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Multiple Indicators of Ambient and Personal Ultraviolet Radiation Exposure and Risk of Non-Hodgkin Lymphoma (United States)

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Abstract

Recent epidemiologic studies have suggested that ultraviolet radiation (UV) may protect against non-Hodgkin lymphoma (NHL), but few, if any, have assessed multiple indicators of ambient and personal UV exposure. Using the U.S. Radiologic Technologists study, we examined the association between NHL and self-reported time outdoors in summer, as well as average year-round and seasonal ambient exposures based on satellite estimates for different age periods, and sun susceptibility in participants who had responded to two questionnaires (1994–1998, 2003–2005) and who were cancer-free as of the earlier questionnaire. Using unconditional logistic regression, we estimated the odds ratio (OR) and 95% confidence intervals for 64,103 participants with 137 NHL cases. Self-reported time outdoors in summer was unrelated to risk. Lower risk was somewhat related to higher average year-round and winter ambient exposure for the period closest in time, and prior to, diagnosis (ages 20–39). Relative to 1.0 for the lowest quartile of average year-round ambient UV, the estimated OR for successively higher quartiles was 0.68 (0.42–1.10); 0.82 (0.52–1.29); and 0.64 (0.40–1.03), p -trend = 0.06, for this age period. The lower NHL risk associated with higher year-round average and winter ambient UV provides modest additional support for a protective relationship between UV and NHL.

INTRODUCTION

Recent epidemiologic studies suggest that sunlight may protect against non-Hodgkin lymphoma (NHL). Most (but not all) 1–2 studies,^{3–10} including a pooled analysis of 10 studies,¹¹ have found inverse associations between NHL risk and individual (personal) sun exposure, evaluated in terms of self-reported time outdoors, sunbathing or other behavioral exposures during various ages. Ultraviolet radiation (UV) exposure is the product of many factors, including not only duration of sun exposure, and host susceptibility characteristics

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(e.g., skin pigmentation), but also season and geographic location, among others. Few analytic studies have examined the environmental or ambient ultraviolet radiation (UV) context in which outdoor behaviors occurred.

None, to our knowledge, has examined average year-round or seasonal ambient UV exposures. Yet ambient UV exposures, which vary markedly throughout the year,¹² may be highly informative of an individual's usual or cumulative UV exposure.

We report here an analysis of the association between NHL risk and both seasonal and average year-round ambient as well as personal sun exposure for different age periods in the U.S. Radiologic Technologists (USRT) cohort, a nationwide study including participants from all 50 states.

MATERIALS AND METHODS

The USRT Study comprises a cohort of U. S. radiological technologists who were certified by the American Registry of Radiological Technologists for at least two years between 1926 and 1982. An initial questionnaire was mailed in 1983-1989, and a second, self-administered questionnaire (1994-1998) ascertained incident cancers and information on demographic and lifestyle risk factors. The current study, relies mainly on data from a third questionnaire self-administered in 2003-2005 with questions on past (lifetime) sun exposure, residence, and cancer diagnoses. The USRT Study was approved by the human subjects review board at the University of Minnesota and the National Cancer Institute (NCI).

Study population

The current study was limited to participants who completed the second questionnaire, were cancer-free (except for non-melanoma skin cancer) at that time and responded to the third questionnaire, $n=64,103$. Seventy-four percent of respondents to the second questionnaire answered the third questionnaire. Eligible cases were those who, in response to the third questionnaire, reported a diagnosis of NHL that was made after the second questionnaire.

We requested pathology and other medical records to validate the self-reported cases of NHL defined as ICD-10 codes (C82-C85). Among the 136 participants reporting NHL, medical record information was obtained for 109 (80%). Of these 109, medical records validated the NHL diagnosis for 105 (96%). We excluded 4 (4%) incorrectly reported. Because a high proportion of self-reported NHL cancers were validated, we also included NHL cancer cases for whom no medical record confirmation could be obtained ($n=27$), as well as cases diagnosed as NHL according to medical records obtained for subjects who reported another type of cancer diagnosis in the self-administered questionnaires ($n=5$). Thus, there were a total of 137 cases. Although we could not assess under-ascertainment of NHL cases in the entire cohort, a USRT study of under-ascertainment in a subgroup of the cohort generally showed few missing cases.¹³

