LYMPHOID NEOPLASIA

Exposure to UV radiation and risk of Hodgkin lymphoma: a pooled analysis

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Key Points

- Our pooled analysis found an inverse association between several measures of UVR exposure and Hodgkin lymphoma.
- Significant UVR-related inverse associations of EBV-positive HL with a dose-response relationship support etiologic heterogeneity in HL.

Ultraviolet radiation (UVR) exposure has been inversely associated with Hodgkin lymphoma (HL) risk, but only inconsistently, only in a few studies, and without attention to HL heterogeneity. We conducted a pooled analysis of HL risk focusing on type and timing of UVR exposure and on disease subtypes by age, histology, and tumor-cell Epstein-Barr virus (EBV) status. Four case-control studies contributed 1320 HL cases and 6381 controls. We estimated lifetime, adulthood, and childhood UVR exposure and history of sunburn and sunlamp use. We used 2-stage estimation with mixed-effects models and weighted pooled effect estimates by inverse marginal variances. We observed statistically significant inverse associations with HL risk for UVR exposures during childhood and adulthood, sunburn history, and sunlamp use, but we found no significant dose-response relationships. Risks were significant only for EBV-positive HL (pooled odds ratio, 0.56; 95% confidence interval, 0.35 to 0.91 for the highest overall UVR exposure category), with a significant linear trend for overall exposure ($P = .03$). Pooled relative risk estimates were not heterogeneous across studies. Increased UVR exposure may protect against HL, particularly EBV-positive HL. Plausible mechanisms involving UVR induction of regulatory T cells or the cellular DNA damage response suggest opportunities for new prevention targets. (*Blood*. 2013;122(20):3492-3499)

Introduction

Classical Hodgkin lymphoma (HL) is a B-cell lymphoma with unusual epidemiologic characteristics.[1] Although rare in most populations, HL is a relatively common cancer of adolescents and young adults, and treatment-related sequelae remain a serious life-long problem.[2-5] Thus, understanding HL etiology is a worthwhile research endeavor with the goal of primary prevention. Numerous epidemiologic studies have identified a variety of putative risk factors as well as substantial etiologic heterogeneity based on age group at diagnosis, tumor histologic subtype, and the presence or absence of Epstein-Barr virus (EBV) in the malignant Hodgkin/Reed-Sternberg cells.[6-10] However, the causes of HL remain poorly understood, in part because its low incidence limits the study sample sizes needed for adequate statistical power, particularly for the stratified analyses necessary to accommodate HL heterogeneity. Further, while the presence of EBV in HL tumors in selected patient subsets has been an important etiologic observation, the etiologic role of this virus in EBV-negative HL, which comprises the majority of cases, remains unclear.[7,9]

Ultraviolet radiation (UVR) exposure has been associated with HL risk, albeit inconsistently and based on only a few studies.[11-16] A large population-based case-control study in Sweden and Denmark detected an inverse association between risk of HL and sunbathing or

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sunburn history within the last 5 to 10 years.[11] A recent French case-control study reported that having light-colored hair and skin or a high propensity to sunburn—indicators for sun sensitivity and potential avoidance[17]—were significantly associated with increased risk of HL.[13] Similarly, a European case-control study observed a positive association of HL risk with increasing skin sensitivity to sun exposure and a nonsignificant inverse association with more recreational days during childhood and adulthood.[14]

No studies have been able to address the role of this common and modifiable behavior in light of the marked heterogeneity of HL. To address this question, we took advantage of an international collaboration under the auspices of the International Lymphoma Epidemiology Consortium (InterLymph) to achieve sufficient numbers of study subjects for meaningful subgroup analyses. We conducted a collaborative pooled analysis of the role of UVR exposure in HL risk focusing on timing and type of exposure and considering epidemiologically distinct disease subtypes defined by age group, histologic subtype, and EBV status of the tumor.

