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Outdoor artificial light at night and risk of non-Hodgkin lymphoma among women in the California Teachers Study cohort

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Abstract

Background: Outdoor artificial light at night (ALAN) has been implicated in a growing number of adverse health outcomes. ALAN is believed to disrupt circadian rhythms and has been associated with increased inflammation, one of the hallmarks of cancer. We examined the association between outdoor ALAN and a cancer strongly associated with autoimmune and inflammatory conditions, non-Hodgkin lymphoma (NHL), in the prospective California Teachers Study cohort.

Methods: Outdoor ALAN was assigned to participant addresses at study baseline (1995-96) through use of the New World Atlas of Artificial Night Sky Brightness. Among 105,937 women followed from 1995-2015, linkage to the California Cancer Registry identified 873 incident cases

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Authorship Contribution

CZ, MF, JW, RMC, SSW, and TL conceived of the study; CZ, MF, NTC, JB, JVL, TL conducted data collection and data analysis; all contributed to data interpretation and manuscript preparation.

Credit Statement

Charlie Zhong: Conceptualization, formal analysis, data curation, software, writing – original draft, visualization, project administration

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of NHL. Age-stratified Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (95%CI) for overall NHL and the most common NHL subtypes; diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Multivariate analyses adjusted for previously reported subtype specific covariates (e.g. body mass index (BMI) for DLBCL).

Results: Compared to the lowest quintile, participants residing in the highest quintile of outdoor ALAN at baseline were more likely to develop NHL (HR=1.32, 95%CI=1.07-1.63), and, in particular, DLBCL (HR=1.87, 95%CI=1.16-3.02). The elevated risk for DLBCL remained statistically significant after adjusting for age, race/ethnicity, BMI, and socioeconomic status (DLBCL:HR=1.87, 95%CI=1.16-3.02, NHL:HR=1.32, 95%CI=1.07-1.63). There was no association between ALAN and FL or CLL/SLL.

Conclusion: DLBCL risk was elevated among women residing in neighborhoods with greater outdoor ALAN. Future research in circadian disruption and DLBCL may clarify potential biological processes implicated in this association.

Keywords

non-Hodgkin lymphoma; light at night; circadian disruption; cohort study

Introduction

Growing scientific evidence indicates that artificial light at night (ALAN) adversely affects human health. Major contributors of outdoor ALAN include commercial lighting, industrial lighting, street lighting, and residential lights[1]. Outdoor ALAN has steadily increased for decades and at accelerating rates. Estimates range from 2-3% per year to as much as 20% in larger cities[2]. For example, the Mount Wilson Observatory in the San Gabriel Mountains of Los Angeles County experienced a rapid decline in utility for nighttime astronomical research due to increasing light pollution from the 1970s through the 2000s[2, 3]. More recent data has shown outdoor ALAN levels have begun to level off in more recent years[4].

Advances in hand-held instrumentation and wearable devices may soon lead to calibrated exposure metrics for ALAN in living environments, but currently such methods are difficult and cost-prohibitive in a large epidemiologic research setting; therefore, many studies make use of satellite measurements as a proxy measure for ground-level exposure. The most commonly used satellite products include the Defense Meteorological Satellite Program's Optical Linescan System (DMSP-OLS) which has been previously utilized in our cohort, the California Teachers Study (CTS)[5]. This satellite detects visible and near-infrared light emissions at a 2.7 km spatial resolution; however, limitations such as the coarse resolution and oversaturation of urban areas led to the launch of its successor, the Visible Infrared Imaging Radiometer Suite (VIIRS), in 2011. VIIRS, onboard the Suomi National Polar-orbiting Partnership (SNPP) satellite obtains nighttime observations in the day-night band (DNB) at ~750 m resolution and provides improved dynamic range[1]. While VIIRS is an improvement over the DMSP-OLS, these satellite-based measures only capture upward radiating light that escapes the atmosphere and may not be as representative of light pollution at a location, which is also influenced by light scattering in the atmosphere. While

no satellite metric captures these sources, researchers at the Light Pollution Science and Technology Institute, led by Dr Fabio Falchi, have developed the New World Atlas of Artificial Night Sky Brightness to address such limitations[6]. The New World Atlas represents an improvement over VIIRS DNB upward radiance through a global measure of zenith brightness (the artificial brightness of the sky directly overhead) coupled with VIIRS observations and validated against thousands of handheld sky quality measurements. Furthermore, exposure to light on the ground includes light from the entire hemisphere of the sky in addition to the zenith brightness measured by the World Atlas and, importantly, direct glare from local sources. Simons et al. have confirmed that total light exposure on the ground is more highly correlated with zenith brightness estimated by the World Atlas than it is with upward radiance from VIIRS DNB in a southern California field study[7].

