Ultraviolet Radiation Exposure and Risk of Malignant Lymphomas

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Background: **The incidence of malignant lymphomas has been increasing rapidly, but the causes of these malignancies remain poorly understood. One hypothesis holds that exposure to ultraviolet (UV) radiation increases lymphoma risk. We tested this hypothesis in a population-based case–control study in Denmark and Sweden.** ***Methods:*** **A total of 3740 patients diagnosed between October 1, 1999, and August 30, 2002, with incident malignant lymphomas, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Hodgkin lymphoma, and 3187 population controls provided detailed information on history of UV exposure and skin cancer and information on other possible risk factors for lymphomas. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by logistic regression. Statistical tests were two-sided.** ***Results:*** **Multivariable-adjusted analyses revealed consistent, statistically significant negative associations between various measures of UV light exposure and risk of non-Hodgkin lymphoma. A high frequency of sun bathing and sunburns at age 20 years and 5–10 years before the interview and sun vacations abroad were associated with 30%–40% reduced risks of non-Hodgkin lymphoma (e.g., for sunbathing four times a week or more at age 20 versus never sunbathing, OR = 0.7, 95% CI = 0.6 to 0.9; for two or more sunburns a year at age 20 versus no sunburns, OR = 0.6, 95% CI = 0.5 to 0.8). These inverse associations increased in strength with increasing levels of exposure (all $P_{trend} \leq .01$). Similar, albeit weaker, associations were observed for Hodgkin lymphoma. There were no clear differences among non-Hodgkin lymphoma subtypes, although associations were stronger for B-cell than for T-cell lymphomas. A history of skin cancer was associated with a doubling in risks of both non-Hodgkin and Hodgkin lymphoma.** ***Conclusions:*** **A history of high UV exposure was associated with reduced risk of non-Hodgkin lymphoma. The positive association between skin cancer and malignant lymphomas is, therefore, unlikely to be mediated by UV exposure. [J Natl Cancer Inst 2005;97:199–209]**

More than 10 years ago, Zheng et al. *(1)* hypothesized that the increasing incidence of non-Hodgkin lymphoma, observed worldwide through decades, may be due, in part, to an increasing trend in ambient ultraviolet (UV) radiation levels and sun exposure habits. Since then, many studies have provided indirect support for this hypothesis, although others have not *(2,3)*. The supportive evidence includes observations of increased risks of non-Hodgkin lymphoma and chronic lymphocytic leukemia after diagnoses of UV-related skin cancers and, conversely, an increased risk of skin cancer after a diagnosis of lymphoma *(4–15)*. In addition, ecologic studies have demonstrated parallel time trends

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in incidence of skin cancer and non-Hodgkin lymphoma *(2,16)* and positive correlations between estimated ambient UV-B radiation levels and/or latitude and non-Hodgkin lymphoma incidence. However, the latter association has primarily been described within Europe *(16–18)* and has not been seen in the United States *(16,19,20)*. Moreover, three recent ecologic analyses [one with data from Europe *(21)* and two with data from the United States *(22,23)*] found inverse associations between estimated UV-B radiation levels and/or latitude and non-Hodgkin lymphoma incidence or mortality rates, respectively. Similarly, studies using outdoor occupation as an indicator of chronic UV exposure have yielded mixed results *(24–27)*.

Experimental studies in both humans and animals have shown that UV exposure induces systemic immune suppression *(3,28,29)*. These findings add biologic credibility to the hypothesis of a link between UV exposure and lymphoma because immune suppression is the strongest known risk factor for this malignancy *(30)*. Given the large public health implications of a causal association between UV light exposure and risk of malignant lymphomas, testing this hypothesis in analytic epidemiologic studies is warranted *(21,31)*. To this end, we carried out a large population-based case–control study in Denmark and Sweden with detailed assessment of UV exposure in relation to all major lymphoma subtypes.

Subjects and Methods

Study Subjects

The SCALE (Scandinavian lymphoma etiology) study base encompassed the entire population between the ages of 18 years and 74 years living in Denmark from June 1, 2000, through August 30, 2002, and in Sweden from October 1, 1999, through April 15, 2002. In Denmark, participants in a regional pilot phase study that started November 1, 1999, and gradually was expanded to national coverage were also included. The source population for the SCALE study was restricted to subjects with sufficient knowledge of the Danish or Swedish language to answer questions in a telephone interview and without a history of organ transplantation, human immunodeficiency virus infection, or other hematopoietic malignancy. Individuals with a first, newly diagnosed malignant lymphoma (non-Hodgkin lymphoma, including chronic lymphocytic leukemia [CLL], or Hodgkin lymphoma) according to the World Health Organization (WHO) classification *(32)* were eligible as case patients. The International Classification of Diseases, 10th Revision (ICD-10) codes used were C82–C85, C88.0, C91.3–5, and C91.7 (non-Hodgkin lymphoma), C91.1 (CLL), and C81 (Hodgkin lymphoma). In both countries, because of the relatively low incidence of Hodgkin lymphoma, patients with prevalent Hodgkin lymphoma diagnosed in 1999 were also included.

We identified patients newly diagnosed with lymphoma through a rapid case ascertainment system set up separately for the purposes of the study in both Denmark and Sweden. A network of contact physicians was established with all hospital clinics in which malignant lymphomas are diagnosed and treated (internal medicine, hematology, oncology, and clinical pathology), involving a total of 39 departments in Denmark and 118 in Sweden. Continuous collaboration with the national pathology registry in Denmark and the six regional cancer registries in Sweden ensured complete reporting through the network. The estimated coverage of the Danish pathology register and the Swedish cancer registries is close to 100% *(33)* (Inge Gram, Danish pathology register, personal communication).

Control subjects were randomly sampled from continuously updated computerized population registers that encompass the entire Danish and Swedish populations. A subset of control subjects was sampled every 6 months during the study period and was frequency-matched within each country on the expected distribution of cases of non-Hodgkin lymphoma, by sex and age (in 10-year intervals). In addition, extra sampling of control subjects was performed in the youngest age groups to ensure at least a 1:1 matching ratio for patients with Hodgkin lymphoma in all age groups.

