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Relationship between ambient ultraviolet radiation and non-Hodgkin lymphoma subtypes: A U.S. population-based study of racial and ethnic groups

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Associations between ultraviolet radiation (UVR) exposure and non-Hodgkin lymphoma (NHL) have been inconsistent, but few studies have examined these associations for specific subtypes or across race/ethnicities. We evaluated the relationship between ambient UVR exposure and subtype-specific NHL incidence for whites, Hispanics and blacks in the United States for years 2001–2010 ($n = 187{,}778$ cases). Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated for UVR quintiles using Poisson regression. Incidence was lower for the highest UVR quintile for chronic/small lymphocytic/leukemia (CLL/SLL) (IRR = 0.87, 95% CI: 0.77–0.97), mantle cell (IRR = 0.82, 95% CI: 0.69–0.97), lymphoplasmacytic (IRR = 0.58, 95% CI: 0.42–0.80), mucosa-associated lymphoid tissue (MZLMALT) (IRR = 0.74, 95% CI: 0.60–0.90), follicular (FL) (IRR = 0.76, 95% CI: 0.68–0.86), diffuse large B-cell (IRR = 0.84, 95% CI: 0.76–0.94;), peripheral T-cell other (PTCL) (IRR = 0.76, 95% CI: 0.61–0.95) and PTCL not otherwise specified (PNOS) (IRR = 0.77, 95% CI: 0.61–0.98). Trends were significant for MZLMALT, FL, DLBCL, BNOS and PTCL, with FL and DLBCL still significant after Bonferroni correction. We found interaction by race/ethnicity for CLL/SLL, FL, Burkitt, PNOS and MF/SS, with CLL/SLL and FL still significant after Bonferroni correction. Some B-cell lymphomas (CLL/SLL, FL and Burkitt) suggested significant inverse relationships in whites and Hispanics, but not in blacks. Some T-cell lymphomas suggested the most reduced risk for the highest quintile of UVR among blacks (PNOS and MF/SS), though trends were not significant. These findings strengthen the case for an inverse association of UVR exposure, support modest heterogeneity between NHL subtypes and suggest some differences by race/ethnicity.

Epidemiology

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer in the United States, with ~70,000 new cases and 19,000 deaths in 2013.[1] The strongest and most consistently identified risk factors are diseases or treatments causing serious immunodeficiency (*e.g.*, HIV and organ transplants), autoimmune conditions, certain infections (*e.g.*, hepatitis C virus and

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Abbreviations: BNOS: B-cell not otherwise specified; Burk: Burkitt lymphoma; CALCL: primary cutaneous anaplastic large cell lymphoma; CLL/SLL: chronic lymphocytic leukemia or small lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; ENNKTL: extranodal natural killer/T-cell lymphoma, nasal-type/aggressive natural killer leukemia; FL: follicular lymphoma; HCL: hairy cell leukemia; LPL: lymphoplasmacytic lymphoma; MZL MALT: marginal-zone lymphoma of mucosa-associated lymphoid tissue; MCL: mantle-cell lymphoma; MF/SS: mycosis fungoides or Sezary syndrome; NMZL: nodal marginal-zone lymphoma; PCM: plasma cell myeloma; Plasma: plasmacytoma; PNOS: PTCL not otherwise specified; PTCL: peripheral T-cell lymphoma other; SMZL: splenic marginal-zone lymphoma; TNOS: T-cell lymphoma not otherwise specified

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What's new?
Studies have yielded mix results as to whether exposure to ultraviolet radiation (UVR) increases or decreases risk of non-Hodgkin lymphoma (NHL). In the present analysis of data from population-based cancer registries in the United States, increasing ambient UVR exposure was associated with a reduction in risk of most NHL subtypes, The reduction occurred for all races, including non-Hispanic whites, Hispanic whites, and blacks. The findings emphasize the importance of exploring NHL etiology according to subtypes and across races and ethnicities, as NHL is increasingly recognized as comprising a diverse group of cancers, each potentially involving unique mechanisms.

Epstein Barr virus) and chemical exposures (*e.g.*, polychlorinated biphenyls, pesticides and hair dyes).[2–5] However, the etiology of most lymphoma subtypes remains unknown.

Exposure to ultraviolet radiation (UVR) has been associated with both increased[6,7] and reduced[8–12] risk of NHL in epidemiologic studies. The different approaches used for UVR exposure assessment include estimating personal exposure (*e.g.*, time spent outdoors, number of sunburns, tanning and occupational exposure) and ambient exposure to solar UVR based on latitude, ground or satellite-based measurements. Studies measuring personal UVR exposure have typically been small retrospective case–control studies, while those estimating ambient UVR have generally either been confined to small geographic areas (*e.g.*, Connecticut[6] and United Kingdom[7,13]) or used latitude as a surrogate.[14,15]

Moreover, NHL is increasingly recognized as a diverse group of cancers with varying etiologies that warrant examination by histological subtype.[5,16] Among the studies that have examined the relationship between UVR and specific NHL histological subtypes,[6,8,14,15,17–23] only one has comprehensively evaluated an extensive number of subtypes.[15] No study has examined these relationships across different races or ethnicities. Examining associations by race may provide possible etiologic clues where risks differ by race.

