Research Article

Cancer Epidemiology, Biomarkers & Prevention

Solar UV Radiation and Cancer in Young Children

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Abstract

Background: Studies have shown that higher solar UV radiation exposure (UVR) may be related to lower risk of some cancers in adults. Recently, an ecologic study reported lower risks of some cancers among children living in higher UVR cities and countries. In a large population-based case–control study in California, we tested the hypothesis that childhood cancers may be influenced by UVR.

Methods: Cancers in children ages 0 to 5 years were identified from California Cancer Registry records for 1988 to 2007 and linked to birth certificate data. Controls were sampled from the birth certificates at a ratio of 20:1. Based on birth address, we assigned UVR exposure in units of Watt-hours/m^2 using a geostatistical exposure model developed with data from the National Solar Radiation Database.

Results: For cases with UVR exposure of 5,111 Watt-hours/m^2 or above, we estimated a reduction in odds of developing acute lymphoblastic leukemia (OR: 0.89, 95% CI: 0.81–0.99), hepatoblastoma (OR: 0.69, 95% CI: 0.48–1.00), and non-Hodgkin's lymphoma (OR: 0.71, 95% CI: 0.50–1.02) adjusting for mother's age, mother's race, and child's year of birth. We also observed a small increase in odds for intracranial/intraspinal embryonal tumors (OR: 1.29, 95% CI: 1.01–1.65).

Conclusions: Our findings suggest that UVR during pregnancy may decrease the odds of some childhood cancers. Future studies should explore additional factors that may be correlated with UVR exposure and possibly include biomarkers of immune function and vitamin D.

Impact: This study shows protective associations of UVR with some childhood cancers. *Cancer Epidemiol Biomarkers Prev; 22(6); 1118–28. ©2013 AACR.*

Introduction

Childhood cancer is a rare disease that may be triggered prenatally. The few known causes of pediatric cancers include ionizing radiation, Down syndrome, and some genetic or chromosomal anomalies (1). Additional potential risk factors have been suggested for specific cancer types, but due to the rarity of the childhood cancers, it has been difficult to establish causes, and preventive measures are similarly lacking.

Solar UV radiation (UVR), a known risk factor for skin cancers, has been identified as a potential protective factor for some cancers. UVB radiation produces vitamin D through reactions occurring in human skin (2). Recent meta-analyses of vitamin D levels and breast (3–5) and colorectal cancer (5–7) have provided some support for protective effects of vitamin D, but there have been inconsistent results for other cancers (8). Also, other UV-induced mechanisms may contribute to potential protection from cancer (9).

As summarized in a review, inverse relationships between UVR and incidence or mortality of cancer of the bladder, breast, colon, esophagus, gallbladder, stomach, lung, ovary, pancreas, prostate, rectum, kidney, thyroid, uterine corpus, and vulva, as well as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma were found in ecologic studies in the United States and other countries (10). An inverse association was also observed for leukemia in the United States (11). First, an ecologic study found an inverse relationship between colon cancer mortality and annual sunlight levels in the United States, and proposed vitamin D as a possible mechanism (12). Subsequently, a landmark study in the United States used ground-level UVB irradiance data from NASA and age adjusted sex- and race-specific cancer mortality rates by state economic area and found inverse associations for 18 cancers in adults (13). Since this study did not adjust for other potential confounders, a later follow up to this study using state-level UVR data adjusted for alcohol consumption, Hispanic heritage, urban/rural residence, poverty level, and, as a proxy for smoking, the lung cancer mortality rate, and found inverse associations for mortality from 13 cancers in adults (14). A study in the United States using the NASA UVR data at the county level found inverse associations with incidence of and mortality from several cancers (11). They also

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found positive associations for some cancer sites (anus, cervix, melanoma, oral cavity, and other skin). Ecologic studies in Europe, Australia, and Asia have also found inverse associations for several cancers in adults (10). In considering these previous studies, it should be noted that mechanisms protecting against cancer mortality may differ from those protecting against cancer incidence.

Multicountry studies, mostly using latitude as a proxy for UVR, showed lower rates of mortality or incidence of breast, lung, ovarian, kidney, brain, and uterine cancer and leukemia in adults residing in countries closer to the equator where UVR levels are higher (10). A recent ecologic study of childhood cancers in several countries found a protective effect of solar UVR on risks for several cancers in children ages 0 to 14 using rates extracted from cancer registries and adjusting for measures of economic development of the country (15). However, it may be difficult to adequately control for possible confounding factors such as smoking, alcohol use, diet, reproductive factors, infections and socioeconomic status (SES) in multicountry studies.

