Title

Hispanic Ethnicity Differences in Birth Characteristics, Maternal Birthplace, and Risk of Early-Onset Hodgkin Lymphoma: A Population-Based Case-Control Study.

Journal

Cancer Epidemiology Biomarkers & Prevention, 31(9)

ISSN

1055-9965

Authors

Graham, Connor
Metayer, Catherine
Morimoto, Libby M
et al.

Publication Date

2022-09-02

DOI

10.1158/1055-9965.epi-22-0335

Peer reviewed

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 March 02.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2022 September 02; 31(9): 1788–1795.

doi:10.1158/1055-9965.EPI-22-0335.

Hispanic Ethnicity Differences in Birth Characteristics, Maternal Birth Place, and Risk of Early-Onset Hodgkin Lymphoma: A Population-Based Case-Control Study

Connor Graham[1], **Catherine Metayer**[2], **Libby M. Morimoto**[2], **Joseph L. Wiemels**[3], **Arfan Siddique**[1], **Mengyang Di**[4], **Rozalyn L. Rodwin**[5], **Nina S. Kadan-Lottick**[6], **Xiaomei Ma**[1], **Rong Wang**[1]

[1]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut, United States

[2]Department of Epidemiology, School of Public Health, University of California, Berkeley, California, United States

[3]Center for Genetic Epidemiology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, United States

[4]Section of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, United States

[5]Section of Pediatric Hematology/Oncology, Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut, United States

[6]Georgetown Lombardi Comprehensive Cancer Center, Washington D.C., United States

Abstract

Background: Hispanic ethnicity differences in the risk of early-onset Hodgkin lymphoma (HL) diagnosed at < 40 years are understudied. We conducted a population-based case-control study to evaluate associations between birth characteristics and early-onset HL with a focus on potential ethnic differences.

Methods: This study included 1,651 non-Hispanic White and 1,168 Hispanic cases with HL endorsing a range of races diagnosed at the age of 0-37 years during 1988-2015 and 140,950 controls without cancer matched on race/ethnicity and year of birth from the California Linkage Study of Early-Onset Cancers. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from multivariable logistic regression models.

Results: Having a foreign-born mother versus a United States-born mother (i.e., the reference group) was associated with an increased risk of early onset HL among non-Hispanic Whites (OR=1.52, 95% CI:1.31-1.76; $P<0.01$) and a decreased risk among Hispanics (OR=0.78, 95% CI:0.69-0.88; $P<0.01$). Among both race groups, risk of early onset HL increased with birthweight

Corresponding author: Rong Wang, PhD, Yale School of Public Health, PO Box 208034, 60 College Street, New Haven, CT 06520-8034, United States, r.wang@yale.edu, Phone: (203) 767-5245, Fax: (203) 785-6980.

Conflict of Interest: The authors declare no potential conflicts of interest

and maternal age (all *P*-trends<0.01). Among Non-Hispanic Whites, each 5-year increase in maternal age (OR = 1.11; 95% CI, 1.04-1.18; *P*-trend < 0.01) and paternal age (OR=1.07, 95% CI:1.02-1.13; *P*-trend=0.01) was associated with increased risk of early onset HL. Compared to female Hispanics, male Hispanics had an increased risk of early onset HL (OR =1.26, 95% CI:1.12-1.42; *P*<0.01).

Conclusion: Maternal birthplace may play a role in risk of early-onset HL that differs by ethnicity.

Impact: The ethnic differences observed between certain birth characteristics, maternal birthplace and early onset HL raise questions about the underlying biological, generational, lifestyle, residential, and genetic contributions to the disease.

INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell malignant neoplasm characterized by the presence of Reed-Sternberg cells (1). The incidence of HL has a bimodal age distribution, with the first peak in late adolescence/young adulthood reflecting early-onset HL (2,3). HL is among the most common cancers in children, adolescents and younger adults (AYAs) in the United States (US) (3,4). Nearly 43% of new cases in the US are diagnosed in people between 0-34 years (5). Besides infection with Epstein-Barr virus, the etiology of HL, especially early-onset HL, is not well understood (6–8). The “late infection model” for HL proposes that early-onset HL may develop as the consequence of relatively common infections, and that the risk increases with increasing age at time of primary infection (9,10). Previous studies have found some birth characteristics, such as high birthweight, high fetal growth, and lower birth order were associated with risk of early-onset HL (<40 years) (11–15).

In the US, prevailing incidence of HL differs between Hispanics and non-Hispanic Whites and varies by age (16). Compared with non-Hispanic Whites, Hispanics have younger mean age at diagnosis (38.0 versus 40.0 years, $P < 0.001$) and are more likely to be male (16). In addition, Hispanics have lower rates of nodular sclerosis HL among AYAs, both of which are types of classical HL, but higher rates of mixed cellularity HL in children and older adults than non-Hispanic Whites (17). Both nodular sclerosis HL and mixed cellularity HL are types of classical HL.

Among Hispanics, incidence variation is also associated with place of birth. Compared with their foreign-born counterparts, US-born Hispanics have higher HL incidence among young adults, but lower in children (16,17). The difference in HL incidence by nativity suggests a possible influence of acculturation. Glaser et al. found that HL incidence was 35% higher for Hispanics residing in less-ethnic, or more acculturated, enclaves relative to those in more-ethnic enclaves, especially among females and those aged 15-39 years (18). These findings indicate environmental factors, such as nativity-related sociodemographic differences, impact HL occurrence.