Classification of Case Patients

In Denmark, review of tumor material took place within the national lymphoma registry organization (LYFO) *(34)*. In this registry, a random 10% sample of all incident cases in the country is reviewed continuously by a panel of expert hematopathologists. In addition, in all but 20% of the study patients in Denmark the diagnostic tumor specimens had been evaluated primarily by a LYFO-approved senior hematopathologist. In Sweden, samples from all case patients were histopathologically evaluated by one of six senior hematopathologists or cytologists and were classified according to the WHO classification *(32)*. Altogether, 70% of all included Swedish patients were reviewed within the study, whereas the remaining 30% had been reviewed already in routine care by one of the six appointed experts. When there was disagreement about a sample, it was referred to a panel of hematopathologists for final evaluation. The original diagnostic slides could not be retrieved for 35 (1.5%) of Swedish patients included in the study. For these patients, the written results of the primary morphologic and immunohistochemical investigation were used for diagnostic evaluation.

Host Factors and Exposure Information

Information on host characteristics, history of sun and artificial UV exposure, history of skin cancer, and potential confounding factors was collected through a telephone interview that used a standardized and computer-aided questionnaire. The computer-based questionnaire allowed the interviewers to fill in the responses of the participants directly in the computer during the course of interview. The questionnaire computer program also included automatic feasibility checks of responses when applicable and guidance through question loops. All questions were identical in the two countries. We were unable to blind the interviewers to case or control status, but they were unaware of the specific hypothesis under study and were instructed to treat case patients and control subjects strictly the same. Most patients (82%) with incident lymphoma were interviewed within 6 months after the date of the diagnostic biopsy (median interval = 2.8 months; range = 0–40 months). Among the patients with prevalent Hodgkin lymphoma, the median time from biopsy to interview was 13 months (range = 1–50 months). The total number of questions asked varied from 93 to 345, depending on the number of "question loops" entered. The median duration of the interview was 25 minutes among case patients (range = 12–121 minutes) and 26 minutes among the control subjects (range = 12–106 minutes).

The questions concerning host factors and UV light exposures were adapted from a validated questionnaire that has previously

been used in studies of sun-related behavior in individuals with dysplastic nevus syndrome *(35)*. Recorded host characteristics included natural hair color (blond, red, red brown, light brown, medium brown, dark brown, or black), eye color (blue, blue/grey, blue/green, green, green/grey, brown, or black), and skin sensitivity to sun exposure (also referred to as skin type). Skin sensitivity was defined as the reaction of skin (without sunscreen protection) to the first sun exposure of the season. Four categories of skin sensitivity were used: type I, the skin always burns and never tans; type II, the skin often burns and is then lightly tanned; type III, the skin sometimes burns and then turns medium tanned; and type IV, the skin seldom burns and always tans deeply. Assessment of sun exposure included sunbathing frequency during summer in Denmark/Sweden 5–10 years before the interview and at age 20 years (seven categories, from never to six to seven times per week); frequency of sunburns 5–10 years before the interview, at age 20 years, and during childhood (five categories, from never to three times or more per year); lifetime history of sun vacations abroad (meaning vacation trips to southern latitudes with sunbathing as the main activity; six categories, from never to more than 20 times); and outdoor occupation lasting 1 year or more (ever/never). Questions about sunbathing and sunburns at age 20 years were asked only of people 40 years old or older.

We also assessed exposure to artificial UV radiation as use of solaria (sun beds) or sun lamps (ever/never, with questions about lifetime frequency, duration, and age of regular use for those who had ever used one or both). Since 1989, only sun beds of UV type 3 (i.e., with low emission of UV-A wavelengths and very low emission of UV-B wavelengths) have been permitted in the Nordic countries. Finally, we recorded history of skin cancer (ever/never), and, if positive, age at diagnosis of skin cancer. However, these self-reports did not allow us to reliably distinguish between the different histopathologic types of skin cancer: malignant melanoma and squamous cell and basal cell carcinoma. The study questionnaire also contained a wide range of questions about, for example, current height and normal weight (for calculation of body mass index), history of autoimmune disorders, medication use, blood transfusions, smoking, occupational exposure to pesticides and solvents, educational level, and family history of cancer *(36)*.

The study was approved by all regional ethics committees in Denmark and Sweden. Verbal informed consent was obtained from each participant before the interview.

Statistical Analyses

We used unconditional logistic regression in both univariate and multivariable analyses. Results are presented as odds ratios (ORs) with 95 percent confidence intervals (CIs); the odds ratio was used as an approximation of relative risk. All analyses were adjusted for the matching factors age (in 5-year intervals), sex, and country. Potential confounders were considered on the basis of prior knowledge of risk factors for non-Hodgkin lymphoma *(36)* and on whether the addition of the covariates to the models changed estimates of relative risk.

The multivariable analyses of lymphoma risk according to host characteristics were mutually adjusted for all other host factors. In the analyses of the different measures of UV exposure, we adjusted for skin type. We further added occupational exposure to pesticides to the multivariable model in the analyses of outdoor occupation. In the analyses of skin cancer, multivariable models included skin type and lifetime number of sun vacations abroad. Overall, the multivariable adjustments changed only a few of the univariate estimates by no more than 10%, and most estimates remained unchanged. Therefore, only multivariable estimates are presented.

Because of the small numbers of subjects in the upper two categories of the variables concerning sunbathing, sunburns at different ages, and use of solaria and sun lamps, we combined these categories. For the same reason, in the analyses of sunbathing we combined three intermediate categories into one category, in the analyses of sun vacations abroad we combined four intermediate categories into two categories, and in the analyses of solaria and sun lamps we combined two intermediate categories into one. In analyses of host characteristics, subjects with red brown, light brown, and medium brown hair were combined in one category. With respect to eye color, categories of brown and black color were combined into the referent category, and the colors blue/grey, grey, green, blue/green, and green/brown were combined into an intermediate category.

Statistical significance of independent variables and interaction effects were tested by the likelihood ratio test. We tested for trend across categories of some variables by assigning equally spaced values (e.g., 1, 2, 3, and 4) to the categories and treating them as continuous variables in the logistic regression analysis. All significance tests were two-sided.

Results

A total of 6927 subjects (3740 case patients and 3187 control subjects) participated in the study. Approximately 37% of the participants were from Denmark, and 63% were from Sweden. The number of individuals enrolled, participation rates, and characteristics of respondents are shown in Table 1. The main reason for nonparticipation among all eligible case patients (n = 4506) was early death (n = 279, 6%), whereas the main reason for nonparticipation among eligible control subjects (n = 4489) was unwillingness to participate (n = 718, 16%). With regard to non-Hodgkin lymphoma, results are presented for the entire group of patients (n = 3055) as well as for patients with each of the four major subtypes of non-Hodgkin lymphoma: diffuse large B-cell lymphoma (n = 796), CLL/small lymphocytic lymphoma (n = 752), follicular lymphoma (n = 586), and T-cell lymphoma (n = 204). Results for all patients with all B-cell types considered together (n = 2812) were virtually identical to those for non-Hodgkin lymphoma overall (data not shown), because these patients made up the vast majority (92%) of all non-Hodgkin lymphoma patients in the study. Most of the Hodgkin lymphoma patients were newly diagnosed during the study period (n = 508, 82%), but 18% (n = 110) were diagnosed in 1999, before the start of the study. Exclusion of the 110 patients with prevalent Hodgkin lymphoma did not change the associations for this disease (data not shown).