These ecologic studies have provided a good foundation for this field, but may still be subject to the ecologic fallacy or residual confounding. Also, several studies have used latitude, which does not capture variation in UVR due to elevation, terrain, or other factors. For example, in the United States UVB levels are higher at higher latitudes and also west of the Rocky Mountains due to a thinner stratospheric ozone layer and higher elevations (10). Other studies have used UVR measures with low spatial resolution such as state- and country-level, which may obscure important exposure differences at a smaller spatial scale. Case–control and cohort study designs have also been used to examine potential protective associations with some cancers, mainly in adults (16–23). In particular several studies investigated non-Hodgkin's lymphoma with some prospective studies showing a protective association (18, 22, 23) with UVR and others showing a harmful (19, 20) or null association (21).

Only 1 previous study examined the association between UVR and cancer in children, and it was limited to ecologic data at the level of cities and countries. Our objective was to assess the associations between UVR during pregnancy and childhood cancers in California in a population-based case–control study using UVR exposures based on mother's address from the birth certificate. Due to its diverse latitudes (32°30′–42° North) and elevations (282 ft below sea level in Death Valley to 14,494 ft at the peak of Mt Whitney), California receives a wide range of UVR. Other studies in California have linked similar UVR measures to increased risk for melanoma (24, 25) and reduced risk of non-Hodgkin's lymphoma (22).

Materials and Methods

Study population

Cancer cases in children ages 0 to 5 years were identified from California Cancer Registry records for 1988 to 2007 and matched to their birth certificates (26, 27). Using first and last names and date of birth, we were able to match 89% of cases to a California birth certificate. Controls without a diagnosis of cancer before age 6 were also sampled from the California birth certificates for the same years at a ratio of 20:1, and frequency matched on year of birth. Maternal address and information on potential confounding variables were obtained from the birth certificates. Using data from California death certificates, we excluded controls who died before age 6 ($n = 1{,}522$). After excluding 9 cases and 610 controls with home addresses outside of California, for whom we lacked UVR exposure information, our study population comprised 10,476 cases and 207,568 controls.

Outcomes were defined on the basis of Surveillance Epidemiology and End Results (SEER) groupings. We included the following cancers in our analysis: acute lymphoblastic leukemia (SEER code 11), acute myeloid leukemia (12), Hodgkin's lymphoma (21), non-Hodgkin's lymphoma (22,23), astrocytoma (32), ependymoma/choroid plexus tumors (31), other gliomas (34), intracranial/intraspinal embryonal tumors (33), other intraspinal/intracranial neoplasms (35,36), neuroblastoma (41), Wilms' tumor (61), hepatoblastoma (71), bone tumors (81, 83–85), rhabdomyosarcoma (91), other soft tissue sarcomas (94,95), germ cell tumors (101,102,103), and retinoblastoma (050). Cases were not limited to first primary incident cancers. As a test of the validity of our exposure measure, childhood melanoma (114) was also examined even though our study only included 39 cases. This study was approved by the University of California, Los Angeles Institutional Review Board.

UV exposure assessment

UVR exposure in units of Watt-hours/m^2 (Wh/m^2) was assigned to subjects based on a geostatistical exposure model (ANUSPLIN) that estimates ground-level UVR exposure using data from the National Solar Radiation Database from over 200 UVR measurement stations and also takes into account elevation, latitude, and longitude (28). Using information from 30 years of data (1961–1990), the model predicts average daily total global solar radiation (AVGLO), which is defined as the total amount of direct and diffuse solar radiation in Wh/m^2 received on a horizontal surface. Annual average UVR was then calculated on the basis of a 20 km buffer around each mother's residential address from the child's birth certificate to capture exposure at home and in nearby areas. These measures serve as a proxy for mothers' exposure to UV light during pregnancy. Exposure was divided into quartiles based on its distribution among control subjects (Q1: 3,133–4,946; Q2: >4,946–5,030; Q3: >5,030–5,111; Q4: >5,111–5,804 Wh/m^2).

Statistical methods

We used unconditional logistic regression to examine associations between UVR exposure and the aforementioned childhood cancers. All models were adjusted for our matching variable, child's birth year. We also adjusted

for maternal race/ethnicity since individuals with more pigmentation in their skin need more UVR to maintain appropriate vitamin D levels, and parental race/ethnicity is associated with most childhood cancers (29, 30). We also adjusted for maternal age in the model because higher maternal age is associated with a greater risk of several childhood cancers and may be related to time spent outdoors and sun protection behaviors (31–33). Lastly, we evaluated parity, neighborhood socioeconomic status, and payment method for prenatal care as potential confounders in our models using a 10% change in estimate criterion for inclusion in the model.

Parity is related to some cancers and could be related to time spent outdoors (34, 35), but did not change OR estimates for any of the cancers. Neighborhood SES was calculated on the basis of an algorithm developed by Yost and colleagues from Census data in California using principal components analysis. This index was created from 7 census indicator variables of SES at the block-group level (education index, median household income, percent living 200% below poverty level, percent blue-collar workers, percent older than 16 years in workforce without job, median rent, and median house value; ref. 36). Only the odds ratios for melanoma changed by 10% or more with the addition of neighborhood SES to our models, but due to the small number of cases these estimates were statistically imprecise. Payment type for prenatal care (private/HMO/Blue Cross-Blue Shield vs. Medi-Cal/other/self-pay) has been found by our research group in previous studies to be a good marker of individual level socioeconomic status (37). Adding it to models changed ORs for other gliomas, Hodgkin's lymphomas, and other intracranial and intraspinal neoplasms. However, we decided not to include this variable in the final models since it only affected estimates for a few cancers and did not meaningfully change the interpretation of results for these cancers. Based on the above considerations, our final models adjusted for maternal race/ethnicity, maternal age, and child's birth year. Participants with missing data for any of the covariates were dropped from the regression models. We assessed trend by running the medians of the UVR quartiles as an ordinal variable in our adjusted models.

