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Relationship between ambient ultraviolet radiation and Hodgkin lymphoma subtypes in the United States

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Background: There are few modifiable risk factors for Hodgkin lymphoma (HL), the most common cancer among young adults in Western populations. Some studies have found a reduced risk with exposure to ultraviolet radiation (UVR), but findings have been inconsistent and limited to HL as a group or the most common subtypes.

Methods: We evaluated UVR and incidence of HL subtypes using data from 15 population-based cancer registries in the United States from 2001 to 2010 ($n = 20021$). Ground-based ambient UVR estimates were linked to county of diagnosis. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated for UVR quintiles using Poisson regression models adjusted for age, sex, race/ethnicity, diagnosis year, and registry.

Results: Hodgkin lymphoma incidence was lower in the highest UVR quintile for nodular sclerosis (IRR = 0.84, 95% CI = 0.75–0.96, P -trend < 0.01), mixed cellularity/lymphocyte-depleted (IRR = 0.66, 95% CI = 0.51–0.86, P -trend = 0.11), lymphocyte-rich (IRR = 0.71, 95% CI = 0.57–0.88, P -trend < 0.01), and nodular lymphocyte predominant HL (IRR = 0.74, 95% CI = 0.56–0.97, P -trend < 0.01), but 'not otherwise specified' HL (IRR = 1.19, 95% CI = 0.96–1.47, P -trend = 0.11).

Conclusions: This is the largest study of UVR and HL subtypes covering a wide range of UVR levels; however, we lack information on personal UVR and other individual risk factors. These findings support an inverse association between UVR and HL.

Hodgkin lymphoma (HL) is the most common cancer in young adults (15–19 years) in the United States. A total of 9190 new cases and 1180 deaths were estimated to occur in the United States in 2014 (Howlander *et al*, 1975–2011). The most consistently identified risk factors are a family history of HL, age (high-risk groups include 15–30 years and over 55 years), male sex, delayed infection with Epstein–Barr virus (EBV), and diseases or treatments resulting in severe immunodeficiency (e.g., human HIV infection and immunosuppressing treatment after organ transplantation; Jarrett, 2002; Yug and Linch, 2003; Cartwright and Watkins, 2004; Hjalgrim *et al*, 2007). Although EBV contributes substantially to the aetiology of classical HL (CHL; Jarrett, 2002), especially the

mixed cellularity/lymphocyte-depleted subtype (Jarrett *et al*, 1996; Glaser *et al*, 1997), the aetiology for much of HL remains unclear.

Solar ultraviolet radiation (UVR) exposure measured in different ways has been related to a reduced risk of HL in some epidemiological studies (Boscoe and Schymura, 2006; Monnereau *et al*, 2013; van Leeuwen *et al*, 2013), whereas others have found no association (Smedby *et al*, 2005; Petridou *et al*, 2007; Boffetta *et al*, 2008; Grandin *et al*, 2008; Chang *et al*, 2011; Wong *et al*, 2012). Studies using self-reported personal UVR measures (e.g., time spent outdoors and sunburn history) have been too small to evaluate the rare HL subtypes (Smedby *et al*, 2005; Petridou *et al*, 2007; Boffetta *et al*, 2008; Grandin *et al*, 2008; Wong *et al*, 2012).

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and have usually been set in locations with limited ambient UVR variability (Smedby *et al*, 2005; Petridou *et al*, 2007; Grandin *et al*, 2008; Wong *et al*, 2012). A pooled analysis with a wide range of ambient UVR found an inverse relationship between several measures of personal UVR exposure and EBV-positive HL, but was not able to evaluate the UVR relationship for the rare HL subtypes (lymphocyte-rich CHL and nodular lymphocyte predominant HL; Monnereau *et al*, 2013). Only one study, from Australia has examined the relationship between UVR and all subtypes of HL, but used latitude as a surrogate for ambient UVR exposure (van Leeuwen *et al*, 2013). Hodgkin lymphoma is increasingly recognised as a heterogeneous group of lymphoid neoplasms with differing etiologies, so investigation by subtype and demographic risk factors is warranted (Morton *et al*, 2007; Mani and Jaffe, 2009).

We evaluated the relationships between solar ambient UVR and the subtype-specific incidence of HL using data from the Surveillance, Epidemiology, and End Results (SEER) Program from 2001 to 2010 linked to United States county-level, ground-based ambient UVR (Tatalovich *et al*, 2006). This is the largest study exploring the association between ambient UVR and HL, containing over eight times more cases than the second largest study (van Leeuwen *et al*, 2013) and uses a refined measure of ambient UVR that has been recently developed for epidemiological study (Tatalovich *et al*, 2006).