Patients and methods

Study population

Four studies collected data on at least 1 measure of personal UVR exposure and contributed data for this analysis (Table 1).[11,13,14,18] All 4 studies were conducted during the early 2000s in Europe and included HL patients age 16 to 80 years at diagnosis, with no history of hematologic or other neoplasms, immunosuppression for organ transplantation, or HIV infection. The 4 studies were the Scandinavian Lymphoma Etiology (SCALE) study in Sweden and Denmark, l'Etude des Facteurs Environnementaux et Genétique des Lymphomes de l'Adulte (Engela) in France, the Epidemiology and Cancer Statistics Group Case-Control Study (ELCCS) in the United Kingdom, and the multi-European-center Epilymph study. Three studies (SCALE, ELCCS, and Epilymph [Italy and Germany]) included population-based controls only, whereas the Engela study and some Epilymph centers included hospital-based controls only (Table 1). Controls were frequency-matched to cases in SCALE and at some Epilymph centers and individually matched in the other studies. All tumors had been classified histologically according to either the 2001 World Health Organization Classification of Hematopoietic and Lymphoid Tumors[19] or the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[20] For this analysis, we considered classical HL overall, which includes all histologic subtypes except nodular lymphocyte-predominant HL and comprises the 2 most common subtypes: nodular sclerosis (ICD-O-3 9663/3 to 9667/3) and mixed cellularity (ICD-O-3 9652/3). Three studies characterized tumor EBV status by using standard immunohistochemistry to detect latent membrane protein 1 (LMP-1) and/or Epstein-Barr nuclear antigen or by in situ hybridization for EBV-encoded RNA (EBER) (Table 1). The sources of controls and matching characteristics are described in Table 1.

All studies obtained informed consent from participants in accordance with the Declaration of Helsinki and ethics approval from their local human research ethics committees; the pooled resource project also obtained ethics approval.

Data collection and exposure definition

Each eligible study provided an electronic dataset containing core subject variables, self-reported measures of personal UVR exposure (sunbathing frequency, sunburn history, vacations/holidays to sunny locations, tanning bed/sunlamp exposure, working time outdoors/outdoor occupation, recreational time outdoors, and use of sun protection), and potential confounding or effect-modifying variables (eg, study site, current socioeconomic status, subject's birth order, day care attendance, history of infectious mononucleosis, pigmentation variables, and cigarette smoking status).

Table 1. Characteristics of participating studies

Study name (reference)	Location	Period of interview/ diagnosis	Cases (n = 1320)					Controls (n = 6381)				
			No.	% Part	Age range (y)	Tumor histology	Classification	Tumor EBV status	No.	% Part	Source	Matching
Epilymph (14)	Spain, France, Italy, Germany, Ireland, Finland, Czech Republic	1998-2004	331	88	17-80	195 NS, 71 MC, 1 other	WHO	18 positive, 27 negative (Spain only)	2540	81	Population registers (Italy and Germany) or hospitals (Spain, France, Ireland, Czech Republic)	Individual (Germany, Czech Republic) or frequency (France, Ireland, Italy, Spain) by sex, age (5-y groups), and area of residence
ELCCS	North, East, and West Yorkshire, Lancashire, South Lakeland, Cornwall, South Devon, Dorset, South Hampshire, England	1998-2004	262	79	16-67	203 NS, 47 MC, 12 other	ICD-O-3	48 positive, 116 negative	237	69	Randomly selected from population registers	Individual by sex, date of birth, and area of residence
SCALE (11)	Denmark, Sweden	1999-2003	585	91	17-75	422 NS, 106 MC, 10 other	WHO	142 positive, 383 negative	3187	71	Randomly selected from population registers	Frequency by country, age (10-y groups), and sex
Engela (13)	Bordeaux, Brest, Caen, Lille, Nantes, Toulouse, France	2000-2004	142	97	18-71	106 NS, 18 MC, 3 other	ICD-O-3	No data	417	93	Hospitals, with no history of hematologic neoplasm	Individual by center, sex, age, and area of residence

% part, participation rate; MC, mixed cellularity; NS, nodular sclerosis; WHO, World Health Organization.