In addition, we conducted stratified analyses to investigate effect measure modification of UVR exposure by mother's race/ethnicity. Only cancers with an $n \geq 20$ were included to ensure adequate sample size.

Table 1. Characteristics of cancer cases and controls in children ages 0 to 5 in California (1988–2007)

	Controls *n* (%)	All cancers *n* (%)
Mother's race/ethnicity		
White, non-Hispanic	75,437 (37)	4,204 (41)
Hispanic, any race	93,267 (46)	4,561 (44)
Black	14,392 (7)	555 (5)
Asian/PI	20,210 (10)	948 (9)
Total	203,306 (100)	10,268 (100)
Mother's age		
<20	22,619 (11)	1,049 (10)
20—24	50,838 (25)	2,292 (22)
25—29	57,662 (28)	2,961 (28)
30—34	48,036 (23)	2,555 (24)
35+	28,375 (14)	1,617 (15)
Total	207,530 (100)	10,474 (100)
Parity		
0	81,616 (39)	4,058 (39)
1 or more	125,816 (61)	6,413 (61)
Total	207,432 (100)	10,471 (100)
Payment type for prenatal care		
Private/HMO/Blue Cross-Blue Shield	91,467 (51)	5,095 (56)
Medi-Cal/Other/Selfpay/Etc	88,594 (49)	4,026 (44)
Total	180,061 (100)	9,121 (100)
Quintiles of neighborhood SES[a]		
1	49,718 (24)	2,376 (23)
2	48,372 (23)	2,436 (23)
3	46,630 (22)	2,367 (23)
4	33,839 (16)	1,727 (17)
5	28,834 (14)	1,559 (15)
Total	207,393 (100)	10,465 (100)
UV quartiles (Wh/m^2)		
3133—4946	51,973 (25)	2,732 (26)
>4946—5030	52,047 (25)	2,597 (25)
>5030—5111	51,822 (25)	2,651 (25)
>5111—5804	51,466 (25)	2,486 (24)
Total	207,308 (100)	10,466 (100)

[a]Based on Yost and colleagues index (36).

Results

Among the childhood cancers we examined, acute lymphoblastic leukemia (ALL) was most common (36%), followed by central nervous system tumors (21%) and neuroblastoma (11%). Characteristics of cases and controls are presented in Table 1. For all cancers combined, case mothers are slightly more frequently white (41%) compared with mothers of controls (37%), and racial/ethnic distributions differed by cancer type; for example, a higher proportion of ALL and Hodgkin's lymphoma case mothers were Hispanic. For all cancers combined, case mothers were older and of higher individual and neighborhood socioeconomic status.

Odds ratios and 95% confidence intervals for quartiles of UVR exposure adjusting for mother's age and race/ethnicity, and child's birth year are shown in Table 2. For children whose mothers were living in areas with UVR exposure in the highest quartile ($\geq$5,111 Wh/m^2), we estimated decreased odds for developing ALL

(OR: 0.89, 95% CI: 0.81–0.99), hepatoblastoma (OR: 0.69, 95% CI: 0.48–1.00), and non-Hodgkin's lymphoma (OR: 0.71, 95% CI: 0.50–1.02). On the other hand, odds of being diagnosed with melanoma were increased for children of mothers with annual average UVR exposures greater than 5,111 Wh/m^2, but our estimate's confidence interval was wide due to the small number of cases ($n = 39$, 13 in the highest quartile of UVR, OR: 2.34, 95% CI: 0.88–6.21). We also observed an increase in odds for intracranial/intraspinal embryonal tumors with UV exposure of 5,111 Wh/m^2 or above (OR: 1.29, 95% CI: 1.01–1.65).

Effect estimates for models stratified by mother's race/ethnicity are shown in Table 3. For ALL, we observed a 16% decrease in odds among Hispanic mothers and a 35% decrease in odds among Black mothers living in counties in the highest quartile of UVR exposure. For Black mothers, a similar decrease in odds was observed in lower quartiles, but the confidence intervals were wide reflecting small cell sizes. The estimated effect for hepatoblastoma was strongest in the top quartile of UVR in Hispanics (OR = 0.60, 95% CI: 0.35–1.02), and children of White mothers in the top quartile of UV exposure were also protected, but by to a lesser degree, and the 95% CI included the null value (OR = 0.79, 95% CI: 0.44–1.41). Effects could not be estimated in children of Black mothers due to a small number of hepatoblastoma cases. For non-Hodgkin's lymphoma, a 39% decrease in odds was observed for children of White mothers in the top quartile of exposure (OR = 0.61, 95% CI: 0.37–1.01), whereas no effects were seen in children of Hispanic mothers, and our sample size was insufficient for children of Black mothers. We also observed protective effects for neuroblastoma and germ cell tumors in Hispanic children only.

