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Prenatal Risk and Protective Factors for Childhood Cancer: Investigating the Effects of Ultraviolet Radiation, Pesticide Exposure, and Maternal Diet

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Prenatal Risk and Protective Factors for Childhood Cancer: Investigating the Effects of Ultraviolet Radiation, Pesticide Exposure, and Maternal Diet

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Christina Lombardi

2013

ABSTRACT OF THE DISSERTATION

Prenatal Risk and Protective Factors for Childhood Cancer: Investigating the Effects of Ultraviolet Radiation, Pesticide Exposure, and Maternal Diet

by

Christina Lombardi

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2013

Professor Beate Ritz, Chair

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. Additional risk factors have been suggested, but due to the rarity of childhood cancers, it has been difficult to establish causes and hence targets for prevention. We investigated ultraviolet radiation (UVR), pesticides, and maternal dietary patterns as possible risk and protective factors. Studies have shown that higher solar UVR may be related to lower risk of some cancers in adults and children. In a large, population-based case-control study we tested the hypothesis that childhood cancers may be influenced by UVR. Cancers in children ages 0 to 5 years were identified from California Cancer Registry records for 1988-2007 and linked to birth certificate data. Controls were sampled from birth certificates. Based on birth address, we

assigned UVR exposure using a geostatistical exposure model developed with data from the National Solar Radiation Database. Our preliminary findings suggest that UVR during pregnancy may decrease the odds of some childhood cancers. In the same study population we evaluated the associations of exposure to specific pesticide types during pregnancy with glial tumors in young children in California using a validated geographic exposure model. We observed increased odds of astrocytoma for residential pesticide exposure to herbicides, insecticides and fungicides, as well as for several chemical classes of pesticides. Additionally, using data from a multi-institutional case-control study of retinoblastoma in the United States and Canada, we investigated the association of maternal prenatal diet with the risk for unilateral retinoblastoma among children less 15 years of age. Previous studies have shown that mother's diet during pregnancy may affect her offspring's risk of cancer. Our results suggest that a dietary pattern with high fruit and vegetable consumption and low consumption of fried foods and sweets during pregnancy, as well as a dietary pattern with high fruit and vegetable consumption and low consumption of red and cured meats, may reduce the odds of unilateral retinoblastoma in offspring.

The dissertation of Christina Lombardi is approved.

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2013

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LIST OF ACRONYMS

ALL	acute lymphoblastic leukemia
CDPR	California Department of Pesticide Regulation
CNS	central nervous system
DES	diethylstilbestrol
OR	odds ratio
PUR	pesticide use reporting
SES	socioeconomic status
UVR	ultraviolet radiation

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1. INTRODUCTION

Childhood cancers are rare diseases that may be initiated prenatally. A powerful example of the carcinogenicity of prenatal exposures is the elevated rates of vaginal and cervical clear-cell adenocarcinoma observed in girls and young women exposed to diethylstilbestrol (DES) in utero. Starting in 1938 DES was prescribed to some pregnant women for the prevention of pregnancy complications, but use declined when it was found to be ineffective in clinical trials.[1] It wasn't until the 1970s that the association between DES and vaginal clear-cell adenocarcinoma was discovered.[2-4]

For most pediatric cancers there are few known causes. Ionizing radiation, Down syndrome, and some genetic or chromosomal anomalies have been identified clearly as risk factors.[5] Additional potential risk factors have been suggested for specific cancer types, but mostly due to the rarity of the childhood cancers, it has been difficult to establish causes, and preventive measures are similarly lacking.

About 10,730 new cases of cancer are diagnosed in children 0–14 years of age each year in the United States (NCI 2009). Leukemia is the most common childhood cancer, followed by brain and other CNS tumors. Through improved diagnosis and treatment methods 5-year survival rates for childhood cancer overall have increased to about 80% in 1996-2003 from 58.1 percent in 1975–77.[6]

Finding protective factors is important, and some studies have indicated that ultraviolet radiation (UVR) exposure may reduce cancer risk. With a large number of cases from the California Cancer Registry, we examined the associations between UVR exposure based on mother's residential address from the child's birth certificate and specific childhood cancers

(Section 4). In the same study population we evaluated the associations of exposure to specific pesticide types during pregnancy with glial tumors in young children in California using a validated geographic exposure model (Section 5). We also investigated the association of maternal prenatal diet with the risk for unilateral retinoblastoma among children less 15 years of age in the United States and Canada in a multi-institutional case-control study (Section 6).

2. BACKGROUND

2.1 Childhood Brain Tumors

Childhood brain tumors are the most common solid tumors found in children and the leading cause of cancer death in children. Most brain tumors in children occur in glial cells (glia is Greek for "glue"), which were once thought to be solely support cells for neurons, but are now understood to perform a wide array of functions, though they do not generate action potentials as neurons do.[7] The most common subtype of brain tumors in children is astrocytoma (52%) followed by primitive neuroectodermal tumors (PNETs) or medulloblastoma (21%), and ependymoma (9%).[8] Other gliomas account for another 15% of tumors. These tumor types peak at different ages in children suggesting distinct etiologies.[8] Also, the predominant subtypes differ from those found in adults.

A small percentage (~5%) of brain tumors can be attributed to family history of brain tumors or genetic syndromes, more specifically neurofibromatosis, Li-Fraumeni syndrome, basal cell nevus (Gorlin's) syndrome, Turcot syndrome, and ataxia telangiectasia.[8] Several possible risk factors have been investigated, but only ionizing radiation has been firmly established. Associations have also been found with high birth weight, pesticides, paternal smoking, viral infection during pregnancy, head trauma, paternal occupational exposure to PAHs (employment

in the motor vehicle-related occupations, the chemical and petroleum industries, and with frequent paint exposures), use of narcotics and penthrane (an anesthetic agent) during delivery, and use of decongestants.[8] A recent pooled analysis does not find much evidence for an association between brain tumors and extremely low-frequency magnetic fields.[9] Air pollution has also been investigated as a possible risk factor with mixed results.[10] With regard to protective factors, maternal multivitamin use and specifically folate supplementation have been identified as potentially reducing risk of childhood brain tumors.[8]

2.2 Childhood Retinoblastoma

Retinoblastoma is a rare childhood tumor of the embryonal retina with a mean age-adjusted incidence rate of 11.8 cases per million children ages 0–4 years in the U.S.[11] It is known for being the basis of Knudson's "two-hit" model of carcinogenesis.[12] It occurs when both alleles of the *RB1* tumor suppressor gene are inactivated in a retinal cell. More recently additional genetic changes such as aneuploidy and genetic instability have been implicated in retinoblastoma tumorigenesis.[13,14] Bilateral disease, which accounts for 27% of cases in children less than 5 years of age, is described either as familial, occurring when an *RB1* mutation is inherited a parent, or sporadic, occurring with a new germline mutation in *RB1*.[11,15] In both of these cases the child will have a mutated *RB1* allele in every cell, and then a second hit inactivates the second *RB1* allele in a retinal cell initiating the disease.[16] Of the children who inherit an RB1 mutation 85% go on to develop bilateral retinoblastoma, usually before age 5. Unilateral retinoblastoma, which accounts for 72% of retinoblastoma cases in children less than 5 years of age, most often results from somatic mutations to the *RB1* gene and peaks at age 6-7 months.[15] In spite of knowledge on some of the genetic mechanisms responsible, the risk factors for retinoblastoma are largely unknown.

3. METHODS

3.1 Environmental Health Tracking and Childhood Cancer Study

The Environmental Health Tracking and Childhood Cancer Study was a large, population-based case-control study based on record linkage (PI: Julia Heck). Cancer cases in children ages 0 to 5 years were identified from California Cancer Registry records for 1988-2007 and matched to their California birth certificates using first and last names and date of birth. A matching rate of 89% was achieved. Controls without a diagnosis of cancer prior to age 6 were also sampled from the California birth certificates for the same years at a ratio of 20:1, frequency matched on year of birth. Maternal address and other parental variables were obtained from the birth certificates. Death certificate data were used to exclude controls who died before age 6.

Subjects were linked to various exposure data sets based on mother's address from the birth certificate, including California Air Resource Board air monitoring data for criteria air pollutants and air toxics, pesticide data, and a UVR geostatistical exposure surfaces created with data from the National Solar Radiation Database. Details regarding exposure measures to be used in these analyses will be provided in subsequent sections. Cases were selected only through age 5 to reduce potential exposure misclassification due to moving after birth and also because many childhood cancers peak during these ages. Additional variables from the child's birth certificate and from census data linked to each subject using mother's residential address from the birth certificate will be considered as potential confounders or effect measure modifiers.

3.2 UV Radiation 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 (5 in California) and also takes into account elevation, latitude and longitude.[17] 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 [18,19] and reduced risk of non-Hodgkin's lymphoma.[20]

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 based on 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: 3133 - 4946; Q2: >4946 - 5030; Q3: >5030 - 5111; Q4: >5111 – 5804 Watt-hrs/m^2). These exposures capture spatial differences in UV exposure, but not temporal differences due to seasonality, which will be addressed in a separate paper by another member of the research team.

3.3 Pesticide Exposure Model

Pesticide reporting requirements started in the 1950s in California on a limited basis, and then expanded in 1970 to requiring reporting of all restricted pesticide use by famers and all pesticide use by commercial pesticide applicators. In 1990, California became the first state to

require reporting of all agricultural pesticide use.[21] California has the most detailed pesticide reporting system in the United States, collecting information on each pesticide's active ingredient, the pounds applied, the crop and acreage of the field, the application method, and the date and location of the application at a resolution of 1 square mile (according to the Public Land Survey System (PLSS) grid). Reporting includes agricultural fields, as well as parks, golf courses, cemeteries, rangeland, pastures, areas along roadsides/railroads, and post-harvest pesticide treatment of crops, treatments in poultry and fish production, and some livestock applications. The principal exclusions are home and garden use, and most industrial and institutional use.[21] Pesticide use is reported monthly to county agriculture commissioners who then report it to the California Department of Pesticide Regulation (CDPR). The Pesticide Use Reporting (PUR) data is made available to researchers through CDPR.

Our GIS-based Residential Ambient Pesticide Estimation System (GRAPES 4.0) combines this detailed PUR data with land use data from the California Department of Water Resources to pinpoint the location of the pesticide application within each 1 square mile land parcel for more accurate exposure assessment.[22] Collection of land use survey data by the State of California started in the 1950s and became annual by the mid-1960s. Its primary purpose was to map agricultural land, defining field boundaries using aerial photos and satellite imagery. Maps were released digitally starting in 1986. Our GIS-based exposure model combines this land use data with the PUR data allowing for more spatially refined exposure estimates. Specifically, the land use data allows us to locate the area (field, orchard, etc) within the 1 square mile grid for PUR data where the pesticides were applied. Without the land use data the same pesticide exposure would be assumed for the entire 1 square mile grid. Since pesticides are thought to drift about 500m or less from the site of application this would lead to exposure misclassification.[22-25]

A simulation study comparing effect estimates from a hypothetical case-control study using our exposure model to those using exposures derived from simpler models, based on PUR or land use only, found ORs were severely attenuated with simpler models.[22] This model has been used successfully in our research group to study associations of pesticide exposures with neural tube defects and Parkinson's disease.[24,26,27]

Using this detailed pesticide exposure model we assessed pesticide exposures within a 500-meter buffer around each mother's residential address from her child's birth certificate. Addresses were assigned latitude and longitude coordinates (geocodes) using our open source geocoder with a manual resolution process for unmatched addresses.[28] In our study population 309 addresses were unknown or unmatchable. For birth years prior to 1998, 500-meter buffers were drawn around residential zip code centroids (the geometric center of a zip code where the mother resided) since full maternal addresses were not available. Using date of last menstrual period and date of birth from the birth certificate, pesticide exposure was assessed for the entire pregnancy and the child's first year of life. Our analyses include 106 pesticides that have been classified by the EPA as possibly or probably carcinogenic based on animal studies and epidemiologic studies when available.[29] These were then grouped by pesticide type based upon the PAN Pesticide Database as: herbicides, insecticides, fungicides, and soil fumigants (see Table 5.1).[30] We also grouped pesticides by their corresponding chemical classes (e.g. organochlorines, halogenated organics) since we expected effects would be similar within these classes.