Table 2. Measures of UVR exposure categories by study

Study	Time spent outdoors not in shade		Routine outdoor leisure activities hours per day, week, month	Sunbathing in summertime frequency per week or month	Sunlamp use		Age or time intervals in analyses	
	Working day	Non-working day			Ever/ never	Frequency	Childhood (age ≤20 y)	Adulthood (age >20 y)
Epilymph	Yes (all but Germany)	Yes (all but Germany)	Yes (only for Germany)		Yes		Ages 10 and 20 y	Ages 30 and 40 y
ELCCS	Yes	Yes			Yes	Yes	Calculated based on age at interview	Calculated based on age at interview
SCALE				Yes	Yes	Yes	Age 20 y	Calculated based on age at interview
Engela			Yes		Yes			Exposure since leaving school

To estimate relative UVR exposure (Table 2), we constructed 5 variables for pooling across studies: overall (ie, lifetime) UVR exposure, childhood UVR exposure, adult UVR exposure, history of sunburn, and history of sunlamp use. Overall UVR exposure was computed as the sum of childhood and adult UVR exposure, except when available data allowed us to include additional lifetime exposure data (eg, the number of times abroad on a sun or beach holiday, as evaluated in SCALE). Variables describing the history of sunburn and the use of a sunlamp/solarium were dichotomized as ever vs never. Childhood UVR exposure (at or before age 20 years) was computed in SCALE, Epilymph, and ELCCS data by summing the non-missing values and creating quartiles for each variable based on available data (eg, hours spent outdoors, hours spent in sun for leisure, or days spent at the water/beach). Because sunlamp users are more likely than nonusers to seek UVR (including sun) exposure,[21] but because sunlamp use was assessed in the contributing studies only as a binary variable, we elevated a subject's assigned quartile by 1 level if that subject also reported using a sunlamp, sunbed, or solarium at or before the age of 20 years (SCALE and ELCCS studies). Adult UVR exposure (after age 20 years) was measured from data provided by all 4 studies in a similar way, averaging measures that were assessed at multiple ages in adulthood.

Statistical analysis

We used a 2-stage estimation method with mixed-effects models, described by Stukel et al,[22] to obtain study-specific odds ratios (ORs) and pooled ORs and 95% confidence intervals (CIs). Since 2 studies (SCALE and Epilymph) were large intercountry efforts that covered study areas of different latitudes, we attempted to better evaluate the impact of between-study variation by producing 2 types of models depending on the definition of study locations. "A" models treated Epilymph and SCALE as single overall studies and adjusted for study location, pooling across 4 study estimates. "B" models treated the 7 study locations of Epilymph and the 2 study locations of SCALE as separate locations, thus pooling across 11 study estimates.

The Stukel approach allows for analysis of each study as originally designed, with study-specific confounder coding. Confounder identification and adjustment procedures were undertaken for each study separately. We used the following criteria, set forth by Rothman et al,[23] to assess a confounding variable: (1) it must be a risk factor for the disease, (2) it must be associated with the exposure, and (3) it must not be on the causal pathway. The first step was to identify variables significantly associated with both outcome and exposure by significance testing with $P \leqslant .10$. The second step was to narrow these variables to confounders that influence the main effect estimates. We used a 10% change in the OR estimate as a criterion to identify confounders that had a large effect on the relationship between the exposure and outcome and that would result in the most parsimonious model. We used a stepwise selection approach, retaining all identified confounders regardless of P value and additional identified covariates that remained significantly associated with the outcome (but not necessarily the exposure) at $P \leqslant .20$ in stepwise modeling. As confounders/effect modifiers, we considered pigmentation variables; education; current or childhood socioeconomic status; number of siblings and birth order; daycare or preschool attendance; body size variables; history of infectious mononucleosis, cancer, or autoimmune disease; and cigarette smoking status. Education for Epilymph and SCALE, a variable combining current socioeconomic status (based on last job held) and education for Engela, and skin pigmentation for Epilymph were included as confounders in final models. The Engela study and 2 centers of the Epilymph study (Germany and the Czech Republic) used individual matching of cases and controls but subsequently analyzed their data ignoring this matching. Because our preliminary analyses for matched and non-matched studies yielded similar results, we opted for non-matched analysis because it provided a larger number of subjects. Data from the ELCCS study allowed us to retain the original individual matching. Effect estimates for each study were obtained by using unconditional logistic models adjusted for age as a continuous variable, sex, and study center for the SCALE, Epilymph, and Engela studies, and conditional logistic models for the ELCCS study.