MATERIALS AND METHODS

Study population and data organisation. The study population is derived from 15 non-overlapping, population-based cancer registries in the SEER 18 database, which contains the widest geographic range and comprises ~26% of the US population. The registries include San Francisco, Los Angeles, San Jose-Monterey, greater California, Seattle-Puget Sound, Utah, New Mexico, Detroit, Iowa, Kentucky, Louisiana (except for cases diagnosed from July–December 2005 which were excluded due to Hurricanes Katrina and Rita), Connecticut, New Jersey, Atlanta, rural Georgia, and greater Georgia (Figure 1; Surveillance, Epidemiology, and End Results (SEER) Program, 2013). Hawaii, Alaska, and Arizona Indian registries were excluded because they were outliers for ambient UVR and/or did not collect information on all races/ethnicities (the Alaska registry contains Native Alaskans, the Arizona registry consists of Native Americans, and Hawaii contains a very small number of cases that fall into the major racial ethnic groups of non-Hispanic White, Hispanic White, and Black). Surveillance, Epidemiology, and End Results registries collect information on patient demographics, tumour characteristics (site and morphology), and year and county of diagnosis. This study included only cases who were diagnosed with a first primary HL before age 85 years and between 2001 and 2010 inclusive. Because of small sample sizes, races/ethnicities other than non-Hispanic White, Hispanic White, and Black were excluded. To protect patient confidentiality, SEER does not have personal identifiers and this study was exempt from IRB review.

As HIV is a strong risk factor for HL, and HIV cases cluster in certain geographical locations, confounding by HIV infection has the potential to substantially bias relative risk estimates (Carbone *et al*, 2009). Therefore, we excluded HL cases that were flagged by SEER as HIV positive. However, HIV status is not reported by the Iowa registry due to privacy concerns stemming from a small number of HIV-positive cases. As sensitivity analyses excluding the Iowa registry did not significantly impact our results, all HL cases from Iowa are included in these analyses. In support of the comprehensiveness of this flag, it has been reported that among HL cases in SEER (200–2010) who died and did not have a positive HIV flag (no HIV or unknown), HIV was found on only 0.2% of death certificates (Shiels *et al*, 2014).

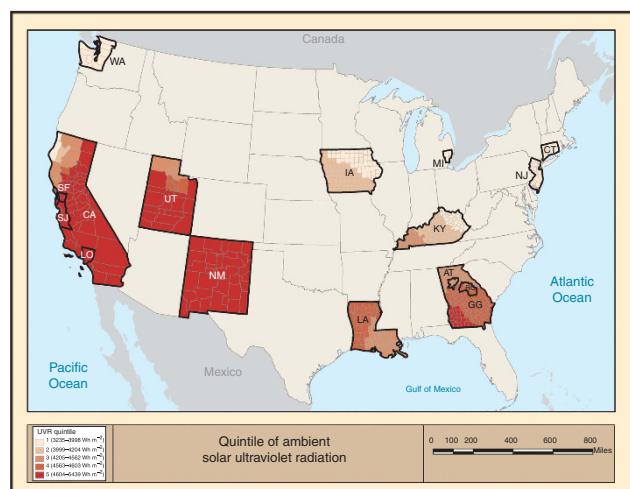
For each county, counts of HL were stratified by year of diagnosis group (2001–2005 and 2006–2010), sex, age group (0–14, 15–24, 25–44, 45–64 and 65–84 years), race (non-Hispanic White, Hispanic White and Black), SEER registry, and ambient annual UVR quintile. The computation of UVR quintiles is detailed below. Corresponding population counts were obtained from the 2000 US census.