For pregnancy and first year of life exposure periods we considered both ever exposure to a pesticide type (ever vs. never) and exposure above the median to a pesticide type (above median vs. median or below). Exposure above the median was defined as being exposed to at

least one pesticide of that specific type (e.g. fungicide) above the median (in lbs per area for 500-meter buffer) for controls. The unexposed group was defined as subjects who were never exposed to any of the carcinogenic pesticides during the relevant time period (pregnancy/first year) since the majority of exposed subjects tended to be exposed to multiple carcinogenic pesticides. Stratified analyses were performed to test for effect measure modification by mother's race/ethnicity, child's birth year and neighborhood SES.

In ongoing analyses, we plan to examine exposure intensity by creating a variable for the number of pesticides each subject was exposed to during pregnancy. Also, we plan to implement a hierarchical linear model with individual pesticides as the first level and pesticide classes as the second.[26] The model weights effect estimates for individual pesticides toward the mean for each pesticide class, which helps address the clustering of effects by chemical class and the issue of multiple comparisons.[26]

3.4 Research on the Environment and Children's Health Study

The Research on the Environment and Children's Health (REACH 2) study was a multi-institutional case-control study of retinoblastoma among children less 15 years of age in the United States and Canada. The primary aim was to investigate the associations of sporadic bilateral retinoblastoma and unilateral retinoblastoma with parental exposures and polymorphisms in DNA repair and carcinogen metabolizing enzyme genes. Parental exposure information was obtained via structured telephone interviews conducted from 2007-2012 with both parents when available. The questionnaire collected information on basic demographics and several possible exposures possibly related to retinoblastoma including, occupational exposures, medical radiation, diet, supplement use, tobacco, alcohol, and residential pesticide use. Blood

samples were collected from cases and their parents, and saliva samples were collected for controls to perform genetic analyses.

Cases of sporadic bilateral retinoblastoma and unilateral retinoblastoma were identified at the following nine large referral centers for retinoblastoma: Wills' Eye Hospital (Philadelphia), Northwestern University Medical Center (Chicago), New York Hospital/Cornell University Medical Center (New York), Children's Hospital of Los Angeles, Hospital for Sick Children (Toronto), Children's Hospital and Regional Medical Center (Seattle), St. Jude Children's Research Hospital (Memphis), the University of Illinois at Chicago, and The Children's Hospital of Philadelphia.

Parents of cases provided lists of their child's friends or relatives under age 15 years to contact as possible controls. The study aimed to match one to two friends and one relative without a previous cancer diagnosis to each case in the same or adjacent age group (0-1, 2-3, 4-5, 6-7, 8-9, 10-11,12-13 and 14-15 years). The study was not able to recruit controls for all cases.[31] Subjects were eligible if they resided in North America, had at least one parent who spoke English or Spanish, and had at least one biological parent available to participate in the study.

3.5 Maternal Dietary Assessment

A 72-item modified Willett food frequency questionnaire was used to assess mother's diet during pregnancy.[32] The food frequency questionnaire was previously validated and has been successfully used for other studies of childhood cancer.[32,33] Mothers were administered the questionnaire 0-13 years after pregnancy, with approximately 83% completing the questionnaire within 5 years after pregnancy. Frequency of consuming specific foods during the second trimester of pregnancy was collected. Since portion size information was not collected, a standard portion size (based on FDA recommendations) was used to calculate total calories per

day, with caloric information taken from the USDA web database.[34] Collecting portion size information in food frequency questionnaires may not add validity to dietary assessment.[35] Food frequencies were converted to servings per day as: (never or less than once per month"=0; "1 to 3 per month"=.08; "1 per week"=.14; "2 to 4 per week"=.43; "5 to 6 per week"=.8; "1 per day"=1[35]; "2 to 3 per day"=2.5; "4 to 5 per day"=4.5; "6+ per day"=6.[36] Servings per day for individual food items were totaled within 13 food groups (number of items): fruit (6), citrus fruit (2), dairy (7), vegetables, excluding potatoes (14), meat and seafood (14), poultry (2), fresh red meat (4), cured meat (3), seafood (5), grains (8), sweets, including beverages (9), fried foods (4), alcohol (3) (Table 6.1).

To capture dietary patterns we created two dietary scales: one capturing a diet high in fruits and vegetables and low in red and cured meats similar to Chuang *et al*; and one capturing a diet high in fruits and vegetables and low in fried foods and sweets.[37] Analysis of dietary patterns has the advantages of not having to separate effects of correlated nutrients, of accounting for interactions between foods, and of capturing combined effects from a diet, which may be easier to detect than those of individual foods or components.[35] The scales were constructed based on food group tertiles, assigning a zero for fruits and vegetable intake in the lowest tertile, 1 for the middle tertile and 2 for the top tertile. The opposite coding was used for red meat, cured meat, fried food and sweets. Hence the scale ranged from 0 to 8, with higher values indicating healthier diets.

4. SOLAR UV RADIATION AS A POSSIBLE PROTECTIVE FACTOR FOR CANCER IN YOUNG CHILDREN

4.1 Introduction

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.[38] Recent meta-analyses of vitamin D levels and breast [39-41] and colorectal cancer [41-43] have provided some support for protective effects of vitamin D, but there have been[43] inconsistent results for other cancers.[44] Also, other UV-induced mechanisms may contribute to potential protection from cancer.[45]

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, and were found in ecological studies in the U.S. and other countries.[46] An inverse association was also observed for leukemia in the U.S.[47] First, an ecological 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.[48] Subsequently, a landmark study in the U.S. 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.[49] 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.[50] A study in the U.S. using the NASA UVR data at the county level found inverse associations with incidence of and mortality from several cancers.[47] They also found positive associations for some cancer sites (anus, cervix, melanoma, oral cavity, and other skin).

Ecological studies in Europe, Australia, and Asia have also found inverse associations for several cancers in adults.[46] In considering these previous studies, it should be noted that mechanisms protecting against cancer mortality may differ from those protecting against cancer incidence.

Multi-country 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.[46] A recent ecological study of childhood cancers in several countries found a protective effect of solar UVR on risks for several cancers in children ages 0-14 using rates extracted from cancer registries and adjusting for measures of economic development of the country.[51] However, it may be difficult to adequately control for possible confounding factors such as smoking, alcohol use, diet, reproductive factors, infections and SES in multi-country studies.

These ecological studies have provided a good foundation for this field, but may still be subject to the ecological 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.[46] 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.[20,52-58] In particular several studies investigated non-Hodgkin's lymphoma with some prospective studies showing a protective association[20,54,58] with UVR and others showing a harmful[55,56] or null association.[57]

Only one previous study examined the association between UVR and cancer in children, and it was limited to ecological 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[18,19] and reduced risk of non-Hodgkin's lymphoma.[20]

4.2 Methods

Study population

Cancer cases in children ages 0 to 5 years were identified from California Cancer Registry records for 1988-2007 and matched to their birth certificates.[59,60] 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 prior to age 6 were also sampled from the California birth certificates for the same years at a ratio of 20:1, 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 nine 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 based on 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), astrocytomas (32), ependymomas/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.[17] 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 based on 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: 3133 - 4946; Q2: >4946 - 5030; Q3: >5030 - 5111; Q4: >5111 – 5804 Watt-hrs/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.[61,62] 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.[63-65] Finally, 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[66,67], but did not change OR estimates for any of the cancers. Neighborhood SES was calculated based on an algorithm developed by Yost et al from Census data in California using principal components analysis. This index was created from seven 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).[68] 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.[69] 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.

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

4.3 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 4.1. For all cancers combined, case mothers are slightly more frequently white (41%) compared to mothers of controls (37%), and racial/ethnic distributions differed by cancer type; e.g. 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.

Table 4.1: Characteristics of cancer cases and controls in children ages 0-5 in California (1988 -2007)

	Controls		All Cancers	
	n	%	n	%
Mother's race/ethnicity				
White, non-hispanic	75437	37	4204	41
Hispanic, any race	93267	46	4561	44
Black	14392	7	555	5
Asian/PI	20210	10	948	9
Total	203306	100	10268	100
Mother's age				
<20	22619	11	1049	10
20-24	50838	25	2292	22
25-29	57662	28	2961	28
30-34	48036	23	2555	24
35+	28375	14	1617	15
Total	207530	100	10474	100
Parity				
0	81616	39	4058	39
1 or more	125816	61	6413	61
Total	207432	100	10471	100
Payment type for prenatal care				
Private/HMO/Blue Cross-Blue Shield	91467	51	5095	56
Medi-cal/Other/Selfpay/Etc	88594	49	4026	44
Total	180061	100	9121	100
Quintiles of neighborhood SES[a]				
1	49718	24	2376	23
2	48372	23	2436	23
3	46630	22	2367	23
4	33839	16	1727	17
5	28834	14	1559	15
Total	207393	100	10465	100
UV quartiles (Watt hrs/m^2)				
3133 - 4946	51973	25	2732	26
>4946 - 5030	52047	25	2597	25
>5030 - 5111	51822	25	2651	25
>5111 - 5804	51466	25	2486	24
Total	207308	100	10466	100

[a]Based on Yost et al index.[68]

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 4.2. For children whose mothers were living in areas with UVR exposure in the highest quartile (≥5111 Watt-hrs/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 5111 Watt-hrs/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 5111 Watt-hrs/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 4.3. For ALL, we observed a 16% decrease in odds among Hispanic mothers and a 35% decrease in odds among African-American 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 African-American 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), while no effects were seen in children of Hispanic mothers, and our sample size was insufficient

for children of African-American mothers. We also observed protective effects for neuroblastoma and germ cell tumors in Hispanic children only.

Table 4.2: Adjusted odds ratios and 95% confidence intervals for the association between quartiles of UV radiation exposure based on mother's address at birth and cancer in offspring ages 0-5 in California (1988-2007)

		Adjusted for birth year (controls n=207308)			Adjusted for mother's age, race, and child's birth year (controls n=203018)			
Cancer	UV quartiles[a] (Watt hrs/m^2)	Cases (n)	OR	95 %CI	Cases (n)	OR	95 %CI	Trend p-value
ALL		3396			3324			
	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		0.7	(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		1.7	(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		
	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		1070			1042		
	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)		0.9	(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: 3133 - 4946; Q2: >4946 - 5030; Q3: >5030 - 5111; Q4: >5111 – 5804 Watt-hrs/m^2.

Table 4.3: Odds ratios and 95% confidence intervals stratified by mother's race/ethnicity[a]

		White (controls n=75262)			Hispanic (controls n=93187)		
Cancer	UV quartiles[b] (Watt hrs/m^2)	Cases (n)	OR[c]	95 %CI	Cases (n)	OR[c]	95 %CI
ALL		1235			1675		
	Q1		ref			ref	
	Q2		0.95	(0.81, 1.12)		0.91	(0.78, 1.06)
	Q3		1.05	(0.90, 1.23)		0.95	(0.82, 1.11)
	Q4		0.98	(0.84, 1.13)		0.84	(0.72, 0.98)
AML		196			254		
	Q1		ref			ref	
	Q2		0.72	(0.47, 1.09)		1.30	(0.86, 1.96)
	Q3		1.00	(0.69, 1.44)		1.34	(0.90, 2.01)
	Q4		0.87	(0.60, 1.26)		1.07	(0.70, 1.63)
Astrocytoma		416			269		
	Q1		ref			ref	
	Q2		0.87	(0.66, 1.14)		1.19	(0.80, 1.78)
	Q3		0.79	(0.60, 1.04)		1.22	(0.82, 1.81)
	Q4		0.95	(0.74, 1.22)		1.26	(0.85, 1.88)
Bone Tumors		30			39		
	Q1		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		
	Q1		ref			ref	
	Q2		1.08	(0.63, 1.84)		1.42	(0.66, 3.07)
	Q3		0.74	(0.41, 1.36)		1.50	(0.70, 3.21)
	Q4		1.23	(0.75, 2.01)		0.95	(0.42, 2.17)
Ependymoma/Choroid Plexus Tumors		99			102		
	Q1		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		
	Q1		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		