UV and other exposures

Personal sun exposure was reported on the third questionnaire (completed during 2003-2005); however, age, race, BMI, physical activity, smoking, and alcohol intake were available from the second questionnaire (completed during 1994-1998, and thus preceding the diagnosis). The questions on sun exposure inquired about five age categories (<13 years; 13-19 years; 20-39 years; 40-64 years; and ≥ 65 years), for which we obtained the city, state, and country in which the participant lived for the longest time during each period. We also asked about amount of time spent outdoors mid-day (9am-3pm) in summer during weekdays (0, <1, 1-2, 3-4, 5-6 hours/day) and separately, during weekends (same hour categories) for each of the age periods. Our study used exposure information self-reported

for ages <13, 13-19, 20-39 years, because these age periods preceded the diagnoses in all of the cases, and thus behavior patterns and residences were more likely to be temporally relevant than exposures for later age periods.

Personal UV exposures were based on summing the time subjects reported that they spent outdoors (9am-3pm) for weekdays and weekends and categorizing time in five groups: 3.5, ≤3.5-7.0, >7.0-14.0, >14.0-21.0 and >21 hours/week. Ambient UV exposures were based on linking the city/state/country locations reported with the Total Ozone Mapping Spectrometer (TOMS) database (<http://toms.gsfc.nasa.gov>). The TOMS database, which is maintained by NASA, provides a daily estimate of UV exposure for a particular location, the erythemal dose, on a global scale in a 1.25° by 1° (longitude by latitude) grid. Values were averaged for the period 1978-1993 to provide stability to the estimates. In particular, summer values were based on June 1st – August 31st; winter values, on December 1st – January 31st; and year-round values, on all months. Winter and summer months were selected because TOMS values were highest for July and next highest (about 10-14% lower) for June and August and they were lowest for December and January, with the second lowest values for November or February, which were 50% higher.

Using the NASA website, we linked geographic location to the most recent, daily (Version 8) dose estimates (the units are considered arbitrary). We created quartiles of UV ambient exposures based on the distribution of doses for the USRT study population during the age period 20-39 years, the time closest, and prior, to the age at self-report. These quartiles cut-points were then applied to exposures for each age group.

We have also included an examination of the association between UV exposure and risk of Basal Cell Carcinoma (BCC) to help validate the exposure variables. BCC is a nonmelanoma skin cancer that is positively related to UV exposure.¹⁴

Statistical analysis

Unconditional logistic regression analysis was used to estimate relative risks (and 95% confidence intervals), while controlling categorically for age (<45, 45-49, 50-54, 55-59, 60-64, 65 yrs.), gender, and race (white/nonwhite). Adjustment for body mass index (BMI, categorically) physical activity (hours walking/hiking, categorically), smoking history (combined status and current pack-year categories) and alcohol intake (drinks/week categorically) did not appreciably modify the risk estimates and were not included in the final models. Finally, we estimated risks for some sun susceptibility factors (e.g., skin tone, hair color; self-reported at LQ3), which were adjusted for age, gender, and race, as well as average year-round TOMS UV data in the age period 20-39 years. Monotonic trends across categorical variables were tested by using an ordinal scale; trends for personal sun exposure was modeled with median values per level (≤3.5; >3.5-7; >7-14; >14-21; >21 hrs/week) as a continuous variable in a logistic model; and trends for ambient exposures were modeled as a continuous variable. All analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

Cases and controls were generally similar in their racial distributions, but a higher proportion of cases than controls were male, older, ever-smokers, non-drinkers, and with higher BMI, (table 1). There was no apparent difference in physical activity as measured by hours/week spent walking or hiking.

Host susceptibility to ultraviolet radiation was associated with risk of NHL only for hair color, with darker color showing significantly higher risks (table 2). There was no

significant association with skin pigmentation, eye color, acute or chronic reaction to sun exposure, such as tanning or burning.