Host Factors

Hair color was not statistically significantly associated with risk of malignant lymphomas (Table 2). Grey, green, or mixed eye color was associated with a statistically significant slightly increased risk of non-Hodgkin lymphoma compared with brown or black color (OR = 1.3, 95% CI = 1.1 to 1.5, Table 2). There were no statistically significant associations between blue eye

Table 1. Characteristics of participants in the SCALE (Scandinavian lymphoma etiology) study

Characteristic	Case patients			Control subjects
	All malignant lymphomas*	Non-Hodgkin lymphomas†	Hodgkin lymphomas	
Total number of participants	3740	3055	618	3187
Country of residence				
Denmark	1393	10751	254	1186
Sweden	2347	980	364	2001
Median age at diagnosis, y (range)‡	59 (18–74)	61 (18–74)	36 (18–74)	59 (18–76)
Sex, n (%)				
Male	2184 (58)	1819 (60)	333 (54)	1767 (55)
Female	1556 (42)	1236 (40)	285 (46)	1420 (45)
Participation rate (%)§	83	81	91	71

*Malignant lymphomas included non-Hodgkin and Hodgkin lymphomas and 67 cases of unspecified lymphoma.

†The non-Hodgkin lymphoma group included 796 patients with diffuse large B-cell lymphoma, 752 patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, 586 patients with follicular lymphoma, 204 patients with T-cell lymphoma, 678 patients with other B-cell lymphoma types, and 39 patients with unspecified non-Hodgkin lymphoma.

‡Or, for control subjects, median age at interview.

§The participation rate reflects the proportion of eligible case patients (n = 4506 for all malignant lymphomas) and eligible control subjects (n = 4489) that were included in the study.

color and risk of any malignant lymphoma types. A U-shaped negative association between skin sensitivity to sun and lymphoma risk was observed for both non-Hodgkin and Hodgkin lymphoma. Subjects whose skin often burns on the first seasonal exposure to the sun (type II) consistently had the lowest relative risk compared with subjects whose skin seldom burns (type IV). For subjects with even more sensitive skin (type I), the risk estimates were higher, approaching unity.

Sunbathing, Solaria and Sun Lamp Use, and Outdoor Occupation

Increasing frequency of sunbathing during summer in Denmark/Sweden and increasing numbers of sun vacations abroad were both associated with a decreasing risk of non-Hodgkin lymphoma (Table 3). Individuals with a history of sunbathing four times a week or more (both during the period 5–10 years before interview and at age 20 years) or a lifetime total of 20 or more sun vacations abroad had approximately 30% lower risks of all non-Hodgkin lymphomas than individuals without such sunbathing or vacation histories; these risk reductions were statistically significant, as were the negative trends (all $P_{trend} \leq .001$). We observed reductions in risk of Hodgkin lymphoma of the same magnitude, but these estimates were based on smaller numbers and were not statistically significant. Similar results were observed for all non-Hodgkin lymphoma subtypes as for non-Hodgkin lymphoma overall, although the data for T-cell lymphomas were less consistent and less precise. Frequent use of solaria or sun lamps was associated with a 20% reduced risk of non-Hodgkin lymphoma of borderline statistical significance and with a statistically significant risk reduction of 30% of Hodgkin lymphoma. Ever having an outdoor occupation for 1 year or more was associated with a slightly increased risk of non-Hodgkin lymphoma (OR = 1.2, 95% CI = 1.0 to 1.3) compared with never having worked outdoors, but this association was weakened (OR = 1.1, 95% CI = 1.0 to 1.2, Table 3) after additional adjustment for occupational exposure to pesticides.

Mutual adjustment for all other measures of UV exposure shown in Table 3 for subjects older than 40 years of age (not all variables were assessed in subjects younger than 40 years) resulted in attenuation of a few estimates (data not shown). Mainly, the negative associations between sunbathing 5–10 years before interview or solaria/sun lamp use and risk of non-Hodgkin lymphoma became weaker and the relative risks no longer reached statistical significance. Further adjustment for hair and eye color, educational level, smoking, body mass index, autoimmune disorders, and history of blood transfusions did not alter the risk estimates (data not shown).

Sunburns

An increasing annual frequency of sunburns during all time periods assessed was clearly inversely associated with risk of all non-Hodgkin lymphomas ($P_{trend} \leq .003$) (Table 4). The association was most pronounced for exposure at 20 years of age; individuals in the highest category of sunburn frequency (twice a year or more) at that age experienced a statistically significant 40% decrease in their risk of non-Hodgkin lymphoma compared with those who had no sunburns (OR = 0.6, 95% CI = 0.5 to 0.8, $P_{trend} < .001$). There was little variation in associations among non-Hodgkin lymphoma subtypes, although the associations appeared slightly stronger for diffuse large B-cell and follicular lymphomas (Table 4). Mutual adjustment for all other measures of UV exposure for subjects at least 40 years old resulted in no association for the period 5–10 years before interview (data not shown).

Analyses of Interaction

We found no statistically significant interactions between any UV exposure variable and age, sex, or skin type. Interactions between sunburns and country were of borderline statistical significance, with risks of non-Hodgkin lymphoma being lower in Sweden than in Denmark for sunburns 5–10 years before interview (P for heterogeneity = .05) and at age 20 years (P for heterogeneity = .007) but not for sunburns in childhood (P for heterogeneity = .26). Importantly, however, protective associations were seen in both countries. For all other UV exposure variables, there was no effect variation by country.