Q1		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	
Q1		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	
Q1		ref		ref	
Q2		1.02	(0.69, 1.50)	1.18	(0.78, 1.77)
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)
Other intracranial/intraspinal neoplasms	46			47	
Q1		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	
Q1		ref		ref	
Q2		0.99	(0.78, 1.26)	0.73	(0.54, 1.00)
Q3		1.12	(0.89, 1.41)	0.65	(0.48, 0.89)
Q4		0.94	(0.75, 1.19)	0.81	(0.60, 1.10)
Rhabdomyosarcoma	141			147	
Q1		ref		ref	
Q2		1.00	(0.64, 1.57)	1.66	(0.96, 2.88)
Q3		0.95	(0.61, 1.50)	1.18	(0.66, 2.09)
Q4		0.78	(0.49, 1.23)	1.43	(0.81, 2.52)
Other Soft Tissue Sarcomas	57			60	
Q1		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	
Q1		ref		ref	
Q2		0.81	(0.61, 1.07)	1.03	(0.72, 1.46)
Q3		0.58	(0.42, 0.79)	1.20	(0.86, 1.70)
Q4		0.73	(0.56, 0.97)	1.15	(0.81, 1.63)
Germ cell tumors	123			155	
Q1		ref		ref	
Q2		1.02	(0.61, 1.69)	0.77	(0.50, 1.20)
Q3		1.31	(0.82, 2.10)	0.62	(0.39, 0.98)
Q4		0.9	(0.55, 1.48)	0.57	(0.35, 0.91)
Retinoblastoma	204			277	
Q1		ref		ref	
Q2		1.25	(0.86, 1.80)	0.93	(0.64, 1.34)
Q3		0.92	(0.62, 1.36)	1.02	(0.71, 1.46)
Q4		0.91	(0.62, 1.32)	0.83	(0.57, 1.20)

		Black (controls n=14381)		
Cancer	UV quartiles[b] (Watt hrs/m^2)	Cases (n)	OR[c]	95 %CI
ALL		96		
	Q1		ref	
	Q2		0.63	(0.39, 1.02)
	Q3		0.67	(0.34, 1.31)
	Q4		0.66	(0.37, 1.16)
AML		36		
	Q1		ref	
	Q2		0.94	(0.42, 2.07)
	Q3		0.40	(0.09, 1.81)
	Q4		1.09	(0.45, 2.63)
Astrocytoma		48		
	Q1		ref	
	Q2		0.78	(0.39, 1.58)
	Q3		1.30	(0.57, 2.98)
	Q4		0.72	(0.31, 1.70)
Bone Tumors		<20		
	Q1		ref	
	Q2		~	~
	Q3		~	~
	Q4		~	~
Other Gliomas		23		
	Q1		ref	
	Q2		0.53	(0.21, 1.33)
	Q3		0.41	(0.09, 1.84)
	Q4		0.25	(0.06, 1.14)
Ependymoma/Choroid Plexus Tumors		<20		
	Q1		ref	
	Q2		~	~
	Q3		~	~
	Q4		~	~
Hepatoblastoma		<20		
	Q1		ref	
	Q2		~	~
	Q3		~	~
	Q4		~	~
Hodgkin's Lymphoma		<20		
	Q1		ref	
	Q2		~	~
	Q3		~	~
	Q4		~	~
Non-Hodgkin's Lymphoma		<20		
	Q1		ref	
	Q2		~	~
	Q3		~	~
	Q4		~	~
Intracranial/intraspinal embryonal tumors		36		
	Q1		ref	
	Q2		1.47	(0.66, 3.27)
	Q3		~	~
	Q4		1.35	(0.53, 3.40)

Other Intracranial/intraspinal Neoplasms	<20		
Q1		ref	
Q2		~	~
Q3		~	~
Q4		~	~
Neuroblastoma	67		
Q1		ref	
Q2		0.77	(0.42, 1.40)
Q3		1.04	(0.49, 2.21)
Q4		0.87	(0.44, 1.71)
Rhabdomyosarcoma	29		
Q1		ref	
Q2		1.47	(0.59, 3.65)
Q3		1.57	(0.50, 4.94)
Q4		0.56	(0.15, 2.18)
Other Soft Tissue Sarcomas	<20		
Q1		ref	
Q2		~	~
Q3		~	~
Q4		~	~
Wilms' Tumor	68		
Q1		ref	
Q2		1.22	(0.64, 2.32)
Q3		1.45	(0.65, 3.22)
Q4		1.57	(0.79, 3.13)
Germ cell tumors	21		
Q1		ref	
Q2		1.04	(0.33, 3.26)
Q3		2.63	(0.80, 8.63)
Q4		0.75	(0.18, 3.13)
Retinoblastoma	45		
Q1		ref	
Q2		1.14	(0.53, 2.43)
Q3		1.79	(0.74, 4.34)
Q4		0.97	(0.39, 2.41)

[a]Only cancers with at least 20 cases are included.
[b]In watt hrs/m2; Q1=0 - 4946; Q2=>4946 - 5030; Q3=>5030 - 5111; Q4=>5111.
[c]Adjusted for mother's age and child's year of birth.

4.4 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 five. Most estimated effect sizes were strongest in the top quartile of exposure (>5111 Watt hrs/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<.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 non-lymphoblastic leukemia, Hodgkin's lymphoma, brain/spinal neoplasms, sympathetic nervous system tumors, retinoblastoma, renal tumors, hepatic tumors, bone tumors, and germ cell/gonadal tumors.[51] 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. Additionally we found a decreased risk for non-Hodgkin's lymphomas, which was not observed by Musselman *et al*.

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 >15 days per year spent at a seaside resort to define high levels of sunlight exposure and found a protective association with childhood NHL.[70] A large pooled analysis of ten case-control studies from several countries participating in the Interlymph Consortium showed a protective effect of recreational sun exposure assessed by questionnaire.[53] 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.[20] 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 non-vitamin D mechanisms such as immunosuppression through regulatory T cells. Recently, another prospective study of adults in six states in the U.S. found a protective association for UVR exposure for NHL incidence as well.[54]

Contrary to these studies, three cohorts did not find protective associations.[55-57] Also, the Vitamin D Pooling Project did not find a protective association for NHL.[71] Whether or not risk or protective factors for adult NHL pertain also to childhood NHL is uncertain since the most common histopathologic types in childhood are different from those in adulthood.

With regard to leukemia, an ecological 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.[72] Another ecological study using UVB data from NASA found inverse associations with leukemia incidence rates at the county level in the U.S.[47] 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 two ecological studies. The first found higher incidence in countries and cities with higher annual ambient UVB[73], while the second study, building upon the first, used more cases from U.S. SEER data and found a null association.[74] In a separate analysis of international data, they also found no association after adjusting for race, climate, and an indicator of economic development.[74] These ecological studies used ambient annual UVR 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.[51]

UVR modulates the immune system through vitamin D and other pathways, and it is known to cause local and systemic immunosuppression.[45] 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.[75] Vitamin D modulates the developing immune system and regulates cytokines related to IgE-mediated allergy.[76] Adverse child health outcomes related to immune function, including asthma and wheezing, have been associated with low maternal vitamin D status during pregnancy.[75,76] Given its effects on the developing immune system and its potential anti-cancer properties it has been hypothesized that maternal vitamin D status may be related to childhood cancer.[76]

Both UVR and vitamin D were shown to be protective against tuberculosis and influenza infections[45], and maternal influenza infection was associated with higher odds of ALL in offspring.[77] 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 (Apr-Sep) to the less sunny season (Oct-Mar). Indeed, for ALL we observed a slightly stronger protective effect for births occurring in the April-September period (results not shown). Month of birth was related to ALL diagnosis in previous studies.[78,79]

We also investigated associations by race/ethnicity (white, Hispanic, and African-American) 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, while 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 to non-Hispanic whites.[80] Studies have also found that sun protection behaviors in Hispanics are related to acculturation, and thus are changing over time.[81,82]

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-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 seven studies conducted in the U.S., 14-32% of the mothers moved during pregnancy[83], but the median distance of moving was <10km. 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 it to be nondifferential with respect to the outcome and likely biased 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.[18,19]

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 three quartiles, while 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.

5. RESIDENTIAL PESTICIDE EXPOSURE AS A POSSIBLE RISK FACTOR FOR CHILDHOOD BRAIN TUMORS

5.1 Introduction

Childhood brain tumors are the most common solid tumors found in children and the leading cause of cancer death in children. Survivors of childhood brain tumors are likely to suffer neurocognitive deficits in several areas: cognitive functioning, academic achievement, attention, psychomotor and visual-spatial skills, verbal memory, and language.[84,85] The most common subtype of brain tumors in children <15 years is astrocytoma (50%) followed by primitive neuroectodermal tumors (PNETs) (23%), and ependymoma (9%).[86] Other rare glioma types account for another 15% of tumors. These tumor types peak at different ages in children suggesting distinct etiologies.[86] A small percentage (~5%) of brain tumors can be attributed to family history or genetic syndromes: neurofibromatosis, Li-Fraumeni syndrome, basal cell nevus (Gorlin's) syndrome, Turcot syndrome, and ataxia telangiectasia.[8] Ionizing radiation is the only established risk factor among those considered to date.[8]

Pesticides have been investigated as possible risk factors for childhood cancer since medical case studies were published in the 1970s.[87,88] The EPA has classified over a hundred pesticides as possible or probable carcinogens based on toxicological and epidemiological data, and many are neurotoxins.[8,29] Pesticides have been found in cord blood indicating placental transfer of these toxins to the developing fetus.[8] As some childhood cancers are initiated in utero, this gives some biological plausibility to the hypothesis that prenatal pesticide exposure may increase childhood brain cancer risk.[89,90]

Several case-control studies[89,91-96] and two cohort studies,[97,98] have found increased risks for childhood brain tumors with parental pesticide exposure.[95,99] However the majority of

studies have focused on parental occupational exposure relying mainly on job title or industry, which are often poor proxies of pesticide exposure.[99] Some case-control studies have found elevated risks of brain tumors with parental home and garden pesticide use and professional pest control treatments at home,[89,100,101] however most of these studies relied on exposure information retrospectively obtained from maternal questionnaires or interviews, which is subject to recall bias. [90] There have been two meta-analyses: one focused on parental occupational exposure, including parental employment in farming or agriculture and reported increased odds of 30% (summary odds ratio (SOR): 1.30; 95% CI: 1.11, 1.53) for case-control studies and 53% for cohort studies (SOR: 1.53; 95% CI: 1.20, 1.95).[99] The other one combined occupational and residential pesticide exposure and observed increased odds for paternal exposure to any pesticide before or after birth (SOR=1.49; 95% CI 1.23,1.79 and SOR=1.66; 95% CI: 1.11, 2.49, respectively).[95] They observed a slight, but non-significant increase in risk for maternal prenatal exposure to pesticides.

Another major source of pesticide exposure is from residential proximity to pesticide application in rural communities. The EPA estimates that in the U.S. an excess of 1.1 billion pounds of pesticides were used in 2006 and 2007.[102] Pesticides have been shown to drift several hundred meters from treatment sites.[22] Only a few studies have examined the relationship between agricultural pesticide exposure and childhood brain tumors and reported mixed results.[98,103,104]

Although the literature has been compelling, there have been few studies adequately powered to investigate childhood brain tumor subtypes. Some studies did find elevated risks specifically for high-grade gliomas[100] and astrocytomas[101,105]. In addition, the majority of studies employed study designs that grouped all pesticides together instead of reporting on specific

pesticides or pesticide classes.[89] In 1990 California became the first state to require reporting of all agricultural pesticide use. California has the most detailed pesticide reporting system in the United States, collecting information on each pesticide's active ingredient, the pounds applied, the crop and acreage of the field, the application method, and the date and location of the application at a resolution of 1 square mile. Our validated exposure model combines this detailed pesticide use reporting data with land use data from the California Department of Water Resources to pinpoint the location of the pesticide application within each 1 mi^2 land parcel for more accurate exposure assessment.[22] Using this detailed pesticide exposure model to assess exposures we conducted a population-based case-control study to evaluate the associations of exposure to specific pesticide types during pregnancy and the first year of life with glial tumor subtypes in young children in California.