We used random effects models to quantify between-study variation in effect estimates. The pooled effect estimates were weighted by the inverse marginal variances (ie, the sum of the individual study-specific variances and the variance of the random study effect). Heterogeneity among studies was tested by using the Cochran Q test and the percentage of variation in ORs attributable to heterogeneity between studies (I^2).

We used a weighted regression approach to assess trends in the log-odds estimates with continuous values to represent quartiles. We fit a trend to the final pooled estimates and alternatively fit a trend to each study and pooled the trend estimates for 1 analysis (overall lifetime exposure). Because the results were similar, we present the former. The weights were based on the proportionate sample size of the pooled results at each ordinal level.

We produced effect estimates for the 5 measures of UVR stratified by age group at diagnosis and/or interview (age <40 years, age 40 years and older), sex, tumor histology (nodular sclerosis, mixed cellularity), and tumor-cell EBV status (positive, negative). We also conducted analyses separately by control type (hospital- or population-based). We tested for effect modification of HL risk by UVR exposure variation by latitude by stratifying analyses by study location; as an indicator of the potential for skin damage, we used the average yearly erythemal UVR index, a simple measure of the UVR level at the earth's surface.[24]

Because the pooled ORs and 95% CIs from both A and B models were consistent for all analyses, we present results only from A models in accordance with the parsimony principle.

To further test hypotheses about etiologic heterogeneity, we performed case analyses to compare exposure-related HL risk across selected histologic subtypes and tumor-cell EBV status. In these comparisons, we adjusted for the same variables as in the case-control analysis. Statistical tests were 2-sided with an α level of .05. All analyses were performed with the open-access software R.

Results

The pooled dataset comprised study data, including UVR information, from 1320 cases and 6381 controls (Table 1). Among all

subjects, 56% were males, 99.7% self-reported their race as white, and the median age at diagnosis was 39 years. As expected, given that the contributing studies were designed to match controls by age to both HL and non-HL (NHL) cases, HL cases tended to be younger and more highly educated than the controls (data not shown). Tumors had been subtyped as nodular sclerosis (53%), mixed cellularity (12%), lymphocyte depletion (4%), or unspecified HL (29%). As expected, mixed cellularity cases were more frequent among the elderly. In all, 208 tumors (28%) were classified as EBV-positive and 526 (71%) as EBV-negative; EBV-positive cases were more likely than EBV-negative cases to be male, to be in the youngest or oldest categories of age, and to have mixed cellularity histology.

UVR exposure and HL risk overall and by age and sex

The associations between measures of UVR exposure and HL risk for subjects overall and for subjects stratified by sex and age at diagnosis are presented in Table 3. For overall UVR exposure, we observed inverse but statistically nonsignificant associations with HL risk (OR, 0.84 [95% CI, 0.67 to 1.04] for high vs low UVR exposure). A significant dose-response association (trend in ORs) was identified for overall UVR exposure with respect to overall HL risk, whereas no significant dose-response associations were observed for childhood or adult UVR exposure separately. For the other 4 measures of UVR of exposure, we observed statistically significant inverse associations with HL risk; results were of similar magnitude for childhood and adult UVR exposures. Adjusted pooled estimates were OR, 0.77 [95% CI, 0.63 to 0.95] for history of sunburn (yes/no) and OR, 0.81 [95% CI, 0.69 to 0.96] for use of sunlamps (ever/never). Similar patterns of association were observed by age at diagnosis and by sex, although not at a statistically significant level in either men or women.

Histologic subtypes and tumor EBV status

Table 4 presents pooled OR estimates for HL risk according to UVR exposure by the 2 most common histologic subtypes and by tumor EBV status. We found little consistent difference in the associations of UVR exposure with risk of nodular sclerosis vs mixed cellularity HL; inverse associations with the latter were stronger for overall and adult UVR exposure but weaker for childhood UVR exposure and history of sunburn. However, risks differed between EBV-positive and EBV-negative HL. ORs in association with EBV-positive HL were lower and statistically significantly inverse for childhood, adulthood, and overall UVR exposure, with a significant linear trend for overall UVR exposure. Results from case-case comparisons by histologic subtype or tumor EBV status were consistent with those for case-control comparisons, showing an inverse association of childhood UVR exposure with EBV-positive vs EBV-negative HL for those in the highest vs lowest quartile (OR, 0.58; 95% CI, 0.33 to 1.02; other data not shown).