Discussion

Our results suggest a possible protective association between UVR and ALL, hepatoblastoma, and non-Hodgkin's lymphoma in children diagnosed with any of these cancers through age 5. Most estimated effect sizes were strongest in the top quartile of exposure (>5,111 Wh/m^2). An exposure–response relationship with increasing quartiles of UVR exposure was observed for ALL, hepatoblastoma, and intracranial/intraspinal embryonal tumors (P-value for trend $P < 0.05$), but not for other cancers possibly because the effect of UVR is only present at higher levels. Even though our estimates were based on a very small number of children with melanoma in this age group, our data suggested a positive association with melanoma development as would be expected if our exposure assessment for UVR was indeed valid; interestingly, with adjustment for neighborhood SES the OR for the top quartile of UVR exposure was 3.17 (95% CI: 1.16–8.70).

The only previous study examining the association between UVR and multiple cancers in children found protective associations for lymphoid leukemia, acute nonlymphoblastic leukemia, Hodgkin's lymphoma, brain/spinal neoplasms, sympathetic nervous system tumors, retinoblastoma, renal tumors, hepatic tumors, bone tumors, and germ cell/gonadal tumors (15). This was an ecologic study based on solar radiation data from NASA relying on age- and sex- stratified rates of cancer from the International Incidence of Childhood Cancer, Vol. II, which includes data provided by 75 registries in 57 countries adjusting for economic inequality (GINI index and gross domestic product). These findings support our results for ALL, Wilms' tumor, hepatoblastoma, neuroblastoma, and retinoblastoma. However, our study did not replicate inverse associations they reported for brain and spinal neoplasms, and counter to this previous study, we observed a positive association for intracranial/intraspinal embryonal tumors. Since we saw no biologic explanation for this result, we interpreted it as a chance finding that needs to be replicated. For germ cell and gonadal tumors, we observed a protective association only among Hispanics. In addition, we found a decreased risk for non-Hodgkin's lymphomas, which was not observed by Musselman and colleagues.

Of the cancers for which we found protective associations, NHL has been studied the most with regard to sun exposure effects, and a number of studies corroborate our finding of a protective effect. A case–control study of Greek children relied on reports of more than 15 days per year spent at a seaside resort to define high levels of sunlight exposure and found a protective association with childhood NHL (38). A large pooled analysis of 10 case–control studies from several countries participating in the Interlymph Consortium showed a protective effect of recreational sun exposure assessed by questionnaire (17). The California Teachers Study (CTS) prospective cohort relied on the same UVR exposure model as our study and similarly found a reduction in non-Hodgkin's lymphoma risk in areas with higher UVR (22). Interestingly, the CTS study did not find any association with dietary vitamin D estimated from a validated food frequency questionnaire, causing speculations about the observed associations being due to nonvitamin D mechanisms such as immunosuppression through regulatory T cells. Recently, another prospective study of adults in 6 states in the United States found a protective association for UVR exposure for NHL incidence as well (18).

Contrary to these studies, 3 cohorts did not find protective associations (19–21). Also, the Vitamin D Pooling Project did not find a protective association for NHL (39). Whether or not, risk or protective factors for adult NHL also pertain to childhood NHL are uncertain since the most common histopathologic types in childhood are different from those in adulthood.

With regard to leukemia, an ecologic study using cancer incidence rates from the International Agency for Research on Cancer's (IARC) GLOBOCAN database and UVR calculated using latitude and cloud cover estimates from NASA found an inverse association between leukemia incidence and UVR (40). Another ecologic study

Table 2. Adjusted odds ratios and 95% confidence intervals for the association between quartiles of UVR exposure based on mother's address at birth and cancer in offspring ages 0 to 5 in California (1988–2007)