Exposure to light at night before sleep has shown to suppress melatonin production and disrupt circadian rhythm[8, 9]. This desynchronization between biological time and clock time has been associated with other proinflammatory conditions such as heart disease and diabetes[10]. Melatonin has also been shown to modulate activation of the inflammatory nuclear transcription factor kappa beta (NF-κβ) pathway, which in turn modulates levels of several immune cytokines such as interleukins (IL) −2, −6, −10, tumor necrosis factor (TNF), and C-reactive protein (CRP)[11], many of which have also been implicated in NHL etiology[12]. Exposure to light at night and disruptions to hormonal and endocrine regulation has been studied more extensively in laboratory settings, where animal studies have shown the role of ALAN in foraging behavior and elevated weight[13] as well as tumor growth[14]. Xenografted rodent models have confirmed a mechanistic pathway of melatonin suppression by light and subsequent cancer growth[15].

Epidemiological studies have linked satellite-measured outdoor lighting to increased breast, lung, colorectal, and prostate cancer risk[5, 16-19]; as well as proinflammatory conditions such as diabetes[20]. Of the studies that have included lymphoma, no association has been found[19]. A few studies to date have suggested potential links between disrupted circadian rhythms and non-Hodgkin lymphoma (NHL) risk. One study evaluated cancer risk based on different U.S. time zones, hypothesizing that those living in the western region of any time zone may result in altered sleep due to later onset of nighttime relative to clock time and earlier waking relative to sunrise. Gu et al reported increased risk of the NHL subtype, chronic lymphocytic leukemia (CLL) among those living closer to the western edge of a time zone[21]. Consistent with this finding is reported evidence of epigenetic silencing of the circadian clock gene, Cryptochrome 1, among CLL patients[22]. Gu et al. also saw increased risk of overall NHL among men residing in more western time zones and a link between sleep disruption from shift work and NHL has been suggested in a Finnish study, again only in men[21, 23].

Here, we sought to investigate any association between outdoor ALAN and non-Hodgkin lymphoma, a cancer of the immune response which takes years to develop. We hypothesized that outdoor ALAN may be a marker of sleep disruption and subsequent chronic inflammation. We selected ALAN as our exposure of interest because it could serve as surrogate exposure for biological processes and be measured at study baseline (1995-1996) by leveraging geospatial data available from the cohort, thus providing critical clues to

whether additional research into the related pathways – sleep disruption, direct measure of circadian rhythm, inflammation – are warranted.

Materials and Methods

Study Population

The California Teachers Study (CTS) is a large prospective cohort recruited from active or retired teachers and members of the California State Teachers Retirement System in 1995. Complete details of the cohort have been published previously [24]. Briefly, 133,477 women returned the baseline questionnaire and have participated in ongoing follow-up activities. The CTS represents a broad age range (22-104 years at baseline, median age 53) in both urban and rural areas. The baseline questionnaire (1995-1996) captured detailed information on diet, alcohol use, height/weight, physical activity, smoking, residential address, environmental exposures, medication use, and personal/family history of cancer including NHL. Each participant's address was assigned a latitude and longitude. For our analysis, participants were excluded if they lived outside of California at baseline or their address could not be geocoded (n=8,343), had prevalent cancer at baseline (n=8,115), or did not answer (n=5,904)/reported sleeping at night with a light on in the bedroom at baseline (n=5,173). The final analytic cohort of consisted of 105,937 participants. Informed consent was obtained according to the Declaration of Helsinki and this study is approved by the Institutional Review Boards of the City of Hope and University of Southern California in accordance with assurances filed and approved by the U.S. Department of Health and Human Services.

Exposure Assessment

We assessed outdoor ALAN using the New World Atlas of Artificial Night Sky Brightness[6], which provides a global measure of luminance at the zenith in millicandela per meter squared (mcd/m^2) at 750 m gridded spatial resolution. The World Atlas was based on VIIRS and handheld measurements taken in 2014. The World Atlas residential outdoor ALAN was retrospectively assigned by linking geocoded residential addresses at study baseline (1995-1996) to the 750 m grid cell in which it fell using the raster package in R version 3.4.3. Cohort-wide quintiles of ALAN were computed to derive the exposure metric for each participant.

