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Ethnic Differences And Risk Of Early-Onset Hodgkin Lymphoma

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ABSTRACT

Ethnic differences in the risk of early-onset Hodgkin lymphoma (HL) have been understudied. We evaluated potential associations between birth characteristics and early-onset HL in the California Linkage Study of Early-onset Cancers, a population-based case-control study that included a large number of non-Hispanic white and Hispanic subjects. This analysis included 2,819 HL cases (non-Hispanic white: 1651, Hispanic: 1168) diagnosed at the age of 0-37 years in California during 1988-2015 and 140,950 controls matched on race/ethnicity and year of birth. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from multivariable logistic regression models. Among non-Hispanic whites, a birthweight of ≥4,000g was associated with an increased risk of HL when compared to normal birthweight (2500-3999g) (OR = 1.25, 95% CI: 1.10, 1.43), while low birthweight (<2500g) decreased the risk (OR = 0.63, 95% CI: 0.48, 0.83). High or low birthweight did not appear to influence HL risk in Hispanics. Compared to those with mothers born in the United States, non-Hispanic whites with mothers born outside the United States had an increased risk of HL (OR = 1.52, 95% CI: 1.32, 1.76), but Hispanics with mothers born outside the United States had a decreased risk of HL (OR = 0.78, 95% CI: 0.69, 0.87). Given the ethnic differences in the etiology of early-onset Hodgkin lymphoma that we observed in this study, future research in diverse populations is warranted.

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INTRODUCTION

In the United States (US), Hodgkin lymphoma (HL) is one of the most commonly diagnosed malignancies among children, adolescents and young adults (1-3). HL is known to have a bimodal incidence with the incidence rising in the early teenage years, peaking in the early 20s, and leveling off until another rise begins in the mid-40s, peaking after the age of 65 (4, 5). Although infection with Epstein-Barr virus has been linked to HL, the etiology of HL, especially early-onset HL, is not well understood (6-8).

The incidence of HL varies by race/ethnicity and age in the US (9, 10). Non-Hispanic whites have a higher incidence of early-onset HL (age of diagnosis: 0-39 years) than Hispanics (3.22 per 100,000 vs. 1.79 per 100,000) (9). This difference is evident among adolescents (15-19 years) and young adults (20-39 years), but little to no difference is seen among children (0-14 years). A California study found that the HL incidence rate was 35% higher for those residing in less-ethnic, or more acculturated, enclaves relative to those in more-ethnic enclaves among adolescents and young adults (15-39 years), but no there were differences among children (11). However, another California study reported that among children diagnosed at 0-5 years, Hispanic children had a more than two-fold increased risk of HL (odds ratio [OR] = 2.43, 95% confidence interval [CI]: 1.14, 5.17) than non-Hispanic white children (12); and compared with children of US-born non-Hispanic white mothers, both children with US-born Hispanic mother and non-US born Hispanic mother had increased risk of HL (13). This finding is very intriguing, but the study was limited to HL diagnosed at the age of 0-5 years.

To investigate the etiology of early-onset HL in both Hispanics and non-Hispanic whites, especially the role of maternal birthplace and birth characteristics more broadly, we conducted

this analysis using data from the California Linkage Study of Early-onset Cancers (CALSEC), a population-based case-control study with diverse race/ethnicity representation.

METHODS

Study population

The CALSEC linked California birth records from 1978-2015 to cancer cases diagnosed at the age of 0-37 years in California during 1988-2015. Included in this analysis were first primary non-Hispanic white and Hispanic HL cases born in California and reported to the California Cancer Registry in 1988-2015. From a total of 2,852 HL cases identified in the CALSEC, we excluded cases whose mother resided outside California (n=4) and cases who had unknown maternal age (n=2), birthweight (n=1), birth order (n=18), mother's birthplace (n=1), mode of delivery (n=2), or status of congenital abnormalities (n=5), resulting in 2,819 cases in the final sample.