Skin Cancer

A self-reported previous diagnosis of skin cancer was associated with a statistically significantly twofold increased risk of non-Hodgkin lymphoma (OR=2.1, 95% CI = 1.6 to 2.9). When we excluded skin cancers diagnosed within 1 year before lymphoma diagnosis among the case patients (and 1 year before interview for the control subjects), to avoid reversed causality, the relative risks did not change appreciably for either non-Hodgkin or Hodgkin lymphoma (Table 5). When non-Hodgkin lymphomas were stratified by subtype, the risk of T-cell lymphoma was increased fourfold in people with a history of skin cancer, whereas we found no association between skin cancer and diffuse large B-cell lymphoma. In analyses stratified according to time between diagnosis of skin cancer and of malignant lymphomas (Table 5), the relative risks were highest within the first 5 years after the diagnosis of skin cancer. With an interval of more

Table 2. Numbers of subjects, multivariable-adjusted odds ratios (ORs)* and 95% confidence intervals (CIs) for major lymphoma subtypes in relation to host sun sensitivity characteristics among participants in the SCALE (Scandinavian lymphoma etiology) study

		Non-Hodgkin lymphoma											
		All non-Hodgkin lymphomas (n = 3055)†		Chronic lymphocytic leukemia (n = 752)‡		Diffuse large B-cell lymphoma (n = 796)		Follicular lymphoma (n = 586)		T-cell lymphoma (n = 204)		Hodgkin lymphoma (n = 618)	
Characteristic	Control subjects (n = 3187), n (%)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)
Hair color													
Dark brown or black	752 (24)	697 (23)	1.0 (Ref.)	182 (24)	1.0 (Ref.)	195 (25)	1.0 (Ref.)	115 (20)	1.0 (Ref.)	49 (24)	1.0 (Ref.)	148 (24)	1.0 (Ref.)
Light, medium or red brown	1477 (47)	1520 (50)	1.1 (1.0 to 1.3)	365 (49)	1.0 (0.8 to 1.2)	371 (47)	1.0 (0.8 to 1.2)	312 (53)	1.4 (1.1 to 1.7)	102 (50)	1.1 (0.7 to 1.6)	285 (46)	0.9 (0.7 to 1.2)
Blond	850 (27)	766 (25)	1.0 (0.8 to 1.1)	187 (25)	0.9 (0.7 to 1.1)	209 (26)	1.0 (0.8 to 1.2)	147 (25)	1.1 (0.8 to 1.5)	48 (24)	0.9 (0.5 to 1.4)	167 (27)	0.9 (0.6 to 1.2)
Red	88 (3)	62 (2)	0.8 (0.5 to 1.1)	16 (2)	0.8 (0.4 to 1.4)	18 (2)	0.8 (0.5 to 1.5)	9 (2)	0.7 (0.3 to 1.4)	5 (2)	0.9 (0.3 to 2.4)	17 (3)	0.8 (0.4 to 1.6)
Eye color													
Brown or black	599 (19)	468 (16)	1.0 (Ref.)	116 (16)	1.0 (Ref.)	128 (16)	1.0 (Ref.)	94 (17)	1.0 (Ref.)	30 (15)	1.0 (Ref.)	117 (19)	1.0 (Ref.)
Grey, green, or mix	888 (28)	881 (30)	1.3 (1.1 to 1.5)	221 (30)	1.3 (1.0 to 1.7)	228 (29)	1.3 (1.0 to 1.6)	161 (28)	1.1 (0.8 to 1.5)	57 (29)	1.4 (0.9 to 2.3)	184 (30)	1.2 (0.9 to 1.6)
Blue	1637 (52)	1632 (54)	1.2 (1.0 to 1.4)	399 (54)	1.1 (0.9 to 1.5)	423 (54)	1.2 (1.0 to 1.5)	312 (55)	1.1 (0.9 to 1.5)	113 (56)	1.6 (1.0 to 2.5)	307 (50)	1.3 (1.0 to 1.7)
Skin reaction to sun (skin type)													
Seldom burns (IV)	916 (29)	1012 (34)	1.0 (Ref.)	245 (33)	1.0 (Ref.)	275 (35)	1.0 (Ref.)	176 (30)	1.0 (Ref.)	74 (36)	1.0 (Ref.)	195 (32)	1.0 (Ref.)
Sometimes burns (III)	966 (31)	865 (29) 610 (20)	0.8 (0.7 to 0.9)	208 (28)	0.9 (0.7 to 1.1)	214 (27)	0.7 (0.6 to 0.9)	170 (29)	0.9 (0.7 to 1.1)	56 (28)	0.6 (0.4 to 0.9)	177 (29)	0.7 (0.5 to 0.8)
Often burns (II)	781 (25)	528 (17)	0.7 (0.6 to 0.8)	157 (21)	0.8 (0.6 to 1.0)	154 (20)	0.7 (0.5 to 0.8)	135 (23)	0.8 (0.6 to 1.1)	36 (18)	0.5 (0.3 to 0.8)	132 (21)	0.6 (0.5 to 0.9)
Always burns (I)	483 (15)		1.0 (0.9 to 1.2) P_{trend} = .22	130 (18)	1.2 (0.9 to 1.6) P_{trend} = .56	142 (18)	1.0 (0.8 to 1.2) P_{trend} = .24	98 (17)	1.0 (0.7 to 1.3) P_{trend} = .51	36 (18)	0.8 (0.5 to 1.3) P_{trend} = .09	112 (18)	0.8 (0.6 to 1.1) P_{trend} =.12

*The analyses included multivariable adjustment for age (5-year intervals), sex, and country and mutual adjustment for the other host characteristics in the table. Ref. = referent.

†In addition to the non-Hodgkin lymphoma subtypes shown, this number includes 678 patients with other B-cell lymphoma types and 39 patients with unspecified non-Hodgkin lymphoma, for whom odds ratios and 95% confidence intervals are not provided.

‡The chronic lymphocytic leukemia group also includes cases with small lymphocytic lymphoma.

Table 3. Numbers of subjects, multivariable-adjusted odds ratios (ORs)* and 95% confidence intervals (CIs) for major lymphoma subtypes according to sun exposure characteristics among participants in the SCALE (Scandinavian lymphoma etiology) study