Our objective is to evaluate the associations between ambient UVR exposure at diagnosis and subtype-specific incidence of NHL for non-Hispanic whites, Hispanic whites and blacks using U.S. population-based registry data from the Surveillance, Epidemiology, and End Results (SEER) Program for years 2001–2010, inclusive. This represents the first study to assess differences in these associations by race/ethnicity. It is the second and largest study of UVR exposure and non-Hodgkin lymphoma subtypes, both common and rare, containing over five times more cases than the previously largest study.[15] The use of SEER county data linked to NASA satellite-based UVR exposure estimates also provides an opportunity to use more refined ambient UVR exposure data than latitude or state of residence.

Material and Methods

Study population

The study population was derived from 15 nonoverlapping population-based cancer registries of the SEER 18 database, which contains the widest geographic coverage and represents ~26% of the U.S. population [registries include San Francisco, Los Angeles, San Jose-Monterey, greater California, Seattle-Puget Sound, Utah, New Mexico, Detroit, Iowa, Kentucky, Louisiana (cases diagnosed from July to December 2005 are excluded from most statistical analyses due to Hurricanes Katrina and Rita), Connecticut, New Jersey and Atlanta, rural Georgia, greater Georgia] (Fig. 1).[24] Hawaii, Alaska Natives and Arizona Indian registries were excluded because they were outliers for ambient UVR and/or did not collect information on non-Hispanic whites, Hispanic whites or blacks. SEER cancer registries collect information on patient demographics, year and county of diagnosis and tumor characteristics (site and morphology). This study comprised patients up to 84 years old who were diagnosed with a first primary NHL between 2001 and 2010, inclusive. In the United States, rates of NHL diagnosed among HIV-uninfected people have been largely stable during the calendar time period included in our study (2001–2010).[25] Races/ethnicities other than non-Hispanic white, Hispanic white and black were excluded owing to small numbers.

As HIV is both a major risk factor for several NHL subtypes and HIV cases cluster in specific locations, confounding by HIV infection may substantially bias relative risk estimates. For this reason, self-reported HIV-positive cases that were flagged by SEER were excluded from this study. HIV status was not collected for mycosis fungiodes or Sezary syndrome (MF/SS), so all cases were included. Because of privacy concerns stemming from very small numbers of cases, HIV status was also not reported by the Iowa registry so all Iowa cases were included. A sensitivity analysis excluding the Iowa registry did not substantially affect our results. The epidemiology of NHL in relation to HIV/AIDS has been previously described in detail for this dataset.[25]

For each county, counts of NHL cases were stratified by calendar year of diagnosis group (2001–2005, 2006–2010), sex, age group (0–44, 45–64, 65–84), race (non-Hispanic white, Hispanic white, black), SEER registry and ambient annual UVR quintile (219–336, 337–403, 404–486, 487–547 and 548–662 mW/m^2). Corresponding population counts were obtained using the 2000 U.S. census. Analyses were restricted to NHL subtypes with a minimum of 50 cases for each racial/ethnic group.

Outcomes

NHL cases consisted of persons diagnosed with B- or T-cell lymphoid neoplasm subtypes. B-cell lymphoid neoplasms

