Title

Gestational and Early Life Exposures as Risk Factors for Childhood Lymphoma, Leukemia, and Wilms' Tumors: an Exploration of Birth Characteristics, Influenza and Respiratory Syncytial Virus Infections, and Pesticide Exposure

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A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Erin Leigh Marcotte

2013

ABSTRACT OF THE DISSERTATION

Gestational and Early Life Exposures as Risk Factors for Childhood Lymphoma, Leukemia, and Wilms' Tumors: an Exploration of Birth Characteristics, Influenza and Respiratory Syncytial Virus Infections, and Pesticide Exposure

by

Erin Leigh Marcotte

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2013

Professor Beate Ritz, Chair

Childhood cancer is the second leading cause of death among children age 0-14 in the United States, but there are very few established risk factors and the etiology of most childhood cancers is still unclear. This dissertation research investigated the associations between birth characteristics and childhood lymphoma, exposure to infections and childhood leukemia, and pesticide exposure and childhood Wilms' tumor among children born in California between 1983 and 2007. We identified all cancer cases among children age 0-5 from the California cancer registry and matched them to California birth certificates. We randomly selected controls from the same birth certificate files. Our analyses included 478 lymphoma cases, 3402 leukemia cases, 863 Wilms' tumor cases, and 215,841 controls. We observed associations between several birth certificate variables, including parental race and some complications of pregnancy and labor/delivery, and childhood lymphoma. We also observed that early life exposure to infections, as estimated by proxies such as timing of birth in relation to community

infections, was protective for acute lymphoblastic leukemia, particularly among first born children. Finally, we found associations between gestational and early life exposure to pesticides and Wilms' tumor. Our findings confirm previous reports on the relationship between race and childhood lymphoma, and Epstein-Barr virus infection may help explain this association. We found evidence in support of the hypothesis that delayed exposure to infections in early life is a risk factor for childhood leukemia. We also report novel associations between several individual pesticides and Wilms' tumor in young children. Due to the rarity of childhood cancers, each of these analyses is limited in sample size and further investigations are necessary to confirm our results.

The dissertation of Erin Leigh Marcotte is approved.

Onyebuchi Arah
Wendie Robbins
Zuo-Feng Zhang
Beate Ritz, Committee Chair

University of California, Los Angeles

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LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoid leukemia
AML	acute myeloid leukemia
BW	birth weight
CA	California
CCR	California Cancer Registry
CDC	Centers for Disease Control
CI	confidence interval
DES	diethylstilbestrol
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EPA	Environmental Protection Agency
GIS	Geographic Information Systems
GRAPES	GIS-based residential ambient pesticide estimation system
HBW	high birth weight
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HMO	Health Maintenance Organization
ICCC-3	International Classification of Childhood Cancer, Third edition
LBW	low birth weight
NHL	non-Hodgkin lymphoma
OR	odds ratio
PLSS	Public Land Survey System
PROM	premature rupture of the membranes
PUR	Pesticide Use Report
RSV	respiratory syncytial virus
SES	socioeconomic status
UCLA	University of California, Los Angeles
US	United States
WT	Wilms' tumor

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1. Introduction

Childhood cancer is the second leading cause of death among children age 0-14 in the United States. In 2013, approximately 11,630 new cases and 1,310 deaths were expected among children age 0-14 in the US.[1] Although improved treatments have led to a decline in mortality rates since 1975, incidence rates have increased slightly over the same period.[2] There are very few established risk factors and the etiology of most childhood cancers is still unclear. Established risk factors are limited to genetic predisposition (< 10% of childhood cancers) [3], Down syndrome, and ionizing radiation [4].

Although childhood cancer is diagnosed throughout the early childhood and adolescent years, prenatal as well as postnatal exposures should be considered as potential etiologic factors. Animal experiments have demonstrated that initiating events can take place in utero with postnatal promotion resulting in malignancies.[5] Furthermore, when a large multicenter consensus group evaluated transplacental carcinogenesis, they found sufficient evidence that preconceptional, in utero, exposures cause cancers in children and adults.[6]

It is generally accepted that there are at least two in utero exposures that have a causal relationship to subsequent development of cancer: ionizing radiation and diethylstilbestrol (DES). The association between fetal exposure to DES and vaginal adenocarcinoma is a classic example of transplacental carcinogenesis. [7] Ionizing radiation acts directly on deoxyribonucleic acid (DNA) and is linked to childhood leukemia. [8]

This proposed research aims to explore the association between childhood cancer and in utero exposure to pesticides and birth and gestational characteristics, such as pregnancy complications and month of birth. The California Cancer Registry and California birth records will be used to identify the study population.

2. Background

2.1 Pediatric Lymphoma

Lymphoma is the third most common childhood malignancy, accounting for approximately 15% of all cancers diagnosed in children. [9] Despite being the third most common form of childhood cancer, pediatric lymphoma is relatively rare, with an incidence rate of 16.5 per million among children 0-14 years of age in the US [10]. Thus, pediatric lymphoma is difficult to study epidemiologically and its etiology remains largely unknown. Pediatric lymphoma consists of two predominant subtypes: Hodgkin lymphoma (HL) and non-Hodgkin's lymphomas (NHL). HL is very rare among young children ages 0-5 and occurs more frequently among adolescents. NHL is the most common lymphoma diagnosed among 1-5 year olds, and its rates also increase with age. Nearly all lymphoma diagnoses among infants < 1 year are miscellaneous lymphoreticular neoplasms. [10]

HL typically arises from B lymphocytes with characteristic Reed-Sternberg cells, which are large, clonal, multinucleated, and sometimes contain Epstein-Barr virus (EBV) genomic sequences [11]. It has been estimated that EBV is found in about 40-50% of all HL cases in developed countries, most commonly among cases diagnosed in 0-10 year olds [12, 13]. MacMahon et al [14] proposed a three disease hypothesis for HL, suggesting that there are three distinct etiologies that contribute to disease, and that these could be distinguished based on age of onset. Armstrong et al [15] provided additional evidence for this hypothesis, stating that the three disease entities may be distinguished on the basis of age at onset and EBV status. They suggest that nearly all early childhood cases of HL are part of the first disease entity, which is EBV-associated and mostly of mixed cellularity subtype.

NHL is a class of lymphoma which includes mature B-cell lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma [11]. While each histological subgroup has unique characteristics, these lymphomas are frequently studied together in epidemiologic contexts. Immunodeficiency,

including immunosuppressive therapy, congenital immunodeficiency syndromes, and HIV/AIDS all predispose to NHL [16, 17]. Maternal and paternal smoking are generally associated with increased risk of NHL. [18-21] A recent meta-analysis on maternal smoking during pregnancy estimated about a 20% increase in risk for children whose mothers smoked during pregnancy (OR 1.22, 95% CI 1.03-1.45).[18]

The number of previous studies reporting on birth and gestational characteristics, complications of pregnancy/delivery, or exposures during pregnancy and pediatric lymphoma is small.

A recent pooled analysis examined the effect of parental age (measured by each 5-year increase in maternal age) and found an increased risk for NHL (OR 1.10, 95% CI 1.02-1.20) for older maternal age, although this association weakened after adjustment for paternal age.[22] No association was observed for increased maternal age and risk of HL. Another pooled analysis of parental race and childhood cancer found an increased risk of HL (OR 1.94, 95% CI 1.36-2.77) and a decreased risk of NHL (OR 0.73, 95% CI 0.55-0.95) among those of Hispanic ethnicity compared to whites.[23]

Previous studies on HL have revealed a racial difference in EBV-associated disease. Several studies among both pediatric and adult HL cases have reported that Hispanic cases are more likely than whites to have EBV-associated HL and that the mixed cellularity subtype is most commonly diagnosed in EBV-related malignancies. [13, 24-26] One pooled analysis that combined data from 14 studies found that the highest percentages of EBV-associated cases occurred among children < 10 and in older adults, and that Hispanics were four times as likely as whites to have EBV-associated HL. [13]

Two previous studies suggest a positive association between previous still birth and NHL. [27, 28] Increased parity is consistently associated with decreased risk of HL among previous studies. [28-30] Other exposures, including birth weight, gestational age, maternal hypertension, and caesarean birth yield inconsistent results. A recent meta-analysis on birth weight (BW) and pediatric lymphoma was inconclusive for both NHL (OR 1.07, 95% CI 0.71-1.62 for low vs normal BW; OR 1.17, 95% CI 0.76-

1.80 for high vs normal BW) and HL (OR 0.94, 95% CI 0.54-1.65 for low vs normal BW; OR 0.94, 95% CI 0.64-1.38 for high vs normal BW). [31]

Due to the rarity of pediatric lymphoma, many previous studies are small and lack the power to stratify by lymphoma subtype. Also, despite evidence that lymphomas diagnosed in young children (< 10 years old) have different etiologies than those diagnosed among older children and adolescents [15], most previous studies have examined lymphomas in children 0-14 years of age together [19, 21, 27-30, 32-35], and one study included all HL cases diagnosed between 0-24 years of age [30].

2.2 Pediatric Leukemia

Leukemia is the most common form of childhood cancer, accounting for approximately 30% of all childhood cancers among those aged 0-14. Its incidence varies with age, with a sharp peak among those aged 1-4.[10] Pediatric leukemia consists of two predominant subtypes: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). ALL occurs much more frequently across all age groups, with the exception of infants less than 1 year old, in whom ALL and AML incidence is nearly equal.[10] ALL accounts for approximately 75% of all pediatric leukemia cases among 0-14 year olds.

Pediatric leukemia arises from a diverse set of chromosomal and molecular changes. There is strong evidence that most of these are acquired, not inherited [36], although a small number (about 5%) of leukemias are associated with inherited genetic syndromes. [36, 37] Evidence from twin studies and studies of neonatal blood spots suggests that most initiating events occur during fetal development in utero. [38-42] Established non-genetic risk factors for ALL include ionizing radiation, male sex, and white race. [8]

There is a growing body of evidence that infections may play a role in pediatric leukemia pathogenesis, and there are two main hypotheses on the nature of this relationship. Greaves has

proposed a 'delayed infection' hypothesis which suggests that delayed exposure to common infections leads to an increased risk of pediatric leukemia.[43] Greaves hypothesized that a minimum of two genetic events are required for the development of ALL and that infection promotes the second genetic event through an abnormal immune response. Kinlen has proposed a 'population mixing' hypothesis which states that pediatric leukemia might arise from a rare response to common infection. [44] Population mixing would result in increased risks due to increased contact between infected and susceptible individuals. While Greaves' hypothesis emphasizes the timing of exposure, Kinlen's hypothesis emphasizes exposure to specific agent(s).

Some of the most compelling evidence in support of an infectious etiology for pediatric leukemia comes from studies of day care attendance, which is considered a proxy for exposure to infection. These studies have consistently shown a decreased risk of pediatric leukemia for regular daycare attenders compared to children who do not attend day care.[45, 46] The two largest studies to examine this relationship have reported similar results. The first, a study from the United Kingdom, reported that any day care contact, regular contact, and formal day care attendance were all protective for ALL (ORs: 0.73, 0.62, and 0.48, respectively) when compared with no day care contact. Results for day care attendance within the first 3 months of life were OR 0.52 (95% CI 0.33-0.84).[47] The second, a large study from Northern California, found that those with the highest levels of day care exposure experienced a risk reduction for both ALL (OR 0.42, 95% CI 0.18-0.99) and common precursor B-cell ALL (OR 0.33, 95% CI 0.11-1.01).[48]

Inconsistent results arise from previous studies on season of birth and childhood leukemia. Four studies have suggested seasonal variation in births for leukemia, and three of the four have suggested that the peak occurs in late winter or spring. A study of ALL among 0-4 year olds from Denmark found that birth month peak and trough occurred in April and October, respectively [49]. One study from

England did not find evidence of seasonality for leukemia cases overall or for ALL cases age 0-14. However, the authors do report a significant sinusoidal variation in birth month when they restricted to ALL cases age 1-6, with a peak in March.[50] Another study examined pediatric leukemia in three different regions of the UK. In each region, they found no association for season of birth and leukemia overall and for ALL among 0-14 year olds. However, two regions exhibited evidence of seasonality among 1-6 year olds, with peaks of February and March and troughs of August and September, respectively. [51] A small study from Hungary found no evidence for seasonality when they checked for a seasonal pattern of one maximum and one minimum level per year. However, when they tested sine and cosine functions within a 6 month period, i.e. allowing for two peaks and two troughs per year, they found that the peak and trough birth months for ALL were February and August, and May and November, respectively. [52] A final study from the UK examined leukemia among 0-14 year olds diagnosed from 1953-1995. The authors did not find an association for birth month and leukemia overall, or in subgroup analyses by age, sex, or disease histology or immunophenotype. Subgroup analyses by birth year revealed that births peaked in February among leukemia cases born before 1960, although this earlier time period included fatal cases only. [53]

2.3 Pediatric Wilms' tumor

Renal tumors represent about 6% of cancer diagnoses among children 0-14 years of age.[10, 54] Wilms' tumor (WT), also called nephroblastoma, is by far the most common type of renal tumor in children, comprising approximately 95% of all renal cancer diagnoses. [10] WT occurs most commonly among children less than 5 years of age, with the highest incidence in the first two years of life. [10] Females have a slightly higher rate of WT than boys (9.7 per million compared to 8.4 per million). [55]

Genetic factors are known to play a role in Wilms' tumor etiology. *WT1*, a gene located on chromosome 11 (11p13), is a tumor suppressor gene involved in kidney and gonadal development.[56, 57] WAGR and Denys-Drash syndromes have *WT1* involvement and are strongly associated with development of WT.[58] However, fewer than 20% of sporadic WT are associated with *WT1* irregularities.[59, 60] *WT2* is a growth regulatory region located on chromosome 11 (11p15) where loss of heterozygosity is found in up to 40% of sporadic WT cases.[56, 61] Beckwith-Wiedemann syndrome, a genetic disorder associated with increased risk of WT, features *WT2* irregularities.[58]

Several environmental, parental, and gestation factors have been implicated as potential risk factors for WT, including paternal occupation as a welder or mechanic, high birth weight, in utero exposure to ionizing radiation, pre-term birth, and maternal hypertension during pregnancy. [54, 62] However, evidence for these factors is inconclusive.

Pesticide exposure has also been examined for possible involvement in WT etiology. [63-68] Exposure to pesticides has been listed as a probable carcinogen (Group 2A) by the International Agency for Research on Cancer.[69] Animal studies have established pesticides as mutagens [69, 70], and exposure has been linked to cytotoxic effects in humans [71-73]. Residential proximity to agricultural fields is one of several factors which may influence pesticide exposure. Pesticide spray drift and post-spray volatilization can spread pesticide residue through the air, sometimes for large distances.[74-76] Factors that influence this exposure include the pesticide used, application method and meteorologic conditions. [77-79] Pesticide residue has been documented indoors in both air and dust, which may persist in carpeting for years.[76, 80, 81] Those living close to agricultural fields, even in non-farmworker families, may be at increased risk of pesticide exposure due to drift.[82-84]

Previous studies on the impact of pesticide exposure on WT risk have yielded mixed results. Three studies have found an increased risk of WT with parental employment involving likely pesticide

exposure [67, 85, 86], while seven studies found no effect [63, 68, 87-91]. Two studies estimated an increased risk for either parental [64] or child [92] exposure to household pesticides, although two other studies did not find an effect with household exposures [68, 93].

Four previous studies have estimated the impact of maternal exposure to pesticides on WT risk. [64, 66-68] These studies vary in exposure assessment methods and exposure periods. Only one study found a statistically significant increase in risk, although point estimates in all studies were above the null.

One small study from Brazil evaluated interview data on maternal farm work with exposure to pesticides at any point from the 6 months prior to pregnancy through birth of the child and found a 3-fold increase in risk (OR 3.09, 95% CI 0.9-10.9).[67] Another study examined self-reported maternal occupational exposure to pesticides during the period from one year pre-conception through diagnosis reference date and found an increased risk (OR 2.52, 95% CI 0.5-12.6), although this result is based on only two exposed cases.[68] One study assessed interview data on maternal occupational and household exposure to pesticides and reported an increased risk for exposures during the two years prior to birth (OR 1.41, 95% CI 0.91-2.20) and pregnancy (OR 1.32, 95% CI 0.83-2.09). [66] Finally, a US study also estimated an increase in WT risk for self-reported maternal pesticide use in the home during the period from one month pre-conception through the diagnosis reference date (OR 1.30 95% CI 1.0-1.7). [64]

A recent review conducted a meta-analysis on these studies and found a combined risk estimate of 1.37 (95% CI 1.09-1.73). [62] However the authors did find evidence of publication bias that may have influenced this result.