Outcomes. The HL cases consisted of patients diagnosed with CHL and non-CHL subtypes using the International Classification of Disease for Oncology third edition (ICD-O-3) morphology codes (Morton *et al*, 2007), which have undergone changes in classification over time (Morton *et al*, 2007). Classical HL subtypes include nodular sclerosis (ICD-O-3 codes: 9663–67), mixed cellularity/lymphocyte depleted (ICD-O-3 codes: 9652–55), lymphocyte rich (ICD-O-3 code: 9651), and not otherwise specified (ICD-O-3 codes: 9650, 9661–62). Hodgkin lymphoma classification is generally based on differences in the pathological findings of Reed–Sternberg cell morphology and the cellular composition of the microenvironment around these cells. Non-CHL consists of the rare nodular lymphocyte predominant subtype (ICD-O-3 code: 9659) in which Reed–Sternberg cells strongly express B lymphocyte markers such as CD20. Only patients diagnosed after the introduction of the World Health Organization Classification (Jaffe *et al*, 1999) and translation into ICD-O-3 (Fritz, 2000) were included in these analyses. Hodgkin lymphoma cases were grouped into subtypes as defined by the InterLymph hierarchical classification for epidemiologic research (Turner *et al*, 2010).

Ambient ultraviolet radiation. Quintiles of ambient UVR were determined by the county of residence at time of HL diagnosis. Ambient UVR was derived using the National Solar Radiation Database, which provided summaries of hourly UVR estimates taken at 239 US radiation stations from 1961 to 1990 (Tatalovich *et al*, 2006). Average annual daily ambient UVR was modelled to represent the biological action spectrum associated with sunburn. This is most heavily weighted towards the UVB spectrum (280–315 nm). Measurements of UVR between weather stations were interpolated based on elevation across the United States to estimate county-level UVR (Tatalovich *et al*, 2006). Annual estimates of UVR have varied little over time as the start of satellite-based measurements in the late 1970s, aside from relatively small fluctuations due to the 11-year solar cycle (Lean *et al*, 1997; Newman *et al*, 2008). Surveillance, Epidemiology, and End Results counties were ranked by UVR and assigned to quintiles 1 (lowest UVR) through 5 (highest UVR) (Figure 1), so that members of a county would all be assigned the same UVR quintile. The ranges of the ambient UVR quintiles were 3235–3998, 3999–4204, 4205–4562, 4563–4603, and 4604–5439 Wh m⁻².

Statistical analysis. We examined the relationship between UVR and total HL and HL subtypes by calculating incidence rate ratios (IRRs) for UVR quintiles (coded as 1–5) and 95% confidence intervals (CIs) using Poisson regression models adjusted for sex, age group, year of diagnosis group, race, and registry. Systematic geographical differences in ascertainment or diagnosis could affect results, thus the SEER registry was included as a random effect in all models. All models contained the natural log of the population size as an offset. In sensitivity analyses, use of zero-inflated Poisson regression models did not change results. Trends were evaluated by examining the linear relationships between continuous UVR (averaged over each quintile) and the incidence of HL and its subtypes.

To evaluate whether these relationships were modified by diagnosis year, age, sex, or race/ethnicity, we included multiplicative interaction terms in the Poisson models. Interaction *P*-values were based on the Wald test and used continuous UVR (averaged over each quintile). We tested for heterogeneity in the relationships between UVR and HL subtypes using the Cochran's



Q statistic for meta-analysis (Cochran, 1954). To describe the potential for misclassification of exposure due to residential movement before residence at diagnosis, we compared UVR from birth state (in tertiles) to UVR at diagnosis among HL cases with information on birth state. Statistical tests were two sided with a specified type-I error of 0.05. Poisson regression was performed with the GLIMMIX procedure and Laplace method using SAS software V9.3 (SAS Institute, Inc., Cary, NC, USA). The Q statistics for heterogeneity were computed in Stata 11 (StataCorp, 2015).

A total of 20 021 cases of HL were included in the study, of which 19 097 (95%) were CHL and 924 (5%) were nodular lymphocyte predominant HL (Table 1). Hodgkin lymphoma was more common among men than women for all subtypes except nodular sclerosis CHL, for which we observed an even sex distribution and nodular sclerosis was the most common subtype among adolescents and young adults (<45 years). Over 70% of all HL cases occurred among non-Hispanic Whites, whereas Hispanic Whites and Blacks comprised 15% and 11% of all cases, respectively.

