study and our previous large case-control study (5) is, however, not obvious. It is, for instance, unlikely that selection bias would have created a spurious strong inverse association between UV radiation and NHL because the study was strictly population based, with high participation rates among both cases and controls (81% and 71%, respectively). It also seems less plausible that differential misclassification (recall bias, arising through over-reporting of UV radiation exposure among controls and/or under-reporting among cases) would create a spurious negative association with an exposure never publically linked to NHL. Alternative explanations include that we had inadequate statistical power to document a presumably weaker true negative association, or that timing of UV radiation exposure in periods with low natural sunlight, and presumably low vitamin D levels, is crucial. Future research should address these issues with high priority, because the answers are likely important both for etiologic understanding and for public health recommendations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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