5.2 Methods

Study population

Cancer cases in children ages 0 to 5 years were drawn from California Cancer Registry records for 1988-2007 and matched to their birth certificates using name and date of birth and we achieved 89% matching success (n=10,914). Twenty controls per case were randomly selected from birth certificate data and frequency matched on birth year to all childhood cancer cases during the study period (n=218,280). We excluded controls who died before age six (n=1674) for equivalence with cases, and in addition subjects with unknown sex (n=3), gestational age less than 20 weeks (n=111), or birth weight less than 500 grams (n=30). We also excluded birth addresses outside California since we do not have exposure information for these addresses (n=632). Methods for the Environmental Health Tracking and Childhood Cancer Study are detailed elsewhere.[59,106,107] We evaluated the following central nervous system subtypes (SEER

code, ICD-O-2 histology code, n): ependymoma (31, n=188), astrocytoma (32, n=829), and other gliomas (34, 9390, n=301).

Pesticide exposures

Pesticide exposures were assessed with the GIS-based Residential Ambient Pesticide Estimation System (GRAPES), which uses California Land Use data from the California Department of Water Resources and pesticide use data reported to the California Department of Pesticide Regulation to locate the precise area within the square mile Public Land Survey System grid where pesticide application occurred, as described in detail previously.[22] A 500-meter buffer around mother's residential address from the birth certificate was used to assess exposure based on previous studies.[23-25] For birth years prior to 1998 zip code centroids were used since full maternal addresses were not available. Using date of last menstrual period and date of birth from the birth certificate, pesticide exposure was assessed for the entire pregnancy and the child's first year of life. Our analyses include 106 pesticides that have been classified by the EPA as possibly or probably carcinogenic.[29] These were then grouped by pesticide type based upon the PAN Pesticide Database as: herbicides, insecticides, fungicides, and soil fumigants (see Table 5.1).[30]

Statistical methods

For pregnancy and first year of life exposure periods we considered both ever exposure to a pesticide type and exposure above the median to any individual pesticide within a pesticide type based on the median for that pesticide among controls. The unexposed group was defined as subjects who were never exposed to any of the carcinogenic pesticides during the relevant time period (pregnancy/first year) since the majority of exposed subjects tended to be exposed to multiple carcinogenic pesticides. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for pesticides and glial tumors, adjusting for child's birth

year (our matching factor), mother's age (<25, 25-34, 35+ years) and race/ethnicity (Non-Hispanic White, Hispanic any race, Black, Asian/PI/Other), and neighborhood socioeconomic status (SES) (quintiles). Neighborhood SES was calculated from California Census data based on an algorithm developed by Yost et al from Census data in California using principal components analysis.[68] This index was created from seven 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).[68] Maternal age, race/ethnicity, and SES have been associated with brain tumors in children and may be associated with pesticide exposure.[62,63] We also tested the following confounders in models for astrocytoma and pesticide class: payment method for prenatal care, mother's education, father's education, child's sex, father's race/ethnicity, father's age, mother born in U.S., rural/urban residence, birth weight, gestational age, parity, region of California, and season of birth. As none of these variables changed our estimates by 10% or more our final models did not include them.

We conducted additional analyses for astrocytoma to explore the elevated odds we observed. Odds ratios were calculated for individual pesticides with at least ten exposed case of astrocytoma, and their corresponding chemical classes (e.g. organochlorines). Stratified analyses were performed to test for effect measure modification by mother's race/ethnicity, child's birth year and neighborhood SES. All analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC). This study was approved by the University of California, Los Angeles, Office of the Human Research Protection Program.

Table 5.1: List of pesticides by type

Herbicides	**Insecticide**
Cacodylic acid	Carbaryl
Bromacil	Bioallethrin
Diuron	Cocamide Diethanolamine(DEA)
Dinoseb	Acephate
Linuron	Methidathion
Molinate	Tetramethrin
Propanil	Dichlorvos
Trifluralin	Pirimicarb
Alachlor	Triforine
Pendimethalin	Diazinon
Cyanazine	Permethrin
Oryzalin	Amitraz
Oxyfluorfen	Resmethrin
Metolachlor	Dimethoate
Oxadiazon	Cypermethrin
Norflurazon	Thiodicarb
Diclofop-methyl	Hydramethylnon
Ethalfluralin	Clofentezine
Prodiamine	Fenoxycarb
Hydrogen cyanamide	Bifenthrin
Isoxaben	Phosmet
Triflusulfuron-methyl	Dicofol
Pyrithiobac-sodium	Lindane
Mecoprop-P	Malathion
s-Metolachlor	Methyl Bromide
Benfluralin	Zeta-Cypermethrin
Chlorthal-dimethyl (DCPA)	Chlorfenapyr
Pronamide	Fipronil
Acifluorfen sodium	Ethoprop
Thiazopyr	Oxythioquinox
Pyraflufen ethyl	Propargite
Metam sodium	Parathion, ethyl-
Penoxulam	Phosphamidon
Simazine	Pymetrozine
Methyl Bromide	Spirodiclofen
	Flonicamid
	Trichlorfon

Fungicide	Soil Fumigant
Cocamide Diethanolamine(DEA)	Metam sodium
Triforine	Methyl Bromide
Oxythioquinox	Telone
Benomyl	
Thiophanate-methyl	
Iprodione	
Mancozeb	
Vinclozolin	
Triadimefon	
Propiconazole	
Uniconazole	
Ferbam	
Maneb	
Tebuconazole	
Fenbuconazole	
Pentachloronitrobenzene (PCNB)	
Pentachlorophenol	
Metiram	
2-Benzyl-4-chlorophenol	
Kresoxim-methyl	
Boscolid	
Terrazole	
Pyrimethanil	
Thiabendazole	
Metam sodium	
Ziram	
Chlorothalonil	
Dicloran	

5.3 Results

Characteristics of cases and controls are shown in Table 5.2. Case mothers for all glial tumor types were less likely to be foreign born and more likely to have private insurance (private/HMO/Blue Cross-Blue Shield) as payment for prenatal care. Mothers and fathers of astrocytoma cases were more likely to be non-Hispanic white and have more years of education than control parents. Astrocytoma cases were more likely to be male, first born, from higher

socioeconomic neighborhoods, born in spring, and from regions of California other than Los Angeles. Astrocytoma cases also had a higher likelihood of herbicide exposure compared to controls.

Odds ratios and 95% confidence intervals for pesticide types (herbicides, insecticides, fungicides, and soil fumigants) adjusted for child's sex and birth year, mother's age and race/ethnicity, and neighborhood SES are shown in Table 5.3. We observed an increase in odds of astrocytoma with herbicide (OR: 1.53, 95% CI: 1.21-1.93), insecticide (OR: 1.26, 95% CI: 0.99-1.61), and fungicide (OR: 1.36, 95% CI: 1.03-1.79) exposure during pregnancy. We did not observe increased odds for ependymoma or other gliomas with pesticide exposure. We further explored the relationship between astrocytoma and pesticide exposure during pregnancy by pesticide chemical class (Table 5.4). Odds were elevated for almost all pesticide classes, and the strongest effect estimate was observed for chloroacetanilide (OR: 3.04 95% CI: 1.75-5.29). Among controls we found moderate correlations between pesticide exposures for several pesticide classes (Table 5.5). Results presented here are for exposure during pregnancy since odds ratios did not change appreciably between pregnancy and first year of the child's life. One exception was that odds of astrocytoma appeared elevated for soil fumigant exposure in the first year of life and not during pregnancy (first year, ever exposed OR: 1.49, 95% CI: 0.98-2.26).

Table 5.2: Characteristics of cancer cases and controls in children ages 0-5 in California (1988-2007)

		Controls		Ependymoma		Astrocytoma	
		n	**%**	n	**%**	n	**%**
Mother's race/ethnicity							
	White, non-Hispanic	79648	**37**	77	**41**	432	**52**
	Hispanic, any race	95867	**44**	73	**39**	273	**33**
	Black	15080	**7**	<20	**9**	53	**6**
	Asian/PI	20861	**10**	<20	**9**	58	**7**
	Other/Refused	4385	**2**	<20	**2**	<20	**2**
Mother's nativity							
	Foreign born	92807	**43**	61	**33**	253	**31**
	US born	122786	**57**	126	**67**	575	**69**
Father's race/ethnicity							
	White, non-Hispanic	75870	**35**	73	**39**	408	**49**
	Hispanic, any race	91852	**43**	72	**38**	265	**32**
	Black	16586	**8**	<20	**9**	61	**7**
	Other/Refused	31533	**15**	26	**14**	95	**11**
Mother's age							
	<25	76808	**36**	63	**34**	265	**32**
	25-34	110011	**51**	96	**51**	451	**54**
	35+	28982	**13**	29	**15**	113	**14**
Father's age							
	<25	46241	**23**	36	**21**	164	**21**
	25-34	105364	**52**	97	**56**	419	**53**
	35+	50489	**25**	40	**23**	203	**26**
Sex of child							
	Male	110140	**51**	107	**57**	452	**55**
	Female	105701	**49**	81	**43**	377	**45**
Urban/Rural							
	Metropolitan	192865	**89**	167	**89**	730	**88**
	Micropolitan	8481	**4**	<20	**4**	42	**5**
	Small town	2289	**1**	<20	**2**	<20	**1**
	Rural	12206	**6**	<20	**5**	48	**6**
Mother's education							
	<12 yrs	57447	**32**	41	**26**	163	**24**
	12 yrs	52245	**29**	48	**31**	201	**29**
	13-15 yrs	35467	**20**	33	**21**	156	**23**
	16+ yrs	34361	**19**	34	**22**	166	**24**
Father's education							
	<12 yrs	49693	**30**	33	**22**	139	**21**
	12 yrs	51964	**31**	53	**36**	195	**30**
	13-15 yrs	29695	**18**	28	**19**	129	**20**
	16+ yrs	36790	**22**	34	**23**	194	**30**
Parity							
	0	85024	**39**	75	**40**	352	**42**
	1	67603	**31**	65	**35**	270	**33**
	2 or more	63063	**29**	48	**26**	207	**25**

Method of delivery							
	Vaginal	158217	**76**	138	**77**	624	**78**
	Cesarean	49090	**24**	41	**23**	177	**22**
Payment type for prenatal care							
	Private/HMO/Blue Cross-Blue Shield	91431	**51**	92	**59**	419	**61**
	Medi-cal/Other/Selfpay/Etc	88541	**49**	63	**41**	270	**39**
Quintiles of neighborhood SES*							
	1	51529	**24**	44	**23**	173	**21**
	2	50348	**23**	38	**20**	199	**24**
	3	48356	**22**	46	**24**	177	**21**
	4	35129	**16**	27	**14**	138	**17**
	5	29994	**14**	33	**18**	141	**17**
Region							
	Northern and sierra	5814	**3**	<20	**2**	34	**4**
	Greater bay area	38796	**18**	44	**23**	162	**20**
	Sacramento area	10204	**5**	<20	**5**	48	**6**
	San Joaquin valley	22967	**11**	<20	**6**	99	**12**
	Central coast	11807	**5**	<20	**6**	44	**5**
	Los Angeles	68679	**32**	64	**34**	236	**28**
	Other southern	57362	**27**	42	**22**	206	**25**
Season of birth							
	Spring	53197	**25**	45	**24**	247	**30**
	Summer	56717	**26**	53	**28**	212	**26**
	Fall	54158	**25**	52	**28**	195	**24**
	Winter	51769	**24**	38	**20**	175	**21**
Herbicide							
	Pregnancy only	929	**0**	<20	**0**	<20	**1**
	First year only	2708	**1**	<20	**1**	<20	**1**
	Both	13537	**6**	<20	**4**	74	**9**
	Neither	198667	**92**	178	**95**	739	**89**
Insecticide							
	Pregnancy only	1123	**1**	<20	**1**	<20	**0**
	First year only	2925	**1**	<20	**1**	<20	**2**
	Both	15116	**7**	<20	**6**	71	**9**
	Neither	196677	**91**	174	**93**	740	**89**
Fungicide							
	Pregnancy only	679	**0**	<20	**1**	<20	**0**
	First year only	2349	**1**	<20	**2**	<20	**1**
	Both	10724	**5**	<20	**4**	53	**6**
	Neither	202089	**94**	177	**94**	762	**92**
Soil fumigant							
	Pregnancy only	693	**0**	<20	**1**	<20	**0**
	First year only	1708	**1**	<20	**1**	<20	**1**
	Both	3526	**2**	<20	**1**	<20	**2**
	Neither	209914	**97**	184	**98**	801	**97**