Outcome Assessment

Cases were obtained through linkage to the California Cancer Registry. Non-Hodgkin lymphoma (NHL) was defined, according to the World Health Organization algorithm[25], as having a diagnosis with the International Classification of Diseases for Oncology, third edition codes of: diffuse large B-cell lymphoma (DLBCL: 9678, 9679, 9680, 9684), follicular lymphoma (FL: 9690, 9691, 9695, 9698), mantle cell lymphoma (MCL: 9673), marginal zone lymphoma (MZL: 9699), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL: 9670, 9823), Burkitt lymphoma (BL: ICD-O-3 codes 9687, 9826), and other B cell lymphomas (other, including not otherwise specified (NOS): 9590, 9591, 9596, 9671, 9675, 9727, 9728, 9833, 9835, 9836, 9761). We identified 873 incident cases of NHL in the cohort from baseline through December 31, 2015.

Covariates

We assessed confounding among several covariates potentially related to either NHL or ALAN, including; age, race/ethnicity (non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, Other), alcohol and smoking status (current, former, never), body mass index (BMI; <18.5, 18.5-25, 25-30, or ≥30 kg/m^2), United States Census block level socioeconomic status (SES; statewide quartiles), United States Census block urban/rural status[26], ultraviolet radiation (UV) level at residence, use of nonsteroidal anti-inflammatory drugs, recreational physical activity (meeting/not meeting American Heart Association recommended physical activity levels[27]), exposure to pesticides, menopausal hormone use, and family history of NHL.

Statistical Methods

We evaluated the association between outdoor ALAN and NHL overall and among the three most common subtypes (DLBCL, FL, CLL/SLL). We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using an age-stratified Cox proportional hazards model. In the Cox regression models, the time scale (in days) was defined by age at entry into the cohort and the first of the following ages: at event (NHL diagnosis), at censoring (e.g., when a participant moved out of California for more than four months), at death, or at end of follow-up (December 31, 2015). We adjusted for subtype specific covariates previously reported; age, race, SES, BMI, and family history of NHL for DLBCL[28], age, race, SES, smoking, alcohol consumption, and family history of NHL for FL[29], and age, race SES, smoking, height, and family history of NHL for CLL/SLL[30]. In addition, we assessed the association between participant residential position (latitudinal and longitudinal degrees) and NHL risk based on the hypothesis outlined by Gu et al[21]. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

For the 105,937 study participants in the analytic sample, the most common NHL subtype was DLBCL (n=212), followed by CLL/SLL (n=216) and FL (n=171). The median level of ALAN in the cohort was 2.40 mcd/m^2 (Table 1). For comparison, a natural, moonless night sky would have a brightness of 0.2 mcd/m^2 and at 2 mcd/m^2 the Milky Way would no longer be visible[31]. The highest levels of ALAN were for participants in Los Angeles County, especially those residing near the Port of Long Beach where levels reached 14 mcd/m^2 (Figure 1). The more rural areas of California exhibited the lowest levels of ALAN.

Compared to participants in the lowest quintile of ALAN, those in the highest quintile had 32% increased risk (HR 1.32, 95% CI 1.07-1.63) of developing NHL (Table 2). Consistent with our previous findings, covariates that were associated with NHL risk included higher SES (HR 1.80, 95% CI 1.16-2.79, Supplemental Table 1) and family history of NHL (HR 1.55, 95% CI 1.21-1.98)[32]. After adjusting for age, race/ethnicity, SES, smoking status, BMI, and family history of NHL, the highest quintile of ALAN was still associated with a 32% increased risk of NHL (95% CI 1.06-1.65). There was no association between longitude of residence and NHL risk (Supplemental Table 2).

Given our hypothesis that outdoor ALAN may drive circadian disruption, we excluded women who reported sleeping with a light on in the bedroom (n=5,173). Of these participants, 39 were diagnosed with NHL, and no association was observed between sleeping with a light on and NHL (HR 0.98, 95% CI 0.71-1.37).

By NHL subtype, the association with ALAN remained statistically significant for DLBCL (HR 1.87, 95% CI 1.16-3.02). There was no association between ALAN and FL (HR 0.84, 95% CI 0.51-1.40) or CLL/SLL (HR 1.28, 95% CI 0.86-1.91). Adjusting for age, race/ethnicity, BMI, family history of NHL, and SES slightly attenuated the association for DLBCL (HR 1.70, 95% CI 1.03-2.79).