		Non-Hodgkin lymphoma											
		All non-Hodgkin lymphomas (n = 3055) †		Chronic lymphocytic leukemia (n = 752) ‡		Diffuse large B-cell lymphoma (n = 796)		Follicular lymphoma (n = 586)		T-cell lymphoma (n = 204)		Hodgkin lymphoma (n = 618)	
Characteristic	Control subjects (n = 3187), n (%)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)
Sunbathing 5–10 years ago													
Never	799 (25)	946 (31)	1.0 (Ref.)	255 (34)	1.0 (Ref.)	235 (30)	1.0 (Ref.)	181 (31)	1.0 (Ref.)	50 (25)	1.0 (Ref.)	122 (20)	1.0 (Ref.)
Once/week or less	1013 (32)	938 (31)	0.9 (0.7 to 1.0)	198 (27)	0.8 (0.6 to 1.0)	269 (34)	0.9 (0.8 to 1.2)	190 (33)	0.8 (0.6 to 1.0)	75 (37)	1.1 (0.7 to 1.6)	236 (38)	0.8 (0.6 to 1.0)
2–3 times/week	666 (21)	555 (18)	0.8 (0.7 to 0.9)	142 (19)	0.9 (0.7 to 1.1)	138 (18)	0.7 (0.6 to 0.9)	99 (17)	0.6 (0.5 to 0.8)	42 (21)	1.0 (0.6 to 1.5)	141 (23)	0.7 (0.5 to 1.0)
4 times/week or more	666 (21)	581 (19)	0.7 (0.6 to 0.9)	147 (20)	0.8 (0.6 to 1.0)	145 (18)	0.7 (0.6 to 0.9)	109 (19)	0.7 (0.5 to 0.9)	35 (17)	0.8 (0.5 to 1.2)	118 (19)	0.7 (0.5 to 1.0)
			P_{trend}<.001		P_{trend} = .11		P_{trend} = .002		P_{trend} = .002		P_{trend} = .18		P_{trend} = .06
Sunbathing at 20 years of age§													
Never	434 (16)	568 (21)	1.0 (Ref.)	168 (23)	1.0 (Ref.)	131 (19)	1.0 (Ref.)	116 (22)	1.0 (Ref.)	21 (13)	1.0 (Ref.)1	49 (19)	1.0 (Ref.)
Once/week or less	931 (35)	918 (33)	0.8 (0.7 to 0.9)	235 (32)	0.7 (0.6 to 0.9)	246 (36)	0.9 (0.7 to 1.2)	157 (30)	0.6 (0.4 to 0.8)	68 (42)	0.5 (0.9 to 2.6)	84 (33)	0.8 (0.5 to 1.2)
2–3 times/week	674 (25)	635 (23)	0.7 (0.6 to 0.9)	157 (22)	0.6 (0.5 to 0.8)	155 (23)	0.8 (0.6 to 1.0)	138 (26)	0.7 (0.5 to 0.9)	28 (18)	0.9 (0.5 to 1.6)	50 (20)	0.6 (0.4 to 1.0)
4 times/week or more	653 (24)	642 (23)	0.7 (0.6 to 0.9)	167 (23)	0.7 (0.5 to 0.9)	143 (21)	0.7 (0.5 to 0.9)	119 (22)	0.6 (0.5 to 1.0)	43 (27)	1.3 (0.8 to 2.3)	73 (28)	0.9 (0.6 to 1.4)
			P_{trend} = .001		P_{trend} = .009		P_{trend} = .01		P_{trend} = .06		P_{trend} = .95		P_{trend} = .84
Sun vacations abroad													
Never	830 (26)	910 (30)	1.0 (Ref.)	255 (34)	1.0 (Ref.)	240 (30)	1.0 (Ref.)	152 (26)	1.0 (Ref.)	60 (30)	1.0 (Ref.)	146 (23)	1.0 (Ref.)
1–5 times	1,002 (32)	1,000 (33)	1.0 (0.9 to 1.1)	218 (29)	0.9 (0.7 to 1.1)	261 (33)	0.9 (0.8 to 1.2)	206 (35)	1.2 (0.9 o 1.5)	69 (34)	0.9 (0.6 to 1.3)	234 (38)	0.8 (0.6 to 1.0)
6–20 times	919 (29)	822 (27)	0.9 (0.8 to 1.0)	201 (27)	0.9 (0.7 to 1.1)	208 (26)	0.8 (0.6 to 1.0)	166 (28)	1.0 (0.7 to 1.2)	55 (27)	0.7 (0.5 to 1.1)	177 (29)	0.7 (0.5 to 0.9)
>20 times	410 (13)	305 (10)	0.7 (0.6 to 0.8)	75 (10)	0.6 (0.5 to 0.8)	83 (10)	0.7 (0.5 to 0.9)	59 (10)	0.7 (0.5 to 1.0)	18 (9)	0.6 (0.3 to 1.0)	60 (10)	0.8 (0.6 to 1.2)
			P_{trend}<.001		P_{trend} = .002		P_{trend} = .001		P_{trend} = .04		P_{trend} = .02		P_{trend} = .06
Solaria/sun lamp use													
Never	1254 (40)	1317 (44)	1.0 (Ref.)	326 (44)	1.0 (Ref.)	358 (46)	1.0 (Ref.)	245 (42)	1.0 (Ref.)	69 (34)	1.0 (Ref.)	203 (33)	1.0 (Ref.)
<10 times	742 (24)	790 (26)	1.0 (0.9 to 1.2)	215 (29)	1.3 (1.0 to 1.6)	185 (24)	0.9 (0.7 to 1.1)	159 (27)	1.0 (0.8 to 1.3)	54 (27)	1.3 (0.9 to 1.8)	134 (22)	0.8 (0.6 to 1.0)
10–49 times	765 (24)	643 (21)	0.9 (0.8 to 1.0)	147 (20)	1.0 (0.8 to 1.3)	163 (21)	0.8 (0.6 to 1.0)	126 (22)	0.7 (0.6 to 1.0)	54 (27)	1.2 (0.8 to 1.8)	161 (26)	0.7 (0.5 to 0.9)
50 times or more	377 (12)	270 (9)	0.8 (0.7 to 1.0)	55 (7)	0.9 (0.6 to 1.2)	77 (10)	0.7 (0.5 to 1.0)	54 (9)	0.6 (0.5 to 0.9)	24 (12)	1.1 (0.6 to 1.8)	116 (19)	0.7 (0.5 to 0.9)
			P_{trend} = .01		P_{trend} = .68		P_{trend} = .007		P_{trend} = .003		P_{trend} = .49		P_{trend} = .004
Outdoor occupation													
Never	2290 (73)	2059 (68)	1.0 (Ref.)	489 (65)	1.0 (Ref.)	528 (67)	1.0 (Ref.)	436 (75)	1.0 (Ref.)	135 (68)	1.0 (Ref.)	437 (75)	1.0 (Ref.)
Ever	846 (27)	965 (32)	1.1 (1.0 to 1.2)	260 (35)	1.1 (0.9 to 1.3)	263 (33)	1.2 (1.0 to 1.4)	144 (25)	1.0 (0.8 to 1.2)	65 (32)	1.2 (0.9 to 1.7)	147 (25)	1.2 (0.9 to 1.6)

*Multivariable models included age (5-year intervals), sex, country, and skin reaction to sun (i.e., skin type). In the analysis of outdoor occupation, there was additional adjustment for occupational exposure to pesticides. Further adjustment for hair and eye color, educational level, smoking, body mass index, autoimmune disorders, and history of blood transfusions did not alter the estimates. Ref. = referent.