In the US, the Hispanic population is the second-largest ethnic group, and nearly 60% of this population is under 35 years old (19). Currently, approximately half of both first and second generation residents of the US are Hispanic (20). Compared with those born in the

US, foreign-born people in the US tend to have larger family size, are less likely to be high school graduates, and have lower median household incomes (21), which indicate possible differences in childhood socioeconomic status between offspring of US-born mothers versus foreign-born mothers.

To understand ethnic disparity of maternal birthplace and birth characteristics in the etiology of early-onset HL, we conducted a large population-based case-control study among non-Hispanic Whites and Hispanics born in California.

MATERIALS AND METHODS

Study population

California Linkage Study of Early-Onset Cancers (CALSEC) was created using a probabilistic record linkage of California birth records maintained by the Center for Health Statistics and Informatics, California Department of Public Health from 1978-2015 with statewide cancer diagnosis data from the California Cancer Registry (CCR) during 1988-2015. Cases were diagnosed from 1988 (the earliest year the CCR data were electronically available) through 2015 (when the linkage was conducted) and born in or after 1978 (the earliest year the California birth data were electronically available). CALSEC captured 76.9%, 70.0% and 44.7%, respectively, of childhood (0-14 years), adolescent (15-19 years) and young adult (20-37 years) cases reported in California between 2000-2015. The current study included first primary HL cases (International Classification of Diseases for Oncology, third edition 9650-9667) among non-Hispanic White and Hispanic people born in California and reported to the California Cancer Registry at ages of 0-37 years.

From 2,852 HL cases identified, we excluded cases: 1) whose mother resided outside California at time of birth (out of concern that these children might not have been reported to the CCR had they developed pediatric cancer) (n=4); and 2) whose birth records with missing information on birthweight (n=1), birth order (n=18), status of congenital abnormalities (n=5), mode of delivery (n=2), maternal age (n=2), or maternal nativity (n=1), resulting in 2,819 cases in the final cohort.

For each case, 50 control subjects of the same ethnicity were randomly selected from the statewide birth records who were born in California during the same year and were not diagnosed with any cancer based on data from the California Cancer Registry up to age 37. The same exclusion criteria for cases were applied to potential controls.

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

Variables of interest

For both cases and controls, we abstracted birth characteristics and parental information from birth records. Maternal birthplace (US or foreign) was a primary variable of interest. We also considered other characteristics including sex, birthweight (low <2500 grams; normal 2500-3999 grams; high ≥4000 grams), gestational age (preterm:22-36, full

term:37-41, post term 42-44 weeks), birth order (1st, 2nd, 3rd or higher), mode of delivery (vaginal or caesarean), plurality (singleton or multiple), maternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years), maternal education (≤12 years, >12 years, or unknown), maternal history of miscarriage or stillbirth (yes, no, or unknown), and paternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years, or unknown). Additionally, we linked with the 1990 US census for those born in 1978-1995, the 2000 US census for those born in 1996-2005 and the 2008-2012 American Community Survey five-year summary for those born in 2006 and later. Percentage of 150 percent of poverty at census block group was obtained from census files and categorized in quartiles based on distribution among controls.

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. As the log-likelihood ratio test for potential interaction between race/ethnicity and maternal birthplace yielded a p value below 0.01, we conducted analyses stratified by race/ethnicity (non-Hispanic White and Hispanic). To compare our findings with previous studies, we further conducted subgroup analyses by age at diagnosis (children 0-14 years, adolescents 15-19 years, and young adults 20-37 years) within each ethnicity. We initially included all variables listed in Table 1 simultaneously in the multivariable logistic regression model and retained variables using the SAS stepwise function with a p-value of less than 0.05. Based on SAS model selection results and findings from previous studies, the final model included sex, birthweight, birth order, mode of delivery, maternal birthplace, maternal age, paternal age and percentage of population below 150% poverty at census block group level. Birthweight, birth order, maternal age, and paternal age as continuous variables were used to assess possible trends. All analyses were conducted in SAS (Version 9.4, SAS Institute, Cary, North Carolina) with 2-sided tests and a type I error of 5%.

Data Availability

We are prohibited by California statutes from publicly sharing data that are derived from the California Department of Public Health. We welcome questions from other investigators or request for additional analyses that are pertinent to the data presented in this manuscript, and potential data sharing when permitted by the California Health and Human Services Agency Committee for the Protection of Human Subjects.

RESULTS

A total of 1,651 non-Hispanic White and 1,168 Hispanic people diagnosed with early-onset HL were included in the study. Of the 2,819 early-onset HL cases, 655 (23.2%), 802 (28.4%), and 1,362 (48.3%) were diagnosed at the age of 0-14, 15-19, and 20-37 years, respectively. Among non-Hispanic Whites, cases were more likely than controls to have higher birthweight ($P < 0.01$), be delivered by cesarean section ($P = 0.02$), and have older fathers ($P < 0.01$) (Table 1). In addition, mothers of non-Hispanic White cases were more likely to be born in the US and tended to be older than those of controls (both $Ps < 0.01$). Among Hispanics, compared with controls, cases were more likely to be male ($P < 0.01$).