A study from Texas used residential proximity to agricultural areas to estimate pesticide exposure and did not observe an association with WT.[94] The authors geocoded residence at birth and

defined those who lived within 1000 meters of agricultural fields as likely exposed to pesticides. Their estimated risk of disease comparing 138 WT cases (19 exposed) to 1802 controls (317 exposed) was OR 0.8 (95% CI 0.5-1.3).

3. Methods

3.1 Data Sources

3.1.1 California Cancer Registry

The California Cancer Registry (CCR) has collected information on all cancers diagnosed in the state of California since 1988. Information collected from the CCR includes age at diagnosis, primary cancer site, histologic type, tumor size, and tumor grade. CCR data also provides enough information to link cases to California birth certificates.

3.1.2 California birth records

A birth certificate is issued for each live birth in California. Each birth certificate contains demographic, residential, and both maternal and paternal information, as well as birth and pregnancy characteristics and information on any prior pregnancies of the mother. While many variables are consistently reported across years, revisions in 1989, 1990, 2000 and 2006 result in availability of some data for only a subset of years.

3.2 Study population

Using data from the California Cancer Registry, we identified all childhood cancer cases diagnosed in California between 1988-2007 among children 0-5 years of age. We successfully matched 89% of cases to their California birth certificate (birth years 1983-2007), resulting in a total case population of 10,914. From the same birth certificate files, we randomly selected twenty controls free of cancer by age 5 for each case, frequency matched on birth year, resulting in 218,280 controls. We cross-checked CA death records and excluded controls who died in before age 6 (n=1674). We also

excluded likely non-viable births among controls, defined as birth weight of < 500 grams (n=29) or birth before 20 weeks of gestation (n=110), resulting in a total control population of 215,841. Since this is a records-based study, we were not required to obtain informed consent from study subjects. However, our use of human subjects data was approved by the UCLA Institutional Review Board and the California Health and Human Services Agency Committee for the Protection of Human Subjects.

4. Birth Characteristics and Risk of Lymphoma in Young Children

4.1 Introduction

Lymphoma is the third most common childhood malignancy, accounting for approximately 15% of all cancers diagnosed in children (0-14 years of age). [9] Pediatric lymphoma is relatively rare, with an incidence rate of 16.5 per million among children in the US. [10] Thus, pediatric lymphomas are difficult to study epidemiologically and their etiologies remain largely unknown. Exposures during the prenatal period may be important for childhood cancers in general due to the highly vulnerable state of the developing fetus. [95, 96] There is a growing body of evidence from animal and epidemiologic studies that exposures during the prenatal period may contribute to development of later pediatric lymphoma. [6, 18, 97]

Pediatric lymphoma comprises two important types: Hodgkin lymphoma (HL) and non-Hodgkin's lymphomas (NHL). HL is very rare among young children ages 0-10 and occurs more frequently among adolescents. NHL is the most common form of lymphoma diagnosed among 0-5 year olds, but its rate increases with age throughout adolescence. Nearly all lymphoma diagnoses among infants younger than 1 year of age are miscellaneous lymphoreticular neoplasms. [10]

HL typically arises from B lymphocytes with characteristic Reed-Sternberg cells, which are large, clonal, multinucleated, and sometimes contain Epstein-Barr virus (EBV) genomic sequences [11]. EBV is found in approximately 40-50% of all HL cases in developed countries and up to 80% in developing countries, most commonly among cases diagnosed 0-10 years of age [12, 13].

NHL as a class includes lymphoblastic lymphoma, Burkitt lymphoma, and large cell lymphoma. [98] While each histological subgroup has unique characteristics, these lymphomas are frequently studied together in epidemiologic contexts. Immunodeficiency, including immunosuppressive therapy, congenital immunodeficiency syndromes, and HIV/AIDS all predispose to NHL. [16, 17]

There are few studies reporting on pregnancy exposures or birth certificate variables (including birth characteristics, demographic factors, and complications of pregnancy and labor/delivery) and pediatric HL or NHL. We hypothesized that cancers in the earliest period of life (0-5 years of age) are most likely to have origins in the prenatal period. Here we present results from a large California population-based case-control study of pediatric lymphoma that employed birth records to examine pregnancy-related risk factors.

4.2 Methods

This data utilized two important sources of population-based data in California: birth certificate and California Cancer Registry. Using the cancer registry, we identified all lymphoma cases diagnosed in California children 0-5 years of age between 1988-2007. Lymphoma cases were defined using the International Classification of Childhood Cancer, Third edition (ICCC-3) [99] classification, including codes 021 (Hodgkin lymphomas), 022 (Non-Hodgkin lymphomas, except Burkitt lymphoma), 023 (Burkitt lymphoma), 024 (miscellaneous lymphoreticular neoplasms), or 025 (unspecified lymphomas). Lymphoma cases were part of a case-control study of all childhood cancers ages 0-5 in California during this period, in which we successfully matched 89% of all cases to their California birth certificate (birth years 1986-2007), resulting in a total case population of 10,485.[100] From the same birth certificate files, we randomly selected twenty controls for each case, frequency matched on birth year, resulting in 209,700 controls. We removed cancer cases from the birth records before frequency matching, to arrive at a set of eligible controls who had not been diagnosed with cancer in California. We cross-checked CA death records and excluded controls who died before age six (n=1,522). We also excluded improbable or likely non-viable births, defined as birth weight of < 500 grams (n=27 controls, n=0 cases) or birth before 20 weeks of gestation (n=136 controls, n=0 cases). The final dataset included 478 lymphoma cases and 208,015 controls.

For exposure information, California birth certificates served as our main data source, providing demographic, reproductive history, and gestational information. Gestational variables included complications of pregnancy and labor/delivery, including abnormal conditions and clinical procedures related to the newborn. Some birth certificate information was only available for a subset of study years due to changes in reporting.

Since our study was based only on existing records, we were not required to obtain informed consent from study subjects. Our use of human subject data was approved by the UCLA Institutional Review Board, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the California Cancer Registry.

We used unconditional multivariate logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) while controlling for the matching factor.

Infants were considered preterm if born at < 37 weeks of gestation and post-term if born at > 42 weeks of gestation.[101] Low birth weight (LBW) and high birth weight (HBW) were defined as birth weights of < 2500 grams and ≥ 4000 grams, respectively.[101] All pregnancy and labor/delivery complications were recorded as dichotomous (yes/no) variables. We created a size for gestational age variable using the method described by Alexander et al [102]. This variable is based on 10^{th} and 90^{th} percentile sex-specific birth weight values for each gestational week between 20 to 45 weeks for each maternal race/ethnicity group (non-Hispanic white, Hispanic of any race, African American, Asian/Pacific Islander, and other). In order to generate the percentile values, we included total singleton live births in California born between 1988 and 2006 with gestational ages between weeks 20 and 45 and birth weight within the range provided by Alexander et al, 1996 (n=10,134,074). These values included separate percentiles for males and females by gestational week for each race/ethnic group. We defined small for gestational age as any birth weight below the 10^{th} percentile for each sex and race group, and large for gestational age as any birth weight above the 90^{th} percentile for each sex and race group.

Other variables considered for inclusion in multivariate regression included maternal age (continuous), race/ethnicity (non-Hispanic White, Hispanic of any race, other), and primary payment source for prenatal care. We used payment source for prenatal care as a proxy for socioeconomic status, as we have previously found it to be associated with income [103], and categorized this variable as private insurance (including Health Maintenance Organizations (HMO), Blue Cross-Blue Shield, and any other private insurance), and other payment methods (including government aid programs, such as Medicare, Medi-Cal, worker's compensation, Title V, CHAMPUS/TRICARE, and self-pay). We adjusted all effect estimates for birth year. In order to avoid sparse data problems, we considered for analysis only those exposures with at least five affected cases, as well as risk factors reported in other studies.

We stratified by lymphoma type, separating HL, NHL (including Burkitt lymphoma and other NHL), and all others, including miscellaneous and unspecified lymphomas. Due to the rarity of some pregnancy complications, we adjusted stratified analyses only for birth year and applied the five affected cases criterion described above. In additional sensitivity analyses, we assessed the impact of US- versus foreign-born status among Hispanics on associations between infant birth weight and size for gestational age and lymphoma. Finally, we examined the distribution of histological subtypes of Hodgkin lymphoma by race/ethnicity to examine the prevalence of the mixed cellularity subtype since previous studies have suggested that this subtype is associated with EBV-related HL.

4.3 Results

Lymphoma cases were more often male and of high birth weight than controls (Tables 4.1 and 4.2). Mothers of cases more frequently reported lower education levels than control mothers and were more likely to report either no prenatal care or prenatal care only after the first trimester.

In multivariate analyses, we observed a strong positive association between maternal Hispanic ethnicity and Hodgkin lymphoma (OR and 95% CI: 2.43 [1.14, 5.17]) and a negative association between

Table 4.1. Demographic Characteristics of Subjects in a Study of Lymphoma Risk Among California Children Diagnosed Between 1988 and 2007

	Controls (n = 208015)		Lymphoma cases, (n = 478)		Hodgkin lymphoma (n = 62)		Burkitt Lymphoma (n = 93)		Other Non-Hodgkin Lymphoma (n = 178)		Misc. and Unspecified Lymphoma (n = 145)	
	N	%†	N	%†	N	%†	N	%†	N	%†	N	%†
Sex												
male	**106108**	**51.0**	**310**	**64.9**	46	74.2	74	79.6	122	68.5	68	46.9
female	**101907**	**49.0**	**168**	**35.1**	16	25.8	19	20.4	56	31.5	77	53.1
Age of mother												
<20	**22637**	**10.9**	**43**	**9.0**	7	11.3	7	7.5	20	11.2	9	6.2
20-29	**108744**	**52.3**	**263**	**55.0**	39	62.9	44	47.3	92	51.7	88	60.7
30-34	**48161**	**23.2**	**115**	**24.1**	12	19.4	27	29.0	44	24.7	32	22.1
35+	**28435**	**13.7**	**57**	**11.9**	4	6.5	15	16.1	22	12.4	16	11.0
missing	**38**		**0**		0		0		0		0	
Age of father												
<20	**8043**	**4.1**	**12**	**2.7**	5	9.4	0	0.0	5	3.0	2	1.4
20-29	**87205**	**44.8**	**209**	**47.1**	23	43.4	40	44.9	78	47.6	68	49.3
30-34	**50070**	**25.7**	**112**	**25.2**	13	24.5	21	23.6	45	27.4	33	23.9
35+	**49160**	**25.3**	**111**	**25.0**	12	22.6	28	31.5	36	22.0	35	25.4
missing	**13537**		**34**		9		4		14		7	
Mother's education												
≤ 8 years	**24469**	**13.6**	**55**	**14.0**	12	24.0	12	14.6	11	8.3	20	15.6
Some high school (9-11 yrs)	**33089**	**18.4**	**86**	**21.9**	10	20.0	17	20.7	26	19.5	33	25.8
High school diploma (12 yrs)	**52382**	**29.1**	**127**	**32.3**	15	30.0	25	30.5	47	35.3	40	31.3
Some college (13-15 yrs)	**35566**	**19.8**	**66**	**16.8**	6	12.0	16	19.5	28	21.1	16	12.5
College diploma or higher (16+ yrs)	**34503**	**19.2**	**59**	**15.0**	7	14.0	12	14.6	21	15.8	19	14.8
missing	**28006**		**85**		12		11		45		17	
Father's education												
≤ 8 years	**24667**	**14.6**	**60**	**16.5**	10	23.3	13	17.1	15	12.1	22	18.3
Some high school (9-11 yrs)	**25123**	**14.9**	**53**	**14.6**	10	23.3	6	7.9	15	12.1	22	18.3
High school diploma (12 yrs)	**52080**	**30.9**	**112**	**30.9**	8	18.6	26	34.2	43	34.7	35	29.2
Some college (13-15 yrs)	**29770**	**17.7**	**67**	**18.5**	7	16.3	12	15.8	27	21.8	21	17.5
College diploma or higher (16+ yrs)	**36954**	**21.9**	**71**	**19.6**	8	18.6	19	25.0	24	19.4	20	16.7
missing	**39421**		**115**		19		17		54		25	

Table 4.1 (continued)

	Controls (n = 208015)		Lymphoma cases, (n = 478)		Hodgkin lymphoma (n = 62)		Burkitt Lymphoma (n = 93)		Other Non-Hodgkin Lymphoma (n = 178)		Misc. and Unspecified Lymphoma (n = 145)	
	N	**%†**	**N**	**%†**	N	%†	N	%†	N	%†	N	%†
Mother's race												
white	**75298**	**36.4**	**165**	**34.7**	13	21.0	46	50.0	72	40.7	34	23.4
hispanic	**93483**	**45.2**	**232**	**48.7**	43	69.4	36	39.1	68	38.4	85	58.6
other	**38024**	**18.4**	**79**	**16.6**	6	9.7	10	10.9	37	20.9	26	17.9
missing	**1210**		**2**		0		1		1		0	
Father's race												
white	**71676**	**36.2**	**150**	**33.0**	10	18.2	43	47.3	66	39.5	31	22.0
hispanic	**89456**	**45.2**	**225**	**49.6**	40	72.7	38	41.8	64	38.3	83	58.9
other	**36928**	**18.6**	**79**	**17.4**	5	9.1	10	11.0	37	22.2	27	19.1
missing	**9955**		**24**		7		2		11		4	
Parental race combination												
white/white	**61040**	**29.5**	**131**	**27.5**	10	16.1	40	43.5	55	31.1	26	17.9
hispanic/hispanic	**79985**	**38.7**	**199**	**41.8**	38	61.3	33	35.9	52	29.4	76	52.4
white/hispanic	**14393**	**7.0**	**33**	**6.9**	2	3.2	6	6.5	16	9.0	9	6.2
other/other	**30464**	**14.7**	**65**	**13.7**	5	8.1	8	8.7	30	16.9	22	15.2
other combination	**20984**	**10.1**	**48**	**10.1**	7	11.3	5	5.4	24	13.6	12	8.3
missing	**1149**		**2**		0		1		1		0	
Mother's birthplace												
US born	**117326**	**56.5**	**269**	**56.3**	31	50.0	58	62.4	115	64.6	65	44.8
foreign born	**90450**	**43.5**	**209**	**43.7**	31	50.0	35	37.6	63	35.4	80	55.2
missing	**239**		**0**		0		0		0		0	
Payment source for prenatal care												
Private insurance	**91600**	**50.8**	**197**	**50.8**	21	44.7	48	59.3	78	57.8	50	40.0
Other	**88856**	**49.2**	**191**	**49.2**	26	55.3	33	40.7	57	42.2	75	60.0
missing	**27559**		**90**		15		12		43		20	
CASE ATTRIBUTES												
Age at diagnosis												
0			**80**	**16.74**	0	0.00	0	0.00	17	9.55	61	45.52
1			**66**	**13.81**	1	1.61	2	2.15	21	11.80	40	29.85
2			**65**	**13.60**	3	4.84	10	10.75	29	16.29	21	15.67
3			**82**	**17.15**	11	17.74	36	38.71	27	15.17	5	3.73
4			**97**	**20.29**	23	37.10	21	22.58	48	26.97	5	3.73
5			**88**	**18.41**	24	38.71	24	25.81	36	20.22	2	1.49

† Percent of non-missing

maternal Hispanic ethnicity and NHL (OR and 95% CI: 0.80 [0.58, 1.10]) (Table 4.3). When we combined maternal and paternal race information, we observed similar associations when both parents reported Hispanic ethnicity (OR and 95% CI: 2.23 [0.99, 5.01]) for Hodgkin lymphoma while for NHL the negative

association was attenuated (OR=0.81; 95% CI 0.57, 1.15). Among birth complications and other indicators for high risk pregnancies, tocolysis, previous preterm birth, and fetopelvic disproportion each conferred an approximately 2-fold increase in estimated risk of any type of lymphoma (Table 4.4). For maternal febrile status, prolonged labor, premature rupture of membranes, moderate to heavy meconium staining of the amniotic fluid, large size for gestational age, high birth weight, and previous stillbirth our data suggested positive associations with lymphoma although confidence intervals included the null value. Including birth weight in the multivariate model for associations between lymphoma and pregnancy and labor complications did not change our estimates more than minimally (< 10% change), (results not shown).

In analyses stratified by lymphoma type, we observed strong associations between Hodgkin lymphoma and moderate to heavy meconium staining, and between non-Hodgkin lymphoma and premature rupture of the membranes (Table 4.5). Positive associations were also observed between high birth weight and both NHL and miscellaneous and unspecified lymphomas.