†In addition to the non-Hodgkin lymphoma subtypes shown, this number includes 678 patients with other B-cell lymphoma types and 39 patients with unspecified non-Hodgkin lymphoma, for whom odds ratios and 95% confidence intervals are not provided.

‡The chronic lymphocytic leukemia group also includes patients with small lymphocytic lymphoma.

§This question was restricted to subjects 40 years old and older (case patients, n = 3177; control subjects, n = 2751).

Table 4. Numbers of subjects, multivariable-adjusted odds ratios (ORs)* and 95% confidence intervals (CIs) for major lymphoma subtypes according to sunburn history among participants in the SCALE (Scandinavian lymphoma etiology) study

	Control subjects, n = 3187	Non-Hodgkin lymphoma										Hodgkin lymphoma (n = 618)	
		All non-Hodgkin lymphomas (n = 3055)†		Chronic lymphocytic leukemia (n = 752)‡		Diffuse large-cell lymphoma (n = 796)		Follicular lymphoma (n = 586)		T-cell lymphoma (n = 204)			
Sunburn history	Subjects, n (%)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)
Sunburns 5–10 years before interview													
Never	2001 (64)	2121 (70)	1.0 (Ref.)	542 (72)	1.0 (Ref.)	540 (69)	1.0 (Ref.)	399 (68)	1.0 (Ref.)	128 (64)	1.0 (Ref.)	308 (51)	1.0 (Ref.)
<1/year	702 (22)	590 (20)	0.9 (0.8 to 1.0)	133 (18)	1.0 (0.8 to 1.3)	174 (22)	1.0 (0.8 to 1.2)	118 (20)	0.9 (0.7 to 1.1)	44 (22)	0.8 (0.6 to 1.2)	186 (30)	0.8 (0.6 to 1.0)
1/year	319 (10)	224 (7)	0.8 (0.6 to 0.9)	46 (6)	0.8 (0.6 to 1.1)	53 (7)	0.6 (0.5 to 0.9)	49 (8)	0.8 (0.6 to 1.1)	20 (10)	0.8 (0.4 to 1.3)	78 (13)	0.7 (0.5 to 0.9)
≥2/year	134 (4)	96 (3)	0.8 (0.6 to 1.1)	29 (4)	1.3 (0.8 to 2.0)	21 (3)	0.6 (0.4 to 1.0)	18 (3)	0.7 (0.4 to 1.2)	7 (4)	0.6 (0.3 to 1.4)	34 (6)	0.7 (0.4 to 1.0)
			P_{trend} = .003		P_{trend} = .92		P_{trend} = .003		P_{trend} = .05		P_{trend} = .14		P_{trend} = .006
Sunburns at 20 years of age§													
Never	1077 (40)	1208 (44)	1.0 (Ref.)	313 (43)	1.0 (Ref.)	305 (45)	1.0 (Ref.)	229 (43)	1.0 (Ref.)	64 (40)	1.0 (Ref.)	108 (43)	1.0 (Ref.)
<1/year	804 (30)	929 (33)	1.0 (0.9 to 1.2)	244 (34)	1.1 (0.9 to 1.3)	220 (32)	1.0 (0.8 to 1.2)	181 (34)	1.0 (0.8 to 1.3)	57 (36)	1.2 (0.8 to 1.8)	79 (31)	0.9 (0.7 to 1.3)
1/year	485 (18)	420 (15)	0.8 (0.7 to 0.9)	109 (15)	0.8 (0.6 to 1.1)	112 (16)	0.8 (0.6 to 1.1)	79 (15)	0.7 (0.6 to 1.0)	30 (19)	1.0 (0.6 to 1.6)	38 (15)	0.8 (0.5 to 1.1)
≥2/year	305 (11)	211 (8)	0.6 (0.5 to 0.8)	61 (8)	0.7 (0.5 to 1.0)	45 (7)	0.5 (0.4 to 0.7)	46 (9)	0.7 (0.5 to 1.0)	9 (6)	0.5 (0.2 to 1.0)	27 (11)	0.8 (0.5 to 1.3)
			P_{trend}<.001		P_{trend} = .03		P_{trend}<.001		P_{trend} = .009		P_{trend} = .19		P_{trend} = .14
Sunburns in childhood													
Never	1570 (59)	1747 (66)	1.0 (Ref.)	429 (66)	1.0 (Ref.)	443 (63)	1.0 (Ref.)	121 (70)	1.0 (Ref.)		1.0 (Ref.)	283 (51)	1.0 (Ref.)
<1/year	546 (20)	461 (17)	0.8 (0.7 to 1.0)	121 (18)	1.0 (0.8 to 1.2)	134 (19)	0.9 (0.7 to 1.2)	24 (14)	0.8 (0.6 to 1.1)		0.5 (0.3 to 0.8)	156 (28)	0.9 (0.7 to 1.2)
1/year	358 (13)	284 (11)	0.8 (0.6 to 0.9)	66 (10)	0.7 (0.5 to 1.0)	79 (11)	0.8 (0.6 to 1.0)	18 (10)	0.7 (0.5 to 1.0)		0.5 (0.3 to 0.9)	79 (14)	0.9 (0.7 to 1.3)
≥2/year	219 (8)	172 (6)	0.7 (0.6 to 0.9)	39 (6)	0.7 (0.5 to 1.0)	51 (7)	0.8 (0.6 to 1.1)	10 (6)	0.6 (0.4 to 0.9)		0.5 (0.2 to 1.0)	39 (7)	0.7 (0.5 to 1.1)
			P_{trend}<.001		P_{trend} = .02		P_{trend} = .07		P_{trend} = .002		P_{trend} = .002		P_{trend} = .14

*Multivariable models included age (5-year intervals), sex, country, and skin reaction to sun (i.e., skin type). Further adjustment for hair and eye color, educational level, smoking, body mass index, occupational exposure to pesticides, autoimmune disorders, and history of blood transfusions did not alter the estimates. Ref. = referent.

†In addition to the non-Hodgkin lymphoma subtypes shown, this number includes 678 patients with other B-cell lymphoma types and 39 patients with unspecified non-Hodgkin lymphoma, for whom odds ratios and 95% confidence intervals are not provided.

‡The chronic lymphocytic leukaemia group also includes patients with small lymphocytic lymphoma.