For each case, 50 control subjects were randomly selected from the statewide birth records and matched to the case on race/ethnicity and year of birth. The same exclusion criteria for cases were applied to potential controls. In addition, none of the controls had been diagnosed with any cancer based on data from the California Cancer Registry.

The study protocol was approved by the institutional review boards at all relevant institutions: the California Health and Human Services Agency; the University of California, Berkeley; and Yale University.

Variables of interest

Birth characteristics and parental information were obtained from birth records. Maternal birthplace (US or outside US) was a primary variable of interest. We also considered other characteristics including sex, birthweight (<2500g, low; 2500-3999g, normal; 4000-7500g, high), birth order (1_{st}, 2_{nd}, 3_{rd}+ higher), gestational age (22-36, 37-41, 42-44 weeks), mode of delivery (vaginal or caesarean), plurality (singleton or multiple), maternal history of miscarriage or stillbirth (yes, no, or unknown), maternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years), paternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years, or unknown), and maternal education (less than 12 years, 12 years or more, or unknown).

Statistical analysis

Categorical variables were presented using frequencies and percentages and compared between cases and controls using Pearson's $\chi 2$ test. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from multivariable logistic regression models. Subgroup analyses were conducted by race/ethnicity (non-Hispanic white and Hispanic) and age at diagnosis (children 0-14 years, adolescents 15-19 years, and young adults 20-37 years). We also conducted a separate analysis for nodular sclerosis the most common histological subtype of HL. All variables listed in Table 1 were included in the initial multivariable model and retained using the SAS stepwise function with a p-value cutoff of 0.05. Models for different subgroup analyses sometimes retained different sets of covariates. We chose a final list of covariates for all analyses if a variable was retained in the model for any analysis, and the final list included sex, birthweight, birth order, mode of delivery, maternal birthplace, maternal age, and paternal age. All analyses were conducted in SAS (Version 9.4, SAS Institute, Cary, North Carolina) with two-sided tests and a type I error of 5% as the threshold for statistical significance.

RESULTS

Of the 2,819 cases, 1,651 were non-Hispanic white, and 1,168 were Hispanic. Cases and controls were comparable in terms of year of birth and race/ethnicity on which they were matched (Table 1). Compared to controls, cases were more likely to be male, to have higher birthweight and to have been delivered by cesarean section. Parents of cases tended to be older than parents of controls. No significant differences were observed between cases and controls with regard to gestational age, birth order, birth plurality, maternal birthplace, history of miscarriage/stillbirth, and maternal education (Table 1).

Table 1. Characteristics of the Study Population by Case-Control Status, California Linkage Study of Early-Onset Cancers, 1988-2015.

Characteristic	Case (N = 2819)[a]	Control (N = 140950)[a]	P[b]
Sex			<.01
Female	1276 (45.3)	68777 (48.8)	
Male	1543 (54.7)	72173 (51.2)	
Race/Ethnicity			1.00
Non-Hispanic White	1651 (58.6)	82550 (58.6)	
Hispanic	1168 (41.4)	58400 (41.4)	
Birth Year			1.00
1978-1982	744 (26.4)	37200 (26.4)	
1983-1987	760 (27.0)	38000 (27.0)	
1988-1992	722 (25.6)	36100 (25.6)	
1993-2009	593 (21.0)	29650 (21.0)	
Birth Weight (grams)			<.01
Low (250-2499)	123 (4.4)	7499 (5.3)	
Normal (2500-3999)	2253 (79.9)	115291 (81.8)	
High (4000-7500)	443 (15.7)	18160 (12.9)	
Gestational Age (weeks)			0.97
22-36	231 (8.2)	11749 (8.3)	
37-41	2051 (72.8)	102062 (72.4)	
42-44	319 (11.3)	15938 (11.3)	
Unknown	218 (7.7)	11201 (8.0)	
Birth Order			0.29
1	1129 (40.1)	58262 (41.3)	
2	926 (32.9)	44551 (31.6)	
3+	764 (27.1)	38137 (27.1)	