Foreign-born status among Hispanics conferred a slight (10-20%) decrease in odds of any lymphoma compared to US-born Hispanics, although confidence intervals included the null value (OR 0.81 95% CI 0.58, 1.12). When we examined birth weight and size for gestational age among Hispanics stratified by maternal birthplace, we did not observe any differences between cases and controls, although among cases, Hispanic mothers born in the US gave birth to more low birth weight infants than foreign-born Hispanic mothers (results not shown).

A higher proportion of Hispanic than white HL cases was diagnosed with the mixed cellularity subtype (27.9% and 7.7% for Hispanics and whites, respectively). The nodular lymphocyte-predominant subtype was more common among whites than Hispanics (4.7% and 30.8% for Hispanics and whites, respectively).

Table 4.2. Birth and Gestational Characteristics of Subjuects in a Study of Lymphoma Risk Among California Children Diagnosed Between 1988 and 2007

	Controls (n = 208015)		Lymphoma (n = 478)		Hodgkin (n = 62)		Burkitt (n = 93)		Other Non-Hodgkin (n = 178)		Misc. and Unspecified (n = 145)	
	N	%†	N	%†	N	%†	N	%†	N	%†	N	%†
Birth weight, g												
< 2500	**12119**	**5.8**	**26**	**5.5**	2	3.2	7	7.5	10	5.6	7	4.9
2500-3999	**173316**	**83.5**	**384**	**80.5**	53	85.5	74	79.6	144	80.9	113	78.5
4000+	**22114**	**10.7**	**67**	**14.0**	7	11.3	12	12.9	24	13.5	24	16.7
missing	**466**		**1**		0		0		0		1	
Gestational age, weeks												
≤ 36	**20118**	**10.2**	**45**	**9.9**	1	1.8	11	12.2	14	8.2	19	13.7
37-42	**168701**	**85.7**	**397**	**87.3**	52	92.9	75	83.3	151	88.8	119	85.6
43+	**8141**	**4.1**	**13**	**2.9**	3	5.4	4	4.4	5	2.9	1	0.7
missing	**11055**		**23**		6		3		8		6	
Size for gestational age												
Small	**20564**	**10.5**	**46**	**10.1**	8	14.3	12	13.3	16	9.4	10	7.2
Normal	**155308**	**79.0**	**349**	**76.9**	45	80.4	67	74.4	132	77.6	105	76.1
Large	**20653**	**10.5**	**59**	**13.0**	3	5.4	11	12.2	22	12.9	23	16.7
missing	**11490**		**24**		6		3		8		7	
Method of delivery												
Vaginal	**158662**	**76.3**	**375**	**78.5**	48	77.4	73	78.5	137	77.0	117	80.7
Caesarean	**49225**	**23.7**	**103**	**21.5**	14	22.6	20	21.5	41	23.0	28	19.3
missing	**128**		**0**		0		0		0		0	
Previous terminations												
None	**172122**	**82.8**	**395**	**82.6**	51	82.3	74	79.6	153	86.0	117	80.7
1+	**35679**	**17.2**	**83**	**17.4**	11	17.7	19	20.4	25	14.0	28	19.3
missing	**214**		**0**		0		0		0		0	
Parity												
first birth	**81785**	**39.3**	**172**	**36.0**	22	35.5	31	33.3	74	41.6	45	31.0
second or third birth	**100143**	**48.2**	**244**	**51.0**	32	51.6	44	47.3	89	50.0	79	54.5
fourth or subsequent birth	**25947**	**12.5**	**62**	**13.0**	8	12.9	18	19.4	15	8.4	21	14.5
missing	**140**		**0**		0		0		0		0	
Prenatal care initiation												
During first trimester	**164378**	**80.1**	**363**	**76.9**	44	72.1	80	86.0	136	77.7	103	72.0
No care or after first trimester	**40958**	**19.9**	**109**	**23.1**	17	27.9	13	14.0	39	22.3	40	28.0
missing	**2679**		**6**		1		0		3		2	

† Percent of non-missing

Table 4.3. Multivariate analysis of select birth certificate variables in relation to lymphoma risk among California children age 0-5

			Hodgkin Lymphoma		Non-Hodgkin Lymphoma	
	Model 1*	Model 2 ‡	Model 1*	Model 2 ‡	Model 1*	Model 2 ‡
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex						
male	1.77 (1.47, 2.14)	1.81 (1.47, 2.23)	2.76 (1.56, 4.88)	2.81 (1.46, 5.42)	2.51 (1.92, 3.28)	2.58 (1.91, 3.49)
female	ref	ref	ref	ref	ref	ref
Birth weight, g						
< 2500	0.97 (0.65, 1.45)	0.89 (0.56, 1.41)	-	-	1.12 (0.68, 1.83)	1.09 (0.62, 1.92)
2500-3999	ref	ref	ref	ref	ref	ref
4000+	1.35 (1.04, 1.76)	1.23 (0.91, 1.67)	1.04 (0.47, 2.28)	1.02 (0.40, 2.77)	1.30 (0.91, 1.84)	1.03 (0.67, 1.59)
Gestational age, weeks						
≤ 36	0.95 (0.70, 1.30)	0.87 (0.60, 1.24)	-	-	0.93 (0.61, 1.40)	0.81 (0.49, 1.34)
37-42	ref	ref	ref	ref	ref	ref
43+	0.66 (0.38, 1.15)	0.59 (0.31, 1.15)	1.20 (0.37, 3.83)	0.96 (0.23, 3.97)	0.83 (0.42, 1.61)	0.70 (0.31, 1.59)
Size for gestational age						
Small	1.00 (0.73, 1.35)	1.06 (0.76, 1.48)	1.34 (0.63, 2.85)	1.53 (0.68, 3.45)	1.06 (0.72, 1.58)	1.13 (0.74, 1.73)
Normal	ref	ref	ref	ref	ref	ref
Large	1.27 (0.96, 1.67)	1.18 (0.85, 1.63)	0.50 (0.16, 1.61)	0.50 (0.12, 2.06)	1.25 (0.86, 1.80)	0.98 (0.62, 1.56)
Age of mother*						
<20	0.79 (0.57, 1.09)	0.80 (0.56, 1.14)	0.86 (0.39, 1.93)	0.94 (0.39, 2.29)	0.95 (0.63, 1.44)	1.05 (0.66, 1.66)
20-29	ref	ref	ref	ref	ref	ref
30-34	1.00 (0.80, 1.25)	0.98 (0.77, 1.26)	0.70 (0.36, 1.33)	1.08 (0.54, 2.15)	1.18 (0.89, 1.57)	1.07 (0.77, 1.49)
35+	0.86 (0.64, 1.14)	0.79 (0.57, 1.10)	0.39 (0.14, 1.10)	0.16 (0.02, 1.18)	1.04 (0.72, 1.50)	0.88 (0.58, 1.35)
Age of father						
<20	0.62 (0.35, 1.12)	0.49 (0.24, 1.00)	2.36 (0.90, 6.20)	0.91 (0.20, 4.16)	0.46 (0.19, 1.13)	0.49 (0.18, 1.37)
20-29	ref	ref	ref	ref	ref	ref
30-34	0.94 (0.75, 1.19)	0.95 (0.72, 1.27)	0.98 (0.50, 1.94)	1.65 (0.70, 3.90)	0.97 (0.72, 1.32)	0.82 (0.56, 1.20)
35+	0.97 (0.77, 1.22)	0.92 (0.66, 1.30)	0.93 (0.46, 1.86)	1.81 (0.64, 5.12)	0.96 (0.71, 1.31)	0.71 (0.45, 1.13)
Mother's education						
≤ 8 years	0.92 (0.67, 1.26)	0.87 (0.61, 1.24)	1.71 (0.80, 3.66)	1.08 (0.46, 2.54)	0.68 (0.43, 1.09)	0.75 (0.44, 1.28)
Some high school (9-11 yrs)	1.08 (0.82, 1.42)	1.11 (0.83, 1.48)	1.06 (0.47, 2.35)	0.74 (0.32, 1.75)	0.95 (0.65, 1.38)	1.16 (0.77, 1.73)
High school diploma (12 yrs)	ref	ref	ref	ref	ref	ref
Some college (13-15 yrs)	0.77 (0.57, 1.03)	0.77 (0.57, 1.04)	0.59 (0.23, 1.52)	0.72 (0.27, 1.88)	0.90 (0.62, 1.31)	0.82 (0.56, 1.21)
College diploma or higher (16+ yrs)	0.72 (0.53, 0.98)	0.70 (0.50, 0.98)	0.71 (0.29, 1.74)	1.22 (0.45, 3.32)	0.70 (0.46, 1.05)	0.58 (0.37, 0.91)
Father's education						
≤ 8 years	1.12 (0.82, 1.54)	1.08 (0.76, 1.52)	2.64 (1.04, 6.69)	1.80 (0.66, 4.93)	0.86 (0.55, 1.33)	0.99 (0.60, 1.62)
Some high school (9-11 yrs)	0.99 (0.71, 1.37)	0.95 (0.67, 1.34)	2.59 (1.02, 6.57)	1.88 (0.70, 5.00)	0.63 (0.39, 1.03)	0.76 (0.46, 1.26)
High school diploma (12 yrs)	ref	ref	ref	ref	ref	ref
Some college (13-15 yrs)	1.05 (0.78, 1.42)	1.09 (0.80, 1.49)	1.53 (0.56, 4.22)	1.83 (0.65, 5.12)	0.99 (0.67, 1.47)	0.94 (0.63, 1.41)
College diploma or higher (16+ yrs)	0.90 (0.67, 1.21)	0.95 (0.68, 1.32)	1.41 (0.53, 3.76)	2.22 (0.76, 6.49)	0.88 (0.60, 1.29)	0.79 (0.52, 1.20)
Mother's race*						
white	ref	ref	ref	ref	ref	ref
hispanic	1.18 (0.96, 1.44)	1.14 (0.90, 1.45)	2.66 (1.43, 4.96)	2.43 (1.14, 5.17)	0.71 (0.55, 0.92)	0.80 (0.58, 1.10)
other	0.97 (0.74, 1.27)	0.94 (0.69, 1.27)	0.91 (0.35, 2.41)	1.21 (0.44, 3.35)	0.79 (0.56, 1.11)	0.74 (0.50, 1.11)
Father's race						
white	ref	ref	ref	ref	ref	ref
hispanic	1.24 (1.01, 1.53)	1.42 (0.98, 2.06)	3.21 (1.60, 6.41)	1.60 (0.50, 5.13)	0.75 (0.57, 0.98)	1.26 (0.78, 2.04)
other	1.04 (0.79, 1.37)	1.03 (0.64, 1.65)	0.97 (0.33, 2.84)	0.98 (0.19, 5.02)	0.84 (0.59, 1.18)	0.85 (0.46, 1.59)
Parental race combination						
white/white	ref	ref	ref	ref	ref	ref
hispanic/hispanic	1.21 (0.97, 1.51)	1.19 (0.91, 1.56)	2.90 (1.45, 5.82)	2.23 (0.99, 5.01)	0.68 (0.51, 0.92)	0.81 (0.57, 1.15)
white/hispanic	1.10 (0.75, 1.61)	1.02 (0.67, 1.58)	0.85 (0.19, 3.87)	-	0.98 (0.62, 1.56)	1.02 (0.61, 1.72)
other/other	1.02 (0.76, 1.37)	0.97 (0.69, 1.36)	1.00 (0.34, 2.93)	1.13 (0.38, 3.39)	0.80 (0.55, 1.17)	0.76 (0.48, 1.18)
Mother's birthplace						
US born	ref	ref	ref	ref	ref	ref
foreign born	1.03 (0.86, 1.23)	0.88 (0.69, 1.11)	1.30 (0.79, 2.13)	0.77 (0.40, 1.47)	0.74 (0.57, 0.94)	0.85 (0.61, 1.19)

Table 4.3 (continued)

			Hodgkin Lymphoma		Non-Hodgkin Lymphoma	
	Model 1*	Model 2 ‡	Model 1*	Model 2 ‡	Model 1*	Model 2 ‡
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Method of delivery						
Vaginal	ref	ref	ref	ref	ref	ref
Caesarean	0.90 (0.72, 1.12)	0.97 (0.76, 1.23)	0.94 (0.52, 1.71)	1.39 (0.73, 2.65)	0.94 (0.70, 1.25)	1.01 (0.74, 1.39)
Previous terminations						
None	ref	ref	ref	ref	ref	ref
1+	1.02 (0.80, 1.29)	1.11 (0.85, 1.44)	1.04 (0.54, 2.00)	1.16 (0.54, 2.52)	0.94 (0.68, 1.29)	0.93 (0.64, 1.34)
Parity						
first birth	ref	ref	ref	ref	ref	ref
second or third birth	1.16 (0.96, 1.41)	1.13 (0.90, 1.42)	1.19 (0.69, 2.04)	1.23 (0.65, 2.34)	1.04 (0.80, 1.34)	0.98 (0.73, 1.32)
fourth or subsequent birth	1.14 (0.85, 1.52)	1.04 (0.72, 1.50)	1.15 (0.51, 2.58)	0.79 (0.24, 2.56)	0.99 (0.67, 1.47)	0.97 (0.59, 1.59)
Prenatal care initiation						
During first trimester	ref	ref	ref	ref	ref	ref
No care or after first trimester	1.16 (0.94, 1.44)	1.19 (0.92, 1.53)	1.55 (0.89, 2.71)	0.90 (0.43, 1.85)	0.97 (0.71, 1.31)	1.07 (0.75, 1.54)
Payment source for prenatal care						
Private insurance	ref	ref	ref	ref	ref	ref
Other	1.00 (0.82, 1.22)	0.95 (0.76, 1.18)	1.28 (0.72, 2.27)	0.86 (0.46, 1.60)	0.74 (0.56, 0.97)	0.78 (0.58, 1.05)

*** Model 1 is adjusted for birth year only**

‡ Model 2 is adjusted for birth year, maternal age and race, and prenatal payment source

We additionally report our observed frequencies of polyhydramnios and anemia, with fewer than five affected cases, because these factors were associated with lymphoma in a previous study. [104] Four case mothers and 1617 control mothers were reported as having suffered from anemia, while one case and 986 control mothers were reported to have suffered from polyhydramnios/oligohydramnios.

Table 4.4. Multivariate Analysis of Pregnancy and Labor/Delivery Complications in Relation to Lymphoma Risk Among California Children Diagnosed Between 1988 and 2007

	Controls N/ N total*	Lymphoma cases, total N/ N total*	Crude OR (95% CI)	Model 1 ‡ OR (95% CI)	Model 2 § OR (95% CI)
Epidural	2980/7780	6/14	1.21 (0.42, 3.49)	0.85 (0.27, 2.68)	0.84 (0.27, 2.65)
Premature labor	4169/174962	10/384	1.10 (0.58, 2.05)	1.15 (0.62, 2.17)	1.31 (0.69, 2.51)
Amniocentisis	4158/174962	6/384	0.65 (0.29, 1.46)	0.68 (0.30, 1.53)	0.69 (0.30, 1.56)
Tocolysis	1536/174962	7/384	2.10 (0.99, 4.44)	2.24 (1.06, 4.75)	2.32 (1.09, 4.92)
Febrile (> 100 F)	2052/174962	6/384	1.34 (0.60, 3.00)	1.40 (0.62, 3.14)	1.39 (0.62, 3.11)
Previous pre-term birth	2013/182742	9/398	2.08 (1.07, 4.03)	2.22 (1.14, 4.32)	2.30 (1.18, 4.47)
Pre-eclampsia	3897/182742	6/398	0.70 (0.31, 1.58)	0.73 (0.33, 1.63)	0.77 (0.34, 1.73)
Prolonged labor (> 20 hours)	1380/182742	5/398	1.67 (0.69, 4.05)	1.73 (0.71, 4.18)	1.70 (0.70, 4.13)
Premature rupture of memb	3505/182742	10/398	1.32 (0.70, 2.47)	1.38 (0.73, 2.58)	1.45 (0.77, 2.74)
Induction of labor	16921/182742	29/398	0.77 (0.53, 1.13)	0.80 (0.56, 1.18)	0.80 (0.55, 1.17)
Stimulation of labor	18144/182742	38/398	0.96 (0.69, 1.34)	0.97 (0.69, 1.36)	0.96 (0.68, 1.35)
Moderate/heavy meconium	7629/182742	22/398	1.34 (0.87, 2.07)	1.39 (0.90, 2.13)	1.37 (0.89, 2.10)
Small for gestational age	20564/196525	46/454	0.97 (0.71, 1.31)	1.04 (0.75, 1.45)	-
Large for gestational age	20653/196525	59/454	1.27 (0.97, 1.67)	1.17 (0.85, 1.62)	-
Preterm birth	20118/196960	45/455	0.97 (0.71, 1.31)	0.88 (0.62, 1.26)	0.92 (0.62, 1.35)
Fetopelvic disproportion	4803/200235	17/464	1.55 (0.95, 2.51)	1.93 (1.15, 3.24)	1.75 (1.02, 3.00)
Breech or other abnormal pr	5944/200235	12/464	0.87 (0.49, 1.54)	0.73 (0.36, 1.47)	0.76 (0.38, 1.54)
Fetal distress	6308/200235	12/464	0.81 (0.46, 1.45)	0.86 (0.46, 1.62)	0.88 (0.47, 1.65)
Low birth weight	12119/207549	26/477	0.93 (0.63, 1.38)	0.87 (0.55, 1.37)	-
High birth weight	22114/207549	67/477	1.37 (1.06, 1.78)	1.24 (0.92, 1.68)	-
Previous still birth	3008/207687	9/478	1.31 (0.68, 2.53)	1.31 (0.62, 2.78)	1.33 (0.63, 2.82)