		Adjusted for birth year (controls $n = 207{,}308$)		Adjusted for mother's age, race, and child's birth year (controls $n = 203{,}018$)		
Cancer	**UV quartiles[a] (Wh/m^2)**	**Cases (*n*)**	**OR (95%CI)**	**Cases (*n*)**	**OR 95%CI**	**Trend *P*-value**
ALL		3,396		3,324		
	Q1		ref		ref	
	Q2		0.93 (0.85–1.03)		0.91 (0.83–1.01)	
	Q3		1.03 (0.94–1.13)		0.97 (0.88–1.07)	
	Q4		0.93 (0.84–1.02)		0.89 (0.81–0.99)	0.042
AML		565		552		
	Q1		ref		ref	
	Q2		0.99 (0.78–1.24)		1.00 (0.79–1.26)	
	Q3		1.02 (0.81–1.29)		1.00 (0.79–1.27)	
	Q4		0.87 (0.69–1.11)		0.90 (0.70–1.15)	0.447
Astrocytoma		801		789		
	Q1		ref		ref	
	Q2		0.82 (0.67–1.00)		0.91 (0.75–1.12)	
	Q3		0.83 (0.68–1.01)		0.92 (0.75–1.12)	
	Q4		0.92 (0.76–1.11)		0.96 (0.79–1.17)	0.648
Bone tumors		79		78		
	Q1		ref		ref	
	Q2		0.83 (0.41–1.67)		0.80 (0.39–1.65)	
	Q3		1.47 (0.80–2.73)		1.37 (0.73–2.57)	
	Q4		1.37 (0.73–2.57)		1.22 (0.64–2.32)	0.411
Other gliomas		220		217		
	Q1		ref		ref	
	Q2		0.93 (0.65–1.33)		0.99 (0.68–1.43)	
	Q3		0.80 (0.55–1.16)		0.90 (0.61–1.32)	
	Q4		0.82 (0.57–1.19)		0.91 (0.62–1.32)	0.568
Ependymoma and choroid plexus tumors		244		241		
	Q1		ref		ref	
	Q2		1.04 (0.74–1.46)		1.08 (0.76–1.53)	
	Q3		0.89 (0.63–1.27)		0.92 (0.64–1.33)	
	Q4		0.84 (0.59–1.21)		0.88 (0.61–1.27)	0.465
Hepatoblastoma		258		256		
	Q1		ref		ref	
	Q2		0.95 (0.69–1.32)		0.95 (0.68–1.32)	
	Q3		0.85 (0.61–1.19)		0.82 (0.58–1.16)	
	Q4		0.70 (0.49–1.00)		0.69 (0.48–1.00)	0.044
Hodgkin's lymphoma		62		62		
	Q1		ref		ref	
	Q2		1.19 (0.51–2.75)		0.90 (0.38–2.10)	
	Q3		2.33 (1.11–4.89)		1.72 (0.81–3.66)	
	Q4		1.70 (0.78–3.71)		1.32 (0.60–2.92)	0.345
Non-Hodgkin's lymphoma		271		268		
	Q1		ref		ref	
	Q2		0.80 (0.57–1.12)		0.84 (0.60–1.18)	
	Q3		1.01 (0.73–1.38)		1.05 (0.76–1.45)	
	Q4		0.72 (0.51–1.01)		0.71 (0.50–1.02)	0.119
Intracranial and intraspinal embryonal tumors		559		550		
	Q1		ref		ref	

(Continued on the following page)

Table 2. Adjusted odds ratios and 95% confidence intervals for the association between quartiles of UVR exposure based on mother's address at birth and cancer in offspring ages 0 to 5 in California (1988–2007) (Cont'd)

		Adjusted for birth year (controls $n = 207{,}308$)		Adjusted for mother's age, race, and child's birth year (controls $n = 203{,}018$)		
Cancer	**UV quartiles[a] (Wh/m^2)**	**Cases (*n*)**	**OR (95%CI)**	**Cases (*n*)**	**OR 95%CI**	**Trend *P*-value**
	Q2		1.19 (0.94–1.52)		1.26 (0.98–1.61)	
	Q3		1.14 (0.89–1.45)		1.20 (0.93–1.54)	
	Q4		1.26 (1.00–1.61)		1.29 (1.01–1.65)	0.047
Other intracranial and intraspinal neoplasms		113		108		
	Q1		ref		ref	
	Q2		0.82 (0.48–1.39)		0.95 (0.55–1.66)	
	Q3		0.93 (0.56–1.55)		1.05 (0.62–1.80)	
	Q4		0.92 (0.55–1.54)		1.05 (0.61–1.79)	0.839
Neuroblastoma		1,070		1,042		
	Q1		ref		ref	
	Q2		0.81 (0.68–0.96)		0.90 (0.76–1.07)	
	Q3		0.81 (0.68–0.95)		0.91 (0.77–1.09)	
	Q4		0.87 (0.74–1.03)		0.93 (0.79–1.11)	0.385
Rhabdomyosarcoma		364		352		
	Q1		ref		ref	
	Q2		1.17 (0.89–1.55)		1.22 (0.91–1.63)	
	Q3		0.92 (0.68–1.23)		1.01 (0.74–1.37)	
	Q4		0.88 (0.65–1.19)		0.97 (0.71–1.33)	0.804
Other soft tissue sarcomas		140		136		
	Q1		ref		ref	
	Q2		1.14 (0.69–1.90)		1.08 (0.64–1.82)	
	Q3		1.54 (0.96–2.48)		1.49 (0.92–2.43)	
	Q4		1.33 (0.82–2.18)		1.26 (0.77–2.09)	0.260
Wilms' tumor		824		812		
	Q1		ref		ref	
	Q2		0.90 (0.75–1.09)		0.91 (0.75–1.11)	
	Q3		0.83 (0.68–1.00)		0.87 (0.71–1.06)	
	Q4		0.91 (0.75–1.09)		0.92 (0.76–1.12)	0.335
Germ cell tumors		370		363		
	Q1		ref		ref	
	Q2		1.10 (0.83–1.46)		1.17 (0.88–1.57)	
	Q3		1.12 (0.85–1.49)		1.17 (0.87–1.56)	
	Q4		0.86 (0.63–1.16)		0.90 (0.66–1.23)	0.666
Retinoblastoma		606		591		
	Q1		ref		ref	
	Q2		1.02 (0.81–1.27)		1.03 (0.82–1.30)	
	Q3		1.01 (0.81–1.26)		1.03 (0.82–1.30)	
	Q4		0.88 (0.70–1.10)		0.88 (0.69–1.11)	0.338