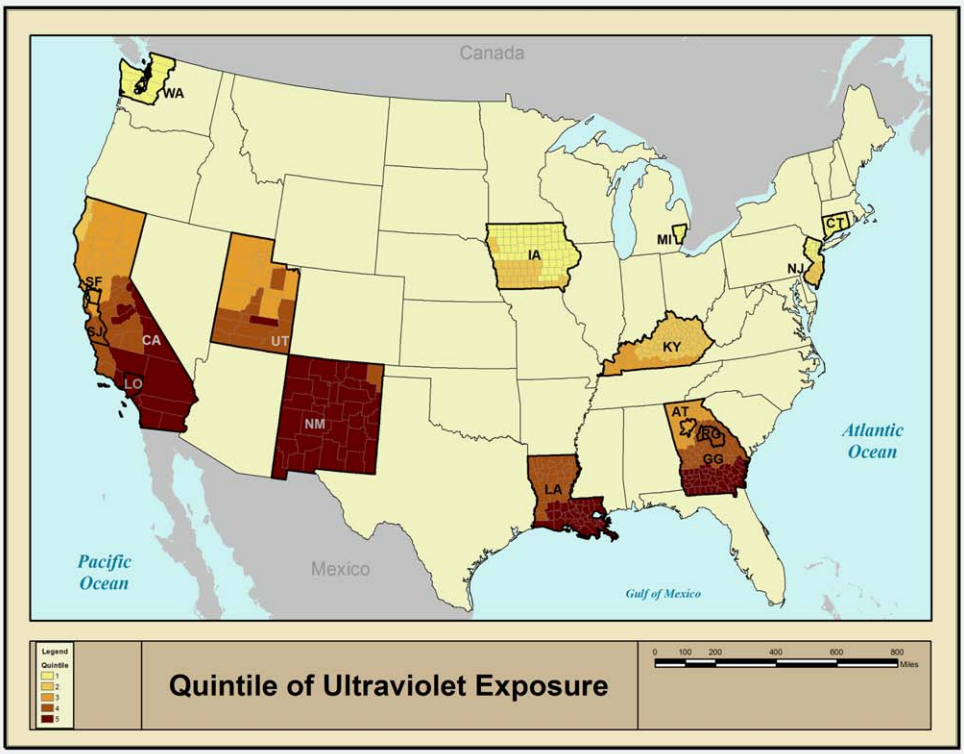

Figure 1. Quintiles of ultraviolet radiation exposure for 15 registries participating in the Surveillance, Epidemiology, and End Results Program between 2001 and 2010.

included chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), mantle-cell lymphoma (MCL), lymphoplasmacytic lymphoma (LPL), marginal-zone lymphoma mucosa-associated lymphatic tissue (MZL MALT), nodal (NMZL) and splenic (SMZL) types, hairy cell leukemia (HCL), plasmacytoma (Plasma), plasma cell myeloma (PCM), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (Burk) and the heterogeneous category of B-cell not otherwise specified (BNOS). Neoplasms originating in the T-cells included extranodal natural killer T-cell lymphoma (ENNKTL), peripheral T-cell lymphoma other (PTCL), PTCL not otherwise specified (PNOS), MF/SS, primary cutaneous anaplastic large cell lymphoma (CALCL) and the heterogeneous category of T-cell not otherwise specified (TNOS). Cases were identified using International Classification of Diseases for Oncology third edition (ICD-O-3) morphology codes.[26] Only patients diagnosed following the introduction of the World Health Organization Classification[27] and translation of this into ICDO-3[28] were included. NHL cases were grouped into lymphoid neoplasm subtypes as defined by the InterLymph hierarchical classification for epidemiologic research.[29]

Ambient ultraviolet radiation

Ambient UVR exposure was derived using the Total Ozone Mapping Spectrometer (TOMS) database maintained by the National Aeronautics and Space Administration (NASA).[30] Cloud-adjusted daily ambient ultraviolet irradiance 305 nm, which is part of the UVB spectrum and therefore related to endogenous vitamin D production,[31] is provided on a 1° latitude × 1° longitude grid. In the continental United States, 1° latitude × 1° longitude grid represents ~111 × 85 km (69 × 53 miles), respectively. Satellite-based estimates of UVR have varied little over time since the start of measurements in the late 1970s, aside from relatively small fluctuations due to the 11-year solar cycle.[32] For this study, daily noon-time estimates over years 1982–1992 were averaged to represent a full 11-year solar cycle. The population centroid of each SEER county was linked to the nearest yearly average UVR estimate using ArcGIS 9.1 software (ESRI 2005). SEER counties were ranked by UVR and assigned quintiles 1 (lowest UVR) to 5 (highest UVR) (Fig. 1).

Statistical analysis

We examined the relationships between ambient UVR and risk of NHL subtypes by calculating incidence rate ratios (IRRs) and 95% confidence intervals (CIs) derived from Poisson regression after adjusting for year of diagnosis group, age group, sex, race and registry. UVR was treated as categorical (quintile) in main effects regression models. To test for trend in NHL rates with increasing UVR quintile, we regressed the log incident rate ratio parameters for UVR quintiles coded in dummies from the Poisson regression models as the outcome variable on the quintile number (2–5) in a linear regression

Table 1. Adjusted incidence rate ratios by quintile of ambient ultraviolet radiation for selected mature B-cell non-Hodgkin lymphoma subtypes, SEER 2001–2010