		Other Gliomas n	%
Mother's race/ethnicity			
	White, non-Hispanic	136	**45**
	Hispanic, any race	109	**36**
	Black	27	**9**
	Asian/PI	26	**9**
	Other/Refused	<20	**1**
Mother's nativity			
	Foreign born	110	**37**
	US born	191	**63**
Father's race/ethnicity			
	White, non-Hispanic	128	**43**
	Hispanic, any race	104	**35**
	Black	29	**10**
	Other/Refused	40	**13**
Mother's age			
	<25	86	**29**
	25-34	151	**50**
	35+	64	**21**
Father's age			
	<25	52	**18**
	25-34	136	**48**
	35+	95	**34**
Sex of child			
	Male	139	**46**
	Female	162	**54**
Urban/Rural			
	Metropolitan	271	**90**
	Micropolitan	<20	**4**
	Small town	<20	**1**
	Rural	<20	**5**
Mother's education			
	<12 yrs	69	**29**
	12 yrs	58	**25**
	13-15 yrs	50	**21**
	16+ yrs	58	**25**
Father's education			
	<12 yrs	57	**26**
	12 yrs	61	**28**
	13-15 yrs	42	**19**
	16+ yrs	58	**27**
Parity			
	0	107	**36**
	1	95	**32**
	2 or more	99	**33**
Method of delivery			
	Vaginal	213	**75**
	Cesarean	72	**25**
Payment type for prenatal care			

	Private/HMO/Blue Cross-Blue Shield	135	**57**
	Medi-cal/Other/Selfpay/Etc	101	**43**
Quintiles of neighborhood SES*			
	1	71	**24**
	2	63	**21**
	3	65	**22**
	4	62	**21**
	5	40	**13**
Region			
	Northern and sierra	<20	**3**
	Greater bay area	55	**18**
	Sacramento area	<20	**6**
	San Joaquin valley	33	**11**
	Central coast	<20	**4**
	Los Angeles	90	**30**
	Other southern	84	**28**
Season of birth			
	Spring	62	**21**
	Summer	88	**29**
	Fall	84	**28**
	Winter	67	**22**
Herbicide			
	Pregnancy only	<20	**0**
	First year only	<20	**1**
	Both	<20	**4**
	Neither	287	**95**
Insecticide			
	Pregnancy only	<20	**1**
	First year only	<20	**1**
	Both	<20	**6**
	Neither	277	**92**
Fungicide			
	Pregnancy only	<20	**0**
	First year only	<20	**0**
	Both	<20	**3**
	Neither	292	**97**
Soil fumigant			
	Pregnancy only	<20	**0**
	First year only	<20	**1**
	Both	<20	**1**
	Neither	295	**98**

*Based on Yost et al index[68]

Table 5.3: Associations (OR (95%CI)) between pesticide exposure during pregnancy and CNS tumors in children ages 0-5 in California

Ever/never exposed[a]	Exposed Cases (n)	Cases (n)	Controls (n)	Crude OR[b]	95% CI	Adjusted OR[c]	95% CI
Herbicides							
Ependymoma	8	181	210214	0.62	(0.30-1.25)	0.64	(0.31-1.30)
Astrocytoma	80	809	210214	1.52	(1.20-1.91)	1.53	(1.21-1.93)
Other gliomas	12	292	210214	0.59	(0.33-1.05)	0.59	(0.33-1.06)
Insecticides							
Ependymoma	13	186	211987	0.89	(0.51-1.56)	0.91	(0.52-1.61)
Astrocytoma	74	803	211987	1.25	(0.99-1.59)	1.26	(0.99-1.61)
Other gliomas	20	300	211987	0.87	(0.55-1.38)	0.88	(0.56-1.39)
Fungicides							
Ependymoma	8	181	207151	0.77	(0.38-1.57)	0.79	(0.39-1.60)
Astrocytoma	56	785	207151	1.36	(1.03-1.79)	1.36	(1.03-1.79)
Other gliomas	8	288	207151	0.50	(0.25-1.01)	0.50	(0.25-1.02)
Soil fumigants							
Ependymoma	3	176	199967	0.79	(0.25-2.49)	0.82	(0.26-2.57)
Astrocytoma	16	745	199967	1.04	(0.63-1.70)	1.07	(0.65-1.76)
Other gliomas	4	284	199967	0.67	(0.25-1.80)	0.69	(0.26-1.86)

[a]Exposed to >=1 pesticide of this type ever during pregnancy.
[b]Adjusted for child's birth year (matching variable).
[c]Adjusted for child's sex and birth year, mother's age and race/ethnicity, and neighborhood SES.

Table 5.4: Associations (OR (95%CI)) between pesticide exposure during pregnancy and Astrocytoma in children ages 0-5 in California

Pesticide class (ever/never exposed during pregnancy)	Exposed cases (n)	Cases (n)	Controls (n)	Crude OR[a]	95% CI	Adjusted OR[b]	95% CI
			Astrocytoma				
Dinitroaniline	49	777	204032	1.52	(1.14-2.04)	1.56	(1.16-2.09)
Azole	19	747	198881	1.45	(0.92-2.30)	1.48	(0.93-2.33)
Benzimidazole	26	754	199914	1.52	(1.02-2.24)	1.53	(1.03-2.27)
Chloroacetanilide	13	741	196324	3.23	(1.86-5.61)	3.04	(1.75-5.29)
Dicarboximide	31	759	201125	1.44	(1.01-2.07)	1.44	(1.00-2.07)
Diphenyl ether	38	766	202082	1.54	(1.11-2.13)	1.55	(1.11-2.16)
Dithiocarbamate	14	742	197669	1.59	(0.93-2.70)	1.62	(0.95-2.76)
Dithiocarbamate inorganic Zn	21	749	199337	1.41	(0.91-2.18)	1.40	(0.91-2.17)
Halogenated organic	12	740	198648	0.96	(0.54-1.69)	0.98	(0.55-1.74)
N-Methyl carbamate	19	747	198468	1.57	(1.00-20.48)	1.60	(1.01-2.53)

Organochlorine	19	747	198189	1.74	(1.10-2.75)	1.84	(1.16-2.91)
Organophosphorus	66	794	208328	1.38	(1.07-1.78)	1.39	(1.08-1.80)
Pyrethroid	23	751	200537	1.21	(0.80-1.84)	1.24	(0.81-1.88)
Substituted benzene	22	750	199530	1.40	(0.92-2.15)	1.42	(0.93-2.17)
Triazine	35	763	201702	1.49	(1.06-2.09)	1.50	(1.07-2.11)
Urea	29	757	200001	1.68	(1.16-2.44)	1.73	(1.19-2.52)

[a]Adjusted for child's birth year (matching variable).
[b]Adjusted for child's sex and birth year, mother's age and race/ethnicity, and neighborhood SES.

Table 5.5: Correlations between pesticide class and type exposure measures[a]

	Dinitroaniline	Benzimidazole	Chloroacetanilide	Dicarboximide	Diphenyl ether	Dithiocarbamate	Dithiocarbamate inorganic Zn	Halogenated organic	N-Methyl carbamate	Organochlorine	Organophosphorus	Pyrethroid	Substituted benzene	Triazine	Urea
Dinitroaniline	**1.0**														
Benzimidazole	0.4	**1.0**													
Chloroacetanilide	0.3	0.2	**1.0**												
Dicarboximide	0.5	0.6	0.2	**1.0**											
Diphenyl ether	0.7	0.4	0.2	0.5	**1.0**										
Dithiocarbamate	0.4	0.3	0.1	0.4	0.4	**1.0**									
Dithiocarbamate inorganic Zn	0.5	0.5	0.2	0.6	0.5	0.3	**1.0**								
Halogenated organic	0.4	0.4	0.1	0.5	0.4	0.3	0.4	**1.0**							
N-Methyl carbamate	0.4	0.3	0.2	0.3	0.4	0.2	0.3	0.3	**1.0**						
Organochlorine	0.4	0.2	0.2	0.2	0.4	0.2	0.2	0.2	0.3	**1.0**					
Organophosphorus	0.6	0.5	0.2	0.6	0.6	0.3	0.5	0.4	0.4	0.4	**1.0**				
Pyrethroid	0.5	0.4	0.2	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.5	**1.0**			
Substituted benzene	0.4	0.4	0.2	0.5	0.4	0.3	0.4	0.3	0.3	0.3	0.5	0.4	**1.0**		
Triazine	0.6	0.4	0.2	0.5	0.6	0.3	0.5	0.4	0.4	0.3	0.5	0.3	0.3	**1.0**	
Urea	0.5	0.3	0.2	0.3	0.5	0.3	0.3	0.3	0.4	0.4	0.5	0.3	0.3	0.6	**1.0**

	Herbicide	Insecticide	Fungicide	Soil Fumigant
Herbicide	**1.0**			
Insecticide	0.8	**1.0**		
Fungicide	0.7	0.7	**1.0**	
Soil Fumigant	0.5	0.5	0.5	**1.0**

[a]Pearson's phi coefficients.

5.4 Discussion

We observed increased odds of astrocytoma for residential pesticide exposure to herbicides (53%), insecticides (26%) and fungicides (36%). Further analysis by pesticide chemical class did not elucidate which classes might be responsible for the increased risk for astrocytoma. This may be due to moderate correlation between exposures to many of the pesticide classes all of which were selected since they are suspected carcinogens. We examined several additional potential confounders related to SES, birth characteristics, and urban/rural residence in our models with none changing estimates by 10% or more. The observed associations for astrocytoma were also robust when we stratified by neighborhood SES and mother's race/ethnicity. We did not observe increased risk for ependymoma or other glial tumors with pesticide exposure during pregnancy.

The few previous studies examining residential pesticide exposure in relation to childhood brain tumors reported conflicting results. Our results differ from two previous studies in California by Reynolds et al.[103,104] The first study was ecological and used California Pesticide Use Report data to estimate agricultural pesticide density by census block group. Cancer cases up to age 15 years from the entire state were identified in the California Cancer Registry for the years 1988-1994 and assigned to block groups based on address at diagnosis. They did not find associations for agricultural pesticide use and risk of childhood gliomas or other childhood cancers, except for an increased risk of leukemia in block groups with the highest propargite use, after adjusting for age, race, and sex.[104] Their second study calculated pounds of selected pesticides and pesticide classes applied in a half-mile radius of mother's address from birth certificates to assess the relationship between prenatal exposure to agricultural pesticides and cancer in young children. Their study population included all cases of cancer in children ages 0-4

years in the state of California born between October 1990 and December 1997, who were diagnosed between 1990 and 1997. They did not show an association with childhood nervous system tumors.[103] Nondifferential exposure misclassification and failure to analyze brain tumor subtypes may account for the differences in findings with our study. Although their case-control study is similar in design to this study, a simulation found that pesticide exposures based on Pesticide Use Report data, such as theirs, trade sensitivity for specificity, which can result in substantial attenuation of effect estimates.

Outside of the US, a cohort study in Norway found an association with parental engagement in horticulture and brain tumors in children residing on farms, which adds support to our findings.[98] Two recent meta-analyses showing elevated risk of childhood brain tumors with parental occupational pesticide exposure and residential pesticide use are consistent with our findings.[95,99] Although results by brain tumor subtype are sparse, a couple of previous case-control studies support our findings of an elevated risk for astrocytoma.[101,105] A case-control study in the U.S and Canada of parental occupational exposures found increased risk of astrocytoma with father's exposure to insecticides, herbicides, agricultural and nonagricultural fungicides, as well as with mother's occupational exposure to all the same categories except agricultural fungicides.[105] The other case-control study using cancer registry data from four east coast states in the U.S. showed increased odds of astrocytoma for residential use of herbicides and fungicides by either parent and for paternal occupational exposure to herbicides.[101]

Pesticides may increase the risk of childhood brain tumors through parental germ line mutations during the preconception period, or gene mutations from prenatal exposure or childhood exposure.[90,95] Associations have been found for preconception, prenatal, and early childhood exposure periods. Due to the difficulty of disentangling these effects, the relevant time

period for exposure is yet to be identified. Although we assessed exposures both during pregnancy and the first year of life, exposures across these periods were too highly correlated in our study to determine which period might be more important in the etiology of glial tumors. In addition to several pesticides being classified as possible/probable carcinogens by the EPA based mainly on animal data, several are neurotoxins and have been associated with neurodevelopmental problems providing another possible biological mechanism.[108]

A study of children enrolled in the West Coast Childhood Brain Tumor Study found interaction effects between children's genotypes for pesticide metabolism genes (PON1 and FMO1) and insecticide treatment in the home for the risk of brain tumors.[109] Genetic factors involved in the metabolism of pesticides may be important modifiers of effects. We did not have genetic data available for this study. Also, we are not able to account for pesticide exposures from occupation, home/garden use, or dietary exposures in this study. We do not have information on whether or not a woman moved during her pregnancy. Residential mobility rates among pregnant women in the U.S. are estimated to be 14-32%.[110] Our study had several strengths. It included a large number of cases, which allowed for the examination of associations for glial tumor subtypes. Linking to birth certificate and census data gave us the ability to adjust for potential several confounders in our models. Our pesticide exposure model provided spatially acute information on individual pesticides and chemical classes. It was objectively assessed, and therefore not subject to recall bias.