Characteristic	Case (N = 2819)[a]	Control (N = 140950)[a]	P[b]
Mode of Delivery			<.01
Vaginal	2159 (76.6)	111216 (78.9)	
Cesarean	660 (23.4)	29734 (21.1)	
Birth Plurality			0.71
Singleton	2761 (97.9)	137903 (97.8)	
Multiple	58 (2.1)	3047 (2.2)	
Mother's Age at Birth			<.01
<20	227 (8.1)	15991 (11.4)	
20-24	704 (25.0)	40041 (28.4)	
25-29	931 (33.0)	42790 (30.4)	
30-34	638 (22.6)	28787 (20.4)	
35+	319 (11.3)	13341 (9.5)	
Father's Age at Birth			<.01
<20	89 (3.2)	5528 (3.9)	
20-24	475 (16.9)	28413 (20.2)	
25-29	831 (29.5)	40759 (28.9)	
30-34	684 (24.3)	33475 (23.4)	
35+	646 (22.9)	26590 (18.9)	
Unknown	94 (3.3)	6185 (4.4)	
Maternal Education			0.37
Less than 12 years	780 (27.7)	40147 (28.5)	
Greater than 12 years	502 (17.8)	23830 (16.9)	
Unknown	1537 (54.5)	76973 (54.6)	
Maternal Birthplace			0.61
United States.	1963 (69.6)	98682 (70.0)	
Other	856 (30.4)	42268 (30.0)	
History of Miscarriage or Stillbirth			0.60
No	2307 (81.8)	115569 (82.0)	
Yes	506 (18.0)	24938 (17.7)	
Unknown	6 (0.2)	443 (0.3)	

[a] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding

[b] P-value is for Chi-squared test

A multivariable logistic regression analysis of the overall study population suggested that males had 13% increased risk of HL (OR = 1.13, 95% CI: 1.05, 1.22) than females (Table 2). Increased risk of HL was also observed with high birthweight (OR = 1.19, 95% CI: 1.07, 1.32) and delivered by cesarean section (OR = 1.10, 95% CI: 1.00, 1.20). Those with a birth order of 3rd or higher had a lower risk of HL compared to firstborns (OR = 0.87, 95% CI: 0.79, 0.97). Compared to individuals born to mothers aged 25-29 years, those delivered by mothers at ages 20-24 years (OR = 0.82, 95% CI: 0.73, 0.91) or <20 years (OR = 0.65, 95% CI: 0.54, 0.78) also had a decreased risk of HL (Table 2).

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Hodgkin Lymphoma (0-37 years), California Linkage Study of Early-Onset Cancers, 1988-2015.

Characteristic	Odds Ratio	95% Confidence interval
Sex		
Female	Ref	
Male	1.14	1.05-1.22
Race/Ethnicity		
Non-Hispanic white	Ref	
Hispanic	1.10	1.00-1.21
Birth Weight (grams)		
Low (250-2499)	1.19	1.07-1.32
Normal (2500-3999)	Ref	
High (4000-7500)	0.83	0.69-1.00
Birth Order		
1	Ref	
2	0.90	0.89-1.07
3+	0.87	0.79-0.97
Mode of Delivery		
Vaginal	Ref	
Cesarean	1.10	1.00-1.20
Mother's Age at Birth		
<20	0.65	0.54-0.78
20-24	0.82	0.73-0.91
25-29	Ref	
30-34	1.01	0.90-1.12
35+	1.04	0.89-1.20
Father's Age at Birth		
<20	1.02	0.79-1.32
20-24	0.93	0.82-1.05
25-29	Ref	
30-34	0.95	0.86-1.07
35+	1.12	0.99-1.27
Unknown	0.81	0.65-1.10
Maternal Birthplace		
United States	Ref	
Other	0.99	0.90-1.09

All variables in the table were mutually adjusted.