B-cell subtype[1,2]		*n*	IRR[3]	95% CI	*p* for trend[4]
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	Q1	11,837	Ref		
	Q2	3,845	0.95	0.90–1.01	
	Q3	7,477	0.89	0.80–0.99	
	Q4	2,956	0.91	0.81–1.02	
	Q5	9,231	0.87	0.77–0.97	0.114
Mantle cell lymphoma (MCL)	Q1	1,570	Ref		
	Q2	547	1.00	0.87–1.15	
	Q3	1,006	0.74	0.63–0.88	
	Q4	434	0.80	0.66–0.96	
	Q5	1,471	0.82	0.69–0.97	0.074
Lymphoplasmacytic lymphoma (LPL)	Q1	1,451	Ref		
	Q2	252	0.69	0.57–0.83	
	Q3	774	0.58	0.42–0.80	
	Q4	269	0.53	0.38–0.75	
	Q5	1,105	0.58	0.42–0.80	0.208
Marginal zone lymphoma of mucosa-associated lymphoid Tissue (MZLMALT)	Q1	2,262	Ref		
	Q2	681	0.94	0.83–1.06	
	Q3	1,483	0.75	0.62–0.92	
	Q4	597	0.75	0.61–0.93	
	Q5	2,181	0.74	0.60–0.90	0.021
Nodal marginal zone lymphoma (NMZL)	Q1	1,381	Ref		
	Q2	306	0.80	0.68–0.94	
	Q3	646	0.60	0.44–0.81	
	Q4	315	0.78	0.57–1.07	
	Q5	1,163	0.77	0.57–1.05	0.77
Splenic marginal zone lymphoma (SMZL)	Q1	360	Ref		
	Q2	108	0.80	0.59–1.10	
	Q3	199	0.59	0.42–0.83	
	Q4	72	0.58	0.39–0.87	
	Q5	324	0.77	0.55–1.09	0.825
Hairy cell leukemia (HCL)	Q1	748	Ref		
	Q2	205	0.87	0.71–1.07	
	Q3	566	0.91	0.73–1.13	
	Q4	212	0.85	0.66–1.09	
	Q5	688	0.81	0.64–1.02	0.507
Plasmacytoma (Plasma)	Q1	696	Ref		
	Q2	239	1.02	0.81–1.28	
	Q3	521	0.89	0.67–1.19	
	Q4	237	0.91	0.67–1.24	
	Q5	741	0.90	0.67–1.20	0.408
Plasma cell myeloma (PCM)	Q1	10,637	Ref		
	Q2	3,308	0.96	0.90–1.02	

Table 1. Adjusted incidence rate ratios by quintile of ambient ultraviolet radiation for selected mature B-cell non-Hodgkin lymphoma subtypes, SEER 2001–2010 (Continued)

B-cell subtype[1,2]		*n*	IRR[3]	95% CI	*p* for trend[4]
	Q3	7,843	0.97	0.88–1.09	
	Q4	3,251	0.93	0.83–1.04	
	Q5	10,123	0.91	0.81–1.02	0.216
Follicular lymphoma (FL)	Q1	8,135	Ref		
	Q2	2,899	0.94	0.87–1.00	
	Q3	5,591	0.77	0.69–0.87	
	Q4	2,222	0.77	0.68–0.87	
	Q5	7,229	0.76	0.68–0.86	<0.001[5]
Diffuse large B-cell lymphoma (DLBCL)	Q1	12,887	Ref		
	Q2	4,217	0.98	0.93–1.04	
	Q3	9,556	0.90	0.81–0.99	
	Q4	3,647	0.84	0.76–0.93	
	Q5	12,429	0.84	0.76–0.94	<0.001[5]
Burkitt lymphoma (Burk)	Q1	581	Ref		
	Q2	155	0.78	0.60–1.00	
	Q3	490	0.84	0.65–1.09	
	Q4	152	0.66	0.49–0.89	
	Q5	673	0.82	0.62–1.07	0.851
B-cell not otherwise specified (BNOS)	Q1	3,167	Ref		
	Q2	943	1.04	0.93–1.15	
	Q3	2,024	0.84	0.71–1.00	
	Q4	827	0.82	0.68–0.98	
	Q5	2,454	0.86	0.72–1.03	0.032

[1]ICD-O-3 codes: CLL/SLL 9670, 9823; MCL 9673; LPL 9671, 9761; MZL_MALT 9699 (excl. C77.0–C77.9), 9764; NMZL 9699 (C77.0–C77.9); SMZL 9689; HCL 9591 (C42.1–C42.2), 9940; Plasma 9731, 9734; PCM 9732–33; FL 9690–91, 9695, 9698; DLBCL 9678–80, 9684, 9688, 9712, 9735, 9737–38; Burkitt 9687; NOSB 9590–91, 9675, 9820, 9970.
[2]Cutoffs for ambient UVR quintile: 219–336, 337–403, 404–486, 487–547, 548–662 mW/m^2.
[3]Adjusted for sex, age group (0–44, 45–64, 65–84), year of diagnosis (2001–2005, 2006–2010), race and a random intercept for SEER registry.
[4]Trend tests use log IRR parameters for UVR quintiles as the outcome variable on the quintile number (2–5) in a linear regression model and estimated that slope using linear least squares with a known variance–covariance matrix.
[5]Significant after Bonferroni correction (19 tests).
Abbreviations: IRR: incidence rate ratio; CI: confidence interval; Ref: reference category; UVR: ultraviolet radiation.