There was no evidence of significant statistical interaction on the multiplicative scale for UVR and HL subtypes or total HL by diagnosis year, sex, or race/ethnicity. However, age category (<45 vs ≥45 years) did significantly modify the association between UVR and risk for total HL (P for interaction <0.001) and the mixed cellularity/lymphocyte-depleted CHL subtype

DISCUSSION

Few studies have evaluated the relationship between UVR and specific subtypes of HL, and only one study has reported risk by all HL subtypes (van Leeuwen *et al*, 2013). In Australia, van Leeuwen *et al* (2013) conducted a cancer registry-based analysis that included ~2400 cases and assessed HL risk by specific subtype using three bands of latitude ($<29^{\circ}$ S, 29° – 36° S and $\geq 37^{\circ}$ S) as a surrogate for ambient UVR exposure. Our findings for an inverse association between UVR and nodular sclerosis CHL and mixed cellularity/lymphocyte-depleted CHL support the significant inverse trends reported in this study (van Leeuwen *et al*, 2013). However, van Leeuwen *et al* (2013) did not find an association between ambient UVR and the rare subtypes such as lymphocyte-rich CHL or nodular lymphocyte predominant HL. The small number of cases of lymphocyte-rich CHL ($n=151$) and nodular lymphocyte predominant HL ($n=118$) in that study limited the power to examine the relationship of UVR for these subtypes. Our null finding for CHL not otherwise specified is consistent with their null finding, but it is difficult to interpret the lack of a UVR relationship for this category because it is believed to mainly reflect difficulties in subclassification of small and suboptimal biopsies (Hjalgrim *et al*, 2007). The confidence bounds for NOS do overlap with most of the HL subtypes (Figure 2), so this null finding may also be due to chance.

Among studies assessing the relationship between UVR and total HL, our findings support some (Boscoe and Schymura, 2006; Monnereau *et al*, 2013), but not all, of the previous research demonstrating a reduced risk of HL with increasing exposure to UVR (Smedby *et al*, 2005; Petridou *et al*, 2007; Boffetta *et al*, 2008; Grandin *et al*, 2008; Chang *et al*, 2011; Wong *et al*, 2012). Our results agree with the only other United States-based study, which found a significantly reduced risk of total HL incidence and mortality in Southern states vs Northern states (Boscoe and Schymura, 2006). Case-control studies in both Europe (Smedby *et al*, 2005; Petridou *et al*, 2007; Boffetta *et al*, 2008; Grandin *et al*, 2008) and Asia (Wong *et al*, 2012) found no relationship between total HL and self-reported UVR exposure. However, the largest of these studies ($n = 618$) reported an inverse association between increasing sunlamp use and total HL risk (P -trend = 0.004; Smedby *et al*, 2005), which agrees with our overall findings for total HL. Four pooled European case-control studies reported a significant inverse trend between increasing UVR exposure and total HL, with the strongest inverse relationship among EBV-positive tumours (odds ratio = 0.56; 95% CI: 0.35–0.91;

Table 1. Distribution of demographic characteristics for Hodgkin lymphoma cases by subtype, SEER 2001–2010

	Total HL		Classical HL								Non-classical HL	
	No. of cases	%	Nodular sclerosis		Mixed cellularity lymphocyte depleted		Lymphocyte rich		Not otherwise specified		Nodular lymphocyte predominant	
			No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Total	20 021	100.0	12 014	60.0	2 581	12.9	638	3.2	3 864	19.3	924	4.6
Age												
0–14 years	936	4.3	606	5.0	117	4.5	30	4.7	110	2.8	73	7.9
15–24 years	4007	20.0	3036	25.3	285	11.0	55	8.6	498	12.9	133	14.4
25–44 years	7415	37.0	5072	42.2	686	26.6	198	31.0	1160	30.0	299	32.4
45–64 years	4461	22.3	2138	17.8	759	29.4	213	33.4	1069	27.7	282	30.5
65–84 years	3202	16.0	1162	9.7	734	28.4	142	22.3	1027	26.6	137	14.8
Sex												
Male	10 764	53.8	6048	50.3	1 593	61.7	390	61.1	2 177	56.3	638	69.0
Female	9 257	46.2	5 966	49.7	988	38.3	248	38.9	1 687	43.7	286	31.0
Race												
White	14 698	73.4	9 031	75.2	1 797	69.6	466	73.0	2 793	72.3	611	66.1
Hispanic	3030	15.1	1 701	14.2	510	19.8	84	13.2	631	16.3	104	11.3
Black	2 293	11.5	1 282	10.7	274	10.6	88	13.8	440	11.4	209	22.6
Annual average UVR quintiles (Wh m⁻²)												
Q1 (3235–3998)	6751	33.7	4158	34.6	833	32.3	233	36.5	1 183	30.6	344	37.2
Q2 (3999–4205)	1251	6.2	744	6.2	222	8.6	34	5.3	202	5.2	49	5.3
Q3 (4206–4562)	2679	13.4	1 538	12.8	319	12.4	101	15.8	593	15.3	128	13.9
Q4 (4563–4603)	1427	7.1	843	7.0	187	7.2	48	7.5	277	7.2	72	7.8
Q5 (4604–5439)	7913	39.5	4 731	39.4	1 020	39.5	222	34.8	1 609	41.6	331	35.8
Diagnosis year												
2001–2002	3891	19.4	2 503	20.8	553	21.4	112	17.6	591	15.3	132	14.3
2003–2004	3922	19.6	2 421	20.2	541	21.0	110	17.2	690	17.9	160	17.3
2005–2006	4062	20.3	2 437	20.3	483	18.7	135	21.2	813	21.0	194	21.0
2007–2008	4185	20.9	2 415	20.1	508	19.7	152	23.8	896	23.2	214	23.2
2009–2010	3961	19.8	2 238	18.6	496	19.2	129	20.2	874	22.6	224	24.2