Mothers of Hispanic cases were more likely to be older ($P < 0.01$) and have ≥12 years education ($P = 0.01$) than those of controls.

Non-Hispanic Whites

Having a foreign-born mother was associated with a 52% (OR = 1.52, 95% CI: 1.31 - 1.76; P < 0.01) increased risk of early-onset HL relative to those with a US-born mother (Table 2). Relative to those with normal birthweight, low birthweight was associated with a 37% decreased risk (OR = 0.63, 95% CI: 0.48 - 0.83; $P < 0.01$) of early-onset HL, while those with high birthweight had a 25% increased risk of early-onset HL (OR = 1.25, 95% CI: 1.10 - 1.43; $P < 0.01$). Moreover, risk of early-onset HL increased 10% with every 500 grams birthweight increase (OR = 1.10, 95% CI: 1.05 - 1.15; P-trend < 0.01). Compared with individuals born to mothers aged 25-29 years, those delivered by mothers at ages <20 years also had a decreased risk of early-onset HL (OR = 0.65, 95% CI: 0.48 - 0.86; $P < 0.01$). The odds ratio for each 5-year increase in maternal age was 1.11 (95% CI: 1.04 - 1.18; P-trend < 0.01). In addition, a 20% (OR = 1.20, 95% CI: 1.03 - 1.41; $P = 0.02$) increased risk of early-onset HL was observed among those non-Hispanic Whites with fathers at ages ≥ 35 years when compared with those with fathers at ages 25-29 years. The odds ratio for each 5-year increase in paternal age was 1.07 (95% CI: 1.02 - 1.13; P-trend = 0.01). Compared with female sex, male sex was not associated with the risk of HL (OR = 1.06, 95% CI: 0.96-1.16; $P = 0.29$).

Hispanics

Having a foreign-born mother was associated with a 22% decreased risk of early-onset HL in offspring (OR = 0.78, 95% CI: 0.69 - 0.88; $P < 0.01$) compared to their counterparts delivered by US-born mothers (Table 3). Males had a higher risk of early-onset HL than females (OR = 1.26, 95% CI: 1.12 - 1.42; $P < 0.01$). Risk of early-onset HL increased 9% with every 500 grams birthweight increase (95% CI: 1.03 - 1.15; P-trend < 0.01). Compared with those born to mothers aged 25-29 years, decreased risks of early-onset HL were observed among Hispanics delivered by mothers at ages <20 years (OR = 0.62, 95% CI: 0.49 - 0.79; $P < 0.01$) and 20-24 yeas (OR = 0.76, 95% CI: 0.64 - 0.89; $P < 0.01$). The odds ratio for each 5-year increase in maternal age was 1.15 (95% CI: 1.07 - 1.24; P-trend < 0.01).

Maternal Birthplace by Age

We further assessed the association between maternal birthplace and risk of early-onset HL at different age groups within each ethnic group (Figure 1). Among non-Hispanic White children and young adults, offspring of foreign-born mothers had an increased risk of HL (children OR = 2.16, 95% CI: 1.60 - 2.92; young adults OR = 1.55, 95% CI: 1.27 - 1.90; both Ps < 0.01) than those of US-born mothers. Among Hispanics, decreased risks of HL among individuals with foreign-born mothers were observed among adolescents (OR = 0.76, 95% CI: 0.61 - 0.96; $P = 0.02$) and young adults (OR = 0.70, 95% CI: 0.58 - 0.85; $P < 0.01$), but the same association was not seen in children (OR = 0.92, 95% CI: 0.74 - 1.15; $P =$ 0.48).

DISCUSSION

In this population-based case-control study, we investigated the etiology of early-onset HL with a focus on maternal birthplace, examining differences by Hispanic ethnicity. The risk of HL associated with having a foreign-born mother (relative to US-born) differed depending on ethnicity: among non-Hispanic Whites, those with foreign-born mothers had an increased risk of HL, while among Hispanics, having a foreign-born mother was associated with decreased risk. Within each race/ethnicity group, the elevated risk among non-Hispanic Whites was limited to children and young adults, while the decreased risk among Hispanics was limited to AYAs. The risks associated with sex also differ in the two race/ethnicity groups, supporting the possibility that non-Hispanic Whites and Hispanics may have different etiological profiles for early-onset HL.

Only limited studies have previously assessed maternal birthplace and risk of HL, and no previous study investigated the impact within a single race/ethnicity group (14,22–24). Although a Texas study observed non-significant association of maternal nativity with risk of HL among children up to 16 years, the trend of their findings was similar to ours (22). They found had a non-significant decreased risk of HL among children of a Mexico-born mother (OR = 0.87, 95% CI: 0.52 - 1.44), but a non-significant increased risk of HL among children of a mothers born in other foreign counties (OR = 1.15, 95% CI: 0.57 - 2.31) than children with a US-born mother. However, in this study, both children of US-born mothers and mothers born in other-foreign countries were of all races/ethnicities. A study among younger California children (0-5 years) reported increased risks of HL among children with non-US born Hispanic mothers (OR = 2.35, 95% CI: 1.24 - 4.47) or US-born Hispanic mothers (OR = 2.49, 95% CI: 1.21 - 5.13) than children of non-Hispanic White US-born mothers, who served as controls (24). This California study did not evaluate impact of maternal birthplace within the non-Hispanic population.