model and estimated that slope using linear least squares with a known variance–covariance matrix (also obtained from the Poisson models). The *p*-value for the slope parameter corresponds to the *p*-trend we report. We then assessed if the slope parameter was different from zero based on a Wald test. To assess whether these relationships were modified by year of diagnosis, age, sex or race/ethnicity, tests for statistical interaction were conducted. Interactions were assessed based on a Wald test using continuous coding for UVR quintiles (with values 1–5). As any systematic geographic difference in NHL ascertainment or diagnosis of the specific subtype could impact our results, SEER registry was included as a random effect in all models. All models contained the natural log of the population size as an offset. Because of overdispersion, we conducted sensitivity analysis using a zero-inflated Poisson model, but this did not affect our results.

Statistical tests were two-sided with a specified type I error of 0.05. Trend and interaction *p*-values were corrected for multiple comparisons testing using Bonferroni adjustment. Poisson regression was performed with the GLIMMIX procedure using SAS software V9.3 (SAS Institute, Cary, North Carolina). For models that did not converge using the GLIMMIX procedure (SMZL, Plasma, Burk and NOSPTCL among combined race groups), the NLMIXED procedure was used.[33]

Results

A total of 187,778 diagnosed cases of NHL were included in the analysis sample. Of these, 176,596 (94%) were mature B-cell NHL (Table 1) and 11,182 (6%) were mature NK/T-cell NHL subtypes (Table 2). There was no consistent evidence of differences in the relationship between UVR and NHL subtypes by year of diagnosis, age or sex. Race/ethnicity did

Table 2. Adjusted incidence rate ratios by quintile of ambient ultraviolet radiation for mature NK-/T-cell non-Hodgkin lymphoma subtypes, 2001–2010

T-cell subtype[1,2]		*n*	IRR[3]	95% CI	*p* for trend[4]
Extranodal natural killer T-cell lymphoma/leukemia (ENNKTL)	Q1	77	Ref		
	Q2	23	0.83	0.46–1.50	
	Q3	81	0.95	0.56–1.61	
	Q4	39	1.26	0.70–2.26	
	Q5	149	1.02	0.60–1.75	0.778
Peripheral T-cell lymphoma, other (PTCL)	Q1	1,340	Ref		
	Q2	394	0.97	0.83–1.13	
	Q3	958	0.82	0.67–1.02	
	Q4	362	0.73	0.58–0.92	
	Q5	1,210	0.76	0.61–0.95	0.05
Peripheral T-cell lymphoma, not otherwise specified (PNOS)	Q1	840	Ref		
	Q2	254	0.92	0.75–1.13	
	Q3	555	0.78	0.62–0.97	
	Q4	211	0.69	0.53–0.90	
	Q5	739	0.77	0.61–0.98	0.101
Mycosis fungoides or Sézary syndrome (MF/SS)	Q1	895	Ref		
	Q2	169	0.85	0.69–1.06	
	Q3	924	1.42	1.00–2.03	
	Q4	232	1.03	0.71–1.51	
	Q5	738	0.79	0.55–1.14	0.561
Primary cutaneous anaplastic large cell lymphoma (CALCL)	Q1	227	Ref		
	Q2	46	0.64	0.43–0.96	
	Q3	146	0.76	0.55–1.06	
	Q4	49	0.64	0.43–0.97	
	Q5	206	0.82	0.58–1.15	0.127
T-cell lymphoma, not otherwise specified (TNOS)	Q1	103	Ref		
	Q2	27	0.74	0.43–1.27	
	Q3	73	1.07	0.56–2.04	
	Q4	23	0.74	0.35–1.58	
	Q5	92	1.33	0.68–2.61	0.257

[1]ICD-O-3 codes: ENNKTL 9719; PTCL 9705, 9708–09, 9714, 9716–17, 9726; PNOS 9675, 9702, 9724, 9725; MF/SS 9700-01; CALCL 9718; TNOS 9590–91, 9684, 9820, 9970.
[2]Cutoffs for ambient UVR quintile: 219–336, 337–403, 404–486, 487–547, 548–662 mW/m^2.
[3]Adjusted for sex, age group (0–44, 45–64, 65–84), year of diagnosis (2001–2005, 2006–2010), race and a random intercept for SEER registry.
[4]Trend tests use log IRR parameters for UVR quintiles as the outcome variable on the quintile number (2–5) in a linear regression model and estimated that slope using linear least squares with a known variance–covariance matrix. None withstood adjustment for multiple comparisons using Bonferroni correction (19 tests).

significantly modify the association of UVR and risk of several of the subtypes before correction for multiple testing (CLL/SLL, FL, Burk, PNOS and MF/SS) and afterward (CLL/SLL and FL), so race/ethnicity-specific estimates are presented for these subtypes (Table 3).