Secondary analyses

No significant interstudy heterogeneity was observed for any measure of UVR exposure (Tables 3 and 4). The percentage of variation in ORs attributable to heterogeneity was low (0% to 25%) in most of our analyses and medium (around 50%) when stratifying on EBV status, mainly due to small numbers and uncertainty in individual risk estimates in 1 study (ELCCS). To address the possibility that hospital controls had less sun exposure due to their disease status, we conducted analyses separately for studies with population-based controls and those with hospital controls. The inverse associations between overall or EBV-positive HL and UVR exposure were observed only in population-based studies (data not shown). We explored modification of the effect of UVR exposure by erythemal UVR index levels by analyzing the relationship of overall UVR exposure with HL risk in 3 regions with a homogeneous UVR index but observed no clear relationship (data not shown).

Discussion

Our pooled analysis of 7701 participants from 4 independent case-control studies of HL found more than a 20% to 30% reduction of risk of HL associated with several measures of UVR exposure over the lifespan (ie, inverse associations of childhood and adulthood UVR exposure, use of sunlamps, and history of sunburns with HL risk). In addition, this analysis provided evidence for a significant inverse exposure-response trend in the association between UVR exposure and EBV-positive HL risk in particular.

Prior research in this area has been scant, and the 3 largest previously published studies were included in this pooled analysis.[11,13,14] Among other studies, neither a case-control study in Singapore involving 74 cases and 829 controls[16] nor a prospective cohort study in California female teachers that included 38 HL cases[15] observed a significant association between UVR exposure and HL. A Greek study of 71 childhood HL cases (mostly patients age 10 to 14 years) and 164 controls also found no association of UVR exposure with HL risk.[12] However, all 3 studies had limited statistical power to demonstrate an effect, and all reported some relative risk estimates below 1, consistent with our findings. The Singapore study, which used a questionnaire adapted from the Epilymph study, reported that having an outdoor occupation (OR, 0.76; 95% CI, 0.39 to 1.47) or having daily or weekly sun exposure in childhood (OR, 0.80 [95% CI, 0.45 to 1.54] for >30 minutes per day on school days and OR, 0.69 [95% CI, 0.40 to 1.22] for >30 minutes per day on non-school days; OR, 0.80 [95% CI, 0.44 to 1.46] for >1 hour per week), but not adulthood, were less frequent among cases than controls.[16] The Californian study reported a nonsignificant inverse association of HL risk with minimum average annual UVR near one's residence (relative risk, 0.86; 95% CI, 0.46 to 1.62), but not with median or maximum average annual UVR.[15] In the Greek study, a nonsignificant inverse association (OR, 0.83; 95% CI, 0.58 to 1.19) was detected with 15 days or more spent annually at seaside resorts.[12] These 3 studies were not included in the present pooled analysis because they were not part of InterLymph at the inception of this project.

Our study is the first to report an inverse association between UVR exposure and EBV-positive HL. The validity of our findings is supported by a significant dose-response relationship and an absence of statistical heterogeneity among studies. Results from case-case comparisons by histologic subtype or tumor EBV status were consistent with those from case-control comparisons. Although information on tumor EBV status was lacking for a proportion of cases, those with EBV information were demographically similar to those without. Because cases classified as EBV-positive were more likely to be male and diagnosed with mixed cellularity HL, our finding of a significant inverse association for EBV-positive HL may explain our observation of a significant inverse association of childhood UVR exposure with HL restricted to males. Due to the limited number of EBV-positive tumors, we were not able to examine associations of UVR exposure with EBV-positive HL stratified simultaneously by age, sex, and histology to better understand these relationships.