As table 3 shows, NHL was not associated with time spent outdoors during the summer (personal UV exposure) during any age category. NHL risk was lowest in those in the two highest quartiles of summer ambient UV exposure in each age group, but there was no dose-response relationship with summer ambient TOMS measures. With regard to winter ambient UV, risk was lowest in the highest ambient quartile in each age group, and the trend reached borderline statistical significance for the age group 20-39 years. A slightly greater disparity in risk between the lowest and highest ambient UV quartiles was seen for average year-round UV exposure, for exposures during the time period nearest to NHL diagnosis, ages 20-39. Relative to the referent category of highest average year-round exposure, odds ratios were 0.68 (95% CI = 0.042-1.10); 0.82 (0.52-1.29); 0.64 (0.40-1.03) for successively higher ambient UV exposure quartiles, p-trend = 0.06.

When we looked at BCC and ambient UV exposure we found highly significant and similar elevated associations with BCC across each age group for summer, winter and annual ambient UV estimates. For example, risks by quartile for increasing annual exposure for ages 20-39 were 1.0; 0.96 (95% CI= 0.86-1.07); 1.18 (1.06-1.32); 1.40 (1.26-1.55), p-trend=<0.0001. Risks were elevated at higher levels of personal UV exposure, but the trend was only significant in those under age 13 years (data not shown).

DISCUSSION

Our study of UV exposure and NHL risk shows a borderline non-significant relationship with average year-round and winter ambient UV exposure. There was no relationship with personal summer time outdoors. Among host susceptibility features, only lighter hair was related to lower risk.

In contrast to several other recent case-control studies, we did not see a gradient in risk related to increasing self-reported summer time outdoors. Recollection of time outdoors, however, is subject to substantial misclassification. A recent study of reproducibility of response about UV exposure within the USRT study showed that when asked at two different times (6 months apart) about total time outdoors during different life periods, the ICC for time outdoors in childhood and in adulthood were only moderately reliable, ICC = 0.56 (ages 0-19) and 0.43 (ages 20).¹⁵

With regard to residential or ambient UV exposure, our results are consistent with the inverse relationships seen in the NCI-SEER Non-Hodgkin Lymphoma Case-Control Study⁴ between NHL and sunlight, as well as in U.S. mortality studies.^{16, 17} The modestly stronger association seen for average year-round ambient and winter UV is of interest. To our knowledge, evaluation of incident risks by ambient or seasonal UV exposure in a large nationwide study has not previously been reported. The relationship between levels of ambient UV in different locations is not fixed, but varies, throughout the year. For example, many locations that are classified in the highest exposure quartiles in one season fall in lower quartiles in another season. The correlations between winter and summer ambient UV exposures for the same locations, although high, are imperfect. The Pearson correlation coefficients between winter and summer ambient TOMS values are 0.75, 0.76, 0.83 for ages <13, 13-19, and 20-39 years, thus accounting for about 56, 58, and 69% respectively of the variability in winter TOMS values given summer values or vice versa. It is plausible that what is most relevant to NHL risk is not a one-time measure of UV exposure, but some indicator of continuous (year-round) UV exposure or possibly low UV (winter) exposure, as is suggested here.

The associations we observe, could, of course, reflect other factors that are related to ambient UV exposure. Although uncontrolled confounding cannot be ruled out, study results were adjusted for age, gender, and race, as well as BMI, physical activity, smoking and alcohol intake. Also, because participants are a relatively homogenous occupational group, SES is less likely to play a confounding role in the associations we observed.

The positive relationship between NHL and dark eye/hair color is similar to that seen in the NCI-SEER Lymphoma Case-Control Study,⁴ but not in the case-control studies in Scandinavia⁸ or New South Wales, Australia.¹⁸ As discussed by Hartge et al.,⁴ it is not clear which type of host susceptibility (light vs dark pigment) would be most indicative of a causal relationship with UV exposure. Propensity to sunburn often leads to sun avoidance, but, at the same time, UV penetration is greatest in those who are constitutionally fair. Possibly the different associations seen between NHL and host susceptibility reflect varying relationships between host susceptibility and sun behavior/protection observed in different populations.

Ambient UV exposures may also be particularly relevant to the hypothesis that the biologic mechanism underlying UV protection against NHL involves cutaneous vitamin D production.^{19, 20} Indeed, Kimlin et al.²¹ found a substantially greater latitude gradient to the relationship between erythemal UV dose and cutaneous production of vitamin D in the U.S. during winter than in summer, thus suggesting that geographic residence may play a greater role in vitamin D status in winter than in summer. In the context of another malignancy, colorectal cancer, Wu et al.,²² found that circulating vitamin D levels in winter were more strongly associated with risk than summer levels, thus also supporting the importance of seasonal exposures. There is also some evidence that vitamin D levels measured in one season are poorly correlated with measures in other seasons.²³ Because potentially available or ambient UV, and thus also vitamin D exposures, vary throughout the year,¹² it may be particularly important to take into account the variability of UV over multiple seasons in assessing risk.