*** The total sample sizes reflected in each row may be smaller than the total number of subjects due to collection of some variables during only a subset of study years**

‡ Model 1 is adjusted for birth year, maternal age and race, and prenatal payment source

§ Model 2 adjusts for all the variables in Model 1, and is further adjusted for birth weight

Table 4.5. Multivariate Analysis of Pregnancy and Labor/Delivery Complications in Relation to Lymphoma Subtype Risk Among California Children Diagnosed Between 1988 and 2007

	Controls	Hodgkin lymphoma		Non-Hodgkin Lymphoma		Misc. & Unspecified	
	N/ N total*	N/ N total*	Crude OR (95% CI)	N/ N total*	Crude OR (95% CI)	N/ N total*	Crude OR (95% CI)
Premature labor	4169/174962	0/50	-	7/214	1.39 (0.65, 2.95)	3/120	-
Premature rupture of memb	3505/182742	0/50	-	9/220	2.18 (1.12, 4.25)	1/128	-
Induction of labor	16921/182742	0/50	-	21/220	1.04 (0.66, 1.62)	8/128	0.65 (0.32, 1.34)
Stimulation of labor	18144/182742	4/50	-	26/220	1.22 (0.81, 1.83)	8/128	0.61 (0.30, 1.24)
Moderate/heavy meconium	7629/182742	5/50	2.55 (1.01, 6.43)	11/220	1.21 (0.66, 2.22)	6/128	1.13 (0.50, 2.57)
Small for gestational age	20564/196525	8/56	1.42 (0.67, 2.99)	28/260	1.03 (0.70, 1.53)	12/138	0.66 (0.35, 1.26)
Large for gestational age	20653/196525	3/56	-	33/260	1.24 (0.86, 1.78)	23/138	1.71 (1.09, 2.67)
Preterm birth	20118/196960	1/55	-	25/260	0.94 (0.62, 1.41)	19/139	1.37 (0.85, 2.23)
Fetopelvic disproportion	4803/200235	2/62	-	10/265	1.60 (0.85, 3.00)	5/137	1.55 (0.63, 3.78)
Fetal distress	6308/200235	1/62	-	8/265	0.96 (0.47, 1.94)	3/137	-
Low birth weight	12119/207549	2/62	-	17/271	1.08 (0.66, 1.76)	7/144	0.80 (0.38, 1.72)
High birth weight	22114/207549	7/62	1.07 (0.49, 2.35)	36/271	1.29 (0.91, 1.83)	24/144	1.68 (1.09, 2.61)

*** The total sample sizes reflected in each row may be smaller than the total number of subjects due to collection of some variables during only a subset of study years**

4.4 Discussion

We investigated associations between pregnancy-related factors reported on birth certificates and pediatric lymphomas in a large, population-based series of children age 0-5 in California. For NHL, the most common form of lymphoma diagnosed among children 0-5, we observed an increase in risk for male sex and a risk reduction for Hispanic ethnicity, foreign-born status, and non-private health insurance, one of our indicators of low SES. Male sex, lower paternal education, and Hispanic ethnicity were related to a risk increase for HL. NHL risk was increased for infants born after premature rupture of the membranes, a potential marker of intra-uterine infection, while HL risk was higher among infants born with meconium staining of the amniotic fluid, a marker of fetal distress, but these estimates were imprecise due to small sample size.

The associations we observed between Hispanic ethnicity and both HL and NHL are consistent with reports from both a recent study that pooled data across the US [23] and the 2000-2008 SEER data[105][105][105][105]. The increased risk of HL among Hispanics may be attributable to Epstein - Barr virus (EBV). Several studies among both pediatric and adult HL cases have reported that Hispanic

cases are more likely than whites to have EBV-associated HL and that the mixed cellularity subtype is most commonly diagnosed in EBV-related malignancies. [13, 24-26] One pooled analysis that combined data from 14 studies found that the highest percentages of EBV-associated cases occurred among children < 10 and in older adults, and that Hispanics were four times as likely as whites to have EBV-associated HL. [13] This study also reported that among cases 0-14 years of age, those from less economically developed regions were six times as likely to have EBV-associated disease as cases from more developed regions. Another study comparing pediatric HL from Honduras and the US found that 100% and 57% of cases, respectively, were EBV-associated. [24] Our case population is among the largest to confirm the strong association between Hispanic ethnicity and HL risk for children 0-5 years of age. While we do not have data on EBV status, the high proportion of mixed-cellularity subtype among Hispanics supports the potential link between EBV and HL in our population. Although latent EBV infection is nearly ubiquitous in adult populations around the world, timing of primary infection may vary. In low resource countries exposure to EBV infection typically occurs during the first few years of life, whereas infection may not occur until the second or third decade of life in high resource areas.[106, 107]

In our analyses of all lymphoma cases combined, we observed an increased risk for those with the birth complications tocolysis and fetopelvic disproportion, as well as previous preterm birth, which is a factor associated with elevated risk for birth complications in subsequent pregnancies. Associations between tocolysis and previous preterm birth with lymphoma have not been reported elsewhere. In 2009, the rate of tocolysis usage in the United States was estimated to be 13.3 per 1000 live births. [108] Tocolysis is most commonly used to inhibit preterm labor, although use of tocolytics has also been suggested for management of fetal distress and during external cephalic version. [101] Fetal distress was not reported to differ among cases and controls, thus tocolysis most likely is an indicator of preterm labor. Previous preterm birth is a strong risk factor for subsequent preterm birth. [109] Additionally,

the positive association between all types of lymphoma and previous stillbirth is similar to results from two previous studies of NHL. [27, 28] Women with previous stillbirth also are at higher risk for preterm birth in subsequent pregnancies. [101, 110, 111] Despite the higher prevalence of these risk factors for preterm birth among cases, frequency of preterm births was similar in cases and controls. Thus it seems that while preterm birth may be more often threatened among cases, we did not find evidence that our cases experienced more preterm births than controls. These associations may therefore point to tocolytic agents used to prevent or manage preterm labor or factors contributing to preterm labor.

Fetopelvic disproportion arises from diminished pelvic capacity, excessive fetal size, or a combination of both. [101] Although fetal size can contribute to fetopelvic disproportion, most cases of disproportion occur in a fetus within the normal weight range. [101] In our population, the mean birth weight of cases and controls affected by fetopelvic disproportion was 3642 g and 4075 g, respectively. Thus, birth weight does not seem to account for the increase of fetopelvic disproportion among cases, and adjusting for birth weight did not remove the association between lymphoma and fetopelvic disproportion.

In analyses stratified by lymphoma type, premature rupture of the membranes (PROM) was associated with NHL. PROM is associated with intra-amniotic infection, low socioeconomic status, low body mass index (< 19.8), nutritional deficiencies, and cigarette smoking. [101] Thus this association could be a proxy for other factors that may influence pediatric NHL risk. We also observed an association between meconium staining of the amniotic fluid and HL risk. Meconium staining, rarely observed in preterm infants, is associated with fetal distress and fetal acidosis and may be an indicator of fetal hypoxia. [101] While meconium staining may not directly contribute to risk of HL in children, it may also act as a proxy for some unknown risk factor.

This study also identified an increased risk of miscellaneous and unspecified lymphomas among those with high birth weight and large size for gestational age. Many factors contribute to fetal growth,

including genetic potential, maternal nutritional status, placental function, and intrauterine hormonal factors.[112] Previous studies have noted a relationship between high birth weight and pediatric leukemia that is particularly strong among young children (< 2 years). [113, 114] Our results may indicate a similar pattern of association between high birth weight and lymphoma given that most miscellaneous and unspecified lymphomas are diagnosed within the first year of life.[10] The underlying biological mechanisms in the association between lymphoma and HBW are unclear, although it may be driven by growth factors such as the insulin-like growth factor (IGF) family, which impact both birth weight and carcinogenic cell proliferation.[114-118]

Our study is restricted to the information provided on California birth certificates. Some variables were collected during only a subset of study years, thereby further limiting our assessments. Birth certificate information has varying levels of validity. [119-125] One study reported a very high sensitivity (>94%) for most race information on California birth certificates. [120] Additionally, birth weight and method of delivery tend to have the highest sensitivity and specificity. [121, 123, 124] Maternal factors such as age, marital status, and education, also have reasonably good validity [119], whereas pregnancy complications generally have high (>95%) specificity but low sensitivity [121-124]. We analyzed a large number of potential risk factors and therefore multiple comparisons may have resulted in false positive findings. Further studies are needed to confirm the novel associations we observed.

Our study represents one of the largest population-based case-control studies of pediatric lymphoma. Our study has additional strengths in that we have a large number of Hispanic mothers (both US and Mexican born) which allowed us to examine risk in these populations separately. Additionally, given the prospective nature of birth certificate data collection with regard to subsequent diagnoses of cancer in children, we do not expect differential misclassification to have influenced our

results. Also our study population is likely to be free of selection bias due to non-participation because of population-based control sampling and the registry-based exposure and outcome assessment.

In this large study of an ethnically diverse population, we demonstrated that several prenatal factors may be related to lymphoma risk among children. Our study confirms previous findings on Hispanic ethnicity and lymphomas and also reports novel associations that merit further investigation. While we found associations between pediatric lymphoma and several birth certificate variables, many of these may be no more than markers of other factors that contribute to lymphoma development. Future research should include studies large enough to distinguish cases not only according to lymphoma type (including histologic classifications more detailed than HL and NHL) but also by age of onset, since lymphomas occurring early in life may have different etiologies than those occurring in older children and adolescents [9, 14, 15]. Our findings corroborate the EBV hypothesis for HL and also suggest that other factors, such as intra-uterine infections and factors associated with preterm labor may be involved in lymphoma pathogenesis.

5. Exposure to infections in Early Life and Risk of Leukemia in Young Children

5.1 Introduction

Leukemia is the most common form of childhood cancer, accounting for more than one third of all childhood cancers among those aged 0-14.[10]

Pediatric leukemia arises from a diverse set of chromosomal and molecular changes. There is strong evidence that most of these are acquired, not inherited, as only a small number (about 5%) of leukemias are associated with inherited genetic syndromes. [36, 37] Evidence from twin studies and studies of neonatal blood spots suggests that most initiating events occur during fetal development in utero. [38-42] Infections may play a role in pediatric leukemia pathogenesis, [45-48, 126] and there are two main hypotheses on the nature of this etiology.

Greaves has proposed the 'delayed infection' hypothesis suggesting that delayed exposure to common childhood infections leads to an increased risk of pediatric leukemia through an abnormal immune response.[43] Greaves hypothesized that lack of immune modulation in the neonatal period and in infancy may predispose the immune system to abnormal responses following subsequent 'delayed' exposure to infection. Within the context of the 'two hit hypothesis', a minimum of two genetic events are required for the development of acute lymphoblastic leukemia (ALL) and infection would promote the second genetic event through an aberrant or pathological immune response. A second hypothesis has been proposed by Kinlen as the 'population mixing' hypothesis which states that pediatric leukemia might arise from a rare response to common infection. [44] Population mixing would result in increased risks due to contact between infected and susceptible individuals. While Greaves' hypothesis emphasizes the timing of exposure, Kinlen's hypothesis emphasizes exposure to specific agent(s) the child has not encountered yet.

Since direct measurement of a child's actual exposure to infection is challenging in an epidemiologic setting, previous studies have employed several proxies of early life exposure to infections in order to examine the link between childhood cancers and infection. Demonstrated predictors of increased early childhood exposure to infection include day care attendance, number of older siblings, and timing of birth with regard to common viral infection seasons.[127, 128] Here we examine the link between risk of ALL and several proxies of early life exposure to infection, including month of birth, timing of birth with regard to influenza and respiratory syncytial virus (RSV) seasons, and birth order among California children age 0-5.

5.2 Methods

Using data from the California Cancer Registry, we identified all acute lymphoid leukemia (ALL) tumor cases diagnosed in California between 1988-2007 among children 0-5 years of age at diagnosis. Leukemia cases were defined as International Classification of Childhood Cancer, Third edition (ICCC-3) [99] code 011 (Lymphoid leukemias). Cases were part of a large case-control study of all childhood cancers ages 0-5 in CA during this period, in which we successfully matched 89% of all cases to their CA birth certificate (birth years 1986-2007), resulting in a total case population of 10,485.[129] From the same birth certificate files, we randomly selected twenty controls free of cancer by age 5 for each case, frequency matched on birth year, resulting in 209,700 controls. We cross-checked CA death records and excluded controls who died before age six (n=1,522). We also excluded improbable or likely non-viable births, defined as birth weight of < 500 grams (n=27 controls, n=0 cases) or birth before 20 weeks of gestation (n=136 controls, n=1 case), resulting in 208,015 controls. To ensure a similar birth year distribution among our subgroup of cases and controls, we randomly chose a separate control series from among this larger control group. This new control series was frequency matched on birth year in a 20:1 ratio to cases. The final dataset included 3402 ALL cases and 68,040 controls.

Since our study was based only on existing records, we did not obtain informed consent from study subjects. Our use of human subject data was approved by the UCLA Institutional Review Board and the California Health and Human Services Agency Committee for the Protection of Human Subjects.

We created a variable reflecting payment source for prenatal care private insurance (including Health Maintenance Organizations (HMO), Blue Cross-Blue Shield, and any other private insurance), and other payment methods (including government aid programs, such as Medicare, Medi-Cal, worker's compensation, Title V, CHAMPUS/TRICARE, and self-pay) as a proxy for socioeconomic status, as we have previously found it to be associated with income. [103] Month of birth information was collected from birth certificate data. We expect that month of birth may be associated with exposure to seasonal infections. Specifically, examples of seasonal infections and the timing of their peak include: winter months: influenza, pneumococcal disease, and rotavirus; spring: respiratory syncytial virus (RSV) and measles; summer: poliovirus and other enteroviruses; and fall: parainfluenza virus type 1. [130]

Since the timing of community infections varies from year to year, we retrieved information on influenza and RSV seasons utilizing surveillance reports from the Centers of Disease Control (CDC) and California Department of Public Health Influenza Surveillance Program. [131, 132] We chose these two infections of interest since detailed surveillance data was available for at least part of the study period. We examined summary reports for Department of Health and Human Services Region 9 (Arizona, California, Nevada, and Hawaii) and these were available beginning with the 1997-1998 season (influenza) and the 1999-2000 season (RSV) through the 2007-2008 season, thus our analyses on these viral seasons are restricted to these years. For each influenza and RSV season we assigned a season peak date, defined as the last day of the calendar week during which the highest percent of samples tested were positive for influenza virus isolates. Some infection seasons experienced two peaks of equal amplitude. In these cases, we assigned two peaks. We then calculated the length of time between birth and first possible exposure to an infection season, using the season peak date as the reference date for

each infection season. We categorized children as having had their first possible exposure to an influenza or RSV season during the first three months of life, three to six months of age, six to nine months of age, nine to twelve months of age, or more than twelve months of age, as previous studies using proxies of infection exposures (such as day care attendance and level of community infections) have used similar 3-month measures. [47, 133, 134]

Since detailed, week-by-week surveillance data was available for influenza, we also created a season intensity variable for each of the eleven influenza seasons from 1997-98 through 2007-08. We categorized each season as having low, medium, or high intensity based on the peak percentage of samples that tested positive for influenza virus isolates during the influenza season. We used cutoffs for the percentage of positive samples of < 20%, 20-29%, and ≥30% for low, medium, and high intensity seasons, respectively, and we examined timing of births in relation to influenza season, stratified by intensity of the season.

Information on the mother's reproductive history is included on the birth certificate, and we used data on the number of previous live births to create a birth order variable, categorized as first birth, second or third birth, and fourth or subsequent birth.