Abbreviations: HL = Hodgkin lymphoma; SEER = Surveillance, Epidemiology, and End Results; UVR = ultraviolet radiation.

Table 2. Adjusted incidence rate ratios by quintile of ambient ultraviolet radiation for HL subtypes, SEER 2001–2010

	Total HL ^a			Classical HL ^b										Non-classical HL ^b				
	n = 20 021			Nodular sclerosis n = 12 014			Mixed cellularity lymphocyte depleted n = 2581			Lymphocyte rich n = 638			Not otherwise specified n = 3864			Nodular lymphocyte predominant n = 924		
	IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI	
UVR quintile ^c	IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI		IRR ^d	95% CI	
Q1			Ref			Ref			Ref			Ref			Ref			Ref
Q2	0.94	0.86	1.02	0.93	0.84	1.04	1.01	0.82	1.25	0.69	0.46	1.03	0.97	0.79	1.19	0.80	0.55	1.17
Q3	0.89	0.82	0.97	0.86	0.76	0.97	0.77	0.60	1.00	0.93	0.72	1.19	1.16	0.94	1.44	0.75	0.55	1.01
Q4	0.84	0.76	0.92	0.83	0.72	0.96	0.88	0.66	1.17	0.76	0.55	1.06	0.93	0.74	1.19	0.72	0.51	1.02
Q5	0.88	0.81	0.95	0.84	0.75	0.96	0.66	0.51	0.86	0.71	0.57	0.88	1.19	0.96	1.47	0.74	0.56	0.97
P for trend ^e			<0.001			<0.001			0.106			0.005			0.503			<0.001

Abbreviations: CI = confidence interval; HL = Hodgkin lymphoma; IRR = incidence rate ratio; Ref = reference category; SEER = Surveillance, Epidemiology, and End Results; UVR = ultraviolet radiation;

^aAll HL subtypes combined.^bICD-O-3 codes: nodular sclerosis: 9663–67; mixed cellularity/lymphocyte depleted 9652–55; lymphocyte rich 9651; not otherwise specified 9650, 9661–62; nodular lymphocyte predominant HL 9659.^cCutoffs for ambient UVR quintile: 3235–3998, 3999–4205, 4206–4562, 4563–4603, and 4604–5439 Wh m⁻².^dAdjusted for sex, age group (0–14, 15–24, 25–44, 45–64, and 65–84 years), year of diagnosis (2001–2005 and 2006–2010), race, and a random intercept for SEER registry.^eTrend tests treat UVR as continuous in Poisson regression models.

Monnereau *et al*, 2013). Our finding that UVR is inversely related to mixed cellularity/lymphocyte-depleted CHL agrees with these results because up to 80% of mixed cellularity/lymphocyte-depleted CHL cases are believed to be EBV positive (Glaser *et al*, 1997).

Although we did not have the EBV status of our cases, we did find the strongest inverse association for the highest quintile of UVR for mixed cellularity/lymphocyte-depleted CHL (IRR = 0.66; 95% CI: 0.51, 0.86).