Among B-cell NHL subtypes, for whites, Hispanics and blacks combined, we observed reduced risk for at least one of the two highest quintiles for the following B-cell subtypes: CLL/SLL, MCL, LPL, MZL MALT, SMZL, FL, DLBCL, Burk and BNOS (Table 1). We found a significantly decreasing trend between UVR and risk of MZLMALT, FL, DLBCL and BNOS, with FL and DLBCL still significant after Bonferroni correction. There was little evidence of a UVR association for Plasma or PCM.

Among T-cell NHL subtypes for all races combined, we observed a significantly reduced risk of at least one of the two highest quintiles for PTCL, PNOS and CALCL (Table 2). There was no evidence of a UVR association for ENNKTL,

Table 3. Adjusted incidence rate ratios by quintile of ambient ultraviolet radiation for non-Hodgkin lymphoma subtypes by race, 2001–2010[1]

		Whites				Hispanics				Blacks				
Subtype		*n*	IRR[2]	95% CI	*p* for trend[3]	*n*	IRR[1]	95% CI	*p* for trend[3]	*n*	IRR[2]	95% CI	*p* for trend[3]	*p* for interaction[4]
Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)	Q1	10,792	Ref			272	Ref			773	Ref			
	Q2	3,625	0.94	0.89–1.00		41	1.15	0.82–1.61		179	1.01	0.82–1.23		
	Q3	6,480	0.89	0.79–0.99		337	0.86	0.69–1.06		660	1.00	0.83–1.20		
	Q4	2,453	0.91	0.81–1.03		166	0.74	0.58–0.94		337	0.90	0.73–1.10		
	Q5	7,466	0.87	0.77–0.97	0.179	944	0.65	0.53–0.80	0.001	821	0.93	0.77–1.12	0.346	<0.001[5]
Follicular lymphoma (FL)	Q1	7,378	Ref			410	Ref			347	Ref			
	Q2	2,734	0.92	0.86–0.99		47	0.87	0.64–1.18		118	1.45	1.13–1.86		
	Q3	4,853	0.77	0.69–0.87		445	0.74	0.61–0.90		293	0.90	0.71–1.15		
	Q4	1,863	0.79	0.70–0.89		229	0.65	0.52–0.81		130	0.77	0.58–1.02		
	Q5	5,433	0.77	0.68–0.87	0.003	1418	0.66	0.55–0.80	0.065	378	0.89	0.70–1.13	0.001	<0.001[5]
Burkitt lymphoma (Burk)	Q1	478	Ref			60	Ref			43	Ref			
	Q2	142	0.85	0.65–1.10		6	0.68	0.29–1.58		7	0.66	0.29–1.50		
	Q3	384	0.83	0.64–1.08		69	0.78	0.55–1.11		37	0.90	0.55–1.46		
	Q4	111	0.68	0.50–0.93		21	0.41	0.25–0.67		20	0.95	0.54–1.69		
	Q5	427	0.84	0.64–1.11	0.673	205	0.67	0.50–0.89	0.574	41	0.87	0.54–1.39	0.506	0.016
Peripheral T-cell lymphoma, not otherwise specified (PNOS)	Q1	637	Ref			49	Ref			154	Ref			
	Q2	214	0.97	0.78–1.20		7	1.02	0.46–2.25		33	0.84	0.56–1.27		
	Q3	401	0.82	0.65–1.04		44	0.64	0.42–0.96		110	0.76	0.53–1.08		
	Q4	127	0.67	0.51–0.89		28	0.69	0.43–1.10		56	0.75	0.50–1.11		
	Q5	454	0.85	0.66–1.08	0.175	181	0.71	0.52–0.98	0.405	104	0.60	0.42–0.86	0.181	0.039
Mycosis fungoides or Sézary syndrome (MF/SS)	Q1	686	Ref			38	Ref			171	Ref			
	Q2	141	0.81	0.64–1.03		7	1.39	0.61–3.17		21	0.68	0.39–1.17		
	Q3	673	1.37	0.92–2.03		86	1.49	0.90–2.48		165	1.29	0.83–2.02		
	Q4	160	1.06	0.69–1.62		29	1.00	0.55–1.82		43	0.72	0.42–1.21		
	Q5	482	0.81	0.53–1.22	0.661	148	0.81	0.49–1.34	0.127	108	0.63	0.39–1.01	0.416	0.033