Table 3. Exposure to UVR and risk of HL by sex and age group

	Overall				Sex								Age group at diagnosis (years)							
					Male				Female				<40				40+			
UVR exposure	Cases (n = 1320)	Controls (n = 6381)	OR	95% CI	Cases (n = 722)	Controls (n = 3518)	OR	95% CI	Cases (n = 598)	Controls (n = 2863)	OR	95% CI	Cases (n = 793)	Controls (n = 1162)	OR	95% CI	Cases (n = 527)	Controls (n = 5219)	OR	95% CI
Overall*																				
Low	281	1323	1.00		155	682	1.00		126	641	1.00		154	188	1.00		127	1135	1.00	
Low-mid	316	1432	0.94	0.76-1.16	167	737	0.95	0.71-1.26	149	695	0.91	0.66-1.25	201	251	1.03	0.75-1.41	115	1181	0.89	0.59-1.34
Mid-high	309	1397	0.87	0.70-1.08	159	795	0.81	0.61-1.09	150	602	0.94	0.68-1.30	189	275	0.81	0.59-1.11	120	1122	0.93	0.69-1.26
High	312	1683	0.84	0.67-1.04	192	982	0.90	0.68-1.20	120	701	0.77	0.55-1.07	182	292	0.77	0.56-1.05	130	1391	0.91	0.67-1.22
P_{trend}†			.01				.33				.14				.09				.39	
P‡			.58				.28				.07				.74				.21	
Childhood																				
Low	271	1373	1.00		133	610	1.00		138	763	1.00		166	217	1.00		105	1156	1.00	
Low-mid	306	1543	0.73§	0.59-0.91	157	861	0.61§	0.45-0.83	149	682	0.87	0.64-1.18	228	294	0.84	0.61-1.17	78	1249	0.89	0.68-1.18
Mid-high	215	1090	0.72	0.48-1.07	109	614	0.62§	0.41-0.95	106	476	0.93	0.66-1.29	161	229	0.96	0.68-1.36	54	861	0.75§	0.55-1.00
High	265	1608	0.80§	0.63-1.00	163	984	0.75	0.55-1.01	102	624	0.85	0.60-1.20	150	241	0.73	0.51-1.06	115	1367	1.04	0.79-1.37
P_{trend}			.41				.51				.22				.25				.90	
P‡			.17				.31				.07				.17				.16	
Adulthood																				
Low	339	1453	1.00		191	813	1.00		148	942	1.00		180	210	1.00		159	1243	1.00	
Low-mid	266	1492	0.80§	0.64-1.00	142	777	0.82	0.60-1.12	124	715	0.77	0.56-1.06	137	236	0.66	0.43-1.01	129	1256	0.60§	0.44-0.82
Mid-high	260	1425	0.76§	0.61-0.95	147	798	0.73§	0.55-0.97	113	627	0.82	0.58-1.15	147	230	0.76§	0.61-0.95	113	1195	0.67	0.39-1.15
High	289	1633	0.87	0.70-1.08	176	942	0.94	0.71-1.24	113	691	0.81	0.58-1.14	134	239	0.65§	0.46-0.93	155	1394	0.90	0.67-1.22
P_{trend}			.51				.72				.35				.26				.95	
P‡			.43				.34				.22				.31				.50	
History of sunburn																				
No	356	1548	1.00		210	801	1.00		146	747	1.00		141	182	1.00		215	1366	1.00	
Yes	714	3681	0.77§	0.63-0.95	390	2077	0.77	0.57-1.03	324	1604	0.79	0.59-1.06	459	678	0.79	0.55-1.12	255	3003	0.75§	0.58-0.97
P‡			.36				.26				.95				.09				.26	
History of sunlamp use																				
No	588	3428	1.00		391	2095	1.00		197	1333	1.00		302	434	1.00		286	2994	1.00	
Yes	633	2501	0.81§	0.69-0.96	285	1139	0.89	0.65-1.23	348	1362	0.81	0.63-1.04	428	586	0.79§	0.62-1.00	205	1915	0.83	0.66-1.04
P‡			.37				.37				.45				.82				.25	

*Education for Epilymph and SCALE, current socioeconomic status for Engela, and skin pigmentation were included as confounders in the final models.
†P_{trend} in ORs.
‡P for heterogeneity among studies.
§$P < .05$.