Potential limitations of this study include the relatively small numbers of NHL cases and the reliance on retrospective reporting of time outdoors and residence. In this regard, we also note that because cases were somewhat older than non-cases, reporting on factors during early life may have involved more misclassification for cases. Nonetheless, it is improbable that reports of past usual locations would be substantially affected by case status (or somewhat greater time since residence). Moreover, the validity of the ambient UV metric is supported by the expected relationships with BCC. In the case of reported time outdoors, the positive associations between personal time outdoors and BCC also provide some support for the exposure instrument. But, as noted, there are inherent difficulties in recalling and synthesizing past behavior over long periods of time, even apart from potential biases due to case status. We also note that our use of reported exposures prior to age 40 (to ensure prediagnostic exposures) meant longer gaps between exposure and diagnosis for older respondents. Finally, because sun exposure history and host characteristics were derived from the third questionnaire, we could not include deaths due to NHL that occurred prior to the third questionnaire. We did, however, run analyses of some risk factors from the second questionnaire (e.g., BMI and physical activity) to compare results between a prospective cohort analysis and the retrospective design required to analyze personal sun exposure, and the two sets of findings were similar.

A strength of the current study is the assessment of multiple indicators of sun exposure and susceptibility. Few studies have examined NHL diagnoses and ambient UV exposure, and none to our knowledge have assessed seasonal or year-round ambient exposures. Using TOMS UV data (collected on a daily basis with global coverage), rather than latitude

positions, provided actual UV estimates – not merely geographic surrogates for UV, and allowed us to estimate seasonal and average year-round exposures. Moreover, that the USRT study enlists participants from across the entire nation ensures a particularly large range of UV exposures (representing latitudes ranging from approximately 20 to 70°).

In sum, we did not find a clear relationship between self-reported time outdoors and NHL. Our finding of a borderline non-significantly reduced risk of NHL associated with year-round average and winter ambient UV exposure during the age period closest to the diagnosis time provides limited support for a relationship with UV. It also highlights the complexity and variability of UV levels that contribute to lifetime or even recent UV exposures, and to the importance of changing vitamin D exposures, if vitamin D is ultimately implicated causally. Further understanding the role of UV (as well as possibly vitamin D) in NHL risk may involve examining a broad constellation of factors determinative of UV exposure throughout the year.

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Table 1

Distribution of NHL cases and non-cases

Characteristics*	Cases (%)	Non-cases (%)
Sex		
Female	91 (66)	50447 (79)
Male	46 (34)	13519 (21)
Race/Ethnicity		
White	132(96)	60847 (95)
Black	4 (3)	1702 (3)
Other	1 (1)	1417 (2)
Age (y)		
<45	32 (23)	28374 (44)
45-49	23 (17)	14171 (22)
50-54	28 (20)	9207 (14)
55-59	23 (17)	5734 (9)
60-64	16 (12)	3402 (5)
≥65	15 (11)	3078 (5)
BMI (kg/m)		
<25	56 (41)	32945 (52)
25-29	48 (35)	19518 (31)
≥30	29 (21)	10223 (16)
Walking/hiking (hrs/week)		
None- <1	60 (44)	28429 (44)
1-3	42 (31)	20889 (33)
≥4	23 (17)	11647 (18)
Smoking history		
Never	65 (47)	39932 (55)
Former	49 (36)	20557 (32)
Current, ≤10 packyrs	2 (1)	1540 (2)
>10 packyrs	16 (12)	6363 (10)
Alcohol intake (past yr)		
Non-drinker	43 (31)	13858 (22)
<1/week	37 (27)	21105 (33)
1-<5/week	41 (30)	19425 (30)
≥ 5/week	16 (12)	9578 (15)

* As of the second (baseline) questionnaire (1994-1998). Some percentages do not add up to 100 due to missing data or rounding.