6. MATERNAL DIETARY PATTERNS DURING PREGNANCY AND UNILATERAL RETINOBLASTOMA

6.1 Introduction

Retinoblastoma is a rare childhood tumor of the embryonal retina with a mean age-adjusted incidence rate of 11.8 cases per million children ages 0–4 years in the U.S.[11] This tumor has been the basis of Knudson's "two-hit" model of carcinogenesis, since it occurs only after inactivation of both alleles of the *RB1* tumor suppressor gene in a retinal cell.[12] More recently additional genetic defects such as aneuploidy and genetic instability have been implicated in retinoblastoma tumorigenesis.[13,14] Bilateral disease, which accounts for 27% of cases in children less than 5 years of age, is considered familial when an *RB1* mutation is inherited from a parent and sporadic when a new germline mutation occurs in *RB1*.[11,15] In both cases the child will have one mutated *RB1* allele in every cell and another mutational event ('second hit') will inactivate the second *RB1* allele in a retinal cell and initiate disease.[16] Among children who inherit an *RB1* mutation, 85% go on to develop bilateral retinoblastoma usually before age 5. Unilateral retinoblastoma, which accounts for 72% of retinoblastoma cases in children less than 5 years of age, most often results from two somatic mutations to the *RB1* gene and peaks at age 6-7 months.[15] In spite of knowledge about some genetic mechanisms responsible for retinoblastoma, risk factors for somatic mutations and retinoblastoma are largely unknown. The five-year survival rate for retinoblastoma in the U.S. is estimated to be over 93%, but treatments may result in loss of vision.[15] Identification of targets for prevention is important to reduce the burden of this disease in the U.S. and in many developing countries where mortality rates are much higher.[111]

In unilateral retinoblastoma the mutations to the *RB1* gene occur mostly after conception, thus prenatal and early childhood exposures are thought to be important for its etiology. In a large, population based case-control study of childhood cancer in California we conducted

previously, among several perinatal characteristics examined, we found elevated odds for unilateral retinoblastoma among children of U.S.-born Hispanic women and decreased odds among children of mothers born in Mexico.[59] We also observed elevated odds in infants born to mothers exposed to higher levels of traffic related air pollution during pregnancy.[112-114] Previously identified possible risk factors for unilateral disease include prenatal x-ray exposure, morning sickness medication use, and low maternal education level.[115]

Mother's prenatal diet and nutrients have been investigated as possible risk and protective factors for childhood cancer.[116,117] Food contains known mutagens such as heterocyclic amines and polycyclic aromatic hydrocarbons in red meat cooked at high temperatures and N-nitroso compounds in cured meats, and probable carcinogens such as acrylamides in baked, grilled, and fried foods.[116,118] Some dietary components such as antioxidants from fruits and vegetables can reduce the risk of somatic mutations potentially conferring some protective benefits.[116,118]

Few studies have examined parental diet and retinoblastoma. Bunin et al assessed the effects of mother's and father's preconception diets on sporadic bilateral retinoblastoma and reported possible protection due to father's consumption of dairy and fruit in the year prior to conception and a harmful effect from cured meats and sweets.[119] No associations were seen with maternal diet, consistent with the observation that 85% of germ line mutations for sporadic bilateral retinoblastoma originate in the father's sperm.[120,121]

Only a single study thus far examined maternal diet and unilateral retinoblastoma. This hospital-based case-control study of children age 6 years or less found an increased risk with maternal consumption of less than 2 servings of vegetables per day during pregnancy.[122] Risk was also increased among children with maternal pregnancy diets low in folate and lutein/zeaxanthin from fruits and vegetables.[122] A U.S. case-control study also found

multivitamin use during pregnancy to reduce unilateral disease risk.[115] Here we investigate associations between maternal prenatal diet and unilateral retinoblastoma among children less than 15 years of age in the United States and Canada in a multi-institutional case-control study.

6.2 Methods

Study population

Data for this study were collected for the Research on the Environment and Children's Health (REACH 2) study, which was an expansion of a previous study and had the primary aim of investigating the associations of sporadic bilateral retinoblastoma and unilateral retinoblastoma with parental exposures and polymorphisms in DNA repair and carcinogen metabolizing enzyme genes. Parental exposure information was obtained via structured telephone interviews conducted from 2007 to 2012 with both parents when available. The questionnaire collected information on basic demographics and preconception and prenatal parental exposures possibly related to retinoblastoma risk including, occupational exposures, medical radiation, diet, supplement use, tobacco, alcohol, and residential pesticide use.

Eligible cases were children less than 15 years of age diagnosed with unilateral retinoblastoma whose physicians gave permission to contact the parents of. Cases were identified at nine large referral centers for retinoblastoma: Wills' Eye Hospital (Philadelphia), Northwestern University Medical Center (Chicago), New York Hospital/Cornell University Medical Center (New York), Children's Hospital of Los Angeles, Hospital for Sick Children (Toronto), Children's Hospital and Regional Medical Center (Seattle), St. Jude Children's Research Hospital (Memphis), the University of Illinois at Chicago, and The Children's Hospital of Philadelphia.

Parents of cases provided lists of their child's friends or relatives under age 15 years to be contacted as possible controls. For unilateral retinoblastoma mother's exposures were the focus, thus, the relatives selected as controls were not allowed to be biologically related to the case's mother. The study aimed to match children without a cancer diagnosis of one or two friends and of one relative to each case in the same or adjacent age group at time of interview (0-1, 2-3, 4-5, 6-7, 8-9, 10-11,12-13 and 14-15 years). Unfortunately, the study was not able to recruit controls for all cases.[31] Subjects were eligible if they resided in North America, had at least one parent who spoke English or Spanish, and had at least one biological parent available to participate in the study. After dropping one control who did not complete the FFQ, 163 unilateral RB cases and 136 controls (but only 85 matched sets) were available for this study. Written consent was provided for blood and saliva samples, and verbal consent was given for telephone interviews. The IRBs at all referring institutions approved the REACH study, and the UCLA Office of the Human Research Protection Program approved this study.

Dietary assessment

A 72-item modified Willett food frequency questionnaire was used to assess mother's diet during pregnancy.[32] Frequency of consuming specific foods during the second trimester of pregnancy was collected. For the calculation of total calories per day a standard portion size (based on FDA recommendations) was assumed since portion size information was not collected, and calorie information was taken from the USDA web database.[34] Thus food frequency was converted to servings per day as: (never or less than once per month"=0; "1 to 3 per month"=.08; "1 per week"=.14; "2 to 4 per week"=.43; "5 to 6 per week"=.8; "1 per day"=1; "2 to 3 per day"=2.5; "4 to 5 per day"=4.5; "6+ per day"=6.[36] Servings per day for individual food items were totaled within 13 food groups (number of items): fruit (6), citrus fruit (2), dairy (7),

vegetables, excluding potatoes (14), meat and seafood (14), poultry (2), fresh red meat (4), cured meat (3), seafood (5), grains (8), sweets, including beverages (9), fried foods (4), alcohol (3) (Table 6.1). To capture dietary patterns we created two dietary scales: one capturing a diet high in fruits and vegetables and low in red and cured meats similar to Chuang et al; and one capturing a diet high in fruits and vegetables and low in fried foods and sweets.[37] The scales were constructed based on food group tertiles, assigning a zero for fruits and vegetable intake in the lowest tertile, 1 for the middle tertile and 2 for the top tertile. The opposite coding was used for red meat, cured meat, fried food and sweets. Hence, the scale ranged from 0 to 8, with higher values indicating healthier diets.

Table 6.1: List of items within each food group

Food Group	Item
Fruit (6)	
	Fresh apples or pears
	Orange juice or grapefruit juice
	oranges
	peach, apricots, nectarines or plums
	bananas
	other fruits
Citrus fruit (2)	
	Orange juice or grapefruit juice
	Oranges
Dairy (7)	
	Skim or low fat milk
	whole milk
	yogurt
	frozen yogurt or light ice cream
	ice cream
	cottage or ricotta cheese
	other cheese
Vegetables--excluding potatoes (14)	
	string beans
	broccoli
	cabbage, cauliflower or brussels sprouts
	raw carrots
	cooked carrots
	corn
	peas or lima beans
	yams or sweet potatoes
	spinach, collard or other greens
	beans
	winter squash
	green salad
	tomatoes or tomato juice
	tomato sauce
Poultry (2)	
	fried chicken or turkey
	chicken or turkey, not fried
Fresh red meat (4)	
	liver
	hamburger
	beef, pork, or lamb as a sandwich or as part of a dish

	beef, pork, or lamb as a main dish
Cured meat (3)	
	bacon
	hot dogs
	processed meats
Seafood (5)	
	oysters
	fried shellfish
	shellfish, not fried
	fried fish, other than shellfish
	fish other than shellfish, not fried
Grains (8)	
	homemade pie
	ready made pie
	cake, sweet rolls or other pastry
	cookies
	white bread, bagels or rolls
	dark or whole wheat bread
	rice or pasta
	cold breakfast cereal
Sweets--including beverages (9)	
	chocolate
	candy without chocolate
	homemade pie
	ready made pie
	cake, sweet rolls or other pastry
	cookies
	regular soda or pop
	fruit drinks with vitamin C added
	other fruit drinks
Fried foods (4)	
	fried chicken or turkey
	fried shellfish
	fried fish, other than shellfish
	french fries
Alcohol (3)	
	beer
	wine
	liquor

Statistical analysis

Both conditional and unconditional logistic regression models were used with unilateral retinoblastoma as the dependent variable. Conditional regression preserved the matched design of the study, while unconditional regression allowed us to include all cases and controls after breaking the matches. Due to the difficulty in control recruitment we chose to use the entire control population in unconditional analyses instead of restricting it to controls selected for unilateral cases. All unconditional regression models controlled for matching variables, i.e. age group at interview (0-<2 yrs, 2-<4 yrs, 4+ yrs). We created tertiles of servings per day for each food group based on the distribution in controls. For the dietary scales we employed continuous and categorical variables (0-2=low, 3-5= medium, 6-8=high). We also calculated Pearson correlation coefficients according to food groups and dietary scores (Table 6.2). We adjusted for mother's race (white non-Hispanic, Hispanic, other) and education (<high school, high school graduate, some college/other training, college graduate or more), whether mothers smoked the month before or during pregnancy (yes/no), household income (≤$35,000, $35000-$50000, $50000-$75000, ≥$75000), total calories per day (continuous), and prenatal vitamin use of at least nine months during pregnancy (yes/no). Marital status was not included in our final adjusted models because it did not change estimates by 10% or more. We conducted all analyses using SAS version 9.3.

Table 6.2: Pearson Correlation Coefficients for food groups among controls, N=144

	Fruit	Citrus	Dairy	Vegetables	Poultry	Red meat	Cured meat	Seafood	Grains	Sweets	Fried foods	High fruit/veg, low fried food/sweets	High fruit/veg, low red/cured meat
Fruit	1.00												
Citrus	0.65	1.00											
Dairy	0.44	0.31	1.00										
Vegetables	0.54	0.34	0.39	1.00									
Poultry	0.28	0.23	0.28	0.29	1.00								
Red meat	0.15	-0.02	0.21	0.24	0.12	1.00							
Cured meat	-0.07	0.00	-0.01	-0.07	0.00	0.12	1.00						
Seafood	0.07	0.09	-0.04	0.10	0.09	0.00	0.08	1.00					
Grains	0.34	0.22	0.40	0.36	0.26	0.25	0.21	-0.08	1.00				
Sweets	-0.03	-0.02	0.27	0.19	0.11	0.21	0.14	-0.05	0.44	1.00			
Fried foods	-0.02	0.06	-0.04	0.19	0.19	0.24	0.19	0.44	0.02	0.27	1.00		
High fruit/veg, low fried food/sweets	0.65	0.36	0.25	0.48	0.12	-0.06	-0.19	-0.01	0.18	-0.41	-0.43	1.00	
High fruit/veg, low red/cured meat	0.62	0.41	0.23	0.54	0.21	-0.32	-0.46	0.04	0.18	-0.11	-0.13	0.69	1.00

6.3 Results

Characteristics of the study population are shown in Table 6.3. Cases were younger than controls. Mothers of controls were more likely than those of cases to have a college or higher education (67% vs 53%), to be non-Hispanic white (76% vs 57%), and to be never smokers (70% vs 58%).