Table 4. Exposure to UVR and risk of HL by histologic subtype and by tumor EBV status

	Histology								Tumor EBV status							
	Nodular sclerosis				Mixed cellularity				Positive				Negative			
UVR exposure	Cases (n = 928)	Controls (n = 6381)	OR	95% CI	Cases (n = 242)	Controls (n = 6381)	OR	95% CI	Cases (n = 208)	Controls (n = 5964)	OR	95% CI	Cases (n = 526)	Controls (n = 5964)	OR	95% CI
Overall*																
Low	182	1323	1.00		55	1323	1.00		56	1323	1.00		121	1323	1.00	
Low-mid	218	1432	1.00	0.78-1.28	49	1432	0.77	0.50-1.18	55	1432	0.80	0.51-1.26	132	1432	0.96	0.70-1.32
Mid-high	214	1397	0.97	0.75-1.26	53	1397	0.83	0.54-1.27	46	1397	0.60†	0.36-0.98	135	1397	0.93	0.67-1.28
High	202	1683	0.88	0.68-1.14	65	1683	0.85	0.56-1.29	51	1683	0.56†	0.35-0.91	138	1683	0.86	0.63-1.19
P_{trend}‡			0.14				0.52				0.03				0,02	
P§			0.40				0.28				0.09				0.36	
Childhood																
Low	186	1373	1.00		42	1373	1.00		50	1373	1.00		109	1373	1.00	
Low-mid	212	1543	0.73†	0.59-0.90	50	1543	0.91	0.63-1.31	52	1543	0.60†	0.37-0.97	143	1543	0.75	0.54-1.03
Mid-high	149	1090	0.84	0.75-1.07	39	1090	1.03	0.60-1.77	30	1090	0.62	0.35-1.07	77	1090	0.70	0.48-1.02
High	166	1608	0.79	0.63-1.00	52	1608	0.90	0.61-1.31	49	1608	0.36	0.10-1.34	129	1608	0.85	0.60-1.21
P_{trend}			0.28				0.59				0.06				0.55	
P§			0.20				0.16				0.14				0.11	
Adult																
Low	231	1453	1.00		57	1453	1.00		58	1247	1.00		107	1247	1.00	
Low-mid	172	1492	0.77	0.55-1.08	47	1492	0.77	0.49-1.20	30	1420	0.43†	0.26-0.73	93	1420	0.69†	0.48-0.98
Mid-high	191	1425	0.87	0.68-1.12	38	1425	0.63	0.40-1.01	33	1354	0.37†	0.21-0.65	101	1354	0.90	0.63-1.27
High	168	1633	0.75†	0.58-0.98	68	1633	1.03	0.68-1.56	45	1565	0.59†	0.36-0.96	104	1565	0.92	0.65-1.29
P_{trend}			0.11				0.94				0.49				0.99	
P§			0.34				0.44				0.10				0.53	
History of sunburn																
No	242	1548	1.00		65	1548	1.00		61	1548	1.00		132	1548	1.00	
Yes	488	3681	0.67†	0.53-0.84	127	3681	0.92	0.59-1.43	132	3681	0.81	0.51-1.29	335	3681	0.65†	0.48-0.89
P§			0.56				0.98				0.27				0.44	
History of sunlamp use																
No	361	3428	1.00		120	3428	1.00		97	3428	1.00		187	3428	1.00	
Yes	455	2501	0.85	0.70-1.03	103	2501	0.80	0.58-1.10	111	2501	0.69	0.47-1.02	338	2501	0.88	0.68-1.13
P§			0.32				0.72				0.10				0.98	

*Education for Epilymph and SCALE, current socioeconomic status for Engela, and skin pigmentation were included as confounders in the final models.
†$P < 0.05$.
‡*P* for trend in ORs.
§*P* for heterogeneity among studies.

This study has several major advantages. As an analysis of pooled data, it includes sufficient numbers of subjects to examine etiologic heterogeneity in risks across subtypes of HL, a relatively rare disease. Our detailed database allowed for adjustment for potential confounding factors across studies, evaluation of interactions, and a robust and complete assessment of selected HL subtypes, which were defined with established laboratory methods.[25,26] Participation bias may have contributed to our observations if individuals with healthy lifestyles were overrepresented among the controls. However, greater participation of healthier controls might be expected to underestimate UVR exposure in the source population because UVR exposure is known to cause skin cancer, and such a bias would attenuate inverse associations with HL.