The mechanism underlying the association between maternal birthplace and risk of HL is complex. First, early-onset HL may develop as the consequence of relatively common infections, the risk increases with older age at time of primary infection (9,10). Foreign born Hispanics have larger family size, lower median household income, and are less educated than their US-born counterparts (21), which may be associated with differing exposure to infectious pathogens among their offspring. It has been reported that a higher number of older siblings (11,12), ≥1 year of nursery school or day care attendance (25), and residence in multiple-family homes (10) reduced the risk of HL. In a nested case-control of U.S servicemen diagnosed with HL between the ages of 17-32 years, low birth order (first born), small sib-ship size, and an interval of at least 5 years between birth and that of a previous or subsequent sibling independently increased the risk of HL (13). These findings support an inverse association between childhood infectious exposure and development of HL in AYA. Second, it is known that, in general, foreign-born Hispanic mothers who immigrate to the US have better pregnancy outcomes than their US-born Hispanic counterparts, with decreased rates of low birthweight, preterm birth and premature mortality (26–28). Compared with their second-generation counterparts, first generation foreign-born Hispanic women who move to the US have been shown to have a healthier diet (29). Foreign born Hispanic women are also less likely to be obese, but this diminishes as more time is spent in

the US (30). A similar relationship has been seen with regards to smoking. One study noted that US born Hispanic women who preferred English as a primary language had higher odds of smoking during pregnancy compared to foreign-born Hispanic or Puerto Rican women with a preference for Spanish (OR = 2.76, 95% CI: 1.36 - 5.63) (31). These prenatal factors may play a role in early-onset cancer, particularly for children (32,33).

Our finding of the higher risk of early-onset of HL among Hispanic males relative to Hispanic females differed from sex-specific incidence rates observed previously, with one study showing that significant differences by sex did not occur until after 40 years of age (13). Evens et al. reported that although both Hispanics and non-Hispanic Whites showed relatively higher incidence in males than in females, there were more males diagnosed with HL among Hispanics compared with non-Hispanic Whites ($P = 0.005$) (16). Both the California early childhood HL study (male vs female: OR = 2.81, 95 % CI 1.46 - 5.42) and the Texas study (female vs male: OR = 0.66, 95 % CI 0.46 - 0.93) reported higher risk of HL among males than females but did not stratify by ethnicity (22,23). The results of our study offer further support that the increased risk of HL associated with the male sex is more pronounced in Hispanics.

The role of birth weight in the etiology of HL has been inconsistent (14,15,23,34–37). As in our previous study among children 0-19 years, we observed an increased risk of HL with increased birthweight(14). Crump et al. reported that every 1,000 grams of birth weight was associated with an 24% increased risk of HL among those age 0-37 years (95% CI: 1.09 - 1.42; $P_{trend} = 0.002$) (15). Milne *et al.* found that a higher proportion of optimal birth weight, a metric for appropriateness of fetal growth (38), was associated with an increased risk of childhood HL (age 0-14 years) in boys. However, other studies have found no relationship between birthweight and childhood HL (23,34–37). None of the studies that provide these null results explicitly compared cases from populations stratified by race or ethnicity. In our study, among non-Hispanic Whites, those with low birth weight had a decreased risk of developing HL compared to those born with a normal birth weight. Conversely, non-Hispanic White children born with a high birth weight showed an increased risk of HL compared to those with normal birth weight, with the risk increasing 10% for each 500-gram increase in birthweight. Within Hispanics, risk of HL increased 9% for each 500-gram increase in birthweight, but there were no significant associations for those born with either low or high birth weight. These findings suggest that when birthweight is measured as a continuous variable it may serve as a useful predictor of risk, but stratifying by categories or low, normal, and high birth weight may lead to varying results.

Previous studies report inconsistent findings on parental age and risk of HL (14,15,22,23,39). In this study, we observed a trend of increased risk of early-onset HL by every 5-year increase in maternal age for both non-Hispanic White and Hispanics, and an 20% increased risk among non-Hispanic Whites with fathers at ages ≥ 35 years. Similarly, our previous study reported a protective impact of younger mother (<20, 20-24 years) and father (20-24 years) independently on the risk of pediatric HL (14). A Swedish study reported that with every 5-year maternal or paternal age increment, risk of any lymphoid neoplasm increased by 3%, but no association was seen between maternal or paternal age and HL when individual subclasses of lymphoid neoplasms were evaluated (39). Our

findings are consistent with regards to 5-year increment in maternal age, but they are more specific and focused on HL. Another Swedish study did not report any association between maternal age and risk of HL among people with cases diagnosed between 0-37 years of age (15). In addition, two childhood HL studies in the US observed no impact of maternal age on the risk of early childhood HL (23) or childhood and adolescent HL (22).