Crude and adjusted odds ratios and 95% confidence intervals for tertiles of food groups (in servings per day) are shown in Table 6.4. For consumption in the top compared to lowest tertile, negative associations were observed for fruit (OR: 0.38, 95% CI: 0.14-1.02), dairy (OR: 0.36, 95% CI: 0.12-1.09), and red meat (OR: 0.35, 95% CI: 0.11-1.13) in adjusted conditional logistic models adjusted for mother's race and education, maternal smoking in the month before or during pregnancy, household income, prenatal vitamin use, and total calories per day. We observed increased odds in the top tertiles of consumption for poultry (OR: 2.33, 95% CI: 0.82-6.63), cured meat (OR: 5.07, 95% CI: 1.63-15.70), seafood (OR: 2.20, 95% CI: 0.92-5.26), sweets (OR: 2.21, 95% CI: 0.8-6.06), and fried foods (OR: 4.89, 95% CI: 1.72-13.89) in adjusted models. Unconditional logistic models for these foods yielded effect estimates in the same direction, but generally lower in magnitude.

Our two dietary scales showed negative associations with increasing scores (Table 6.5). Odds of unilateral retinoblastoma decreased by 25% with every 1 point increase in our 8 point scale capturing a maternal diet with high fruit and vegetable and *low fried foods and sweets* intake during the second trimester of pregnancy. For every 1 point increase in our score measuring high fruit and vegetable intake and *low red and cured meat* intake we observed a 16% decrease in odds of unilateral retinoblastoma.

Table 6.3: Characteristics of unilateral retinoblastoma cases and controls

	Controls		Cases		
	n	**%**	**n**	**%**	**Chi Sq P-value**
Child's age					
0-<2 yrs	42	29	68	37	0.01
2-<4 yrs	43	30	68	37	
4+ yrs	59	41	47	26	
Total	144		183		
Household income					
≤$35,000	29	21	56	34	0.10
$35000-$50000	19	14	17	10	
$50000-$75000	29	21	30	18	
≥$75000	59	43	61	37	
Total	136		164		
Mother's education					
<High School	6	4	15	8	0.05
High School graduate	15	10	31	17	
Some college/other training	26	18	40	22	
College graduate or more	97	67	97	53	
Total	144		183		
Mother's race					
White non-Hispanic	109	76	104	57	0.00
Hispanic	18	13	45	25	
Other	17	12	34	19	
Total	144		183		
Mother smoked mo before or during pregnancy					
Never smoker	101	70	107	58	0.03
Yes	17	12	41	22	
No	26	18	35	19	
Total	144		183		
Took prenatal vitamin 9+ mos of pregnancy					
Yes	89	62	98	54	0.15
No	55	38	84	46	
Total	144		182		
Fruit (servings per day)					
0 - 1.37	48	33	75	41	0.15
>1.37 - 2.43	49	34	65	36	
>2.43 - 8	47	33	43	24	
Total	144		183		
Citrus (servings per day)					
0 - 0.16	52	36	65	36	0.18

>0.16 - 0.86	50	35	79	43	
>0.86 - 3.5	42	29	39	21	
Total	144		183		
Dairy (servings per day)					
0 - 1.57	48	33	73	40	0.46
>1.57 - 2.73	48	33	57	31	
>2.73 - 6.51	48	33	53	29	
Total	144		183		
Vegetables (servings per day)					
0.44 - 1.66	48	33	56	31	0.51
>1.66 - 2.66	48	33	72	40	
>2.66 - 6.94	48	33	54	30	
Total	144		182		
Poultry (servings per day)					
0 - 0.16	48	33	59	32	0.01
>0.16 - 0.43	63	44	57	31	
>0.43 - 1.08	33	23	67	37	
Total	144		183		
Red meat (servings per day)					
0 - 0.30	50	35	75	41	0.51
>0.30 - 0.65	53	37	62	34	
>0.65 - 2.22	41	28	46	25	
Total	144		183		
Cured meat (servings per day)					
0 - 0.08	64	44	65	36	0.22
>0.08 -0.16	32	22	42	23	
>0.16 - 1.31	48	33	76	42	
Total	144		183		
Seafood (servings per day)					
0 - 0	57	40	58	32	0.23
>0 - 0.14	40	28	50	27	
>0.14 - 2.22	47	33	75	41	
Total	144		183		
Grains (servings per day)					
0.14 - 1.65	48	33	66	36	0.85
>1.65 - 2.37	50	35	59	32	
>2.37 - 6	46	32	58	32	
Total	144		183		
Sweets (servings per day)					
0 - 0.88	49	34	52	28	0.54
>0.88 - 1.75	47	33	67	37	
>1.75 - 4.58	48	33	64	35	
Total	144		183		

Fried foods (servings per day)					
0 - 0.08	59	41	48	26	0.01
>0.08 - 0.24	38	26	49	27	
>0.24 - 1.51	47	33	86	47	
Total	144		183		
Eat fried food out					
Never/≤1 time per week	79	55	90	49	0.55
1-3 times per week	62	43	86	47	
4+ times per week	3	2	6	3	
Total	144		182		
Alcohol during pregnancy					
No	133	92	171	93	0.70
Yes	11	8	12	7	
Total	144		183		
Total energy (calories)					
467 - 1179	36	25	42	23	0.95
>1179 - 1560.5	36	25	50	27	
>1560.5 - 1964.5	36	25	44	24	
>1964.5 - 3938	36	25	47	26	
Total	144		183		
High fruits/vegetables, low fried food/sweets					
Mean	144	4.08	182	3.54	
0-2	30	21	50	27	0.17
3-5	81	56	103	57	
6-8	33	33	29	16	
Total	144		182		
High fruits/vegetables, low red/cured meat					
Mean	144	4.17	182	3.92	
0-2	27	19	39	21	0.45
3-5	82	57	109	60	
6-8	35	24	34	19	
Total	144		182		

Table 6.4: Associations (OR (95%CI)) between tertiles of food groups (servings per day) during the 2nd trimester of pregnancy and unilateral retinoblastoma

		Conditional Logistic Model					
		n=92 matched sets			n=85 matched sets		
	Food group tertiles (servings per day)	**Crude OR**	95% C.I.		**Adj OR[b]**	95% C.I.	
Fruit							
	0 - 1.37	**ref**	~	~	**ref**	~	~
	>1.37 - 2.43	**1.17**	0.60	2.26	**0.86**	0.38	1.94
	>2.43 - 8	**0.70**	0.34	1.46	**0.38**	0.14	1.02
Citrus							
	0 - 0.16	**ref**	~	~	**ref**	~	~
	>0.16 - 0.86	**2.17**	1.04	4.51	**2.23**	0.94	5.29
	>0.86 - 3.5	**1.58**	0.70	3.56	**1.98**	0.72	5.44
Dairy							
	0 - 1.57	**ref**	~	~	**ref**	~	~
	>1.57 - 2.73	**1.06**	0.52	2.15	**0.61**	0.25	1.52
	>2.73 - 6.51	**0.83**	0.39	1.76	**0.36**	0.12	1.09
Vegetables							
	0.44 - 1.66	**ref**	~	~	**ref**	~	~
	>1.66 - 2.66	**2.03**	0.96	4.27	**2.39**	0.93	6.19
	>2.66 - 6.94	**1.46**	0.70	3.03	**1.04**	0.39	2.74
Poultry							
	0 - 0.16	**ref**	~	~	**ref**	~	~
	>0.16 - 0.43	**0.91**	0.42	1.93	**0.92**	0.36	2.38
	>0.43 - 1.08	**1.90**	0.88	4.10	**2.33**	0.82	6.63
Red meat							
	0 - 0.30	**ref**	~	~	**ref**	~	~
	>0.30 - 0.65	**0.58**	0.27	1.23	**0.53**	0.22	1.30
	>0.65 - 2.22	**0.44**	0.19	1.03	**0.35**	0.11	1.13
Cured meat							
	0 - 0.08	**ref**	~	~	**ref**	~	~
	>0.08 -0.16	**1.77**	0.77	4.07	**2.90**	0.99	8.55
	>0.16 - 1.31	**2.83**	1.24	6.44	**5.07**	1.63	15.70
Seafood							
	0 - 0	**ref**	~	~	**ref**	~	~
	>0 - 0.14	**1.48**	0.71	3.09	**1.44**	0.60	3.45
	>0.14 - 2.22	**1.46**	0.71	2.99	**2.20**	0.92	5.26
Grains							
	0.14 - 1.65	**ref**	~	~	**ref**	~	~
	>1.65 - 2.37	**0.84**	0.43	1.64	**0.59**	0.25	1.38
	>2.37 - 6	**0.92**	0.46	1.83	**0.59**	0.21	1.61
Sweets							
	0 - 0.88	**ref**	~	~	**ref**	~	~
	>0.88 - 1.75	**1.39**	0.68	2.83	**1.78**	0.75	4.23
	>1.75 - 4.58	**1.31**	0.64	2.72	**2.21**	0.81	6.06
Fried							
	0 - 0.08	**ref**	~	~	**ref**	~	~
	>0.08 - 0.24	**2.86**	1.28	6.39	**6.34**	2.14	18.83

	>0.24 - 1.51	**2.65**	1.21	5.82	**4.89**	1.72	13.89
Fried food out							
	Never/<=1 time per wk	**ref**	~	~	**ref**	~	~
	1-3 times per wk	**1.80**	0.91	3.56	**1.82**	0.83	4.00
	4+ times per wk	**5.18**	0.56	48.26	**6.39**	0.47	87.86
Alcohol							
	Never/<1 time per mo	**ref**	~	~	**ref**	~	~
	1 per mo or more	**1.40**	0.44	4.41	**1.44**	0.35	5.86

		Unconditional Logistic Model[a]					
		Cases: n=183, Controls: n=144			Cases: n=163, Controls: n=136		
	Food group tertiles (servings per day)	**Crude OR**	95% C.I.		**Adj OR[b]**	95% C.I.	
Fruit							
	0 - 1.37	**ref**	~	~	**ref**	~	~
	>1.37 - 2.43	**0.87**	0.51	1.47	**0.84**	0.46	1.54
	>2.43 - 8	**0.60**	0.35	1.05	**0.56**	0.28	1.12
Citrus							
	0 - 0.16	**ref**	~	~	**ref**	~	~
	>0.16 - 0.86	**1.30**	0.78	2.18	**1.34**	0.75	2.39
	>0.86 - 3.5	**0.78**	0.44	1.39	**0.76**	0.39	1.50
Dairy							
	0 - 1.57	**ref**	~	~	**ref**	~	~
	>1.57 - 2.73	**0.83**	0.49	1.42	**0.79**	0.43	1.48
	>2.73 - 6.51	**0.78**	0.46	1.35	**0.62**	0.30	1.27
Vegetables							
	0.44 - 1.66	**ref**	~	~	**ref**	~	~
	>1.66 - 2.66	**1.26**	0.74	2.16	**1.68**	0.90	3.15
	>2.66 - 6.94	**0.97**	0.56	1.69	**1.07**	0.54	2.12
Poultry							
	0 - 0.16	**ref**	~	~	**ref**	~	~
	>0.16 - 0.43	**0.72**	0.42	1.22	**0.82**	0.44	1.53
	>0.43 - 1.08	**1.62**	0.91	2.87	**1.71**	0.86	3.40
Red meat							
	0 - 0.30	**ref**	~	~	**ref**	~	~
	>0.30 - 0.65	**0.80**	0.48	1.34	**0.80**	0.45	1.43
	>0.65 - 2.22	**0.78**	0.45	1.37	**0.68**	0.35	1.33
Cured meat							
	0 - 0.08	**ref**	~	~	**ref**	~	~
	>0.08 -0.16	**1.27**	0.71	2.29	**1.41**	0.75	2.67
	>0.16 - 1.31	**1.64**	0.99	2.73	**1.53**	0.85	2.77
Seafood							
	0 - 0	**ref**	~	~	**ref**	~	~
	>0 - 0.14	**1.21**	0.69	2.13	**1.45**	0.78	2.71
	>0.14 - 2.22	**1.65**	0.97	2.79	**2.03**	1.12	3.69
Grains							
	0.14 - 1.65	**ref**	~	~	**ref**	~	~
	>1.65 - 2.37	**0.76**	0.44	1.31	**0.75**	0.40	1.43

