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# Birth characteristics and risk of lymphoma in young children

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ABSTRACT

*Background:* Lymphoma is the third most common childhood malignancy and comprises two types, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The etiology of pediatric lymphomas is largely unknown, but has been suggested to have prenatal origins.

*Methods:* In this population-based study, California birth certificates were identified for 478 lymphoma cases diagnosed in children 0–5 years of age between 1988 and 2007; 208,015 controls frequency-matched by birth year were randomly selected from California birth records.

*Results:* Compared to non-Hispanic whites, Hispanic children had an increased risk of HL (odds ratio (OR) and 95% confidence interval (CI) 2.43 [1.14, 5.17]), and in particular, were diagnosed more often with the mixed cellularity subtype. For all types of lymphoma, we observed an about twofold risk increase with indicators for high risk pregnancies including tocolysis, fetopelvic disproportion and previous preterm birth. NHL risk doubled with the complication premature rupture of membranes (OR and 95% CI 2.18 [1.12, 4.25]) and HL with meconium staining of amniotic fluids (OR and 95% CI 2.55 [1.01, 6.43]).

*Conclusion:* These data support previously reported associations between Hispanic ethnicity and HL and suggest that pregnancy related factors, such as intra-uterine infections and factors associated with preterm labor, may be involved in lymphoma pathogenesis.



## 1. Introduction

Lymphoma is the third most common childhood malignancy, accounting for approximately 15% of cancers diagnosed in children (0–14 years of age) [1]. Pediatric lymphoma is relatively rare, with an incidence rate of 16.5 per million in the US [2]. Thus, pediatric lymphomas are difficult to study epidemiologically and their etiologies remain largely unknown. There is a growing body of evidence that exposures during the prenatal period, which is a highly vulnerable period of development [3,4], may contribute to development of pediatric lymphoma [5,6].

Pediatric lymphoma comprises two main types: Hodgkin lymphoma (HL) and non-Hodgkin's lymphomas (NHL). HL is 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 years olds. Nearly all lymphoma diagnoses among infants younger than 1 year of age are miscellaneous lymphoreticular neoplasms [2].

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 [7]. 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 [8,9].

NHL includes lymphoblastic lymphoma, Burkitt lymphoma, and large cell lymphoma [10]. Immunodeficiency, including immunosuppressive therapy, congenital immunodeficiency syndromes, and HIV/AIDS all predispose to NHL [11,12].

There are few studies reporting on pregnancy exposures or birth certificate variables and pediatric lymphoma [13–21]. 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.

## 2. Materials and methods

### 2.1. Subjects

The study utilized two 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 and 2007.

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Lymphoma cases were defined using International Classification of Childhood Cancer, Third edition (ICCC-3) [22] classification, 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 [23]. From CA birth certificate files, we randomly selected twenty controls per 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 ($n = 1522$). We also excluded likely non-viable births, defined as birth weight of <500 g ($n = 27$ 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.

California birth certificates provided 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, and month of prenatal care initiation. Because some birth certificate variables, specifically those related to pregnancy and labor/delivery complications, were not collected each year, we included information in Table 4 which indicates the set of study years that each variable is available.

As our study used de-identified records, we were not required to obtain informed consent from study subjects. Use of human subject data was approved by the UCLA Institutional Review Board, California Health and Human Services Agency Committee for the Protection of Human Subjects, and California Cancer Registry.

### 2.2. Statistical methods

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 and post-term at >42 weeks of gestation [24]. Low birth weight (LBW) and high birth weight (HBW) were defined as birth weights <2500 g and ≥4000 g, respectively [24]. All pregnancy and labor/delivery complications were recorded as dichotomous (yes/no) variables. We created a sex- and race-adjusted size for gestational age variable using the method described by Alexander et al. [25]. This variable is based on 10th and 90th percentile sex-specific birth weight values for each gestational week between 20 and 45 weeks for 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 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. [25] ($n = 10,134,074$). These values included separate percentiles for males and females by gestational week for each race/ethnic group. For each sex and race group, we defined small for gestational age as any birth weight below the 10th percentile, and large for gestational age as any birth weight above the 90th percentile.

Other variables included 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 [26], 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, worker's compensation, Title V, CHAMPUS/TRICARE, and self-pay). We adjusted all effect estimates for birth year. We considered 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 miscellaneous and unspecified lymphomas. Due to the rarity of some pregnancy complications, we adjusted stratified analyses only for birth year. In additional sensitivity analyses, we assessed the impact of US-versus foreign-born status among Hispanics on analysis of infant birth weight and size for gestational age. Finally, we examined the distribution of histological subtypes of HL 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.

## 3. Results

Lymphoma cases were more often male and of high birth weight (HBW) than controls (Tables 1 and 2). When considering all lymphoma cases combined, 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 HL (OR and 95% CI: 2.43 [1.14, 5.17]) and a negative association between maternal Hispanic ethnicity and NHL (OR and 95% CI: 0.80 [0.58, 1.10]) (Table 3). We observed similar associations when both parents reported Hispanic ethnicity (ORs and 95% CIs: 2.23 [0.99, 5.01] for HL and 0.81 [0.57, 1.15] for NHL). Among birth complications and other indicators for high risk pregnancies, tocolysis, previous preterm birth, and fetopelvic disproportion conferred an approximately 2-fold increase in risk of any type of lymphoma (Table 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, HBW, and previous stillbirth our data suggested positive associations with lymphoma although confidence intervals included the null value. Conversely, for pre-eclampsia, induction of labor, and breech or other abnormal presentation our data suggested negative associations, with confidence intervals again including the null. Including birth weight in the multivariate model for associations between lymphoma and pregnancy and labor complications and, separately, including child's sex in the multivariate model for birth weight did not change our estimates more than minimally (<10% change) (results not shown).

In analyses stratified by lymphoma type, we observed positive associations between HL and meconium staining (OR and 95% CI: 2.55 [1.01, 6.43]), and between NHL and premature rupture of the membranes (OR and 95% CI: 2.18 [1.12, 4.25]) (Table 5). Positive associations were also observed between HBW and miscellaneous and unspecified lymphomas (OR and 95% CI: 1.68 [1.09, 2.61]).

Foreign-born status among Hispanics conferred a slight 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), and this result is similar to our estimate for foreign-born mothers of any race. When we examined birth weight and size for gestational age among Hispanics stratified by maternal birthplace, we did not observe 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).