[a]Q1: 3,133–4,946; Q2: >4,946–5,030; Q3: >5,030–5,111; Q4: >5,111–5,804 Wh/m^2.

using UVB data from NASA found inverse associations with leukemia incidence rates at the county level in the United States (11). Both of these studies focused on adults and grouped all types of leukemia together, thus subtypes such as ALL could not be investigated. The relationship between retinoblastoma and UVR was examined in 2 ecologic studies. The first found higher incidence in countries and cities with higher annual ambient UVB (41), whereas the second study, building upon the first, used more cases from U.S. SEER data and found a null association (42). In a separate analysis of international data, they also found no association after adjusting for race, climate, and an indicator of economic development (42). These ecologic studies used ambient annual UVR

Table 3. Odds ratios and 95% confidence intervals stratified by mother's race/ethnicity[a]

		White (controls $n = 75,262$)		Hispanic (controls $n = 93,187$)		Black (controls $n = 14,381$)	
Cancer	UV quartiles[b] (Wh/m^2)	Cases (n)	OR[c] 95%CI	Cases (n)	OR[c] 95%CI	Cases (n)	OR[c] 95%CI
ALL		1,235		1,675		96	
	Q1		ref		ref		ref
	Q2		0.95 (0.81–1.12)		0.91 (0.78–1.06)		0.63 (0.39–1.02)
	Q3		1.05 (0.90–1.23)		0.95 (0.82–1.11)		0.67 (0.34–1.31)
	Q4		0.98 (0.84–1.13)		0.84 (0.72–0.98)		0.66 (0.37–1.16)
AML		196		254		36	
	Q1		ref		ref		ref
	Q2		0.72 (0.47–1.09)		1.30 (0.86–1.96)		0.94 (0.42–2.07)
	Q3		1.00 (0.69–1.44)		1.34 (0.90–2.01)		0.40 (0.09–1.81)
	Q4		0.87 (0.60–1.26)		1.07 (0.70–1.63)		1.09 (0.45–2.63)
Astrocytoma		416		269		48	
	Q1		ref		ref		ref
	Q2		0.87 (0.66–1.14)		1.19 (0.80–1.78)		0.78 (0.39–1.58)
	Q3		0.79 (0.60–1.04)		1.22 (0.82–1.81)		1.30 (0.57–2.98)
	Q4		0.95 (0.74–1.22)		1.26 (0.85–1.88)		0.72 (0.31–1.70)
Bone tumors		30		39		<20	
	Q1		ref		ref		ref
	Q2		0.46 (0.13–1.65)		1.13 (0.34–3.77)		∼
	Q3		1.01 (0.38–2.64)		2.13 (0.71–6.37)		∼
	Q4		1.14 (0.47–2.77)		1.56 (0.50–4.91)		∼
Other gliomas		103		73		23	
	Q1		ref		ref		ref
	Q2		1.08 (0.63–1.84)		1.42 (0.66–3.07)		0.53 (0.21–1.33)
	Q3		0.74 (0.41–1.36)		1.50 (0.70–3.21)		0.41 (0.09–1.84)
	Q4		1.23 (0.75–2.01)		0.95 (0.42–2.17)		0.25 (0.06–1.14)
Ependymoma/choroid plexus tumors		99		102		<20	
	Q1		ref		ref		ref
	Q2		0.85 (0.50–1.46)		1.59 (0.82–3.07)		∼
	Q3		0.79 (0.46–1.36)		1.52 (0.79–2.95)		∼
	Q4		0.72 (0.42–1.23)		1.11 (0.55–2.23)		∼
Hepatoblastoma		96		127		<20	
	Q1		ref		ref		ref
	Q2		1.26 (0.75–2.12)		0.76 (0.46–1.25)		∼
	Q3		0.95 (0.54–1.67)		0.71 (0.43–1.16)		∼
	Q4		0.79 (0.44–1.41)		0.60 (0.35–1.02)		∼
Hodgkin's lymphoma		<20		43		<20	
	Q1		ref		ref		ref
	Q2		∼		2.58 (0.56–11.76)		∼
	Q3		∼		4.16 (0.96–18.02)		∼
	Q4		∼		3.91 (0.89–17.21)		∼
Non-Hodgkin's lymphoma		120		104		<20	
	Q1		ref		ref		ref
	Q2		0.82 (0.50–1.33)		0.63 (0.34–1.19)		∼
	Q3		0.83 (0.52–1.35)		1.14 (0.65–1.98)		∼
	Q4		0.61 (0.37–1.01)		0.79 (0.43–1.44)		∼
Intracranial/intraspinal embryonal tumors		244		237		36	
	Q1		ref		ref		ref
	Q2		1.02 (0.69–1.50)		1.18 (0.78–1.77)		1.47 (0.66–3.27)