[1]Cuttoffs for ambient annual UVR quintile: 219–336, 337–403, 404–486, 487–547, 548–662 mW/m^2.
[2]Adjusted for sex, age group (0–44, 45–64, 65–84), year of diagnosis (2001–2005, 2006–2010) and a random intercept for SEER registry.
[3]Trend tests use log IRR parameters for UVR quintiles as the outcome variable on the quintile number (2–5) in a linear regression model and estimated that slope using linear least squares with a known variance–covariance matrix.
[4]Interaction tests treat UVR quintile as a continuous variable (coded 1–5).
[5]Significant after Bonferroni correction (included 57 tests for trend *p*-values and 19 tests for interaction *p*-values).
Abbreviations: IRR: incidence rate ratio; CI: confidence interval; Ref: reference category; UVR: ultraviolet radiation.

MF/SS or TNOS for all races combined. A significant trend was found for PTCL, but this did not withstand Bonferroni correction.

Interaction by race was significant for the following subtypes: CLL/SLL (p for interaction < 0.001), FL (p for interaction < 0.001), Burk (p for interaction $= 0.016$), PNOS (p for interaction $= 0.039$) and MF/SS (p for interaction $= 0.033$), with CLL/SLL and FL race interactions withstanding correction for multiple comparisons (19 tests). Of these subtypes, the B-cell lymphomas (CLL/SLL, FL and Burk) demonstrated significant inverse relationships in both whites and Hispanic whites for at least one of the two highest quintiles, but not in blacks. For example, UVR was most protective in the highest quintile for CLL/SLL (IRR = 0.65; 95% CI: 0.53–0.80) and FL (IRR = 0.66; 95% CI: 0.55–0.80) among Hispanics. In contrast, the T-cell lymphomas (PNOS and MF/SS) suggested the most protective relationship for the highest quintile of UVR among blacks (IRR for PNOS = 0.60; 95% CI: 0.42–0.86 and IRR for MF/SS = 0.63; 95% CI: 0.39–1.01), though MF/SS was not significantly reduced.

Discussion

In this U.S. population-based study of ambient UVR and NHL subtypes, we report a reduction in risk of most NHL subtypes (CLL/SLL, MCL, LPL, MZLMALT, SMZL, FL, DLBCL, Burk, BNOS, PTCL, PNOS and CALCL) associated with high levels of ambient UVR, with trends for FL and DLBCL still significant after Bonferroni correction for all races combined. The following subtypes, however, were not associated with ambient UVR for all races combined: Plasma, PCM, ENNKTL, MF/SS and TNOS. These results strengthen the evidence for UVR involvement in many NHL subtypes and support the case for modest etiologic heterogeneity among NHL subtypes with regard to UVR exposure. This is the only study we are aware of to assess the relation between UVR and NHL subtypes by race and ethnicity. Our results suggest little evidence of a reduced risk of CLL/SLL and Burk associated with UVR exposure in blacks, whereas IRRs were reduced for these subtypes in Hispanics and whites, though trends were only significant for CLL/SLL in Hispanics. There was evidence of reduced risk of FL associated with UVR for each racial group. We also observed a greater reduction in risk for PNOS and MF/SS in relation to UVR in blacks compared with the risks of these types of NHL in other racial groups, though tests of interaction did not withstand Bonferroni correction.

Exposure to UVR has been hypothesized to influence the risk of NHL because UVR is associated with a number of immunological changes.[34,35] A protective role for UVR in NHL has been proposed *via* immune modulation, specifically through depressing T-helper 1-mediated immune response and enhancing T-helper 2 activity.[34,36] UVR exposure also contributes to vitamin D production, which has been linked to lower risk of some cancers, although the few epidemiologic studies of NHL and circulating vitamin D have found limited or no evidence of an overall association.[37–39] In addition, there are racial differences in incidence of several subtypes of NHL,[40] measures of immune function,[4,41] relationships between immune system-related gene polymorphisms and NHL[42] and circulating vitamin D levels.[43]

Overall, epidemiologic studies have found UVR to be inversely associated with diffuse large B-cell lymphoma (DBCL),[8,15,17,18,20–22] as they were in this study. In contrast, the associations with the other two main B-cell subtypes, FL and CLL/SLL, have been inconsistent.[13,15,17,18,22] In this study, UVR was inversely related to risk of both CLL/SLL and Burk in whites and Hispanics, but not in blacks, while UVR was inversely associated with FL in all three race/ethnicities. The largest and most comprehensive study preceding our study is a registry-based analysis in Australia which used latitude as a surrogate for ambient UVR exposure.[15] In that study, van Leeuwen *et al.* suggest that their failure to find an association with FL, which has no established relationship to infection or immune dysfunction, provides evidence that UVR plays a protective role specifically in those NHL subtypes where infection or immune dysfunction are involved. Our finding that UVR is inversely related to FL does not support the hypothesis that UVR reduces the risk of specific NHL subtypes only associated with immune dysfunction or infection-related mechanisms.