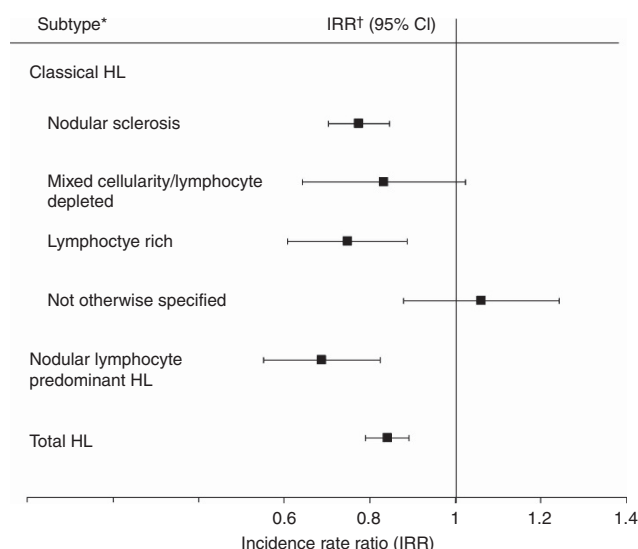


Figure 2. Incidence rate ratios (IRRs) and 95% confidence intervals (CI) of Hodgkin lymphoma subtypes for 1000 Wh m⁻² of UVR in the Surveillance, Epidemiology, and End Results Program between 2001 and 2010. *ICD-O-3 codes: nodular sclerosis 9663-67; mixed cellularity/lymphocyte depleted 9652-55; lymphocyte rich 9651; classical not otherwise specified 9650, 9661-62; nodular lymphocyte predominant HL 9659. †Model contains sex, age group (0–14, 15–24, 25–44, 45–64, 65–84 years), continuous UVR (1000 Wh m⁻²), race, year of diagnosis (2001–2005, 2006–2010), and SEER registry. Note: 1000 Wh m⁻² corresponds to approximately a 600-mile north-south distance on the east coast of the United States. CI = confidence interval; HL = Hodgkin lymphoma; IRR = incidence rate ratio; UVR = ultra-violet radiation.

Exposure to UVR is associated with a number of systemic immunologic changes (Clydesdale *et al*, 2001; Hart *et al*, 2011; Ullrich and Byrne, 2012). Ultraviolet radiation causes the induction of regulatory T cells (Schwarz, 2008), which inhibit chronic inflammation and may potentially reduce cancer risk (Erdman and Poutahidis, 2010). Exposure to ambient UVR also contributes to the production of endogenous vitamin D, which has been shown to be protective for other lymphoid cancers (Lim *et al*, 2009; Luczynska *et al*, 2013). However, 25-hydroxyvitamin D is not known to be associated with risk of HL. It has also been suggested that the induction of nitric oxide by UVR, independently of vitamin D, may be responsible for a number of circulatory system changes (Liu *et al*, 2014). Numerous studies have suggested an inverse relationship between UVR and some B-cell non-HL subtypes (Smedby *et al*, 2005; Boffetta *et al*, 2008; Chang *et al*, 2011; van Leeuwen *et al*, 2013; Cahoon *et al*, 2014). Shared clinicopathological and molecular features between some HL and B-cell non-HL subtypes suggest that UVR may have a similar role in these two major types of lymphoma (Menon *et al*, 2012; Hartmann *et al*, 2013).

An important strength of this study is a sample size large enough to examine all HL subtypes and evaluate potential modifying effects by sex, age, and race/ethnicity. This study encompasses a broad range of ambient UVR for a geographically dispersed population, and uses county-level ground-based ambient UVR estimates recently made available for epidemiological research. Despite these strengths, our study also has several limitations. We lack information on individual-level risk factors such as EBV status, autoimmune disorders (Fallah *et al*, 2014), alcohol consumption (Tramacere *et al*, 2012), body mass index (Murphy *et al*, 2013), and individual measures of sun exposure (e.g., sun protective behaviours, time outdoors, and location of residence throughout the lifetime). We found significant inverse

associations of total HL and mixed cellularity/lymphocyte-depleted CHL with UVR for individuals <45 years of age but not those 45 years and older. Ambient UVR may be assigned more accurately to people who are younger because they have had less opportunity to move before cancer diagnosis. As UVR was linked to the location of residence only at the time of diagnosis, greater misclassification may explain the null findings in older people. However, an analysis among HL cases in SEER with information on birth state suggested that the large majority of cases lived in a similar UVR at diagnosis and birth.

In summary, this US population-based study of ambient UVR and HL showed a significant reduction in risk for all HL subtypes except CHL not otherwise specified. Our results support and expand the limited evidence for an association between UVR and HL, especially the rare subtypes of lymphocyte-rich CHL and nodular lymphocyte predominant HL. Future research should focus on more detailed personal UVR exposure assessment and control for individual-level HL risk factors such as EBV status.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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