Discussion

Outdoor artificial light at night was associated with an increased risk NHL for the DLBCL subtype. We did not observe statistically significant associations for either FL or CLL/SLL, but the increased risk of NHL overall was also significant on the basis of DLBCL cases. In contrast to the Gu et al study[21], we observed no association between NHL or NHL subtypes with longitude (Supplemental Table 2), but we did observe a nonsignificant increase in CLL/SLL risk for the highest quintile of ALAN. At present, it is unclear what exposure; ALAN, altered circadian rhythm, sleep disruption, or something else altogether, is the true underlying exposure that might explain the adverse health effects associated with ALAN, including increased NHL risk. Strengths of our study include the large sample size and length of followup. We were also able to examine individual-level, subtype specific covariates, including BMI, smoking, and exercise. Our linkage to the California Cancer Registry provides high quality case ascertainment with subtype information. We used the New World Atlas as a proxy for ground-level light exposure, a more accurate measure of outdoor ALAN exposure, which is both higher resolution than previous studies that were conducted with the DMSP-OLS and correlates more highly with ground-based exposure than the VIIRS DNB data [7] . Weaknesses to our study include relatively few cases to be powered to detect an association for individual subtypes. Also, our study was conducted in California, so all participants resided in the western portion of the Pacific time zone, making it difficult to assess light zone position as a contributor. We also lack additional features of the participants'-built environment such as housing and use of blinds or shades, but believe this would introduce nondifferential bias.

The New World Atlas of Artificial Night Sky Brightness does have its shortcomings when assessing exposure to ALAN. First, it only estimates brightness at the zenith and does not incorporate light from the whole hemisphere and especially on the horizon, which drives light exposures in human settlements[7]. Second, there is no distinction between the different wavelengths of light among the current satellite-based ALAN tools. Light in the blue spectrum (500-450 nm) has been shown to be especially disruptive to sleep[35], including suppression of melatonin[36]. A recently published study utilized high resolution color photography from the International Space Station to help address this limitation, though availability of such imagery is likely limited in both time and locations covered[37]. While the New World Atlas is a better measure of exposure to ALAN[7] it is based on the VIIRS data from 2014 of ALAN and was applied retrospectively to our cohort. Street

lighting, the major contributor to outdoor ALAN, is fairly stable over time, therefore use of the World Atlas to retroactively assign exposure, particularly during the study follow-up period where ALAN has leveled off, is expected to be stable[2, 3, 38]. The few studies that have been conducted comparing direct satellite measured ALAN and bedroom exposure have found little to no correlation during sleep[39, 40], but this has not been examined for the New World Atlas. Disruptions to melatonin levels persist hours after exposure to a light source[41, 42], so continuous exposure to ALAN while asleep may not be necessary to contribute to disruption of circadian pathways. Finally, we do not have information on behavioral factors such as grading assignments at night, preparing for teaching the next day, television use in the bedroom, or handheld screen-based computing device usage in the cohort; the latter of which have been shown to delay onset of sleep[35], however, such exposures would likely be nondifferential as they are not expected to be associated with outdoor ALAN.

Future studies need better measures of circadian rhythm and sleep disruption. In the CTS, questions were not asked at baseline that could provide a more direct measure of circadian disruption. Although we had limited information on study participants who slept with a light on in the bedroom, the sample size was too small to detect an association with NHL risk. Additionally, this question was asked to ascertain exposure to electromagnetic fields so did not ask about other sources of light such as televisions. New technologies such as genome and epigenome wide studies could further elucidate the mechanism behind ALAN, sleep disruption, and disease risk. Both polymorphisms in circadian rhythm genes and epigenetic silencing have been associated with increased breast cancer risk[43].

In conclusion, we observed an increased risk for DLBCL, and NHL overall, among those living in the highest quintile of outdoor ALAN exposure compared to the lowest. As we are continuing to better understand the effects of our environment on sleep disruption, further studies assessing the risk associated with NHL and its subtypes are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The New World Atlas of Artificial Night Sky Brightness was used to assess exposure to light at night
- There was increased risk of NHL for those in highest quintile of light at night
- The risk association was strongest for the DLBCL subtype
- The World Atlas is a unique resource for studying health effects associated with light at night