(Continued on the following page)

Table 3. Odds ratios and 95% confidence intervals stratified by mother's race/ethnicity[a] (Cont'd)

		White (controls $n = 75{,}262$)		Hispanic (controls $n = 93{,}187$)		Black (controls $n = 14{,}381$)	
Cancer	UV quartiles[b] (Wh/m^2)	Cases (n)	OR[c] 95%CI	Cases (n)	OR[c] 95%CI	Cases (n)	OR[c] 95%CI
	Q3		1.32 (0.93–1.88)		0.97 (0.64–1.47)		∼
	Q4		1.40 (1.00–1.95)		1.10 (0.73–1.67)		1.35 (0.53–3.40)
Other intracranial/intraspinal neoplasms		46		47		<20	
	Q1		ref		ref		ref
	Q2		0.92 (0.38–2.23)		0.85 (0.36–2.00)		∼
	Q3		1.34 (0.61–2.94)		0.73 (0.31–1.74)		∼
	Q4		1.29 (0.59–2.82)		0.83 (0.35–1.94)		∼
Neuroblastoma		537		357		67	
	Q1		ref		ref		ref
	Q2		0.99 (0.78–1.26)		0.73 (0.54–1.00)		0.77 (0.42–1.40)
	Q3		1.12 (0.89–1.41)		0.65 (0.48–0.89)		1.04 (0.49–2.21)
	Q4		0.94 (0.75–1.19)		0.81 (0.60–1.10)		0.87 (0.44–1.71)
Rhabdomyosarcoma		141		147		29	
	Q1		ref		ref		ref
	Q2		1.00 (0.64–1.57)		1.66 (0.96–2.88)		1.47 (0.59–3.65)
	Q3		0.95 (0.61–1.50)		1.18 (0.66–2.09)		1.57 (0.50–4.94)
	Q4		0.78 (0.49–1.23)		1.43 (0.81–2.52)		0.56 (0.15–2.18)
Other soft tissue sarcomas		57		60		<20	
	Q1		ref		ref		ref
	Q2		1.03 (0.48–2.23)		1.03 (0.44–2.44)		∼
	Q3		1.09 (0.52–2.31)		1.49 (0.66–3.32)		∼
	Q4		1.38 (0.70–2.72)		1.00 (0.42–2.38)		∼
Wilms' tumor		355		337		68	
	Q1		ref		ref		ref
	Q2		0.81 (0.61–1.07)		1.03 (0.72–1.46)		1.22 (0.64–2.32)
	Q3		0.58 (0.42–0.79)		1.20 (0.86–1.70)		1.45 (0.65–3.22)
	Q4		0.73 (0.56–0.97)		1.15 (0.81–1.63)		1.57 (0.79–3.13)
Germ cell tumors		123		155		21	
	Q1		ref		ref		ref
	Q2		1.02 (0.61–1.69)		0.77 (0.50–1.20)		1.04 (0.33–3.26)
	Q3		1.31 (0.82–2.10)		0.62 (0.39–0.98)		2.63 (0.80–8.63)
	Q4		0.90 (0.55–1.48)		0.57 (0.35–0.91)		0.75 (0.18–3.13)
Retinoblastoma		204		277		45	
	Q1		ref		ref		ref
	Q2		1.25 (0.86–1.80)		0.93 (0.64–1.34)		1.14 (0.53–2.43)
	Q3		0.92 (0.62–1.36)		1.02 (0.71–1.46)		1.79 (0.74–4.34)
	Q4		0.91 (0.62–1.32)		0.83 (0.57–1.20)		0.97 (0.39–2.41)

[a]Only cancers with at least 20 cases are included.
[b]Q1: 3,133–4,946; Q2: >4,946–5,030; Q3: >5,030–5,111; Q4: >5,111–5,804 Wh/m^2.
[c]Adjusted for mother's age and child's year of birth.

averages for cities, states or countries, in contrast to our case–control study using UVR measures based on a 20-km radius around a mother's address. For hepatoblastoma, our study is only the second one to show a protective association from UVR exposure and these findings need to be confirmed in other studies (15).