	>2.37 - 6	**0.88**	0.51	1.51	**0.79**	0.38	1.67
Sweets							
	0 - 0.88	**ref**	~	~	**ref**	~	~
	>0.88 - 1.75	**1.31**	0.76	2.26	**1.50**	0.81	2.78
	>1.75 - 4.58	**1.25**	0.72	2.16	**1.24**	0.61	2.49
Fried							
	0 - 0.08	**ref**	~	~	**ref**	~	~
	>0.08 - 0.24	**1.66**	0.93	2.97	**1.81**	0.95	3.44
	>0.24 - 1.51	**2.41**	1.42	4.11	**2.01**	1.08	3.76
Fried food out							
	Never/<=1 time per wk	**ref**	~	~	**ref**	~	~
	1-3 times per wk	**1.22**	0.78	1.92	**0.99**	0.59	1.64
	4+ times per wk	**2.13**	0.50	9.03	**2.03**	0.38	10.81
Alcohol							
	Never/<1 time per mo	**ref**	~	~	**ref**	~	~
	1 per mo or more	**0.92**	0.39	2.18	**1.42**	0.56	3.61

[a]Adjusted for matching variable age group
[b]Adjusted for mother's race and education, mother smoked month before or during pregnancy, household income, prenatal vitamin use, total calories per day.

Table 6.5: Associations (OR (95%CI)) between dietary patterns during the 2nd trimester of pregnancy and unilateral retinoblastoma

	Conditional Logistic Model						Unconditional Logistic Model[a]					
	n=91 matched sets			n=84 matched sets			Cases: n=182, Controls: n=144			Cases: n=162, Controls: n=136		
	Crude OR	95% C.I.		**Adj OR[b]**	95% C.I.		**Crude OR**	95% C.I.		**Adj OR[b]**	95% C.I.	
High fruit/veg, low fried food/sweets												
Continuous	**0.89**	0.76	1.04	**0.75**	0.61	0.92	**0.85**	0.75	0.96	**0.88**	0.77	1.01
0-2	**ref**	~	~	**ref**	~	~	**ref**	~	~	**ref**	~	~
3-5	**1.09**	0.52	2.31	**0.95**	0.42	2.13	**0.75**	0.44	1.30	**0.97**	0.52	1.81
6-8	**0.71**	0.30	1.65	**0.40**	0.14	1.11	**0.53**	0.27	1.05	**0.70**	0.33	1.49
High fruit/veg, low red/cured meat												
Continuous	**0.97**	0.81	1.15	**0.84**	0.67	1.04	**0.92**	0.81	1.04	**0.95**	0.83	1.09
0-2	**ref**	~	~	**ref**	~	~	**ref**	~	~	**ref**	~	~
3-5	**0.95**	0.46	1.97	**0.78**	0.35	1.74	**0.94**	0.53	1.67	**0.99**	0.52	1.90
6-8	**0.89**	0.35	2.29	**0.66**	0.23	1.88	**0.65**	0.32	1.29	**0.73**	0.34	1.58

[a]Adjusted for matching variable age.
[b]Adjusted for mother's race and education, mother smoked month before or during pregnancy, household income, prenatal vitamin use of 9 or more months and total calories per day.

6.4 Discussion

Our results suggest that a dietary pattern with high fruit and vegetable consumption and low consumption of fried foods and sweets, as well as a dietary pattern with high fruit and vegetable consumption and low consumption of red and cured meats during pregnancy, may reduce the odds of unilateral retinoblastoma in offspring. Considering individual food groups we observed protective associations among children of mothers who consumed higher amounts of fruit, dairy and surprisingly red meat. Harmful associations were detected for highest maternal intake of poultry, cured meat, seafood, sweets and fried foods. Thirty-five percent of our study participants reported no seafood consumption, and another 28% consumed seafood once a week

or less. Servings per day of seafood were moderately correlated with fried foods (Pearson's correlation coefficient=0.44), which may account for the increased risk we observed. The counterintuitive findings for seafood and red meat may be chance findings, or attributable to frequency alone not reflecting portion size adequately, food preparation methods not being taken into account or individual food groups not being as relevant to risk as overall dietary patterns.

Our results for the dietary scales showed –as one would expect - diets higher in fruits and vegetables to be protective. This is in line with a previous hospital-based case-control study of children age ≤6 years which found an increased risk of unilateral retinoblastoma in children of mothers who consumed less 2 servings of vegetables per day during pregnancy adjusting for maternal education and socioeconomic status indicators.[122] Although they did not observe an association with fruit consumption alone as we did, they found increased risk for lower maternal consumption folate, B6, α-carotene, and lutein/zeazanthine from fruit and vegetables. The slight differences in results may reflect differences in dietary patterns between our predominantly non-Hispanic white population and this population of mothers in Mexico City or differences in dietary assessment. The Mexico City study assessed diet by interview with three open-ended questions about the foods mothers typically consumed for breakfast, lunch and dinner and per week consumption frequencies for each food. Vegetable consumption may have been particularly important in this population because only 43% of case mothers and 53% of control mothers took multivitamins at any time during pregnancy, and this study took place before folic acid fortification of food in Mexico. [122,123] Fruit and vegetable consumption has been associated with lower risk of several cancers in adults.[116] Protective associations were also found for maternal fruit and vegetable consumption during pregnancy and acute lymphoblastic leukemia

(ALL), childhood brain tumors and germ cell tumors.[124-127] The protective effects have been attributed to dietary fibers, antioxidants, flavonoids, and salicylic acid contents.[116]

The effect sizes for the consumption of fried foods and unilateral retinoblastoma were strong in this study and increased further in sensitivity analyses restricted to non-Hispanic Whites only (OR for the top tertile: 8.24, 95% CI 1.91-35.51). We also observed elevated risks for consumption of sweets during pregnancy. These findings could be due to acrylamide, which has been classified as a probable carcinogen, and is found in baked goods and fried foods, especially fried potatoes.[116,118] Acrylamide acts as a mitotic spindle inhibitor in the nucleus and could interfere with chromosome segregation and DNA repair leading to DNA mutations and carcinogenesis.[118]

Although we observed a possibly inverse association for frequent red meat consumption alone, our dietary scale results showing diets lower in red and cured meats and higher in fruits and vegetables as possibly protective are consistent with previous findings showing associations between cancer in adults and higher red meat consumption.[116] Heterocyclic aromatic amines (HAAs) and polycyclic aromatic hydrocarbons are carcinogens formed when cooking meats at high temperatures and have been suggested as possible components responsible for the observed harmful effects.[116,118] Cured meats contain nitrates which are transformed into N-nitroso compounds, known carcinogens, in the body.[116,118] The harmful association we found for maternal consumption of cured meats is supported by several studies of childhood brain tumors showing associations with mothers' consumption of cured meats during pregnancy.[128]

Studies have found both increased and decreased risk of cancers in adults with poultry and dairy consumption.[116] Among controls in our study dairy consumption was moderately correlated with fruit and vegetable consumption (Pearson correlation coefficients = 0.44 and 0.39,

respectively), which may account for the inverse association observed. Diets high in fast food may also be lower in dairy.[129] Our findings of decreased risk with higher dairy consumption and increased risk with higher poultry consumption are hard to interpret and need to be investigated in future studies. Although the etiology of bilateral retinoblastoma differs from that of unilateral retinoblastoma it is interesting to note that reductions in risk of sporadic bilateral retinoblastoma were observed for higher paternal dairy consumption and dairy-related nutrient consumption during the year prior to conception in the same study population.[33,119] Dairy may be associated with healthier eating patterns in this study population, and mothers' and fathers' diets are likely to be correlated.

When using friend and relative controls in case-control studies overmatching on life-style related factors is likely. Indeed, a simulation study conducted for the first REACH study previously suggested overmatching on demographic factors, but to a lesser degree on parental smoking.[31] Overmatching on diet would be expected to result in reduced statistical power to detect associations between diet and the outcome. The previous difficulties with control recruitment resulted in some differences between case and control characteristics; specifically, cases without a matched control were more likely to be non-White and of lower socioeconomic status, and thus were dropped in all analyses of matched pairs.[31] This would further limit the exposure distribution in terms of diet in the restricted population, while analyses based on all cases and controls may be more affected by confounding due to SES, which we attempted, but may not have succeeded in controlling for completely. Given these limitations, we provided results from both conditional and unconditional analyses for comparison.

We expect diet measurement error because food frequency questionnaires were administered to mothers 0-13 years after pregnancy with approximately 83% completing the

questionnaire within 5 years after pregnancy. Differential recall bias may have occurred if case mothers recalled diet more or less accurately than control mothers. If case mothers were more likely to underreport consumption of foods perceived to be unhealthy to minimize feeling of guilt regarding their child's cancer then associations for unhealthy foods could be biased downward. A previous study found that quintile based agreement in diet reported during pregnancy with pregnancy diet reported 3-7 years after pregnancy was 60-69% for telephone interviews and 69-79% for self-administered questionnaires, which is similar to or slightly lower than recall for diet in adult life in general.[130] Interviewer bias also may have occurred because it was not possible to blind interviewers to case-control status. Since this was not a population-based study, selection bias may have occurred due to control selection. As discussed previously more health conscious friends and family may have participated in the study as suggested by the higher educational status among all controls creating false protective associations for healthier foods.[119] Given the young age of retinoblastoma onset we do not expect child's diet to bias results.

In spite of these limitations, this study is one of only a few on this topic for retinoblastoma. For a very rare cancer a relatively large number of cases were accumulated at major referral institutions in the U.S. and Canada. Detailed information on socioeconomic factors allowed us to control for possible confounding. The food frequency questionnaire was previously validated and has been successfully used for other studies of childhood cancer.[32,33]

PUBLIC HEALTH RELEVANCE

Although survival rates of childhood cancer have been increasing and exceed 90% for some cancer types, the rates of recurrence are high, and the late effects of treatment can range from mild to debilitating. For adult survivors of childhood brain tumors in particular the late

effects occur due to damage of the developing brain, and therefore touch several domains--medical, neurocognitive, psychosocial, and economic.[131] Hence, identification of risk and preventive factors is of utmost importance.

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 [132]. 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.

Using a spatially refined exposure model in California, an agricultural center, we observed increased risk of astrocytoma among children 0-5 years of age with residential pesticide exposure during pregnancy. Risks appeared elevated for several pesticide types and chemical classes. In spite of controlling for several possible confounders, residual confounding cannot be ruled out. Future studies should attempt to incorporate exposures from multiple sources including application near residence, residential use, and occupational exposure, as well as consider including biomarkers of exposure. To protect the health of children policy interventions can be initiated to reduce pesticide exposure and the associated negative health outcomes.

The five-year survival rate for retinoblastoma in the U.S. is estimated to be over 93%, but treatments may result in loss of vision.[15] Identification of targets for prevention is important to reduce the burden of this disease in the U.S. and in many developing countries where mortality rates are much higher.[111] Our study provides preliminary evidence that mothers who consume diets higher in fruits and vegetables and lower in fried foods, sweets, red and cured meats during pregnancy may reduce the risk of unilateral retinoblastoma in their offspring. The associations with fried foods and sweets are interesting and should be investigated further in relation to childhood cancer. Future studies should consider additional methods of dietary assessment. Given the low number of retinoblastoma cases diagnosed in the U.S. each year, approximately 300 children <20 years of age, and the difficulty of obtaining detailed dietary information inclusion of biomarkers is unlikely, and studies on this topic will continue to be challenging.[15] Dietary interventions with pregnant women should be explored to potentially reduce the risks of childhood cancer and possibly other negative health outcomes.

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