Maternal birthplace showed different association with the risk of HL in the two ethnic groups. Compared with individuals whose mothers were born in the US, those with mother born outside the US had a 22% decreased risk of HL (OR = 0.78, 95% CI: 0.69, 0.87) among Hispanics, but a

52% increased risk of HL (OR = 1.52, 95% CI: 1.32, 1.76) among non-Hispanic whites (Figure 1). Among Hispanics, males had an increased risk of HL (OR = 1.26, 95% CI: 1.12, 1.42) than females; among non-Hispanic whites, sex did not appear to be associated with HL risk. Among non-Hispanic whites, high birthweight was associated with an increased risk of HL when compared to normal birthweight (OR = 1.25, 95% CI: 1.10, 1.43), while low birthweight had reduced risk (OR = 0.63, 95% CI: 0.48, 0.83). In contrast, birthweight did not influence HL risk in Hispanics. Those delivered by younger mothers had a lower risk of HL among both Hispanics and non-Hispanic whites (Figure 1).

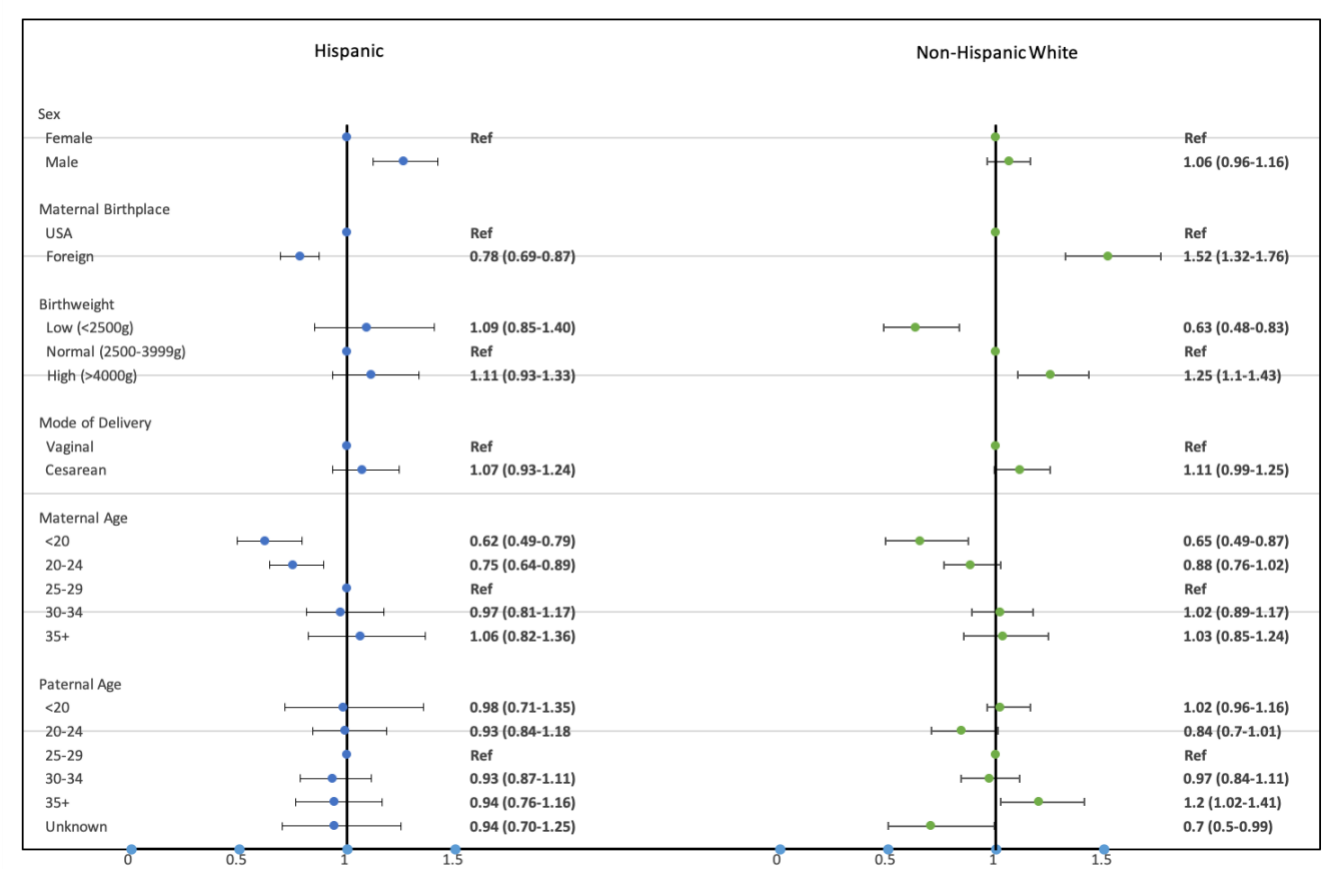

Figure 1. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Hodgkin Lymphoma (0-37 years) by ethnicity, California Linkage Study of Early-Onset Cancers, 1988-2015

As maternal birthplace, sex, and birthweight showed different associations with HL in the two ethnic groups, we conducted age-specific analyses for the two ethnic groups separately. As shown in Figure 2, non-Hispanic whites whose mothers were born outside the US were at an increased risk for HL among children (OR = 2.16, 95% CI: 1.60, 2.92) and young adults (OR = 1.55, 95% CI: 1.23, 1.90). Among Hispanics, a decreased risk of HL among individuals whose mothers were born outside the US was observed among adolescents (OR = 0.76, 95% CI: 0.60, 0.95) and young adults (OR = 0.70, 95% CI: 0.58, 0.84).