We used unconditional logistic regression analyses to obtain odds ratios (OR) and 95% confidence intervals (CI) for risk of leukemia. We calculated measures of association for each month of birth, using the month of November as the reference value because we hypothesized that infants born in November would be most likely to be exposed to seasonal infections that peak in winter or spring months within the first few months of life. Since we do not have *a priori* evidence that any factors in our dataset are associated with timing of birth, we adjusted only for birth year in analyses related to birth month and timing of birth around infectious season peaks. For birth order analyses, we adjusted for birth year, mother's race and mother's age. In our analyses of the timing of births in relation to

infection seasons, we stratified on mother's parity (first birth versus second or subsequent birth) and age at diagnosis (<1 year, 1-5 years) to examine their impact on our results. Because a previous study reported racial differences in the effect of birth order on ALL risk [135], we examined these groups separately in subgroup analyses of birth order. Due to changes in vaccination recommendations during the study years, we conducted a sensitivity analysis, limiting all analyses to those born between 1997 and 2003. Finally, in separate sensitivity analyses, we excluded preterm births, defined as any birth prior to 37 weeks of gestation, and we limited analyses to B-cell leukemia cases.

5.3 Results

ALL cases were more frequently male than their respective controls, and a higher proportion had private health insurance compared to controls. ALL cases were more frequently Hispanic. (Table 5.1)

In analyses of ALL, cases were more frequently born in spring or summer months (March, June or July) compared to November. When we stratified by mother's parity, results were stronger among first births, and we did not observe an association between ALL and month of birth among second or subsequent births. Excluding cases diagnosed in infancy (less than one year of age) did not change our results (not shown).

When we examined the timing of births in relation to influenza and RSV seasons, we observed an increased risk of ALL among those whose first exposure to an influenza season occurred at nine to twelve months of age compared to those exposed within the first three months of life (OR and 95% CI 1.16 [1.00, 1.35]). (Table 5.2) We observed a similar pattern with a stronger effect estimate among first births (OR and 95% CI 1.44 [1.13, 1.82]) and we did not observe an association among second or later births. Excluding cases diagnosed in infancy (less than one year of age) did not change our results (not shown). We observed very similar associations in analysis of age at first potential exposure to an RSV

Table 5.1. Birth and Demographic Characteristics of Subjects in a Study of Leukemia Risk Among California Children Diagnosed Between 1988 and 2007

	Controls (n = 68040)		ALL cases (n = 3402)	
	N	%†	N	%†
Sex				
male	34788	51.1	1921	56.5
female	33252	48.9	1481	43.5
Gestational age, weeks				
≤ 36	6557	10.2	332	10.3
37-42	55191	85.6	2761	85.6
43+	2692	4.2	131	4.1
missing	3600		178	
Age of mother				
<20	7466	11.0	325	9.6
20-29	35669	52.4	1705	50.1
30-34	15674	23.0	826	24.3
35+	9222	13.6	546	16.0
missing	9		0	
Mother's education				
≤ 8 years	8166	13.8	410	13.8
Some high school (9-11 yrs)	10673	18.0	511	17.2
High school diploma (12 yrs)	17519	29.6	895	30.2
Some college (13-15 yrs)	11616	19.6	553	18.7
College diploma or higher (16+ yrs)	11203	18.9	596	20.1
missing	8863		437	
Mother's race				
white	24695	36.5	1233	36.4
hispanic	30526	45.1	1680	49.6
other	12439	18.4	472	13.9
missing	380		17	
Season of birth				
Spring	16713	24.6	864	25.4
Summer	17500	25.7	924	27.2
Fall	17400	25.6	807	23.7
Winter	16427	24.1	807	23.7

Table 5.1 (continued)

	Controls (n = 68040)		ALL cases (n = 3402)	
	N	%†	N	%†
Parity				
first birth	26803	39.4	1288	37.9
second or third birth	32651	48.0	1669	49.1
fourth or subsequent birth	8549	12.6	443	13.0
missing	37		2	
Payment source for prenatal care				
Private insurance	30074	50.7	1656	55.6
Other	29238	49.3	1321	44.4
missing	8728		425	
Age at diagnosis (cases only)				
0			196	5.8
1			499	14.7
2			882	25.9
3			820	24.1
4			623	18.3
5			382	11.2

† Percent of non-missing

season. Children who were nine to twelve months of age at their first exposure to an RSV season experienced increased risk of ALL (OR and 95% CI 1.18 [1.02, 1.37]) compared to those with potential exposure during the first three months of life. Among first births, children nine to twelve months of age at first exposure had a 30% increase in risk (OR and 95% CI 1.30 [1.03, 1.65]) compared to those exposed at zero to three months of age. We did not observe an association between ALL and age at first exposure to RSV season among children of second or higher birth order. (RSV results not shown)

Among all ALL cases combined, risk estimates decreased with increasing birth order, although confidence intervals include the null. In non-Hispanic white children, we observed a statistically significant decrease in risk for children of fourth or high birth order (OR and 95% CI 0.76 [0.59, 0.96]). We did not observe a birth order effect in Hispanic children.

Table 5.2. Analysis of age at First Exposure to an Influenza Season in a Study of Leukemia Risk Among California Children Diagnosed Between 1988 and 2007

	All cases and controls			First births			Second or subsequent births		
	Controls	Cases	OR* (95% CI)	Controls (n=26803)	Cases (n=1288)	OR* (95% CI)	Controls (n=41200)	Cases (n=2112)	OR* (95% CI)
All ALL cases combined									
Age at first exposure to influenza season									
0 to 3 months	9792	455	ref	3814	163	ref	5973	292	ref
3 to 6 months	8018	416	1.12 (0.97, 1.28)	3151	153	1.14 (0.91, 1.42)	4864	263	1.11 (0.93, 1.31)
6 to 9 months	7543	380	1.08 (0.94, 1.25)	2896	130	1.05 (0.83, 1.33)	4645	250	1.10 (0.93, 1.31)
9 to 12 months	5444	294	1.16 (1.00, 1.35)	2087	128	1.44 (1.13, 1.82)	3355	166	1.01 (0.83, 1.23)
> 12 months	663	28	0.91 (0.62, 1.34)	278	11	0.93 (0.50, 1.73)	385	17	0.90 (0.55, 1.49)
missing	36580	1829		14577	703		21978	1124	
*ORs adjusted for birth year									

Table 5.3. Analysis of age at first exposure to an influenza season and the intensity of that season

	Low intensity influenza season			Medium intensity influenza season			High intesnity influenza season		
	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Age at first exposure to influenza season									
0 to 3 months	2923	139		3689	164		3180	152	
3 to 6 months	2140	109	1.07 (0.83, 1.39)	3066	150	1.10 (0.88, 1.38)	2812	157	1.17 (0.93, 1.47)
6 to 9 months	1990	99	1.05 (0.80, 1.36)	2904	158	1.22 (0.98, 1.53)	2649	123	0.97 (0.76, 1.24)
9 to 12 months	2010	101	1.06 (0.81, 1.37)	1977	117	1.33 (1.04, 1.70)	837	49	1.23 (0.88, 1.71)
> 12 months	189	9	1.00 (0.50, 2.00)	474	19	0.90 (0.56, 1.46)	0	0	-
First births									
Age at first exposure to influenza season									
0 to 3 months	1122	48		1409	54		1283	61	
3 to 6 months	859	38	1.03 (0.67, 1.60)	1195	53	1.16 (0.79, 1.70)	1097	62	1.19 (0.83, 1.71)
6 to 9 months	743	35	1.10 (0.71, 1.72)	1118	53	1.24 (0.84, 1.82)	1035	42	0.85 (0.57, 1.28)
9 to 12 months	766	37	1.13 (0.73, 1.75)	762	52	1.78 (1.21, 2.63)	313	24	1.61 (0.99, 2.63)
> 12 months	88	2	-	190	9	1.24 (0.60, 2.54)	0	0	-
Second or subsequent births									
Age at first exposure to influenza season									
0 to 3 months	1799	91		2280	110		1894	91	
3 to 6 months	1280	71	1.10 (0.80, 1.51)	1871	97	1.08 (0.81, 1.42)	1713	95	1.15 (0.86, 1.55)
6 to 9 months	1247	64	1.02 (0.73, 1.41)	1786	105	1.22 (0.93, 1.60)	1612	81	1.05 (0.77, 1.42)
9 to 12 months	1243	64	1.02 (0.73, 1.41)	1215	65	1.11 (0.81, 1.52)	524	25	0.99 (0.63, 1.56)
> 12 months	101	7	1.37 (0.62, 3.03)	284	10	0.73 (0.38, 1.41)	0	0	-

Table 5.4. Analysis of Birth Order in a Study of Leukemia Risk Among California Children Diagnosed Between 1988 and 2007

	All cases			non-Hispanic white			Hispanic		
	Controls (n=68040)	Cases (n=3402)	OR* (95% CI)	Controls (n=24695)	Cases (n=1233)	OR** (95% CI)	Controls (n=30526)	Cases (n=1680)	OR** (95% CI)
Birth order									
First	26803	1288	ref	10562	534	ref	10904	563	ref
Second	21131	1076	1.00 (0.92, 1.09)	8327	420	0.95 (0.83, 1.09)	8838	490	1.03 (0.90, 1.17)
Third	11520	593	0.95 (0.85, 1.05)	3814	195	0.94 (0.79, 1.12)	5888	326	0.99 (0.85, 1.15)
>= Fourth	8549	443	0.91 (0.81, 1.03)	1978	84	0.76 (0.59, 0.96)	4887	300	1.05 (0.89, 1.24)
missing	37	2		14	0		9	1	

* Adjusted for birth year, maternal race, and mother's age
** Adjusted for birth year and maternal age

When we examined age at first exposure to influenza by season intensity, we observed that infants exposed at 6 months of age or older during a medium-intensity season had increased risk of ALL. There was a strong association between delayed exposure to influenza during medium- and high-intensity seasons among first births. Influenza season intensity did not impact ALL risk among second or higher births, and delayed age of exposure did not increase ALL risk in low-intensity influenza seasons.

Limiting leukemia analyses to the B-cell subtype and, in separate analyses, excluding preterm births, and limiting to birth years 1997-2003 did not change results for any of our analyses (results not shown).

5.4 Discussion

In this large population-based study of childhood cancer in children age 0-5 in California, we investigated associations between several indirect measures of infection in early life, including month of birth, timing of birth around influenza and RSV seasons, birth order, and childhood leukemia tumors. Although we do not have direct data on individual infection burden for our population, previous studies have demonstrated that month of birth, timing of birth around infection seasons, and birth order all increase risk of exposure to several different infections in childhood.[127, 128] For ALL, we observed

positive associations for births in the spring and summer months, births that occurred nine to twelve months prior to influenza and RSV seasons, and negative associations for higher birth orders. The associations for birth month and timing of birth around infection seasons were stronger for first births.

Previous reports on the influence of season on childhood leukemia have not been consistent. Four studies have suggested seasonal variation in births for leukemia, and three of the four have suggested that the birth peak occurs in late winter or spring(February [136], March [136, 137], and April [138]), while the fourth suggested two distinct peaks in February and August [139]. The association we observed between ALL and birth in the spring and summer months is similar to these previous results and may be indicative of delayed exposure to seasonal infections that peak during winter months, since these infants would experience the longest timespan between birth and subsequent influenza or other infection season. Our results utilizing influenza and RSV surveillance data support this hypothesis as well, since we observed an increased risk estimate for those born 9 to 12 months prior to these infection seasons. Both of these associations were observed among first births only, which may indicate that children with older siblings experience greater exposure to infections year-round and that timing of birth is less important for these children.

Children with older siblings may have greater exposure to infections in early life than those without siblings. Several studies have reported reduced risk of ALL associated with higher birth order [21, 135, 140-145], although many other studies have reported either no association [136-139, 146-151] or a positive association[134, 152, 153]. A recent pooled analysis of data from five US states examined associations between birth order and childhood cancers and found a decreased risk of ALL among third (OR and 95% CI 0.90 [0.82, 0.99]) and fourth or higher (OR and 95% CI 0.90 [0.80, 1.01]) births. [154] We observed a reduced risk of ALL associated with higher birth order among non-Hispanic whites but not Hispanics. This is consistent with a previous study from Northern California [135] and may indicate that

birth order is a reliable predictor of infection exposure among non-Hispanic whites but not Hispanics. Cultural variations may account for this difference, as Hispanic populations are more likely to have larger family households that include extended family members or unrelated individuals.[155, 156] Thus even first born children in Hispanic families may live with other non-sibling children.

Some studies that have tested the delayed infection hypothesis by examining medical or hospital records for history of infections in early life.[157] However, maternal immunoglobulins, mostly IgG1, are transferred across the placenta in the third trimester of pregnancy, with maximal transport beginning at 32 weeks of gestation.[158, 159] These antibodies provide passive immunity for infections to which the mother has been exposed, and their presence in the first months of life serves to protect the infant from severe disease. Nonetheless there is evidence that the neonatal system is able to mount a response to immune challenge despite passive immunity from the mother.[160-162] Thus even exposure to infections in the earliest stages of life may elicit some stimulation of the immune system and, according to Greaves' hypothesis, may contribute to a decreased risk of ALL.

We hypothesized that infants whose first exposure to influenza was during a particularly high intensity season would experience decreased risk of ALL due to a higher community burden of infection and therefore a high likelihood of exposure. We observed that infants exposed during the second half of their first year (6 months or older) during a medium-intensity season were at increased ALL risk, particularly among first births. First born children with delayed exposure (at nine to twelve months of age) during high-intensity seasons also experienced substantial increased risk for ALL. There is evidence from the 2009 influenza pandemic that although infants did not experience an increased burden of respiratory infections during the pandemic, parent-initiated visits for respiratory symptoms increased during that time.[163] Increased parental awareness due to media reports and public health campaigns

during a particularly high intensity influenza season may result in increased precautions among parents to protect their young children and thus lead to decreased exposures.

Breastfeeding may impact exposure to infections and immune response among infants, and it has been suggested that breastfeeding may modulate the infant's immune system thereby helping it to respond effectively to infection later in life.[164, 165] Previous studies have shown that long-term (> 6 months) breastfeeding is associated with decreased risk of ALL, with a meta-analysis estimating an approximate 25% decrease in risk (OR 0.76 95% CI 0.68, 0.84).[164] However a case-control study in northern California did not observe an association between breastfeeding and risk of ALL.[166] Breastfeeding rates in the United States have risen during the study period, and in a national survey, the percentage of California infants who were still breastfed at 6 months was about 40-49% in the year 2000.[167] We did not have information on breastfeeding among our study population and thus we were unable to examine it in our analyses.

Some of the most compelling evidence in support of an infectious etiology in early childhood stems from studies of day care attendance. These studies have consistently shown a decreased risk of pediatric leukemia for regular daycare attenders, who would have a high level of exposure to infectious agents, compared to children who do not attend day care.[45-48] A recent meta-analysis also found a reduced risk of ALL for day care attenders compared to non-attenders (OR 0.76 and 95% CI 0.67, 0.87).[168] We did not have information on day care attendance among our study population.

The proxies used in this and other studies for exposure to infections in early life have limitations in that they do not predict an individual's actual exposures. While we do not have individual-level data on true exposure, high quality influenza surveillance data was available for a subset of study years to inform our analysis and help verify the specific timing of possible exposure to infection. We also examined birth order which is another marker of exposure to infections in childhood. Future studies

using a biological measure of early life exposure to infections would provide a more direct examination of this association.

Our study is the largest to examine the effect of season of birth and exposure to infection seasons in childhood leukemia among young children 0-5 years old. We do not expect any misclassification of our main exposure variables, which were based on date of birth. Since we have data available for a wide range of years, we do not expect that our results could be influenced by chance fluctuations in monthly birth rates of a single year. In this study of a large population of childhood cancer cases, we demonstrated that timing of birth and its proximity to influenza season may impact risk for childhood leukemia and astrocytoma. Our results support the hypothesis that delayed exposure to infections in early childhood increases risk of ALL.

6. Pesticide exposure as a risk factor for Wilms tumor in young children: an examination of maternal exposure during pregnancy and infant exposure during the first year of life

6.1 Introduction

Renal tumors represent about 6% of cancer diagnoses among children 0-14 years of age.[10, 54] Wilms' tumor (WT), also called nephroblastoma, is by far the most common type of renal tumor in children, comprising approximately 95% of all renal cancer diagnoses in children less than 14 years of age. [10] WT occurs most commonly among children less than 5 years of age, with the highest incidence in the first two years of life. [10] Females have a slightly higher rate of WT than males (9.7 per million compared to 8.4 per million). [55]

Several environmental, parental, and prenatal development factors have been implicated as increasing the risk for WT, including paternal occupation as a welder or mechanic, high birth weight, in utero exposure to ionizing radiation, pre-term birth, and maternal hypertension during pregnancy. [54, 62] However, the evidence is inconclusive due to the small number of studies and their generally limited statistical power.