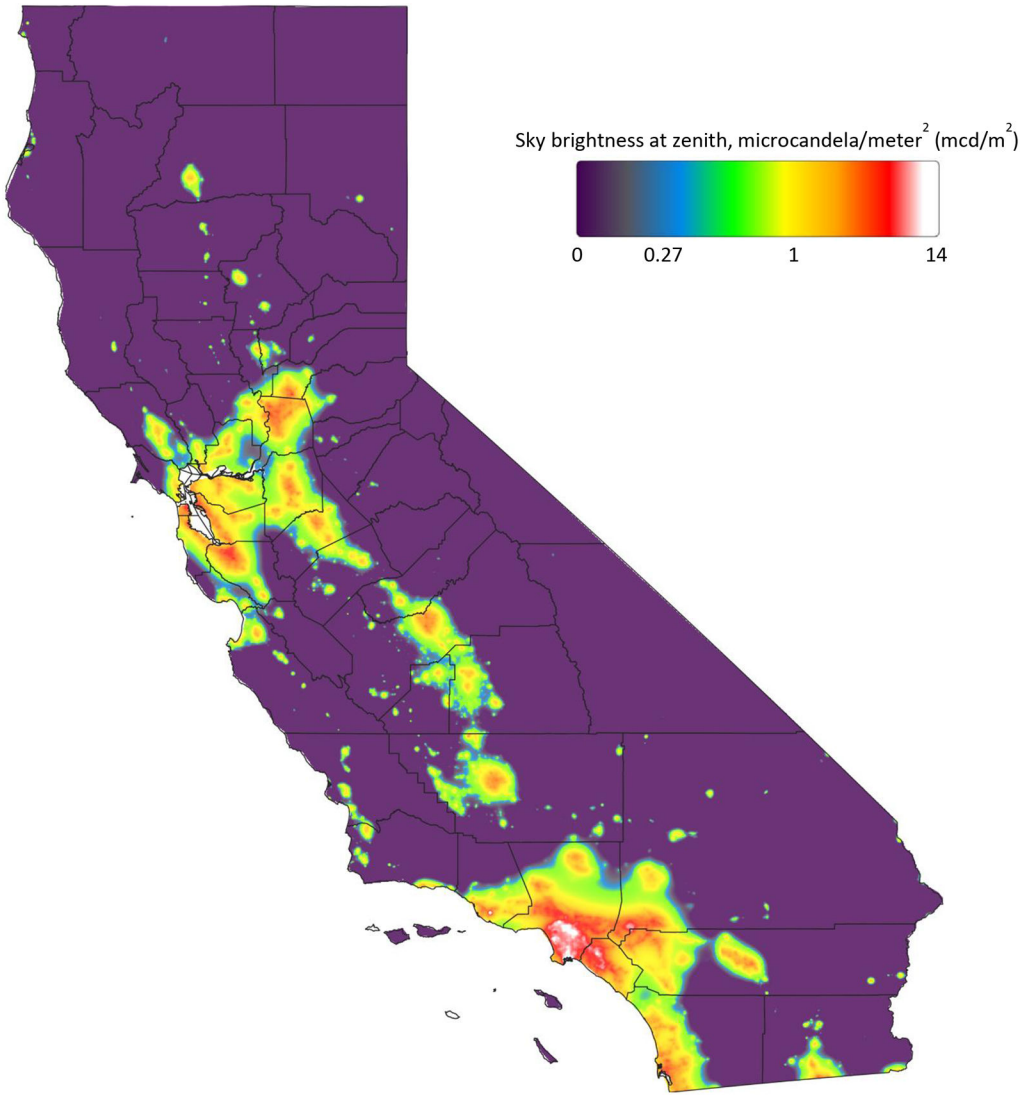

Figure 1.

Outdoor artificial light at night in California based on the New World Atlas of Artificial Night Sky Brightness

Table 1.

Self-reported demographic characteristics and New World Atlas of Artificial Night Sky Brightness among 105,937 women in the California Teachers Study Cohort at baseline (1995-1996)