Study limitations include the loss of granularity resulting from the data harmonization required of pooled analyses. There was substantial variation across studies in the wording of questions about UVR exposure (except for dichotomized variables). Nevertheless, the information on individual UVR exposure was mostly collected as number of hours daily at a specific age, such that quantifying exposures into the broad categories of quartiles should accurately capture the gradient in UVR exposure. Furthermore, any exposure misclassification should not have been differential between cases and controls. We could neither distinguish occupational from recreational exposure nor evaluate cumulative lifetime UVR exposure or the use of UVR-protective clothing or lotion. However, the lack of clear differences in pooled risk estimates for UVR exposure before and after age 20 years suggests a potential biological effect of UVR on HL development independent of age at exposure, although our data do not rule out a cumulative effect of UVR. Given the large difference in age distributions between cases and controls, we cannot rule out residual confounding by age, although our models were adjusted for age as a continuous variable. However, age-stratified results, which are less likely to be confounded by age within strata, were similar to overall results, suggesting minimal, if any, residual confounding by age.

Given the known health risks for UVR exposure, recall bias might have led to underreporting of UVR exposure among cases. However, this possibility was potentially reduced by the studies' including many questions on other exposures and not emphasizing UVR exposure in the questionnaires, as well as by the lack of a previously known association between UVR exposure and HL risk.

Reverse causality, with an HL diagnosis leading to more time spent indoors, may also have contributed to spurious inverse associations with adulthood UVR exposure. However, the inverse associations with both childhood and adulthood UVR exposure, heterogeneity between risks of EBV-negative and EBV-positive HL (and consistent results from the case-case analysis), which would be expected to have an equivalent impact on reverse causality, and an observed dose-response relationship for EBV-positive HL make this possibility unlikely.

Given the inverse associations of UVR exposure with both HL and NHL development, several biological hypotheses can be considered for our study findings. Until recently, the strongest evidence came from the observation that the induction of vitamin D_3 synthesis in the skin by UVR[27] could have a protective effect against lymphoma development. This hypothetical mechanism is supported by the observation that vitamin D_3 promotes differentiation and inhibits proliferation of lymphoma cells in vitro,[28] and by the strong expression of the vitamin D receptor on HL tumor cells.[29] However, a pooled analysis of 10 cohort studies found no association between prediagnostic serum 25-hydroxyvitamin D levels and risk of NHL or its major histologic subtypes.[30]

Two other plausible pathways could explain a protective effect of UVR on HL. First, the immune system could be modulated by UVR induction of regulatory T cells,[31] which are critical to inhibiting inflammation.[32,33] In HL, the tumor microenvironment, which represents 99% of the tumor, comprises reactive cells that help maintain an inflammatory milieu,[34] and individual traits affect the tumor microenvironment in HL.[35] UVR appears to induce regulatory T cells through antigen presentation by UVR-damaged Langerhans cells in the lymph nodes[36] leading to an immunosuppressed state that may be protective, as suggested by the inverse association observed between the use of aspirin and HL risk.[37-39] Second, the cellular DNA damage response activated by viral oncogenes such as those associated with EBV[40] could cause tumor suppression by effector T cells when enhanced by UVR exposure,[41] which is known to induce multiple defense mechanisms to counterbalance its potential mutagenic and cytotoxic effects.[42] The DNA damage response acts as an innate barrier to tumorigenesis,[43] whereas a disordered response may lead to lymphomas, including EBV-associated lymphoma.[44] Further research is clearly needed to explore these speculative mechanisms.

In conclusion, this analysis of HL risk across contemporaneous European case-control studies found UVR exposure to be inversely associated with HL risk overall. The stronger associations for EBV-positive HL, with a clear dose-response relationship, further support etiologic heterogeneity in HL. A clearer understanding of biological pathways related to UVR exposure could illuminate the pathogenesis of HL and facilitate the development of new targets to enhance the DNA damage response or regulatory T-cell activity for the purpose of reducing the occurrence of HL and other malignancies.

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Authorship

Contribution: E.T.C. designed the research; A.M. drafted the manuscript; C.W.S. performed the statistical analysis; A.M., K.E.S., S.d.S., E.K., M. Melbye, L.F., M. Maynadié, A.S., N.B., A.N., P. Boffetta, P.C., I.G., J.C., and H.H. contributed data; A.M., E.T.C., and S.L.G. interpreted

the results; E.T.C. and S.L.G. obtained funding for the research; and all the authors critically reviewed and revised the manuscript.

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