Our study has several limitations. First, the California Linkage Study of Early-Onset Cancers includes only cases born in California beginning in 1978 (when California birth records first became computerized) and diagnosed in California beginning in 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, Hispanics have a younger mean age at diagnosis of HL than non-Hispanic Whites (38.0 versus 40.0 years) (16). The oldest age of diagnosis was 37 years in our study. It is likely that a slightly higher percentage of Hispanic cases were included in our study than non-Hispanic White cases, creating an imbalance in our analysis. Thirdly, 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 cancer incidence in 2000-2015 from 22 registries in the Surveillance, Epidemiology, and End Results Program (40), we estimate that 603 out of 140,950 controls would have developed cancer by the age of their matched cases if they had all moved out of California the day after birth. Therefore, the impact of this misclassification would be small. In addition, there is no reason to believe that the likelihood of misclassifying actual cases as controls would be different based on a child's birth characteristics, and nondifferential misclassification would have biased the risk estimates toward the null. We did not have data on when foreign-born mothers moved to the US. There may have been a different impact on whether the mother moved when she was a child versus as an adult. 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 (6–8,41–43).

The study also has multiple strengths. The size and racial/ethnic diversity of the California population resulted in a large number of non-Hispanic White and Hispanic cases which 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 California Linkage Study of Early-Onset Cancers is record linkage-based which obviates the need for participant contact and therefore we were able to obtain preexisting, non-identifying data from all eligible subjects. As a result, this study was less prone to selection bias due to non-participation and differential recall between cases and controls.

In summary, this large population-based case-control study identified multiple risk factors for HL in children, adolescents, and young adults from California. Among Hispanics,

adolescents and young adults with foreign-born mothers were at a decreased risk of HL compared to individuals with US-born mothers, Among non-Hispanic Whites, children and young adults of foreign-born mothers had an increased 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.

Acknowledgments:

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

Rozalyn L. Rodwin was a trainee of the Yale Cancer Prevention and Control Training Program, which was funded by the National Cancer Institute (T32 CA250803).

Funding

Part of this work was funded by the National Cancer Institute (T32 CA250803).

REFERENCES

1. Mathas S, Hartmann S, Kuppers R. Hodgkin lymphoma: Pathology and biology. Semin Hematol 2016;53(3):139–47 doi 10.1053/j.seminhematol.2016.05.007. [PubMed: 27496304]
2. Zhou L, Deng Y, Li N, Zheng Y, Tian T, Zhai Z, et al. Global, regional, and national burden of Hodgkin lymphoma from 1990 to 2017: estimates from the 2017 Global Burden of Disease study. J Hematol Oncol 2019;12(1):107 doi 10.1186/s13045-019-0799-1. [PubMed: 31640759]
3. Punnett A, Tsang RW, Hodgson DC. Hodgkin lymphoma across the age spectrum: epidemiology, therapy, and late effects. Semin Radiat Oncol 2010;20(1):30–44 doi 10.1016/j.semradonc.2009.09.006. [PubMed: 19959029]
4. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020. Bethesda, MD: National Cancer Institute. .
5. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Hodgkin Lymphoma. https://seer.cancer.gov/statfacts/html/hodg.html. Accessed 10/27/2019.
6. Armstrong AA, Alexander FE, Paes RP, Morad NA, Gallagher A, Krajewski AS, et al. Association of Epstein-Barr virus with pediatric Hodgkin's disease. Am J Pathol 1993;142(6):1683–8. [PubMed: 8389527]
7. Nakatsuka S, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. Int J Hematol 2006;83(5):391–7 doi 10.1532/IJH97.05184. [PubMed: 16787868]
8. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. J Intern Med 2008;264(6):537–48 doi 10.1111/j.1365-2796.2008.02031.x. [PubMed: 19017178]
9. Gutensohn N, Cole P. Epidemiology of hodgkin's disease in the young. Int J Cancer 1977;19(5):595–604 doi 10.1002/ijc.2910190502. [PubMed: 863541]
10. Gutensohn N, Cole P. Childhood social environment and Hodgkin's disease. N Engl J Med 1981;304(3):135–40 doi 10.1056/NEJM198101153040302. [PubMed: 6255329]