§This question was restricted to subjects 40 years old and older (case patients, n = 3177; control subjects, n = 2751).

Table 5. Numbers of subjects, multivariable odds ratios (ORs)* and 95% confidence intervals (CIs) for major lymphoma subtypes in relation to self-reported skin cancer among participants in the SCALE (Scandinavian lymphoma etiology) study

Years between skin cancer and lymphoma diagnosis	Control subjects (n = 3187)	Non-Hodgkin lymphoma										Hodgkin lymphoma (n = 618)	
		All non-Hodgkin lymphomas (n = 3055)†		Chronic lymphocytic leukemia (n = 752)‡		Diffuse large B-cell lymphoma (n = 796)		Follicular lymphoma (n = 586)		T-cell lymphoma (n = 204)			
	Subjects, n (%)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)	Subjects, n (%)	OR (95% CI)
No skin cancer	2987 (98)	2810 (96)	1.0 (Ref.)	692 (92)	1.0 (Ref.)	742 (98)	1.0 (Ref.)	541 (96)	1.0 (Ref.)	178 (90)	1.0 (Ref.)	582 (99)	1.0 (Ref.)
0–1	12 (0.4)	35 (1.2)	3.2 (1.6 to 6.4)	10 (1.4)	3.1 (1.3 to 7.4)	5 (0.7)	1.9 (0.6 to 5.5)	6 (1.1)	3.1 (1.1 to 8.6)	9 (4.6)	15 (5.6 to 39)	0	—
2–5	13 (0.4)	39 (1.3)	3.2 (1.7 to 6.1)	13 (1.8)	4.3 (1.9 to 9.6)	6 (0.8)	1.6 (0.5 to 4.5)	4 (0.7)	2.1 (0.6 to 6.5)	5 (2.5)	9.2 (3.1 to 28)	0	—
>5	38 (1.2)	53 (1.8)	1.4 (0.9 to 2.2)	12 (1.6)	1.1 (0.6 to 2.2)	7 (0.9)	0.6 (0.3 to 1.5)	12 (2.1)	1.7 (0.9 to 3.3)	5 (2.5)	2.7 (1.0 to 7.1)	8 (1.4)	2.8 (1.3 to 6.2)
>1	51 (1.7)	92 (3.1)	1.9 (1.3 to 2.7)	25 (3.4)	1.8 (1.1 to 3.0)	13 (1.7)	0.9 (0.4 to 1.7)	16 (2.8)	1.8 (1.0 to 3.2)	10 (5.1)	4.2 (2.0 to 8.6)	8 (1.4)	2.1 (1.0 to 4.6)

*Multivariable models included age (5-year intervals), sex, country, skin reaction to sun (i.e., skin type), and lifetime number of sun vacations abroad. Further adjustment for sun bathing in Denmark/Sweden, sunburns, solaria/sun lamp use, hair and eye color, educational level, smoking, body mass index, family history of cancer, occupational exposure to pesticides, autoimmune disorders, and history of blood transfusions did not alter the estimates. The odds ratios are presented according to years from reported age at diagnosis of skin cancer to age at diagnosis of malignant lymphoma. Ref. = referent.

†In addition to the non-Hodgkin lymphoma subtypes shown, this number includes 678 patients with other B-cell lymphoma types and 39 patients with unspecified non-Hodgkin lymphoma, for whom odds ratios and 95% confidence intervals are not provided.

‡The chronic lymphocytic leukemia group also includes patients with small lymphocytic lymphoma.

than 5 years, the risk estimates for all non-Hodgkin lymphomas, CLL, and follicular lymphoma approached unity, whereas the risks of T-cell lymphoma and Hodgkin lymphoma remained statistically significantly increased. Multivariable adjustment for skin type and total number of sun vacations abroad increased a few risk estimates slightly. Further adjustment for other measures of UV exposure, smoking, educational level, occupational exposure to pesticides, autoimmune disorders, family history of cancer, and history of blood transfusions did not change the results (data not shown). There was no statistically significant interaction between history of skin cancer and sex, age, or country. In exploratory analyses (data not shown), high levels of UV exposure were generally positively associated with history of skin cancer, as expected.

Discussion

Results from this large population-based case–control study do not support a positive association between UV exposure and risk of Hodgkin lymphoma, non-Hodgkin lymphoma, or the major subtypes of non-Hodgkin lymphoma. In fact, our results instead indicate that this common exposure is associated with a reduced risk of malignant lymphomas. Specifically, a high frequency of sunbathing, domestically or abroad, and a high frequency of sunburns at age 20 years or in childhood were associated with statistically significantly reduced relative risks of non-Hodgkin lymphoma. We found similar, albeit weaker, evidence of an association between various measures of UV exposure and risk of Hodgkin lymphoma. The major non-Hodgkin lymphoma subtypes showed associations similar to those for non-Hodgkin lymphoma overall, although reduced risks were more consistently observed for B-cell lymphomas (CLL, diffuse large B-cell lymphoma, and follicular lymphoma) than for T-cell lymphoma. These findings are supported by recent data from an Australian case–control study *(37)*, about one-fifth the size of this study, in which high levels of sun exposure were also found unexpectedly to be inversely associated with risk of non-Hodgkin lymphoma overall.

We also observed an approximately twofold increased risk of both non-Hodgkin and Hodgkin lymphoma associated with a self-reported history of skin cancer. This finding is consistent with those of numerous registry-based cohort studies, in which a history of skin cancer has been associated with 1.5- to 3-fold increased risks of non-Hodgkin lymphoma, including CLL. These previous observations pertained not only to squamous cell skin cancer *(4,6,10,12,15)* but also to basal cell carcinoma *(5–7,13)* and malignant melanoma *(4,6,8,9,11)*. In addition, several studies have observed two- to ninefold increased risks for skin cancer associated with a diagnosis of non-Hodgkin lymphoma *(4,6,8,9,14)*. Data on risk of Hodgkin lymphoma after skin cancer are scarce, but non–statistically significant twofold increased risks have been reported *(3,5, 10, 12)*. In these earlier reports, proposed explanations for the observed association between skin cancer and lymphomas include shared etiologic factors such as chronic immune suppression resulting from genetic or environmental factors, in particular UV exposure. A link between the two groups of malignancies might also arise spuriously because of closer surveillance and thereby higher detection rate of a second primary malignancy.