Table 2

Estimated OR and 95% CI according to various indicators of personal sun susceptibility*

	No. cases	No. controls	OR	95% CI
Hair color				
Blond	11	9568	1.00	
Red	2	1689	0.99	0.22-4.47
Reddish Brown	9	3712	2.12	0.88-5.13
Light Brown	29	12130	2.14	1.07-4.29
Medium-dark brown or black	86	36375	1.97	1.05-3.70
P-trend			0.04	
Eye color				
Blue	27	15732	1.00	
Green/blue or green/grey	32	11334	1.90	1.13-3.17
Hazel	17	8747	1.19	0.65-2.18
Light Brown	9	3978	1.42	0.67-3.03
Dark Brown	38	13918	1.77	1.07-2.93
P-trend			0.11	
Skin tone				
Light	49	22986	1.00	
Medium	68	28375	1.05	0.73-1.52
Dark	6	2530	0.92	0.38-2.23
P-trend			0.93	
Skin reaction to first sun				
Severe burning	8	4384	1.00	
Painful burning	35	17309	1.17	0.54-2.52
Mild sunburn	69	32512	1.17	0.56-2.44
Tanned, no sunburn	22	8045	1.41	0.62-3.20
No change	1	1279	0.36	0.04-3.01
P-trend			0.82	
Skin reaction to repeated sun				
Deepest tan	35	17732	1.00	
Moderate tan	63	29837	1.03	0.68-1.56
Light tan	30	13597	1.13	0.69-1.85
Not tanned	8	2169	1.70	0.78-3.71
P-trend			0.31	

* Adjusted for age, gender, race/ethnicity and average year-round quartiles for sun exposure.

Numbers do not add to 137 or 64,103 due to missing data.

Table 3

Risk of NHL associated with personal and summer, winter, and year-round ambient sun exposure according to age*

	ages <13			ages 13-19			ages 20-39		
	No. cases	No. controls	OR	95% CI	No. cases	No. controls	OR	95% CI	No. controls
Personal sun exposure (hrs/wk)									
≤7	11	5537	1.00		14	6166	1.00		15759
>7-14	17	8468	1.02	0.48-2.19	19	10468	0.83	0.42-1.66	16503
>14-21	32	8991	1.89	0.95-3.77	35	12708	1.31	0.70-2.45	14949
>21	65	36308	0.91	0.48-1.74	58	30083	0.82	0.46-1.49	12367
P-trend**			0.10				0.25		0.09
Summer (s) ambient exposure (TOMS) (quartiles)									
<177	40	16695	1.00	39		16525	1.00		14803
177-<188	40	18169	0.97	0.62-1.50	37	18025	0.92	0.58-1.44	15598
188-<228	31	15718	0.81	0.51-1.30	32	15661	0.86	0.54-1.37	15070
≥228	18	10163	0.76	0.43-1.33	19	10627	0.77	0.44-1.34	15104
P-trend**			0.22				0.19		0.09
Winter (w) ambient exposure (TOMS) (quartiles)									
<23	46	18004	1.00		44	17822	1.00		15131
23-<31	33	18494	0.73	0.46-1.14	31	18235	0.72	0.45-1.14	16464
31-<52	30	12781	0.95	0.60-1.51	31	12813	1.01	0.63-1.60	13619
≥52	20	11466	0.69	0.41-1.18	21	11878	0.73	0.43-1.24	15460
P-trend**			0.09				0.14		0.06
Average annual ambient exposure (TOMS) (quartiles)									

	ages <13			ages 13-19			ages 20-39					
	No. cases	No. controls	OR	95% CI	No. cases	No. controls	OR	95% CI	No. cases	No. controls	OR	95% CI
<99	46	18005	1.00		45	17853	1.00		43	15520	1.00	
99-<111	33	17424	0.77	0.49-1.21	32	17253	0.77	0.49-1.21	28	15236	0.68	0.42-1.10
111-<143	31	14410	0.85	0.54-1.34	30	14368	0.83	0.52-1.32	32	14366	0.82	0.52-1.29
≥143	19	10906	0.70	0.41-1.20	20	11364	0.71	0.42-1.22	28	15553	0.64	0.40-1.03
P-trend**			0.11				0.14				0.06	

* Adjusted for age, gender, and race/ethnicity. Numbers do not add to 137 or 64,103 due to missing data.

** P-trend based on continuous values for ambient exposure and median categorical values for personal exposure.