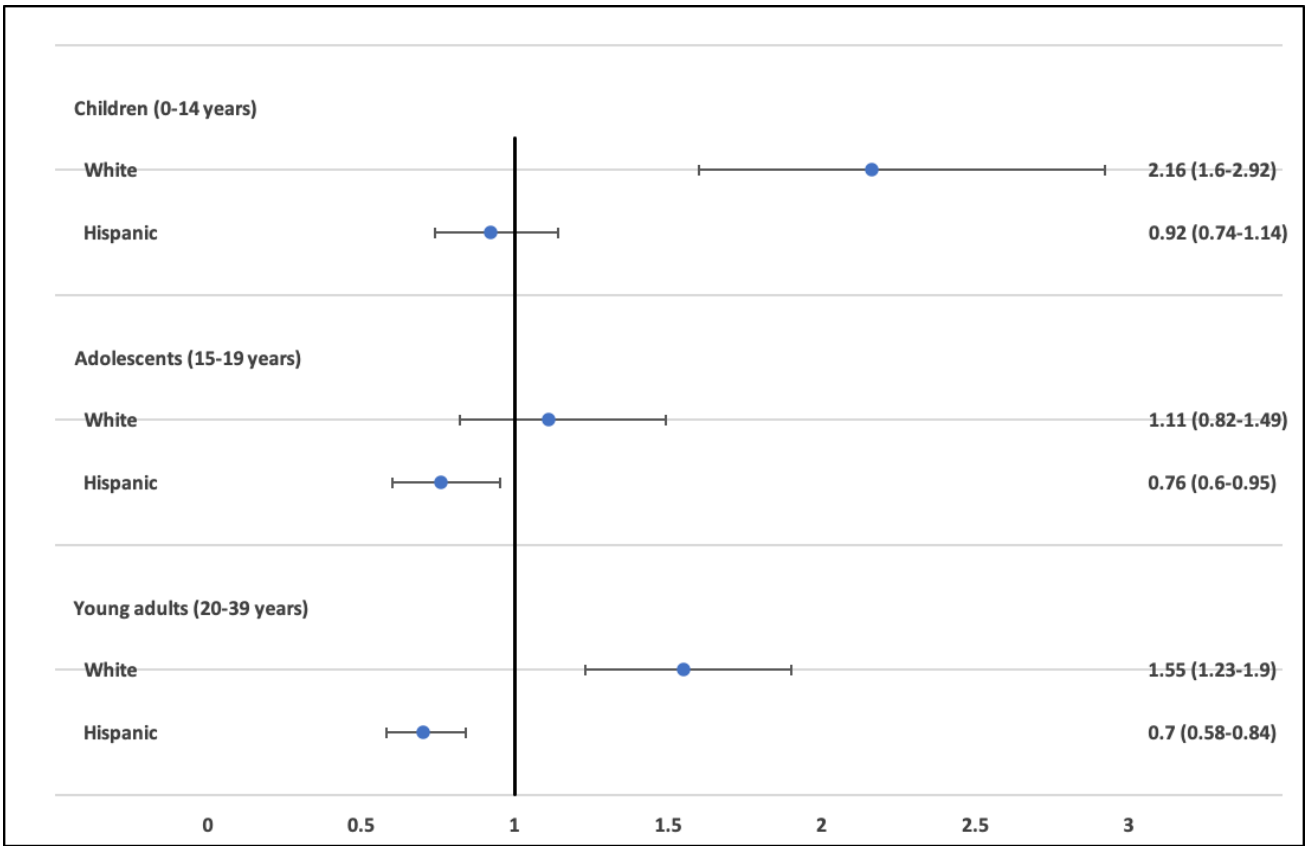

Figure 2. Association between maternal birthplace and risk of Hodgkin lymphoma by age and ethnicity, California Linkage Study of Early-Onset Cancers, 1988-2015

Our analysis of the most common histological subtype of HL generated results that were extremely similar to those from the analysis of HL as a single entity, so we decided not to present the results separately.

DISCUSSION

In this large population-based case-control study, we investigated the etiology of early-onset HL, with a focus on potential ethnic differences. Compared to those with US-born mother, among non-Hispanic whites, children and young adults with non-US born mothers were at an increased risk of HL; but among Hispanics, adolescents and young adults of non-US born mother had a decrease risk of HL. The association between sex, birthweight and HL risk also exhibited ethnic heterogeneity, supporting the possibility that non-Hispanic whites and Hispanics may have distinct etiological profiles for HL.

Only limited studies have assessed maternal birthplace and risk of HL. A Texas study reported no difference in risk of HL (OR = 0.87, 95% CI: 0.52, 1.44) between children with Mexican-born mothers and those with US-born mothers (14). This study was limited to children up to 16 years and did not further stratify by ethnicity. Also, in this study, although 73 of 143 HL cases were Hispanic, only a total of 42 (28.7%) mothers were born outside the US (14). In our study, mothers of about 30% participants were born outside the