11. Chang ET, Montgomery SM, Richiardi L, Ehlin A, Ekbom A, Lambe M. Number of siblings and risk of Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 2004;13(7):1236–43. [PubMed: 15247136]
12. Altieri A, Castro F, Bermejo JL, Hemminki K. Number of siblings and the risk of lymphoma, leukemia, and myeloma by histopathology. Cancer Epidemiol Biomarkers Prev 2006;15(7):1281–6 doi 10.1158/1055-9965.EPI-06-0087. [PubMed: 16835324]
13. Mack TM, Norman JE Jr., Rappaport E, Cozen W. Childhood determination of Hodgkin lymphoma among U.S. servicemen. Cancer Epidemiol Biomarkers Prev 2015;24(11):1707–15 doi 10.1158/1055-9965.EPI-15-0145. [PubMed: 26324069]
14. Triebwasser C, Wang R, DeWan AT, Metayer C, Morimoto L, Wiemels JL, et al. Birth weight and risk of paediatric Hodgkin lymphoma: Findings from a population-based record linkage study in California. Eur J Cancer 2016;69:19–27 doi 10.1016/j.ejca.2016.09.016. [PubMed: 27814470]
15. Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and family risk factors for Hodgkin lymphoma in childhood through young adulthood. Am J Epidemiol 2012;176(12):1147–58 doi 10.1093/aje/kws212. [PubMed: 23171883]
16. Evens AM, Antillon M, Aschebrook-Kilfoy B, Chiu BC. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. Ann Oncol 2012;23(8):2128–37 doi 10.1093/annonc/mdr578. [PubMed: 22241896]
17. Glaser SL, Clarke CA, Chang ET, Yang J, Gomez SL, Keegan TH. Hodgkin lymphoma incidence in California Hispanics: influence of nativity and tumor Epstein-Barr virus. Cancer Causes Control 2014;25(6):709–25 doi 10.1007/s10552-014-0374-6. [PubMed: 24722952]
18. Glaser SL, Chang ET, Clarke CA, Keegan TH, Yang J, Gomez SL. Hodgkin lymphoma incidence in ethnic enclaves in California. Leuk Lymphoma 2015;56(12):3270–80 doi 10.3109/10428194.2015.1026815. [PubMed: 25899402]
19. United States Census Bureau. The Hispanic Population in the United States: 2019. https://www.census.gov/data/tables/2019/demo/hispanic-origin/2019-cps.html. Assessed 10/20/2020.
20. Trevelyan E, Gambino C, Gryn T, Larsen L, Acosta Y, Grieco E, et al. Characteristics of the U.S. Population by Generational Status: 2013. Washington, DC: U.S. Census Bureau; 2016. Report nr P23-214
21. Grieco EM, Acosta YD, Cruz GPdl, Gambino C, Gryn T, Larsen LJ, et al. The Foreign-Born Population in the United States: 2010. Washington, DC: US Census Bureau; 2012. Report nr ACS-19.
22. Peckham-Gregory EC, Danysh HE, Brown AL, Eckstein O, Grimes A, Chakraborty R, et al. Evaluation of maternal and perinatal characteristics on childhood lymphoma risk: A population-based case-control study. Pediatr Blood Cancer 2017;64(5) doi 10.1002/pbc.26321.
23. Marcotte EL, Ritz B, Cockburn M, Clarke CA, Heck JE. Birth characteristics and risk of lymphoma in young children. Cancer Epidemiol 2014;38(1):48–55 doi 10.1016/j.canep.2013.11.005. [PubMed: 24345816]
24. Heck JE, Park AS, Contreras ZA, Davidson TB, Hoggatt KJ, Cockburn M, et al. Risk of Childhood Cancer by Maternal Birthplace: A Test of the Hispanic Paradox. JAMA Pediatr 2016;170(6):585–92 doi 10.1001/jamapediatrics.2016.0097. [PubMed: 27110958]
25. Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, et al. Childhood social environment and Hodgkin's lymphoma: new findings from a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2004;13(8):1361–70. [PubMed: 15298959]
26. Engel T, Alexander GR, Leland NL. Pregnancy outcomes of U.S.-born Puerto Ricans: the role of maternal nativity status. Am J Prev Med 1995;11(1):34–9 doi 10.1016/s0749-3797(18)30498-7.
27. Wingate MS, Alexander GR. The healthy migrant theory: variations in pregnancy outcomes among US-born migrants. Soc Sci Med 2006;62(2):491–8 doi 10.1016/j.socscimed.2005.06.015. [PubMed: 16039025]
28. DeSisto CL, McDonald JA. Variation in Birth Outcomes by Mother's Country of Birth Among Hispanic Women in the United States, 2013. Public Health Rep 2018;133(3):318–28 doi 10.1177/0033354918765444. [PubMed: 29653068]

29. Guendelman S, Abrams B. Dietary intake among Mexican-American women: generational differences and a comparison with white non-Hispanic women. Am J Public Health 1995;85(1):20–5 doi 10.2105/ajph.85.1.20. [PubMed: 7832256]
30. Akresh IR. Dietary assimilation and health among hispanic immigrants to the United States. J Health Soc Behav 2007;48(4):404–17 doi 10.1177/002214650704800405. [PubMed: 18198687]
31. Detjen M, Nieto F, Trentham-Dietz A, Fleming M, Chasan-Taber L. Acculturation and Cigarette Smoking Among Pregnant Hispanic Women Residing in the United States. American Journal of Public Health 2007;97(11):2040–7 doi 10.2105/AJPH.2006.095505. [PubMed: 17901446]
32. John E, Savitz D, Sandler D. Prenatal Exposure to Parents' Smoking and Childhood Cancer. American Journal of Epidemiology 1991;133(2):123–32 doi doi: 10.1093/oxfordjournals.aje.a115851. [PubMed: 1822074]
33. Clarke MA, Joshu CE. Early Life Exposures and Adult Cancer Risk. Epidemiol Rev 2017;39(1):11–27 doi 10.1093/epirev/mxx004. [PubMed: 28407101]
34. O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. Int J Epidemiol 2015;44(1):153–68 doi 10.1093/ije/dyu265. [PubMed: 25626438]
35. Papadopoulou C, Antonopoulos CN, Sergentanis TN, Panagopoulou P, Belechri M, Petridou ET. Is birth weight associated with childhood lymphoma? A meta-analysis. Int J Cancer 2012;130(1):179–89 doi 10.1002/ijc.26001. [PubMed: 21351088]
36. Smith A, Lightfoot T, Simpson J, Roman E, investigators U. Birth weight, sex and childhood cancer: A report from the United Kingdom Childhood Cancer Study. Cancer Epidemiol 2009;33(5):363–7 doi 10.1016/j.canep.2009.10.012. [PubMed: 19932649]
37. Petridou ET, Dikalioti SK, Skalkidou A, Andrie E, Dessypris N, Trichopoulos D, et al. Sun exposure, birth weight, and childhood lymphomas: a case control study in Greece. Cancer Causes Control 2007;18(9):1031–7 doi 10.1007/s10552-007-9044-2. [PubMed: 17653828]
38. Milne E, Laurvick CL, Blair E, de Klerk N, Charles AK, Bower C. Fetal growth and the risk of childhood CNS tumors and lymphomas in Western Australia. Int J Cancer 2008;123(2):436–43 doi 10.1002/ijc.23486. [PubMed: 18412242]
39. Larfors G, Glimelius I, Eloranta S, Smedby KE. Parental Age and Risk of Lymphoid Neoplasms. Am J Epidemiol 2017;186(10):1159–67 doi 10.1093/aje/kwx185. [PubMed: 29149251]
40. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Limited-Field Data, 22 Registries, Nov 2021 Sub (2000-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission. Accessed 5/13/2022.
41. Fugl A, Andersen CL. Epstein-Barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract 2019;20(1):62 doi 10.1186/s12875-019-0954-3. [PubMed: 31088382]
42. Bakkalci D, Jia Y, Winter JR, Lewis JE, Taylor GS, Stagg HR. Risk factors for Epstein Barr virus-associated cancers: a systematic review, critical appraisal, and mapping of the epidemiological evidence. J Glob Health 2020;10(1):010405 doi 10.7189/jogh.10.010405. [PubMed: 32257153]
43. Rostgaard K, Balfour HH Jr., Jarrett R, Erikstrup C, Pedersen O, Ullum H, et al. Primary Epstein-Barr virus infection with and without infectious mononucleosis. PLoS One 2019;14(12):e0226436 doi 10.1371/journal.pone.0226436. [PubMed: 31846480]