	Cohort n=105,937		NHL n=873		p-value
Race					
White	92,393	87.2%	792	90.7%	
Black	2,487	2.3%	16	1.8%	
Hispanic	4,616	4.4%	22	2.5%	
Asian/Pacific islander	4,483	4.2%	29	3.3%	
Other	1,958	1.8%	14	1.6%	0.049
Light at Night					
Median (IQR)	2.40	(1.22-3.95)	2.50	(1.27-4.29)	
Quintile 1	21,186	20.0%	158	18.1%	
Quintile 2	21,189	20.0%	181	20.7%	
Quintile 3	21,187	20.0%	172	19.7%	
Quintile 4	21,188	20.0%	163	18.7%	
Quintile 5	21,187	20.0%	199	22.8%	0.14
UV					
Quintile 1	18,096	20.0%	143	19.4%	
Quintile 2	18,095	20.0%	150	20.4%	
Quintile 3	17,978	19.9%	170	23.1%	
Quintile 4	18,103	20.0%	163	22.1%	
Quintile 5	18,149	20.1%	110	14.9%	0.01
SES					
Quartile 1	4,578	4.4%	23	2.7%	
Quartile 2	18,214	17.5%	131	15.1%	
Quartile 3	34,409	33.0%	267	30.8%	
Quartile 4	46,944	45.1%	445	51.4%	<0.001
Rural Census Block					
Rural	14,956	14.4%	111	12.8%	
Suburban	23,002	22.1%	169	19.5%	
Urban	66,231	63.6%	586	67.7%	0.016
BMI					
<20	11,319	11.1%	68	8.2%	
20-24.9	51,496	50.6%	405	48.9%	
25-29.9	25,025	24.6%	227	27.4%	
30+	13,913	13.7%	128	15.5%	0.4
Smoking					
Never	70,547	67.0%	535	61.7%	
Former	29,541	28.1%	294	33.9%	
Current	5,185	4.9%	38	4.4%	0.005
Alcohol					

	Cohort n=105,937		NHL n=873		p-value
Never	33,606	33.4%	287	34.0%	
Former	58,546	58.3%	492	58.3%	
Current	8,316	8.3%	65	7.7%	0.22
Any Daily NSAID					
no	73,331	70.2%	603	70.1%	
yes	31,091	29.8%	257	29.9%	0.57
Exercise					
did not meet AHA guidelines	35,991	34.2%	277	32.1%	
met AHA guidelines	69,202	65.8%	585	67.9%	0.088
Family History of NHL					
no	97,154	95.2%	779	91.8%	
yes	4,894	4.8%	70	8.2%	<0.001
Any exposure to pesticides					
no	66,555	80.9%	585	78.8%	0.11
yes	15,711	19.1%	157	21.2%	
Histology					
DLBCL			212	22.7%	
FL			171	18.3%	
CLL/SLL			216	23.2%	
Marginal Zone			84	9.0%	
Other			190	20.4%	

NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma

Table 2.

Association between light at night and non-Hodgkin lymphoma and major subtypes (DLBCL, FL, CLL/SLL) among 105,937 women in the California Teachers Study Cohort followed from 1995-2015

	Overall NHL (n=873)		**DLBCL (n=212)**		**FL (n=171)**		**CLL/SLL (n=216)**	
Univariate age adjusted								
Light at Night	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Quintile 1	1.00	-	1.00	-	1.00	-	1.00	-
Quintile 2	1.20	(0.97-1.49)	**1.79**	**(1.11-2.89)**	1.32	(0.84-2.07)	0.90	(0.58-1.40)
Quintile 3	1.10	(0.89-1.38)	**1.74**	**(1.07-2.82)**	1.13	(0.70-1.80)	0.79	(0.50-1.24)
Quintile 4	1.03	(0.83-1.29)	1.52	(0.93-2.49)	0.82	(0.50-1.37)	0.93	(0.61-1.44)
Quintile 5	**1.32**	**(1.07-1.63)**	**1.87**	**(1.16-3.02)**	0.84	(0.51-1.40)	1.28	(0.86-1.91)
Multivariate								
Light at Night	HR[α]	95% CI	HR[β]	95% CI	HR[γ]	95% CI	HR[δ]	95% CI
Quintile 1	1.00	-	1.00	-	1.00	-	1.00	-
Quintile 2	1.14	(0.90-1.44)	1.57	(0.96-2.59)	1.44	(0.87-2.38)	0.88	(0.55-1.40)
Quintile 3	1.04	(0.82-1.32)	1.51	(0.91-2.48)	1.33	(0.79-2.23)	0.73	(0.45-1.19)
Quintile 4	0.94	(0.74-1.20)	1.27	(0.76-2.13)	0.92	(0.53-1.62)	0.86	(0.54-1.37)
Quintile 5	**1.32**	**(1.05-1.66)**	**1.70**	**(1.03-2.79)**	1.06	(0.61-1.84)	1.30	(0.84-2.00)

[α] Age, race, SES, BMI, smoking, alcohol, family history of NHL

[β] Age, race, SES, BMI, family history of NHL

[γ] Age, race, SES, smoking, alcohol, family history of NHL

[δ] Age, race, SES, height, family history of NHL

NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma