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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 1988–2007; 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 two-fold 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.

MeSH Keywords

Children; Epidemiology; Hispanics; Hodgkin Lymphoma; Lymphoma, Non-Hodgkin; Pregnancy

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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 year 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.

Materials and Methods

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 1988-2007. 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=1,522). We also excluded 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.

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.

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 grams and 4000 grams, 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 to 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, 1996 (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.

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).

A higher proportion of Hispanic than white HL cases was diagnosed with the mixed cellularity subtype (27.9% and 7.7%, respectively). The nodular lymphocyte-predominant subtype was more common among whites than Hispanics (4.7% and 30.8% for Hispanics and whites, respectively) (Supplemental Table 1).

Although we observed fewer than five affected cases for polyhydramnios and anemia, these factors were associated with lymphoma in a previous study (27), thus we report our observed frequencies of these factors here. Four case mothers and 1617 control mothers suffered from anemia, while one case and 986 control mothers suffered from polyhydramnios/oligohydramnios.

Discussion

We investigated associations between pregnancy-related factors and pediatric lymphomas in a large, population-based series of children age 0-5 in California. For NHL, we observed an increase in risk for male sex and a risk reduction for Hispanic ethnicity, foreign-born status, and non-private health insurance, an indicator 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 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. Generally these estimates were imprecise and had wide confidence intervals due to small sample size, although the association between HL and meconium staining was statistically significant.

The associations we observed between Hispanic ethnicity and both HL and NHL are consistent with reports from a recent study that pooled data across the US (28) and the 2000-2008 SEER data (29)(29)(29)(32)(31)(30)(29)(28)(27)(26)(25)(24)(23)(22)(21)(20, 21). 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. (9, 30-32) One pooled analysis 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. (9) Another study comparing pediatric HL from Honduras and the US found that 100% and 57% of cases, respectively, were EBV-associated. (30) 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.

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 reports of 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. Tocolytics are most commonly used to inhibit preterm labor, although use of tocolytics has also been suggested for management of fetal distress. (24) Fetal distress was not reported to differ among cases and controls, thus tocolysis most likely is an indicator of preterm labor. Many different agents are available for use as tocolytics, including beta-mimetics, magnesium sulfate, calcium channel blockers, prostaglandin inhibitors, and oxytocin receptor blockers.(33) These classes of drugs not only differ in mechanism of action, but also in contraindications and potential side effects. We do not have information on the type of tocolytic used and thus are unable to assess whether a particular agent is driving the association between tocolysis and lymphoma in our data. Previous preterm birth is a strong risk factor for subsequent preterm birth. (34) Additionally, the positive association between all types of lymphoma and previous stillbirth is similar to results from two previous studies of NHL. (14, 21) Women with previous stillbirth also are at higher risk for preterm birth in subsequent pregnancies. (24, 35, 36) Despite the higher prevalence of these risk factors for preterm birth among cases, frequency of preterm births was similar in cases and 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. (24) Although fetal size can contribute to fetopelvic disproportion, most cases of disproportion occur in a fetus within normal weight range. (24) 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 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 stratified analyses, 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. (24) We also observed an association between meconium staining of the amniotic fluid and HL risk. Meconium staining is associated with fetal distress and fetal acidosis and may indicate fetal hypoxia. (24) These factors may not directly contribute to risk of lymphoma, instead acting as a proxy for other risk factors.

This study also identified an increased risk of miscellaneous and unspecified lymphomas among those with HBW and large size for gestational age. Many factors contribute to fetal growth, including genetic potential, maternal nutritional status, placental function, and intrauterine hormonal factors.(37) Previous studies have noted a relationship between HBW and pediatric leukemia that is particularly strong among young children (<2 years). (20, 38) Our results may indicate a similar pattern given that most miscellaneous and unspecified lymphomas are diagnosed within the first year of life.(2) The underlying biological mechanisms in this association may be driven by growth factors such as the insulin-like

growth factor (IGF) family, which impact both birth weight and carcinogenic cell proliferation.(38, 39)

Our study is restricted to information provided on California birth certificates. Some variables were collected during a subset of study years, thereby further limiting our assessments. We conducted many tests of association and some of our results may be due to chance. Further research is needed to confirm positive results. Furthermore, due to limited sample sizes we were not able to stratify our results for some birth characteristics by lymphoma subtypes, thus we are not able to determine whether these associations are be specific to certain subtypes using these data. Birth certificate information has varying levels of validity. (40-44) One study reported a very high sensitivity (>94%) for most race information on California birth certificates. (41) Additionally, birth weight and method of delivery tend to have the highest sensitivity and specificity. (42-44) Maternal factors also have good validity (40), whereas pregnancy complications generally have high (>95%) specificity but low sensitivity (42-44).

Our study represents one of the largest population-based case-control studies of pediatric lymphoma. This study has strengths in that we have a large number of Hispanic mothers which allowed us to examine risk in these populations separately. Additionally, given the prospective nature of birth certificate data collection, we do not expect differential misclassification to have influenced our results. Our study population is likely to be free of selection bias due to non-participation because of records-based control sampling.

Our study confirms previous findings on Hispanic ethnicity and lymphomas and also reports novel associations. While we found associations between pediatric lymphoma and several birth certificate variables, many of these may be 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 but also by age of onset, since lymphomas occurring early in life may have different etiologies than those occurring in older children (1, 45). 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Demographic Characteristics of Study Control Subjects and Lymphoma Cases Diagnosed in California Between 1988 and 2007

	Controls (n = 208015)		Lymphoma cases, total (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

	Controls (n = 208015)		Lymphoma cases, total (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	% [†]
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	
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												

	Controls (n = 208015)		Lymphoma cases, total (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	% [†]
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

Table 2
Birth and Gestational Characteristics of Study Control Subjects and Lymphoma Cases Diagnosed in California Between 1988 and 2007

	Controls (n = 208015)		Lymphoma cases, total (n = 478)		Hodgkin lymphoma (n = 62)		Burkitt Lymphoma (n = 93)		Non-Hodgkin Lymphoma (n = 178)		Misc. and Unspecified Lymphoma (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

	Controls (n = 208015)		Lymphoma cases, total (n = 478)		Hodgkin lymphoma (n = 62)		Burkitt Lymphoma (n = 93)		Non-Hodgkin Lymphoma (n = 178)		Misc. and Unspecified Lymphoma (n = 145)	
	N	% [†]	N	% [†]	N	% [†]	N	% [†]	N	% [†]	N	% [†]
fourth or subsequent birth missing	25947	12.5	62	13.0	8	12.9	18	19.4	15	8.4	21	14.5
	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 3
Multivariate Analysis of Select Birth Certificate Variables in Relation to Lymphoma Risk
Among California Children Age 0-5 Diagnosed Between 1988 and 2007

	Any Lymphoma OR [‡] (95% CI)	Hodgkin Lymphoma OR [‡] (95% CI)	Non-Hodgkin Lymphoma OR [‡] (95% CI)
Sex			
male	1.81 (1.47, 2.23)	2.81 (1.46, 5.42)	2.58 (1.91, 3.49)
female	ref	ref	ref
Birth weight, g			
< 2500	0.89 (0.56, 1.41)	-	1.09 (0.62, 1.92)
2500-3999	ref	ref	ref
4000+	1.23 (0.91, 1.67)	1.02 (0.40, 2.77)	1.03 (0.67, 1.59)
Gestational age, weeks			
36	0.87 (0.60, 1.24)	-	0.81 (0.49, 1.34)
37-42	ref	ref	ref
43+	0.59 (0.31, 1.15)	0.96 (0.23, 3.97)	0.70 (0.31, 1.59)
Size for gestational age			
Small	1.06 (0.76, 1.48)	1.53 (0.68, 3.45)	1.13 (0.74, 1.73)
Normal	ref	ref	ref
Large	1.18 (0.85, 1.63)	0.50 (0.12, 2.06)	0.98 (0.62, 1.56)
Age of mother *			
<20	0.80 (0.56, 1.14)	0.94 (0.39, 2.29)	1.05 (0.66, 1.66)
20-29	ref	ref	ref
30-34	0.98 (0.77, 1.26)	1.08 (0.54, 2.15)	1.07 (0.77, 1.49)
35+	0.79 (0.57, 1.10)	0.16 (0.02, 1.18)	0.88 (0.58, 1.35)
Age of father			
<20	0.49 (0.24, 1.00)	0.91 (0.20, 4.16)	0.49 (0.18, 1.37)
20-29	ref	ref	ref
30-34	0.95 (0.72, 1.27)	1.65 (0.70, 3.90)	0.82 (0.56, 1.20)
35+	0.92 (0.66, 1.30)	1.81 (0.64, 5.12)	0.71 (0.45, 1.13)
Mother's education			
8 years	0.87 (0.61, 1.24)	1.08 (0.46, 2.54)	0.75 (0.44, 1.28)
Some high school (9-11 yrs)	1.11 (0.83, 1.48)	0.74 (0.32, 1.75)	1.16 (0.77, 1.73)
High school diploma (12 yrs)	ref	ref	ref
Some college (13-15 yrs)	0.77 (0.57, 1.04)	0.72 (0.27, 1.88)	0.82 (0.56, 1.21)
College diploma or higher (16+yrs)	0.70 (0.50, 0.98)	1.22 (0.45, 3.32)	0.58 (0.37, 0.91)
Father's education			
8 years	1.08 (0.76, 1.52)	1.80 (0.66, 4.93)	0.99 (0.60, 1.62)
Some high school (9-11 yrs)	0.95 (0.67, 1.34)	1.88 (0.70, 5.00)	0.76 (0.46, 1.26)
High school diploma (12 yrs)	ref	ref	ref
Some college (13-15 yrs)	1.09 (0.80, 1.49)	1.83 (0.65, 5.12)	0.94 (0.63, 1.41)
College diploma or higher (16+yrs)	0.95 (0.68, 1.32)	2.22 (0.76, 6.49)	0.79 (0.52, 1.20)

	Any Lymphoma OR [‡] (95% CI)	Hodgkin Lymphoma OR [‡] (95% CI)	Non-Hodgkin Lymphoma OR [‡] (95% CI)
Mother's race *			
white	ref	ref	ref
hispanic	1.14 (0.90, 1.45)	2.43 (1.14, 5.17)	0.80 (0.58, 1.10)
other	0.94 (0.69, 1.27)	1.21 (0.44, 3.35)	0.74 (0.50, 1.11)
Father's race			
white	ref	ref	ref
Hispanic	1.42 (0.98, 2.06)	1.60 (0.50, 5.13)	1.26 (0.78, 2.04)
other	1.03 (0.64, 1.65)	0.98 (0.19, 5.02)	0.85 (0.46, 1.59)
Parental race combination			
white/white	ref	ref	ref
hispanic/hispanic	1.19 (0.91, 1.56)	2.23 (0.99, 5.01)	0.81 (0.57, 1.15)
white/hispanic	1.02 (0.67, 1.58)	-	1.02 (0.61, 1.72)
other/other	0.97 (0.69, 1.36)	1.13 (0.38, 3.39)	0.76 (0.48, 1.18)
Mother's birthplace			
US born	ref	ref	ref
foreign born	0.88 (0.69, 1.11)	0.77 (0.40, 1.47)	0.85 (0.61, 1.19)
Method of delivery			
Vaginal	ref	ref	ref
Caesarean	0.97 (0.76, 1.23)	1.39 (0.73, 2.65)	1.01 (0.74, 1.39)
Previous terminations			
None	ref	ref	ref
1+	1.11 (0.85, 1.44)	1.16 (0.54, 2.52)	0.93 (0.64, 1.34)
Parity			
first birth	ref	ref	ref
second or third birth	1.13 (0.90, 1.42)	1.23 (0.65, 2.34)	0.98 (0.73, 1.32)
fourth or subsequent birth	1.04 (0.72, 1.50)	0.79 (0.24, 2.56)	0.97 (0.59, 1.59)
Prenatal care initiation			
During first trimester	ref	ref	ref
No care or after first trimester	1.19 (0.92, 1.53)	0.90 (0.43, 1.85)	1.07 (0.75, 1.54)
Payment source for prenatal care			
Private insurance	ref	ref	ref
Other	0.95 (0.76, 1.18)	0.86 (0.46, 1.60)	0.78 (0.58, 1.05)

[‡]ORs are adjusted for birth year, maternal age and race, and prenatal payment source

* Maternal age analyses are adjusted for birth year, maternal race, and prenatal payment source. Maternal race analyses are adjusted for birth year, maternal age, and prenatal payment source

Table 4
Multivariate Analysis of Pregnancy and Labor/Delivery Complications in Relation to
Lymphoma Risk Among California Children Age 0-5 Diagnosed Between 1988 and 2007

	Controls	Lymphoma cases, total	
	N/ N total*	N/ N total*	OR [†] (95% CI)
Years collected 2006+			
Epidural	2980/7780	6/14	0.85 (0.27, 2.68)
1989-2005			
Premature labor	4169/174962	10/384	1.15 (0.62, 2.17)
Amniocentesis	4158/174962	6/384	0.68 (0.30, 1.53)
Tocolysis	1536/174962	7/384	2.24 (1.06, 4.75)
Febrile (> 100 F)	2052/174962	6/384	1.40 (0.62, 3.14)
1989+			
Previous pre-term birth	2013/182742	9/398	2.22 (1.14, 4.32)
Pre-eclampsia	3897/182742	6/398	0.73 (0.33, 1.63)
Prolonged labor (> 20 hours)	1380/182742	5/398	1.73 (0.71, 4.18)
Premature rupture of membrane	3505/182742	10/398	1.38 (0.73, 2.58)
Induction of labor	16921/182742	29/398	0.80 (0.56, 1.18)
Stimulation of labor	18144/182742	38/398	0.97 (0.69, 1.36)
Moderate/heavy meconium staining of amniotic fluid	7629/182742	22/398	1.39 (0.90, 2.13)
All study years			
Small for gestational age	20564/196525	46/454	1.04 (0.75, 1.45)
Large for gestational age	20653/196525	59/454	1.17 (0.85, 1.62)
Preterm birth	20118/196960	45/455	0.88 (0.62, 1.26)
1986-2005			
Fetopelvic disproportion	4803/200235	17/464	1.93 (1.15, 3.24)
Breech or other abnormal presentation	5944/200235	12/464	0.73 (0.36, 1.47)
Fetal distress	6308/200235	12/464	0.86 (0.46, 1.62)
All study years			
Low birth weight	12119/207549	26/477	0.87 (0.55, 1.37) 1.37)
High birth weight	22114/207549	67/477	1.24 (0.92, 1.68)
Previous still birth	3008/207687	9/478	1.31 (0.62, 2.78)

* 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

[†] ORs are adjusted for birth year, maternal age and race, and prenatal payment source

Table 5
Multivariate Analysis of Pregnancy and Labor/Delivery Complications in Relation to Lymphoma Subtype Risk Among California Children Diagnosed Between 1988 and 2007

	Controls N/ N total*	Hodgkin lymphoma			Non-Hodgkin Lymphoma			Misc. & Unspecified Lymphoma		
		N/ N total*	OR	95% CI	N/ N total*	OR	95% CI	N/ N total*	OR	95% CI
Premature labor	4169/174962	0/50	-	-	7/214	1.39	0.65, 2.95	3/120	-	-
Premature rupture of membrane	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 staining of amniotic fluid	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