Pesticide exposure has previously been examined for its possible involvement in WT etiology. [63-68] Many pesticides are listed as a probable carcinogens (Group 2A) by the International Agency for Research on Cancer.[69] Animal studies have established that some pesticides are mutagens [69, 70], and some are cytotoxic in humans [71-73]. Several previous studies have focused on parental occupational exposure as a potential risk factor for WT.[67, 85-91] Some previous studies have found an increased risk of WT with parental employment involving likely pesticide exposure during the pre-conception and pregnancy periods [67, 85, 86], while several others found no effect [63, 68, 87-91].

Those living close to agricultural fields, even in non-farmworker families, may also be at increased risk of pesticide exposure due to drift.[82-84] Residential proximity to agricultural fields may

influence pesticide exposure due to pesticide spray drift and post-spray volatilization that spreads pesticide residue through the air, sometimes over large distances of 1000ft or more.[74-76] Residential exposure is also influenced by application method and meteorologic conditions. [77-79, 169] Pesticide residues can enter nearby homes through the air or on the clothing or shoes of inhabitants. Pesticide residue has been documented indoors in both air and dust, which may persist in carpeting for years.[76, 80, 81] A study from Texas used residential proximity to agricultural areas to estimate pesticide exposure and did not observe an association with WT.[94]

Other previous studies estimated an increased risk for either parental [64] or child [92] exposure to household pesticides, although some studies did not find an effect with household exposures [68, 93]. Four previous studies have estimated the impact of maternal exposure to pesticides on WT risk. [64, 66-68] These studies vary in exposure assessment methods and exposure periods (pre-conception, pregnancy, and prior to the child's diagnosis). Although point estimates in all studies were above the null, only one study found a formally statistically significant increase in risk. A recent review conducted a meta-analysis on these studies and reported a combined risk estimate of 1.37 (95% CI 1.09-1.73). [62] However the authors did find evidence of publication bias that may have influenced this result.

Many of these previous studies relied on parental occupation as an indicator for likely pesticide exposure, and although some previous studies have examined pesticide types (e.g., herbicides, insecticides, fungicides) separately, no previous studies have had data on exposure to specific pesticides. Using our study population and a unique spatial approach to exposure assessment that utilizes statewide data on pesticide use in California, land use maps, and geocoded residential addresses, here we examine the association between exposure to pesticides and risk of WT.

6.2 Methods

Using data from the California Cancer Registry, we identified all Wilms tumor (WT) cases diagnosed in California (CA) between 1988-2007 among children 0-5 years of age at diagnosis. WT cases were defined as International Classification of Childhood Cancer, Third edition (ICCC-3) [99] code 061 (Nephroblastoma and other non-epithelial renal tumors). Cases were part of a large population-based case-control study of all childhood cancers diagnosed in children ages 0-5 in CA during this period, in which we successfully matched 89% of all cases to their CA birth certificate (birth years 1983-2007), resulting in a total case population of 10,914.[129] For each case, we randomly selected twenty controls, frequency matched by birth year, who were cancer-free by age 6 using CA birth records, resulting in 218,280 controls. We cross-checked CA death records and excluded controls who died before age six (n=1,674). We also excluded improbable or likely non-viable births, defined as birth weight of < 500 grams (n=29 controls, n=0 cases) or birth before 20 weeks of gestation (n=110 controls, n=0 cases), and those for whom sex was unclear (n=3 controls, n=0 cases) or with a birth address outside of CA (n=623 controls, n=0 cases). Our final dataset contained 863 Wilms tumor cases and 215,841 controls.

Since our study was based solely on existing records, we did not obtain informed consent from study subjects. Our use of human subject data was approved by the UCLA Institutional Review Board and the California Health and Human Services Agency Committee for the Protection of Human Subjects.

The state of California has mandated pesticide use reporting by law for professional applications including farming since 1974. Initially, reporting was required only for restricted-use pesticides[170], with reporting requirements expanded to all commercial uses of pesticides in 1990. Pesticide Use Reports (PUR) record the date, location, amount, type of crop and acreage of the field, and specific type of pesticide used. The location documented on each PUR is based on the Public Land Survey System (PLSS), a nationwide system that divides land into rectangular sections up to 6 square-miles in size.

The state of California also conducts periodic surveys of land use and agricultural crop cover. These land use maps delineate field boundaries and include over 70 different crops or crop categories. Using Geographic Information Systems (GIS) software, we overlaid each PLSS grid with its corresponding land use map, allowing us to point to the location of each pesticide application reported in PURs by linking to crop type within the PLSS section.

CA birth certificates collected home address at the time of birth from 1998 onward, which we used to geocode each address with manual resolution of unmatched addresses, as described previously.[171] For births prior to 1998, residential address was not available on electronic birth records, and as such we used zip code centroid as a proxy for residential location. We created a 500m buffer around each residence and calculated pounds of pesticide per acre applied within each buffer and averaged these over relevant time periods for each subject. We investigated pesticide exposure during both pregnancy (all-pregnancy and trimester-specific) and early childhood (age ≤ 1) using residential addresses or zip codes. For each pesticide and time period of interest, we created a variable indicating ever exposure and, separately, we identified the median amount of exposure in controls and created a variable indicating whether exposure above or below the median level.

We selected pesticides included in the Environmental Protection Agency's (EPA) 2011 classification of chemicals evaluated for carcinogenic potential including pesticides that contain chemicals listed as 'probable' (Group B) or 'possible' (Group C) human carcinogens, or comparable categories for chemicals evaluated under previous versions of chemical classifications (n=174 pesticides).[172] Of those 174, our GRAPES program found that children in our sample had been exposed to 106. We classified each pesticide according to use type (herbicide, insecticide, fungicide, soil fumigant, or other) and chemical class. We classified exposure to individual pesticides and pesticide

types and classes. Risk for WT was assessed for individual pesticides, pesticide types and classes with at least 5 exposed cases.

We used unconditional logistic regression to calculate both unadjusted and adjusted odds ratios and 95% confidence intervals. All analyses were adjusted for birth year. In separate analyses we additionally adjusted for maternal age (continuous), race/ethnicity (White, Hispanic, other), whether birth address was in an urban or rural community (dichotomous indicator for urban/rural), and neighborhood socioeconomic (SES) index. The urban/rural county variable was created using the US Department of Agriculture Economic Research Service Rural-Urban commuting area codes.[173] These codes use measures of population density, urbanization, and daily commuting from the 2000 census to classify US census tracts. We used those codes to create a dichotomous urban/rural variable for each census tract. We created a variable estimating SES quintiles using the method outlined by Yost et al[174] that uses principal components analysis of census tract indicators of SES (education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value). For each pesticide, we created a three-level variable indicating whether a child was never exposed, exposed during either pregnancy or the first year of life, or exposed during both pregnancy and the first year of life.

Due to small numbers of exposed cases when we separated our data into trimester-specific exposure estimates and to limit multiple comparisons, we investigated trimester-specific associations only for chemical classes, pesticide types, and those individual pesticides that were associated with WT risk in our overall pregnancy analyses.

We limited all analyses to birth years 1990 and later since comprehensive pesticide use reporting was not mandated until that time. We did not have a sufficient number of exposed cases to

conduct a sensitivity analysis limiting to birth years 1998 and later. To assess whether there are differences between exposures assessed using residential address or using zip code centroids.

6.3 Results

Wilms tumor cases were more often female and mothers of cases were more frequently of white race than controls. (Table 6.1) A slightly higher proportion of cases lived in rural areas than controls.

In multivariate analysis of pesticide exposure during pregnancy (ever vs never), vinclozolin, triforine, and linuron exposure were associated with an over two-fold increase in WT risk (Table 6.2). When we examined exposures above the median level in controls during pregnancy, the association between triforine and WT risk strengthened (OR and 95% CI 2.98 [1.22, 7.30]). Above-median level exposures to diuron (n=15 exposed cases) and norflurazon (n=11 exposed cases) were also positively associated with WT risk (ORs and 95% CIs 1.65 [0.98, 2.77] and 2.10 [1.14, 3.86], respectively). We did not have sufficient power to examine pregnancy exposure to above-median levels for vinclozolin or linuron (n=3 exposed cases for each). We did not observe associations between WT risk and exposure according to chemical classes or pesticide types during pregnancy.

Table 6.1. Demographic characteristics of Subjects in a Study on Wilms tumor risk Among Children age 0-5 in California

	Controls (n=215,841)		Cases (n=863)	
	n	%	n	%
Sex				
Male	110140	51.03	410	47.51
Female	105701	48.97	453	52.49
Maternal age				
Less than 20	23504	10.89	86	9.98
20-24	53304	24.70	181	21.00
25-29	60343	27.96	240	27.84
30-34	49668	23.02	245	28.42
35 and older	28982	13.43	110	12.76
missing	40		1	
Urban or rural county				
Urban	171366	79.56	669	77.70
Rural	44035	20.44	192	22.30
missing	440		2	
Maternal race				
non-Hispanic white	79648	36.90	377	43.68
Hispanic	95819	44.39	349	40.44
other	40374	18.71	137	15.87
Socioeconomic index				
1 (low)	51529	23.93	178	20.67
2	50348	23.38	201	23.34
3	48356	22.45	190	22.07
4	35129	16.31	157	18.23
5 (high)	29994	13.93	135	15.68
missing	485		2	
Age at diagnosis				
0			137	15.87
1			195	22.60
2			173	20.05
3			158	18.31
4			125	14.48
5			75	8.69

Although the numbers of exposed cases during specific trimesters were small, we tended to observe greater risks for exposures during the first and third trimesters (Table 6.3). First trimester exposure (ever vs never) to vinclozolin (OR and 95% CI 3.22 [1.33, 7.81]), the halogenated organic chemical class (OR and 95% CI 1.85 [1.04, 3.28]), and the urea chemical class (OR and 95% CI 1.82 [0.97, 3.42]), which includes linuron and diuron, increased WT risk. Third-trimester exposures to triforine (OR and 95% CI 3.05 [1.35, 6.89]), the dicarboximide chemical class (OR and 95% CI 1.74 [1.02, 2.97] for above the median exposure), and herbicides (OR and 95% CI 1.31 [0.98, 1.75]) increased risk.

Triforine exposures (ever vs never) during the first year of life were also associated with a strongly increased risk for WT (OR and 95% CI 2.82 [1.44, 5.51]). Ever exposure to vinclozolin, ziram, methidathion, pesticides in the 2,6-Dinitroaniline chemical class, and the herbicides were also associated with increased risk estimates, although confidence intervals included the null.

For first year exposure levels above the control median level, the risk estimates for triforine and methidathion were stronger (ORs and 95% CIs: 3.80 [1.67, 8.65] and 2.28 [1.17, 4.48], respectively). There was no association between above-median level exposure to ziram, and we did not have sufficient

Table 6.2: Associations between maternal pesticide exposure during pregnancy and child's exposure during the first year of life and Wilms tumor in children ages 0-5 in California, birth years 1990-2007

		Ever exposure during pregnancy								Ever exposure during the first year of life							
	Chemical name	Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI		Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI	
2,6-Dinitroaniline		8808	42	1.20	0.88	1.64	1.20	0.87	1.65	10416	43	1.29	0.94	1.77	1.311	0.95	1.81
	Trifluralin	4184	21	1.22	0.79	1.88	1.17	0.75	1.84	5100	19	1.1	0.69	1.74	1.067	0.66	1.72
	Oryzalin	4610	23	1.23	0.81	1.86	1.14	0.75	1.75	5565	24	1.32	0.87	1.99	1.247	0.82	1.9
	Pendimethalin	2153	5	0.55	0.23	1.32	0.50	0.21	1.21	2766	7	0.74	0.35	1.57	0.69	0.33	1.47
Aldehyde	Metaldehyde	1938	8	0.97	0.48	1.96	0.96	0.48	1.94	2197	9	1.19	0.61	2.3	1.169	0.6	2.27
Azole		3656	15	0.99	0.59	1.66	0.96	0.57	1.61	4510	19	1.28	0.81	2.03	1.245	0.78	1.98
	Triadimefon	1723	9	1.24	0.64	2.41	1.16	0.60	2.25	2125	10	1.37	0.73	2.58	1.289	0.68	2.43
	Propiconazole	1217	6	1.20	0.53	2.69	1.16	0.52	2.61	1489	7	1.44	0.68	3.05	1.395	0.66	2.97
Benzimidazole		4689	23	1.19	0.78	1.81	1.14	0.75	1.74	5631	23	1.22	0.8	1.85	1.174	0.77	1.79
	Benomyl	2405	13	1.29	0.74	2.25	1.20	0.69	2.10	2990	13	1.25	0.72	2.18	1.178	0.67	2.07
	Thiophanate-methyl	2903	13	1.06	0.61	1.84	0.99	0.57	1.73	3503	13	1.09	0.63	1.89	1.021	0.59	1.78
Chloroacetanilide										1498	7	1.34	0.63	2.83	1.239	0.58	2.63
	Metolachlor									905	5	1.55	0.64	3.77	1.34	0.55	3.27
Dicarboximide		5900	30	1.25	0.87	1.81	1.21	0.83	1.75	7212	30	1.26	0.87	1.83	1.226	0.84	1.78
	Iprodione	5667	29	1.26	0.87	1.83	1.19	0.81	1.73	6965	29	1.26	0.87	1.84	1.204	0.82	1.76
	Vinclozolin	802	8	2.36	1.17	4.76	2.22	1.10	4.48	1005	7	1.99	0.94	4.2	1.879	0.89	3.99
Diphenyl ether		6857	35	1.26	0.89	1.77	1.24	0.87	1.75	8143	27	1	0.68	1.47	0.982	0.66	1.46
	Oxyfluorfen	6821	35	1.26	0.90	1.78	1.22	0.86	1.73	8076	27	1	0.68	1.48	0.971	0.65	1.45
Dithiocarbamate		5575	23	1.00	0.66	1.52	0.96	0.63	1.47	6873	26	1.14	0.77	1.69	1.106	0.74	1.65
	Maneb	1561	6	0.92	0.41	2.05	0.82	0.37	1.85	1971	6	0.88	0.39	1.97	0.793	0.35	1.79
	Metam sodium	1131	5	1.04	0.43	2.52	0.98	0.40	2.38	1471	5	0.97	0.4	2.35	0.928	0.38	2.25
	Mancozeb	2179	8	0.87	0.43	1.75	0.81	0.40	1.63	2680	8	0.87	0.43	1.75	0.813	0.4	1.64
	Ziram	2133	12	1.33	0.75	2.37	1.21	0.68	2.16	2763	16	1.7	1.03	2.8	1.579	0.95	2.63
Halogenated organic		3424	17	1.20	0.74	1.94	1.16	0.71	1.88	4266	18	1.25	0.78	1.99	1.219	0.76	1.96
	Methyl Bromide	2955	17	1.39	0.86	2.26	1.31	0.80	2.13	3630	18	1.47	0.92	2.36	1.399	0.87	2.26
N-Methyl Carbamate		3244	16	1.20	0.73	1.98	1.16	0.70	1.92	4098	14	1.01	0.59	1.71	0.974	0.57	1.67
	Carbaryl	3105	16	1.25	0.76	2.06	1.17	0.71	1.94	3914	14	1.05	0.61	1.78	0.983	0.57	1.69
Organoarsenic	Cacodylic acid	788	3	0.90	0.29	2.82	0.80	0.25	2.51	1103	6	1.55	0.69	3.49	1.403	0.62	3.19
Organochlorine		2964	13	1.06	0.61	1.84	1.03	0.59	1.80	3728	11	0.86	0.47	1.56	0.839	0.46	1.54
	Dicofol	2800	12	1.03	0.58	1.83	0.97	0.54	1.73	3566	11	0.89	0.49	1.63	0.846	0.46	1.56
Organophosphorous		13104	53	1.03	0.78	1.37	1.02	0.77	1.36	14835	51	1.09	0.81	1.45	1.082	0.81	1.45
	Tribufos	759	5	1.55	0.64	3.76	1.38	0.56	3.38	1112	4	1.01	0.38	2.72	0.897	0.33	2.44
	Diazinon	5962	26	1.07	0.72	1.58	1.00	0.67	1.50	7186	27	1.12	0.76	1.66	1.072	0.72	1.59
	Dimethoate	4558	17	0.90	0.56	1.46	0.85	0.52	1.39	5503	17	0.92	0.56	1.49	0.877	0.54	1.44
	Phosmet	2428	12	1.19	0.67	2.10	1.09	0.61	1.95	3084	12	1.15	0.65	2.04	1.064	0.59	1.91
	Malathion	3786	18	1.14	0.71	1.83	1.10	0.69	1.77	4585	12	0.76	0.43	1.36	0.74	0.42	1.32
	Acephate	3776	9	0.56	0.29	1.09	0.54	0.28	1.05	4397	12	0.8	0.45	1.42	0.768	0.43	1.37
	Methidathion	1744	10	1.38	0.73	2.58	1.28	0.68	2.40	2180	12	1.6	0.9	2.85	1.506	0.84	2.7