US, with a higher percentage among Hispanics (54.6% in cases and 60.1% in controls). Among California children aged 0-5 years, compared with children of non-Hispanic white mothers, children with US-born Hispanic mothers (OR = 2.49, 95% CI: 1.21, 5.13) or non-US born Hispanic mothers (OR = 2.35, 95% CI: 1.24, 4.47) both had increased risk of HL (13). As HL is rare among young children, this study only

included a total of 66 HL cases and did not specifically evaluate the role of maternal birthplace among Hispanics (13).

The mechanism underlying the association between maternal birthplace and risk of HL is challenging to fathom. The influence of the Hispanic paradox and stress of immigration are seen in many aspects of life and health, ranging from cancer to mental health and beyond (13, 15-17). How this paradox might play a role in early-onset cancer, particularly for children and adolescents is unclear. It is known that in general, as Hispanic people immigrate to the US their diets and behaviors gradually shift to those common to the US, and their health may decline (18, 19). One recent study found that as acculturation increased for migrant mothers to the US, so did the number of adverse pregnancy outcomes reported (20). Furthermore, another study revealed that when comparing native and migrant populations in Spain, the natives were more likely to develop chronic conditions and cancer in adulthood (21). These findings support the current view that both genetic and environmental factors play a role in the etiology of HL (22, 23).