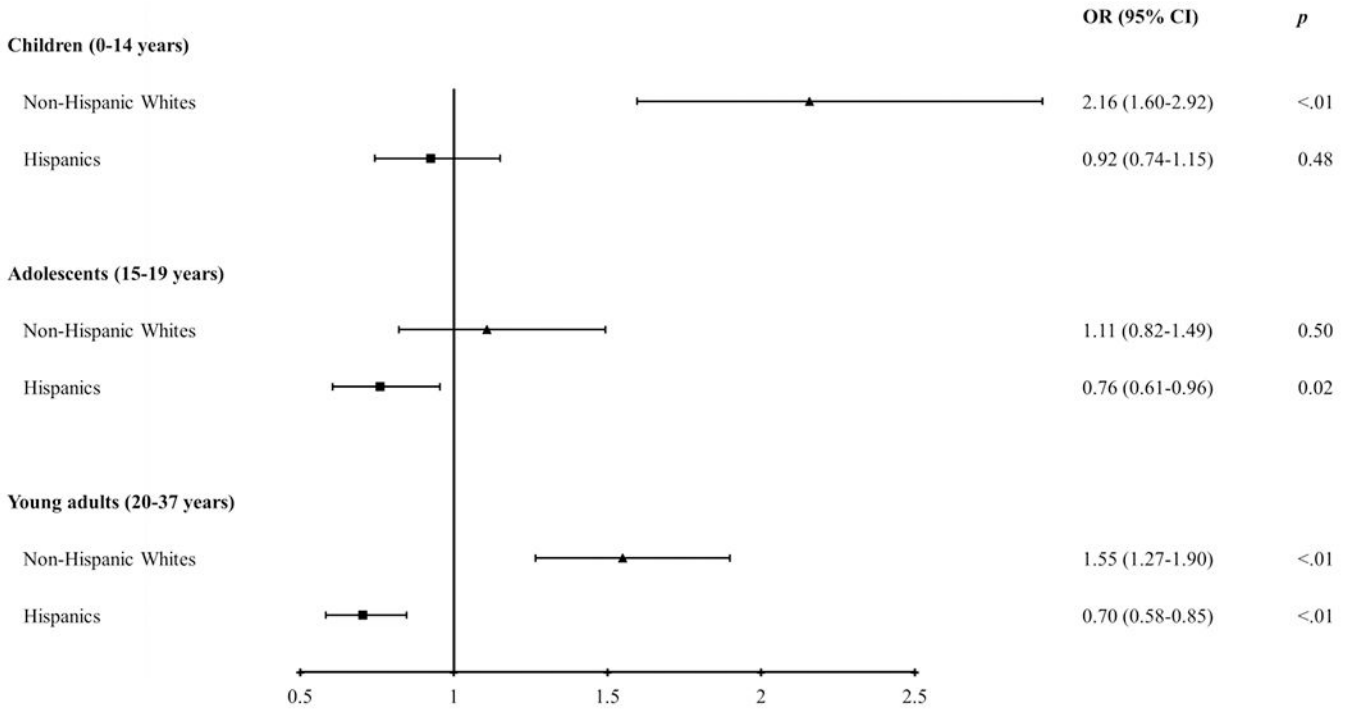

Figure 1.

Association between foreign-born mother and risk of Hodgkin lymphoma by age and ethnicity, California Linkage Study of Early-Onset Cancers, 1988-2015

Table 1.