Table 6.2 (continued)

		Ever exposure during pregnancy								Ever exposure during the first year of life							
	Chemical name	Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI		Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI	
Pyrethroid										6546	21	0.96	0.62	1.49	0.942	0.61	1.47
	Permethrin	3253	15	1.10	0.66	1.84	1.02	0.61	1.72	4068	14	1.01	0.59	1.72	0.945	0.55	1.62
	Bifenthrin	2188	9	0.97	0.50	1.87	0.92	0.48	1.79	2805	8	0.83	0.41	1.68	0.801	0.4	1.62
Pyridazinone	Norflurazon	2371	14	1.41	0.83	2.39	1.30	0.76	2.24	2930	15	1.48	0.88	2.48	1.395	0.82	2.36
Substituted Benzene		4305	21	1.17	0.76	1.82	1.14	0.74	1.77	5136	22	1.27	0.83	1.95	1.245	0.81	1.92
	Chlorothalonil	3810	19	1.20	0.76	1.89	1.14	0.72	1.81	4577	20	1.29	0.82	2.02	1.242	0.79	1.95
Tetrazine	Clofentezine									832	5	1.71	0.7	4.13	1.533	0.63	3.74
Triazine		6477	27	1.02	0.69	1.49	0.98	0.66	1.45	7724	25	0.97	0.65	1.45	0.942	0.63	1.42
	Simazine	5542	23	1.00	0.66	1.52	0.94	0.62	1.44	6577	21	0.95	0.61	1.47	0.897	0.58	1.4
Unclassified		8020	34	1.04	0.74	1.48	1.02	0.72	1.45	9655	34	1.07	0.76	1.52	1.061	0.75	1.51
	Propargite	4824	21	1.05	0.68	1.62	0.98	0.63	1.54	6145	25	1.21	0.81	1.8	1.168	0.77	1.78
	Piperonyl butoxide	1115	5	1.06	0.44	2.55	1.01	0.42	2.45								
	Triforine	771	7	2.18	1.03	4.63	2.03	0.96	4.31	875	9	3.00	1.54	5.85	2.815	1.44	5.51
Urea		4776	26	1.33	0.90	1.98	1.31	0.88	1.95	6023	21	1.04	0.67	1.61	1.026	0.66	1.6
	Diuron	4272	22	1.25	0.82	1.92	1.19	0.77	1.83	5400	17	0.93	0.57	1.51	0.883	0.54	1.45
	Linuron	513	5	2.32	0.96	5.62	2.28	0.94	5.54								
Pesticide Type																	
Fungicide		11403	47	1.04	0.77	1.40	1.02	0.75	1.37	13073	44	1.05	0.77	1.44	1.039	0.76	1.42
Herbicide		14466	63	1.13	0.87	1.46	1.13	0.86	1.47	16245	62	1.23	0.94	1.6	1.244	0.95	1.63
Insecticide		16239	67	1.07	0.83	1.38	1.07	0.83	1.38	18041	60	1.07	0.82	1.4	1.072	0.82	1.41
Soil fumigant		4219	21	1.20	0.78	1.86	1.17	0.76	1.82	5234	22	1.25	0.82	1.92	1.232	0.8	1.9
Other		4830	20	0.99	0.64	1.55	0.97	0.62	1.52	5853	15	0.75	0.45	1.26	0.739	0.44	1.24

† adjusted for birth year

‡ adjusted for birth year, urban/rural, SES quintile, maternal age and maternal race

Table 6.3: Trimester-specific associations between pesticide exposure during pregnancy and Wilms tumor in children ages 1-5 in California, birth years 1990-2007

		First trimester							Second trimester							Third trimester						
	Pesticide	Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI		Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI		Exposed controls	Exposed cases	OR†	95% CI		Or_{adj} ‡	95% CI	
2,6-Dinitroaniline		4239	16	0.94	0.57	1.54	0.92	0.56	1.52	5370	21	0.97	0.63	1.50	0.95	0.61	1.48	5288	29	1.38	0.95	2.01	1.37	0.93	2.00
Aldehyde										1337	6	1.09	0.49	2.43	1.07	0.48	2.40								
Azole		1751	6	0.84	0.37	1.87	0.81	0.36	1.82	2211	6	0.66	0.30	1.48	0.64	0.29	1.44	2299	11	1.18	0.65	2.15	1.15	0.63	2.09
Benzimidazole precursor		2417	13	1.32	0.76	2.29	1.28	0.73	2.22	2929	13	1.08	0.62	1.88	1.04	0.60	1.81	2908	17	1.44	0.89	2.34	1.39	0.85	2.25
Dicarboximide		2805	13	1.14	0.66	1.98	1.10	0.63	1.91	3568	15	1.03	0.62	1.73	0.99	0.59	1.66	3527	22	1.56	1.02	2.38	1.50	0.98	2.30
	Vinclozolin	355	5	3.41	1.41	8.27	3.22	1.33	7.81																
Diphenyl ether		3553	17	1.18	0.73	1.91	1.14	0.70	1.86	4274	20	1.15	0.74	1.80	1.12	0.71	1.76	4244	22	1.28	0.84	1.96	1.24	0.81	1.92
Dithiocarbamate		2547	10	0.96	0.52	1.80	0.93	0.50	1.74	3228	14	1.06	0.62	1.81	1.02	0.60	1.73	3232	13	0.99	0.57	1.71	0.95	0.55	1.65
Halogenated organic		1531	12	1.91	1.08	3.39	1.85	1.04	3.28	1886	9	1.16	0.60	2.24	1.12	0.58	2.16	1872	8	1.05	0.52	2.10	1.01	0.50	2.03
N-Methyl Carbamate		1250	7	1.37	0.65	2.88	1.33	0.63	2.81	1634	8	1.20	0.60	2.41	1.16	0.57	2.34	1768	8	1.12	0.56	2.25	1.08	0.53	2.18
Organochlorine		1112	5	1.10	0.46	2.66	1.08	0.44	2.61	1532	5	0.80	0.33	1.93	0.78	0.32	1.88	1567	8	1.26	0.63	2.54	1.23	0.61	2.48
Organophosphorous		7383	31	1.06	0.74	1.52	1.04	0.72	1.50	8948	32	0.90	0.63	1.28	0.89	0.62	1.27	9025	40	1.14	0.83	1.57	1.12	0.81	1.55
Pyrethroid		2487	11	1.08	0.59	1.96	1.05	0.58	1.91	3232	10	0.75	0.40	1.40	0.73	0.39	1.36	3373	14	1.02	0.60	1.73	0.99	0.58	1.68
Pyridazinone	**Norflurazon**	1019	6	1.43	0.64	3.21	1.37	0.61	3.08	1242	7	1.35	0.64	2.86	1.29	0.61	2.74	1203	9	1.81	0.93	3.50	1.74	0.90	3.40
Substituted Benzene		2188	8	0.89	0.44	1.79	0.86	0.43	1.74	2675	11	1.00	0.55	1.81	0.97	0.53	1.76	2646	17	1.57	0.97	2.55	1.54	0.95	2.49
Triazine		3014	12	0.97	0.55	1.73	0.94	0.53	1.67	3750	15	0.97	0.58	1.63	0.94	0.56	1.57	3848	18	1.15	0.72	1.84	1.11	0.69	1.78
Unclassified		3669	20	1.34	0.86	2.10	1.31	0.84	2.06	4743	15	0.77	0.46	1.29	0.75	0.45	1.26	4909	20	1.01	0.65	1.58	0.98	0.63	1.54
	Triforine																	475	6	3.17	1.41	7.13	3.05	1.35	6.89
Urea		2172	13	1.47	0.85	2.56	1.44	0.83	2.51	2631	13	1.21	0.70	2.10	1.19	0.68	2.07	2703	15	1.37	0.82	2.29	1.34	0.80	2.25
	Diuron	1959	9	1.12	0.58	2.17	1.09	0.56	2.11	2379	11	1.13	0.62	2.05	1.10	0.60	2.00	2393	13	1.34	0.77	2.32	1.30	0.75	2.26
Pesticide Type																									
Fungicide		6457	24	0.93	0.62	1.40	0.91	0.60	1.36	7721	31	1.01	0.70	1.45	0.98	0.68	1.42	7776	38	1.25	0.90	1.74	1.22	0.88	1.70
Herbicide		8910	42	1.21	0.89	1.66	1.21	0.88	1.66	10393	42	1.03	0.76	1.41	1.03	0.75	1.41	10416	52	1.30	0.98	1.73	1.31	0.98	1.75
Insecticide		9875	42	1.09	0.80	1.49	1.08	0.79	1.48	11655	41	0.90	0.65	1.23	0.89	0.64	1.22	11878	56	1.24	0.94	1.64	1.24	0.94	1.63
Soil fumigant		1916	13	1.66	0.96	2.88	1.61	0.93	2.81	2389	14	1.43	0.84	2.44	1.39	0.82	2.38	2362	11	1.14	0.63	2.08	1.11	0.61	2.02
Other		2544	10	0.96	0.51	1.79	0.94	0.50	1.76	3067	14	1.11	0.65	1.89	1.09	0.64	1.86	3180	8	0.61	0.30	1.23	0.60	0.30	1.20

† adjusted for birth year

‡ adjusted for birth year, urban/rural, SES quintile, maternal age and maternal race

power to examine above-median level exposure to vinclozolin (median results not shown). First year of life above-median exposure to cacodylic acid, chlorothalon, and propargite were also associated with increased WT risk (ORs and 95% CIs 2.35 [0.96, 5.78], 1.67 [0.95, 2.92], and 1.61 [0.97, 2.68], respectively). Exposure above the median level to pesticides in the dicarboximide class also increased WT risk estimates (OR and 95% CI 1.53 [0.96, 2.44]).

When we categorized children according to exposure during either time period (pregnancy or the first year of life) or exposure during both time periods, analyses did not provide evidence that exposure during both periods was associated with higher risk estimates than exposure during one time period (results not shown).

6.4 Discussion

In this large, population-based study of Wilms tumor in children age 0-5 in California, we observed increased risk estimates for exposures to a small number of pesticides during pregnancy and the first year of life. Our study is unique in that we were able to combine data from California pesticide use reports, land use maps, and residential addresses to create individual-level exposure estimates for over 100 potentially carcinogenic pesticides during pregnancy and the first year of life. Previous studies that utilized either interview data or death or birth records of parental employment generally did not have information on exposure to specific pesticides[63, 66-68, 85-91, 93, 94], and only a few studies were able to examine pesticide exposure by type (e.g. herbicide, insecticide, fungicide)[64, 92]. Ours is the first study to implicate specific pesticides as risk factors for Wilms tumor in children. Previous studies have found increased risk with likely parental occupational exposure to pesticides[67, 85, 86] and household exposure to insecticides[64, 92]. Our findings provide support for the role of several pesticides in Wilms tumor etiology, although they should be interpreted with caution as we conducted many comparisons and some findings may be due to chance.

Triforine was strongly associated with risk of WT for both maternal exposures during pregnancy and child exposures during the first year of life. Triforine is found in many commercial fungicides. It was first registered for use in the US in 1976 [175] and was once used on almonds, apples, asparagus, blueberries, cherries, hops, ornamentals, peaches, and roses.[176-178] In 1996, all food uses were cancelled and since that time, triforine has been used only on roses and other ornamentals.[175] Animal studies on the health effects of triforine have shown an increase in liver and lung tumors among exposed mice[175, 176], and a study of teratogenicity on pregnant rats found evidence that triforine may have embryotoxic effects (post-implantation losses and fetal deaths among the exposed group) [176]. A metabolism study of triforine fed to rats found that 78% was excreted via renal excretion.[179] At present, the EPA lists triforine as having 'suggestive evidence of carcinogenicity'.[172]

Vinclozolin was also associated with WT risk during pregnancy and early childhood. It is a fungicide that was registered in the US in 1981 and is used on raspberries, lettuce, kiwi, canola, beans, onions, ornamentals, and turf.[180] Animal studies have reported that liver, testicular, and adrenal tumors were caused by vinclozolin exposure in mice and rats.[181] A study on developmental toxicity in rabbits found evidence for fetotoxicity at moderate doses, and genotoxicity studies have suggested that vinclozolin may act as a promotor in rat liver.[181, 182] Vinclozolin has antiandrogenic properties that may account for its association with testicular tumors.[180] A study comparing the acute renal effects in rats of three dicarboximide fungicides (succinimide, vinclozolin, and iprodione), found that succinimide exposure produced changes in renal function, but vinclozolin and iprodione had minimal effects.[183] However a recent study on viclozolin-exposed minnows found renal effects, including changes in size of the glomerulus and of Bowman's space in the kidneys.[184] A study on canines also found renal effects for vinclozolin,[182] with dogs exposed at low levels experiencing changes in weight and fat content of the kidney, and at higher exposure levels fat droplets were found in kidney tubules.

Linuron and diuron, both substituted urea herbicides, were associated with WT risk when mothers were exposed during pregnancy. They were registered in 1966 and 1983, respectively, and they are used to control broad-leaved and grassy weeds on both crop and non-crop sites.[185, 186] Animal studies of rats, mice and dogs have shown liver and testicular tumors to be associated with linuron exposure, and linuron residue was found in the kidneys of exposed rats and dogs.[187] Researchers did not observe effects of linuron exposure on pregnant rabbits [187], but rats exposed to diuron during pregnancy had offspring with birth defects and low birth weight, and both embryotoxic and developmental effects were observed when pregnant mice were exposed to diuron.[188] Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea] has a chemical structure similar to one that has caused Wilms tumor in rats (N-nitroso-N'-methylurea). [189] Chronic toxicity studies for linuron have shown increased liver tumors in mice and increased testicular tumors in rats.[185] Importantly, diruon exposure has been linked to kidney and bladder tumors in rats [186], and it may also be a promoter in bladder carcinogenesis in mice [190].

We also observed associations between Wilms tumor and exposure to norflurazon, ziram, methidathion, cacodylic acid, chlorothalon, and propargite. These associations were not consistent in our analyses and may represent chance findings.

Kidney formation begins in the very early stages of gestation. The precursors of the urinary system, the pronephros and the mesonephros, are formed by 5 weeks of gestation.[101] The ureteric bud and nephrogenic blastema interact between weeks 9 and 12 to form to metanephros, which will become the permanent kidney. By week 14 the loop of Henle is functional and reabsorption occurs, and nephrons in all stages of development are present.[101, 191] Primitive metanephric blastemal cells give rise to Wilms tumors, and these cells would have normally differentiated into nephric components.[189] In humans, the process of terminal differentiation of renal structures is complete around 36 weeks of

gestation. Many Wilms tumors are associated with nephrogenic rests, which consist of embryonic blastemal cells with varying degrees of differentiation.[192, 193] Our trimester-specific analyses indicated that the first and third trimesters may be the most sensitive periods for pesticide exposure associated with increased WT risk in offspring.

To our knowledge, this study is the first to utilize data on specific pesticides to explore their association with WT. To date, most studies that have explored the relationship between pesticides and childhood cancer have asked about personal use of pesticides in the home or garden, relying on data gathered via parental interview, which is subject to recall bias, although a recent study examined reliability of maternal reports on household pesticide use and did not find differences between cases and controls.[194] Our study did not rely on interview data and therefore we expect any misclassification to be non-differential. Furthermore, California is well-suited for a study on pesticide exposures. The state ranks first in US agricultural production and pesticides applied in CA account for about 25% of total US agricultural pesticide use.[195, 196] The California Department of Pesticide Regulation has the most extensive pesticide use reporting system in the United States and oversees one of the most comprehensive pesticide regulatory programs in the world.

Although we have residential address information at the time of birth only, it is reasonable to expect that these may be used to estimate residential exposures throughout the perinatal period. A recent review on residential mobility during pregnancy reported that mobility estimates ranged from 9-32%, although the median distance moved was < 10 km.[197] We did not have information on maternal employment status during pregnancy, time spent at the residence, or whether the child attended day care outside of the residence, and these factors may impact residential exposures due to spray drift from neighboring fields. Also our pesticide exposure assessment includes only residential exposures and therefore we are not able to estimate any occupational exposures.

We found associations between several Wilms tumor in young children and exposure to several pesticides during the pre- and perinatal period. Due to the small numbers of exposed cases and the large number of associations we tested, the results we observed should be interpreted with caution. Further studies are necessary to confirm the associations we observed.