Geographic and temporal correlations between incidence of skin cancer and non-Hodgkin lymphoma *(2,16)* support a

relationship between the two malignancies but do not convey any information about the mechanism(s). Other ecologic studies of latitude and/or estimated UV-B radiation levels and incidence or mortality from non-Hodgkin lymphoma have shown either positive *(16–18)*, negative *(19,21–23)*, or no correlations *(20)*. Not only are these results far from clear, but ecologic studies are also often difficult to interpret due to the lack of individual-level information on exposure and possible confounders. Moreover, studies on occupational exposure to UV light and risk of non-Hodgkin lymphoma mostly provide evidence of no association *(26,27,38)* or of weak positive *(24)* or weak negative associations *(25)*. However, because none of these studies had data on recreational sun exposure, a potentially large exposure misclassification might have biased the results.

Given the indirect nature of almost all previously published evidence for a possible relationship between UV exposure and risk of malignant lymphomas, the strength of our study lies in the detailed and individual assessment of this exposure. Other strengths include the population-based design, the complete and rapid case ascertainment, and the thorough and uniform classification of malignant lymphomas. Moreover, the large study size permitted us to analyze relative risks of major non-Hodgkin lymphoma subtypes and of Hodgkin lymphoma.

One limitation of the study is the nonparticipation rate (17% versus 29% among eligible case patients and control subjects, respectively), which could have introduced selection bias. However, it is not likely that nonparticipation would be differently linked to UV exposure among case patients nd control subjects. Another possible bias in a case–control study design is differential recollection of exposure between case patients and control subjects (i.e., recall bias). However, there are presently no firmly established or widely known associations between UV exposure and malignant lymphoma. Therefore, it is unlikely that patients would have been influenced to link their disease to UV exposure or, further, that they would have systematically underreported their exposure—even more so at age 20 years than 5–10 years before interview—in such a way that a true positive association became convincingly inverse. Given the limitations of self-reported data on past exposures and the challenging task of capturing all aspects of UV exposure, it is more likely that our study suffers to some extent from imprecise exposure assessment, which is likely to affect case patients and control subjects equally. Such nondifferential exposure misclassification generally attenuates any true differences between case patients and control subjects, biasing the results toward no association, i.e., causing associations to be underestimated.

We cannot exclude the possibility that our results were influenced by residual confounding of unknown etiologic factors related to UV exposure or were due to chance. However, adjustment for a number of known and suspected risk factors for malignant lymphomas had little or no impact on the risk estimates. Although there is a possibility that some of the statistically significant associations arose by chance (especially given that multiple comparisons were carried out), the consistency of the results across UV exposure variables and the highly statistically significant inverse dose–response relationships indicate that chance alone is unlikely to explain our findings. The similarity of results between Denmark and Sweden and between the sexes and the independence of the associations from skin type further decrease the possibility that our findings would have arisen as a result of bias or chance. The fact that inverse associations were observed for all skin types may further imply that our findings are generalizable beyond a Scandinavian population. In contrast with the rest of the findings, we observed no associations with ever having an outdoor occupation. This could be due to de facto low levels of UV light exposure associated with outdoor occupation, insufficiently detailed information about job history, or residual confounding.

Subtypes of lymphatic malignancies show considerable heterogeneity with respect to clinical behavior, histopathology, and molecular biology *(32)*. There is increasing awareness that etiologic factors might also differ between subtypes *(31,39)*. Interestingly, risk factors for some uncommon lymphoma types are well established, for example, Epstein-Barr virus for Burkitt's lymphoma and non-Hodgkin lymphoma in strongly immunosuppressed individuals, *Helicobacter pylori* for gastric lymphoma, and human herpes virus 8 for pleural effusion lymphomas. Much less is known about risk factors for more common non-Hodgkin lymphoma subtypes. Most consistently, a number of autoimmune and chronic inflammatory disorders have been positively associated with non-Hodgkin lymphoma *(40)*. There is also evidence of a degree of familiar clustering *(40)*. Hence, although primary and acquired suppression of cell-mediated immunity are the most well-known risk factors for non-Hodgkin lymphoma, lymphomagenesis also appears to involve immune stimulation and/or dysfunction, driven by exogenous as well as endogenous factors.

It is unclear whether our data indicate that UV-induced systemic immune modulation, which involves alterations of T-cell subsets ($CD4^+$, $CD8^+$, and natural killer cells) *(28)*, can confer a reduced risk of non-Hodgkin lymphoma (or perhaps only B-cell lymphoma), rather than a risk increase as previously believed *(1–3,31)*. However, because systemic immune effects by UV radiation appear to be modulated by skin type *(28)*, this mechanism would be consistent with our finding of an association between skin type and lymphoma risk. Another possible biologic mechanism by which UV exposure could inhibit lymphomagenesis is photo-initiation of vitamin D production by UV-B radiation *(22,41)*. Vitamin D deficiency may have a role in the development of several common cancers, including cancers of the prostate, colon, breast, and ovary *(41)*. The active vitamin D hormone calcitriol (1,25-dihydroxyvitamin D_3) promotes differentiation and has an antiproliferative effect on a variety of cell lines, including those derived from the hematopoietic system *(42)*. Treatment with alpha-calcidiol, which is metabolized to calcitriol, has also been shown to produce tumor regression in follicular low-grade lymphomas *(42)*. It has been proposed that this action is enhanced through a modulation of $CD4^+$ T cells *(42)*. An increase in skin pigmentation is also known to be associated with diminished cutaneous production of cholecalciferol (vitamin D_3) after UV exposure *(41)*.

In light of our finding that UV exposure is inversely associated with the risk of non-Hodgkin lymphoma, the link between malignant lymphomas and skin cancer is intriguing. Decreasing relative risks of non-Hodgkin lymphoma with increasing time from diagnosis of skin cancer, both in previous reports *(4,9,10)* and in this study, may indicate shared predisposing factors, such as acquired dysfunction of the cellular immune system or of DNA repair. This possibility is indirectly supported by observations that skin cancer is associated with poor prognosis in patients with second cancers (non-Hodgkin lymphoma and breast, prostate, colon, and lung cancer) *(43,44)*. Moreover, skin cancer patients appear to be at increased risk, not only of non-Hodgkin lymphoma

but also of carcinomas of the upper aerodigestive tract, breast, kidney, lung, and brain *(5,10–12,45)*. Our results further indicate that different subtypes of malignant lymphoma may have different associations with skin cancer.

To conclude, our data do not support the a priori hypothesis that UV exposure is associated with an increased risk of malignant lymphomas. Rather, the results suggest an inverse association between UV light exposure and non-Hodgkin lymphoma risk. However, before this association can be considered causal we need further confirmatory data from other epidemiologic studies and, ideally, a better understanding of possible biologic mechanisms.

Appendix

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