Our finding on the higher risk of HL among male children was consistent with sex-specific incidence rates observed in the Surveillance, Epidemiology and End Results (SEER) program. Williams et al. calculated the incidence rate ratio for HL using data from SEER 18 (2000-2015) and showed that male sex was associated with a higher rate than female sex (incidence rate ratio = 1.25, 95% CI: 1.20, 1.30) (24). We also observed an increased risk of HL among those with high birthweight which was consistent with our previous findings in the pediatric population (25). Similarly, a Swedish study reported that high fetal growth was associated with an increased risk of HL among those age 0-37 years (26). However, other studies have found no relationship between birthweight and childhood HL (12, 27-30). Given the ethnic differences we

observed in the association between sex, birthweight and the risk of HL, it would be important to conduct more etiological studies of HL in racially/ethnically diverse populations and accommodate potential ethnic disparity in statistical analysis. In our study, higher birth order was associated with decreased risk of HL, especially among adolescents and young adults. Findings from a Danish study suggested that increasing birth order increased the relative risk of childhood HL (0-14 years) but decreased the relative risk of HL in young adults (≥15 years) (31, 32). Nevertheless, other studies have found no association between birth order and risk of HL (14, 26, 33, 34). Possible explanations for the inconsistent findings might include the varying ages of HL diagnosis included in different studies and the relatively small sample sizes in many existing studies. For example, only one of these studies has an age range of 1-37 years (26), while the others are more varied, ranging from 0-16 years to 15 years and older (14, 33, 34). The largest sample size from these studies is 943 cases, with the others all falling below 400.

Our study has several limitations. Firstly, the CALSEC linkage consisted of birth records from 1978 (when California birth records first became computerized) and cancer diagnoses from 1988 (when the statewide cancer reporting was fully implemented). All cases had to be born in California, which accounted for 61% of all HL cases diagnosed at the age of 0-37 years and reported to the California Cancer Registry (the coverage is 77.2% for HL in children). However, there is no reason to believe that HL cases diagnosed in California but not born there have a systematically different etiology. Alternatively, our design can be conceptualized as a case-cohort study, in which we identified cases from a cohort consisting of all California births. Second, there was potential for misclassification of controls who might have moved out of California and been diagnosed with early-onset HL elsewhere. Based on the age-specific incidence rate of HL in California from 2000-2015, we estimate that 35 out of 140,950 controls

would have developed HL by the age of 37 years if they had all moved out of California the day after birth. Lastly, we were limited to data available in existing records, and therefore could not adjust for additional risk factors for HL such as history of Epstein-Barr virus infection or infectious mononucleosis (6-8, 35-37).

The study also has multiple strengths. The large size and racial/ethnic diversity of the California population resulted in a large number of non-Hispanic white and Hispanic cases, and we also had access to 50 times as many controls, which helped to improve statistical power and allowed us to conduct stratified analyses by ethnicity and age of diagnosis (children, adolescents, and young adults). Previous studies on the etiology of HL have mostly been conducted in European/Caucasian populations, so the analysis of HL risk factors among Hispanics is a major strength of our study. The CALSEC is record linkage-based which obviated the need for participant contact and therefore we were able to obtain preexisting, non-identifying data without active consent. As a result, this study was less prone to selection bias due to non-participation due to differential recall between cases and controls.

CONCLUSION

In summary, this large population-based case-control study identified multiple risk factors for HL in children, adolescents, and young adults from California. Compared to individuals with US-born mothers, among Hispanics, children and young adults with non-US born mothers were at an increased risk of HL; but among non-Hispanic whites, adolescents and young adults of non-US born mother had a decrease risk of HL. The association between sex, birthweight and HL risk also varied by ethnicity. These findings underscore the importance of accounting for potential ethnic differences in the etiology of early-onset HL in future studies.

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