7. Public Health Implications

This dissertation research investigated the associations between birth characteristics and childhood lymphoma, exposure to infections and childhood leukemia, and pesticide exposure and childhood Wilms' tumor among children age 0-5 born between 1983-2007.

We observed associations between several birth certificate variables, including parental race and some complications of pregnancy and labor/delivery, and childhood lymphoma. While these results may not represent causal effects, they may help to generate hypotheses about the etiology of chodlhood lymphoma and provide insights directing future research.

Our results on exposure to infections in the first year of life and childhood leukemia suggest that exposure to community infections, such as influenza and RSV, may play a role in successful immune modulation during the first months of life, particularly among first born children. Our data also suggests that there are racial differences in some proxies for exposure to infection, such as birth order. These results lend support to the hypothesis that early life exposure to infections is protective for childhood leukemia.

We reported several novel associations between pesticide exposure in utero and during early life and childhood Wilms' tumor. Our study is the first to examine the link between individual pesticides and WT. Exposure misclassification should be a consideration when interpreting these findings, as

should the role of chance and multiple comparisons. If further studies confirm our findings, these data may have important implications for pesticide regulatory bodies.

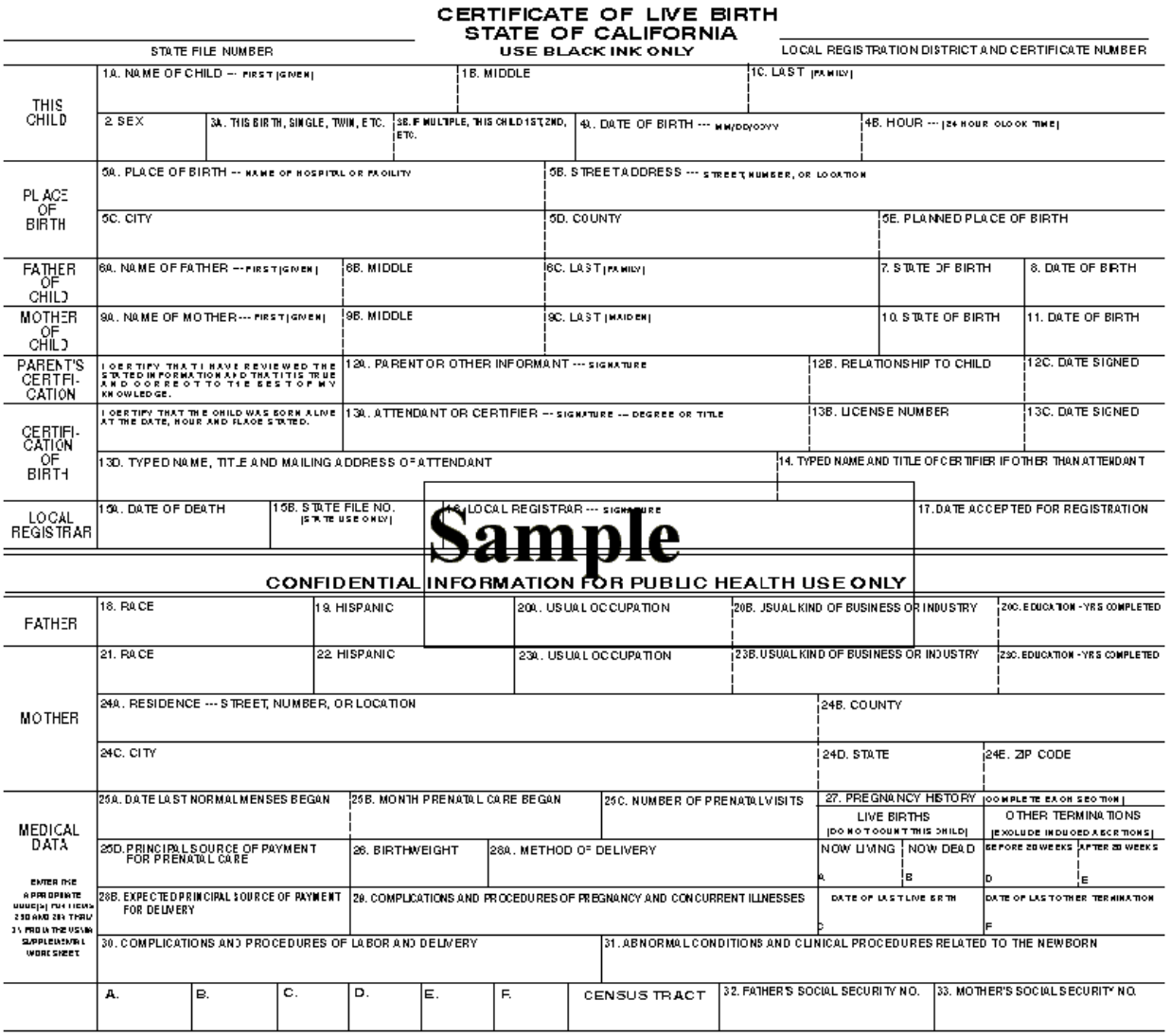
Since our data was records-based, we did not have measurements for all variables or exposures of interest. Future research on these topics may be able to further elucidate the findings we observed with the use of interview or other detailed data. Although we may have had misclassification of the exposures we investigated, we expect that it would be non-differential. Because cases were identified from cancer registry data, we do not expect significant misclassification of our outcomes. Selection bias due to non-participation did not affect our study population which was based on record linkage. It is possible that our controls differed from the source population of children born in California who, if they were diagnosed with cancer in the first 5 years of life, would also have been diagnosed in California. However we compared the distribution of important demographic and gestational factors among our controls to all California births and we did not find evidence of selection bias.

Cancer is the second leading cause of death among children. Although childhood cancer mortality has steadily declined in recent years, approximately 1,310 new deaths are expected in 2013.[1] The economic burden of childhood cancer is considerable. In 2005, childhood cancers were responsible for over 100,000 hospital stays costing about $1.7 billion.[198] The impact of cancer during childhood is reaches into adult life. Survivors of childhood cancer have a high risk of late effects, including complications with vital organ function and reproduction, and poor psychological health.[199] Secondary neoplasms and cancer recurrence are also among the serious potential risks for survivors.[199]

This research aimed to further elucidate risk factors and exposures associated with certain childhood cancers. As we further the understanding of pathways that lead to childhood cancer, future

efforts can be made to develop environmental or therapeutic interventions that might prevent or mitigate cancers among children.

8.1 Appendix I: California Birth Certificate



CERTIFICATE OF LIVE BIRTH
STATE OF CALIFORNIA
USE BLACK INK ONLY

STATE FILE NUMBER

LOCAL REGISTRATION DISTRICT AND CERTIFICATE NUMBER

THIS CHILD

1A. NAME OF CHILD — FIRST (GIVEN)
1B. MIDDLE
1C. LAST (FAMILY)
2. SEX
3A. THIS BIRTH, SINGLE, TWIN, ETC.
3B. IF MULTIPLE, THIS CHILD 1ST, 2ND, ETC.
4A. DATE OF BIRTH — MM/DD/CCYY
4B. HOUR — (24 HOUR CLOCK TIME)

PLACE OF BIRTH

5A. PLACE OF BIRTH — NAME OF HOSPITAL OR FACILITY
5B. STREET ADDRESS — STREET, NUMBER, OR LOCATION
5C. CITY
5D. COUNTY
5E. PLANNED PLACE OF BIRTH

FATHER OF CHILD

6A. NAME OF FATHER — FIRST (GIVEN)
6B. MIDDLE
6C. LAST (FAMILY)
7. STATE OF BIRTH
8. DATE OF BIRTH

MOTHER OF CHILD

9A. NAME OF MOTHER — FIRST (GIVEN)
9B. MIDDLE
9C. LAST (MAIDEN)
10. STATE OF BIRTH
11. DATE OF BIRTH

PARENT'S CERTIFICATION

I CERTIFY THAT I HAVE REVIEWED THE STATED INFORMATION AND THAT IT IS TRUE AND CORRECT TO THE BEST OF MY KNOWLEDGE.
12A. PARENT OR OTHER INFORMANT — SIGNATURE
12B. RELATIONSHIP TO CHILD
12C. DATE SIGNED

CERTIFICATION OF BIRTH

I CERTIFY THAT THE CHILD WAS BORN ALIVE AT THE DATE, HOUR AND PLACE STATED.
13A. ATTENDANT OR CERTIFIER — SIGNATURE — DEGREE OR TITLE
13B. LICENSE NUMBER
13C. DATE SIGNED
13D. TYPED NAME, TITLE AND MAILING ADDRESS OF ATTENDANT
14. TYPED NAME AND TITLE OF CERTIFIER IF OTHER THAN ATTENDANT

LOCAL REGISTRAR

15A. DATE OF DEATH
15B. STATE FILE NO. (STATE USE ONLY)
16. LOCAL REGISTRAR — SIGNATURE
17. DATE ACCEPTED FOR REGISTRATION

Sample

CONFIDENTIAL INFORMATION FOR PUBLIC HEALTH USE ONLY

FATHER

18. RACE
19. HISPANIC
20A. USUAL OCCUPATION
20B. USUAL KIND OF BUSINESS OR INDUSTRY
20C. EDUCATION - YRS COMPLETED

MOTHER

21. RACE
22. HISPANIC
23A. USUAL OCCUPATION
23B. USUAL KIND OF BUSINESS OR INDUSTRY
23C. EDUCATION - YRS COMPLETED
24A. RESIDENCE — STREET, NUMBER, OR LOCATION
24B. COUNTY
24C. CITY
24D. STATE
24E. ZIP CODE

MEDICAL DATA

ENTER THE APPROPRIATE LETTER(S) FOR ITEMS 28B AND 28C FROM THE WORK SUPPLEMENTAL WORKSHEET

25A. DATE LAST NORMAL MENSES BEGAN
25B. MONTH PRENATAL CARE BEGAN
25C. NUMBER OF PRENATAL VISITS
27. PREGNANCY HISTORY (COMPLETE EACH SECTION)
LIVE BIRTHS (DO NOT COUNT THIS CHILD)
NOW LIVING — A
NOW DEAD — B
OTHER TERMINATIONS (EXCLUDE INDUCED ABORTIONS)
BEFORE 20 WEEKS — D
AFTER 20 WEEKS — E
25D. PRINCIPAL SOURCE OF PAYMENT FOR PRENATAL CARE
26. BIRTHWEIGHT
28A. METHOD OF DELIVERY
28B. EXPECTED PRINCIPAL SOURCE OF PAYMENT FOR DELIVERY
29. COMPLICATIONS AND PROCEDURES OF PREGNANCY AND CONCURRENT ILLNESSES
DATE OF LAST LIVE BIRTH — C
DATE OF LAST OTHER TERMINATION — F
30. COMPLICATIONS AND PROCEDURES OF LABOR AND DELIVERY
31. ABNORMAL CONDITIONS AND CLINICAL PROCEDURES RELATED TO THE NEWBORN

A. | B. | C. | D. | E. | F. | CENSUS TRACT | 32. FATHER'S SOCIAL SECURITY NO. | 33. MOTHER'S SOCIAL SECURITY NO.

VS 10D (REV. 1/95)

PRIVACY NOTIFICATION

This information is collected by the State of California, Department of Health Services, Office of Vital Records and Statistics, 304 S Street, Sacramento, CA 95814, telephone number (916) 322-1356. The information is required by Division 9 of the Health and Safety Code. This record s open to public access except where prohibited by statute. Every element on this form, except tems 18 through 23C, 32, and 33, is mandatory. Failure to comply is a misdemeanor. Ths principal purposes of this recorc are to: 1) Establish a legal record of each vital event; 2) Provide certified copies for personal use; 3) Furnish information for demographic and epidemiological studies; and 4) Supply data to the National Center for Health Statistics for federal reports. Items 32 and 33 are included pursuant to Section 10125 (b) (14) of the Health and Safety Code, and may be used for child support enforcemen: purposes, or for linking the birth information database with other databases for statistical and epdemiological purposes.

Definition of Live Birth

"Live Birth" means the complete expulsion or extraction from its mother of a product of conception (irrespective of duration of pregnancy) which, after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached.

8.2 Appendix II: Pesticide Use Report

STATE OF CALIFORNIA
DEPARTMENT OF PESTICIDE REGULATION
PR-ENF-017C (REV. 08/08) Page 1 of 2

PRODUCTION AGRICULTURE MONTHLY PESTICIDE USE REPORT

Submit to the Agricultural Commissioner within 10 days of the month following application.

Month 1 ________ Year 2 ________

☐ Nursery 3

Operator ID/Permit No. 4	Operator (Grower) 5	Address 6	City 7	Zip Code 8

Site Identification No. 9	Total Planted Acres/Units 10	County Number 11	Section 12	Township 13 ☐ N ☐ S	Range 14 ☐ E ☐ W	Base & Meridian 15 ☐ S ☐ M ☐ H

Commodity/Site Treated 16	Field Location 17

Date/Time Application Completed 18	Acreage/ Units Treated 19	Application Method (Check One) 20	Block ID (If Applicable) 21	EPA or State Registration Number (From Label) 22	Total Product Used 23	Days Reentry 24	Rate Per Acre 25	Dilution 26	Product and Manufacturer 27
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				
		☐ Ground ☐ Air ☐ Fume ______ ☐ Other			☐ LB ☐ OZ ☐ PT ☐ QT ☐ GA				

Report Prepared By ______________________ Date ____________

Reviewed By ______________________
For Agency Use Only

Use Report Completion Instructions

Production Agriculture Monthly Pesticide Use Report (PR-ENF-017C)

These instructions will assist you in completing this form. The completed forms must be submitted to the county agricultural commissioner (CAC) in the county where the pest control work was performed by the 10th day of the month following the month of application.

1-2. Enter the month and year of the pesticide applications.

3. Check this box if all of the pesticide applications were made in a nursery.

4. Enter the Operator Identification Number/Restricted Material Permit Number assigned by the CAC.

5-8. Identify the property operator (grower) and complete the address information.

9. Each commodity/site is assigned a unique identification number of one to eight characters. Enter this number exactly as it was issued by the CAC.

10. Indicate the total planted acres, square feet or units at the treatment site. For pre-plant applications, enter the total acreage, square feet or units to be treated.

11. Indicate the county number. This is available from the CAC.

12-14. Indicate the section, township, and range designation for each site that is treated. These designations must be the same as those on your restricted materials permit or the Operator Identification form issued by the CAC. Otherwise, a coordinate map showing the designations must be used to determine the appropriate information. The respective compass points, e.g., "N", "S", should be checked as well.

15. There are only three base and meridians in California. One of the following code letters must be used to complete this section: H-Humboldt; M-Mount Diablo; S-San Bernardino.

16. Enter the commodity/site by common name. Identify the specific type of commodity, e.g., head lettuce, loose leaf lettuce, table grapes, wine grapes. Do not use general terms such as "herbs", "citrus" or "cole crops."

17. Enter the location of the field treated. Use the system utilized by the CAC to designate the specific property treated.

18. For each pesticide application, indicate the date and hour it was completed. Use a 24-hour clock or military time, e.g., write 7:00 a.m. as 0700, 4:00 p.m. as 1600.

19. For each application, report the total acreage treated. For band applications or strip spraying, report the total acreage at the site. For spot spraying or partial applications, e.g., border treatments, indicate only the acreage that was actually treated.

20. Check the method of application that represents each application. If checking "FUME" (fumigation), include the four-digit numeric field fumigation method (FFM) code.

21. Enter the appropriate number to identify a block within a field, if applicable.

22. Each pesticide is assigned an "EPA Regis. No." or "Calif. Reg. No." that appears on the label. Record the entire number including the alpha code, e.g., "AA," "ZA," "ZB," for each pesticide that is used. Do not use the "EPA Est. No." Spreader stickers, adjuvants, and drift control agents are registered as pesticides in California and must also be reported. Do not report nutrients, fertilizers, buffers, etc., that have no EPA or California Registration Number. Record the number from the label on the container that was used, not a number from a specimen label book.

23. Record the total amount of formulated (packaged) product that was used for each application. Do not report the total the total mixture after dilution. Check only one unit of measure (if not on form, write it in this box). If necessary, decimals and fractions may be used.

24. Enter the reentry interval as required by the pesticide label or regulation. (Optional)

25-26. Indicate the rate at which the pesticide was applied per acre, e.g., 1 pound in 100 gallons, 3 pints in 250 gallons. (Optional)

27. Write in the name of the pesticide product and the manufacturer as identified on the label. Include the brand or trade name name and type of formulation if it is indicated on the label, e.g., Pestkill 30W, NoGro 6E, Mildex SP.

Remember to sign and date the report. If you have any questions or need additional assistance in completing this form, please contact your local CAC.

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