As noted, we also found a significant inverse trend of CLL/SLL risk by increasing level of UVR quintile in Hispanics and significant protective association in whites with the highest level of UVR, but not in blacks. In one of the few studies of NHL and circulating vitamin D, Lim et al. found that CLL/SLL was more inversely related to 25(OH)D, the major circulating form of vitamin D, than other common subtypes of NHL.[38] Luczynska et al. also found that circulating vitamin D was statistically significantly inversely related to CLL, but not other subytpes.[39] A recent genome-wide study found that regions of the genome associated with CLL also contain a disproportionately large number of vitamin D receptor-binding sites, providing additional evidence of an etiological role of 25(OH)D for this subtype.[44]

In the two previous studies that have examined T-cell lymphomas, UVR associations have been generally inverse, but the two studies use different classification systems for NHL and thus cannot be easily compared.[15,18] In our study, statistically significant inverse associations with UVR include PTCL, PNOS and CALCL, with the inverse association for PNOS largely driven by the association in blacks, though trends were not significant. As noted, race is significantly related to circulating vitamin D, with blacks having lower levels of circulating mean serum 25(OH) than whites.[41,43] Experimental evidence has also demonstrated that a low dose of UVB radiation increases serum vitamin D3 concentrations in whites, but not in blacks.[45] Our finding of stronger inverse relationships for PNOS and MF/SS in blacks argues against a biologic mechanism involving vitamin D in this group. However, racial differences in immune-related conditions and risk

of non-Hodgkin lymphoma have been observed, possibly due to differences in immune system regulatory genes.[4] Also, experimental evidence involving whole body irradiation with low levels of UVB in blacks and whites has been associated with differences in immunological responses consisting of increased B-cells (CD19) and helper T-cells (CD4 and CD29) in whites and decreased CD3 T-cells in blacks.[45] Although whites have higher overall incidence of NHL,[5] blacks have had notably higher incidence rates of peripheral T-cell lymphomas and mycosis fungoides.[40] In addition, race is a well-established modifier of the relationship between UVR and skin cancer risk.

Our findings should be interpreted within the context of several limitations. Our study lacked data on personal UVR exposure; however, ambient UVR based on TOMS satellites, as estimated here, has been significantly positively associated with UVR exposure measured by personal dosimeter.[46] Misclassification of exposure may also have resulted because ambient UVR was linked to location of residence only at time of diagnosis. The direction of this potential bias is difficult to ascertain, but could be particularly relevant to NHL subtypes with longer latency periods, such as CLL/SLL. Residual confounding due to unmeasured confounders may also bias our results; however, there are few strong personal risk factors that have been established for NHL.[47] In addition, as most of the observed associations were not significantly different by race and race is known to be related to a number of lifestyle factors, there is additional evidence that residual confounding by these lifestyle factors did not play a large role in the UVR NHL relationships we observed.

One of the major advantages of this study is a sample size large enough to look at many NHL subtypes by racial/ethnic groups. To our knowledge, this analysis is the largest to date of UVR and NHL subtypes, comprising over five times the number of cases as the previous largest study.[15] The large population included in the U.S. SEER registries has both a substantial number of Hispanics and blacks and a broad range of ambient UVR exposures. Although incidence of NHL subtypes varies by race,[48] race/ethnicity has not been previously examined in terms of its role in the relationship between UVR and NHL. Racial/ethnic differences may reflect differences in genes, other physiological characteristics, behaviors and sun sensitivity.

In summary, this U.S. population-based study of ambient UVR and NHL, the largest reported to date, showed a statistically significant reduction in risk of most NHL subtypes by all racial groups combined for increasing ambient UVR exposure, with trends for FL and DLBCL withstanding Bonferroni correction for multiple comparisons. There was evidence of differences in risk for CLL/SLL, FL, Burk, PNOS and MF/SS associated with UVR by race/ethnicity, though only CLL/SLL and FL withstood Bonferroni correction. Our results support and expand previous findings of a protective association of UVR on NHL subtypes and serve as a starting point for understanding the differences in the relationship between UVR and specific NHL subtypes by race/ethnicity. Epidemiological studies with personal UVR exposure are needed to confirm these findings and investigate potential roles of UVR on immunologic mechanisms. Experimental studies of the effect of UVR exposure are also needed to elucidate mechanistic differences by race/ethnicity.

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