UVR modulates the immune system through vitamin D and other pathways, and it is known to cause local and systemic immunosuppression (9). The role of vitamin D during pregnancy in the health of the child has not been well characterized aside from the documented increased risk of rickets among children born to vitamin D-deficient mothers (43). Vitamin D modulates the developing immune system and regulates cytokines related to IgE-mediated allergy (44). Adverse child health outcomes related to immune function, including asthma and

wheezing, have been associated with low maternal vitamin D status during pregnancy (43, 44). Given its effects on the developing immune system and its potential anticancer properties, it has been hypothesized that maternal vitamin D status may be related to childhood cancer (44).

Both UVR and vitamin D were shown to be protective against tuberculosis and influenza infections (9), and maternal influenza infection was associated with higher odds of ALL in offspring (45). This provides support for a potential role of UVR in reducing cancer risk via reducing susceptibility to viral infections. If this is the mechanism then we might expect to see seasonality in the effect of UVR. To investigate the issue of seasonality we conducted stratified analyses for ALL cases by season of birth, comparing the sunny season in California (April–September) to the less sunny season (October–March). Indeed, for ALL we observed a slightly stronger protective effect for births occurring in the April to September period (results not shown). Month of birth was related to ALL diagnosis in previous studies (46, 47).

We also investigated associations by race/ethnicity (White, Hispanic, and Black) to examine the potential influence of skin pigmentation. UVR appeared to be protective for ALL among children of Black and Hispanic mothers, though the confidence intervals were very wide for children of Black mothers due to a small sample size. The negative associations for NHL and Wilms' tumor were observed mainly among white children, whereas for hepatoblastoma the effect of UVR seems stronger among children of Hispanic than White mothers. These differences in UVR effects may not only be due to skin pigmentation but also to time spent outdoors, sun protection or other behaviors that may affect UVR exposures in these women and their children or other race/ethnicity specific cultural or behavioral factors that interact with UVR exposure effects. A nationally representative survey reported lower use of sunscreen, but higher use of shade and long sleeves for sun protection in Hispanics compared with non-Hispanic whites (48). Studies have also found that sun protection behaviors in Hispanics are related to acculturation, and thus are changing over time (49, 50).

The measure of UVR employed in this study is a composite of several years of data and therefore does not allow us to look at trimester-specific exposures. This is problematic if there are narrow windows of susceptibility when a mother's UVR exposure may be particularly important for protection against cancer in their offspring. Also, we were not able to assess the relative importance of prenatal and postnatal UVR exposures in childhood cancer etiology. However, in our stratified analyses for ALL cases by season of birth, the stronger protective effect for births occurring in the April to September period might indicate the importance of late pregnancy or early life UVR exposures in the etiology of ALL.

If a mother moved during pregnancy, we may have misclassified her exposure if UVR levels for the new residence were different. A recent review found that in 7 studies conducted in the United States, 14% to 32% of the mothers moved during pregnancy (51), but the median distance of moving was less than 10 km. Since our UVR exposure metric represents a 20 km buffer around the mother's home, we would not expect moves to be a strong source of exposure misclassification in this study, and we would expect misclassification to be nondifferential with respect to the outcome and to bias estimates toward the null. Also, the increased melanoma risk in our study supports the validity of our exposure measure, as does the increased risk for melanoma in adults based on the same UVR exposure data for California in previous studies (24, 25).

Beyond the variables we were able to control for, unmeasured risk factors for childhood cancer that vary by region similarly to UVR may be causing residual confounding. To investigate possible differences by region for ALL, we conducted stratified analyses based on statewide UVR quartiles separately for Southern California, which in general has higher UVR, and Northern California (results not shown). In Southern California, UVR exposure was found to decrease odds of ALL in the top 3 quartiles, whereas in Northern California only the top quartile of exposure was found to be protective. This suggests that in Northern California, only those living in areas with the highest exposures receive enough UVR for a protective effect. There may also be confounding from other risk factors that vary regionally, such as diet or health behaviors that account for the observed associations. Also, we did not adjust for multiple comparisons.

Conclusion

These preliminary findings suggest that UVR during pregnancy is related to lower likelihood of some childhood cancers. The mechanism may be through vitamin D production or through other UVR-mediated immune pathways. It is also possible that the observed associations are due to residual spatial confounding from yet unknown protective factors that we should try to investigate. Further studies are needed before any specific public health recommendations can be made, and any prevention messages must be carefully tailored to balance the possible benefits of UVR with skin cancer prevention (52). Future studies should collect residential history, explore additional factors that may be correlated with UVR exposure, investigate trimester-specific effects, and possibly include biomarkers of immune function and vitamin D to further explore possible pathways for the observed associations. Distinguishing the effects of UVR and vitamin D will be necessary to identify the best manner in which to protect children from these cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: C. Lombardi, J.E. Heck, M. Cockburn, B. Ritz
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Lombardi, B. Ritz
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.E. Heck, M. Cockburn, B. Ritz
Writing, review, and/or revision of the manuscript: C. Lombardi, J.E. Heck, M. Cockburn, B. Ritz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Cockburn
Study supervision: J.E. Heck

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