Characteristics of the Study Population, California Linkage Study of Early-Onset Cancers, 1988-2015.

	Non-Hispanic White Case		Non-Hispanic White Control			Hispanic Case		Hispanic Control		
Characteristic	**No.**	**%[a]**	**No.**	**%[a]**	***P***	**No.**	**%[a]**	**No.**	**%[a]**	***P***
Total	1,651		82,550			1,168		58,400		
Maternal birthplace										
United States	1,433	86.8	75,401	91.3	<0.01	530	45.4	23,281	39.9	<0.01
Foreign	218	13.2	7,149	8.7		638	54.6	35,119	60.1	
Sex										
Female	773	46.8	40,175	48.7	0.14	503	43.1	28,602	49.0	<0.01
Male	878	53.2	42,375	51.3		665	56.9	29,798	51.0	
Age at diagnosis (years)										
0-14	291	17.6				364	31.2			
15-19	479	29.0				323	27.7			
20-37	881	53.4				481	41.2			
Birth weight										
Low	54	3.3	4,314	5.2	<0.01	69	5.9	3,185	5.5	0.13
Normal	1,304	79.0	66,584	80.7		949	81.3	48,707	83.4	
High	293	17.7	11,652	14.1		150	12.8	6,508	11.1	
Gestational age (weeks)										
Preterm	118	7.1	6,067	7.3	0.28	113	9.7	5,682	9.7	0.19
Full term	1,224	74.1	59,968	72.6		827	70.8	42,094	72.1	
Post-term	176	10.7	9,781	11.8		143	12.2	6,157	10.5	
Unknown	133	8.1	6,734	8.2		85	7.3	4,467	7.6	
Birth order										
1st	710	43.0	36,707	44.5	0.45	419	35.9	21,555	36.9	0.64
2nd	573	34.7	27,585	33.4		353	30.2	16,966	29.1	
≥ 3rd	368	22.3	18,258	22.1		396	33.9	19,879	34.0	
Mode of delivery										
Vaginal	1,249	75.7	64,393	78.0	0.02	910	77.9	46,823	80.2	0.06
Cesarean	402	24.3	18,157	22.0		258	22.1	11,577	19.8	
Birth plurality										
Singleton	1,613	97.7	80,618	97.7	1.00	1,148	98.3	57,285	98.1	0.75
Multiple	38	2.3	1,932	2.3		20	1.7	1,115	1.9	
Maternal age (years)										
<20	79	4.8	6,621	8.0	<0.01	148	12.7	9,370	16.0	<0.01
20-24	360	21.8	21,126	25.6		344	29.5	18,915	32.4	
25-29	559	33.9	26,640	32.3		372	31.8	16,150	27.7	
30-34	437	26.5	19,386	23.5		201	17.2	9,401	16.1	
≥ 35	216	13.1	8,777	10.6		103	8.8	4,564	7.8	
Maternal education										

	Non-Hispanic White Case		Non-Hispanic White Control			Hispanic Case		Hispanic Control		
Characteristic	**No.**	**%[a]**	**No.**	**%[a]**	***P***	**No.**	**%[a]**	**No.**	**%[a]**	***P***
≤12 years	292	17.7	15,039	18.2	0.51	488	41.8	25,108	43.0	0.01
> 12 years	378	22.9	18,468	22.4		124	10.6	5,362	9.2	
Unknown	981	59.4	49,043	59.4		556	47.6	27,930	47.8	
Maternal history of miscarriage/stillbirth										
No	1,342	81.3	66,236	80.2	0.33	965	82.6	49,333	84.5	0.07
Yes	303	18.4	15,966	19.3		203	17.4	8,972	15.4	
Unknown	6	0.4	348	0.4		0	0.0	95	0.2	
Paternal age (years)										
<20	30	1.8	2,068	2.5	<0.01	59	5.1	3,460	5.9	0.32
20-24	199	12.1	13,589	16.5		276	23.6	14,824	25.4	
25-29	474	28.7	23,816	28.9		357	30.6	16,943	29.0	
30-34	450	27.3	22,163	26.8		234	20.0	11,312	19.4	
≥ 35	460	27.9	17,823	21.6		186	15.9	8,767	15.0	
Unknown	38	2.3	3,091	3.7		56	4.8	3,094	5.3	
Percentage of population below 150% poverty at census block group level										
1st quartile (lowest)	388	23.5	18,966	23.0	0.75	175	15.0	7,465	12.8	0.12
2nd quartile	354	21.4	17,170	20.8		189	16.2	9,232	15.8	
3rd quartile	276	16.7	13,849	16.8		234	20.0	12,572	21.5	
4th quartile (highest)	152	9.2	8,149	9.9		357	30.6	18,262	31.3	
Unknown	481	29.1	24,416	29.6		213	18.2	10,869	18.6	

Table 2.

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

Characteristic	Odds Ratio	95% Confidence interval	*P*
Maternal birthplace			
United States	Referent		
Foreign	1.52	1.31 - 1.76	<.01
Sex			
Female	Referent		
Male	1.06	0.96 - 1.16	0.29
Birth weight			
Low	0.63	0.48 - 0.83	<.01
Normal	Referent		
High	1.25	1.10 - 1.43	<.01
Per 500 grams	1.10	1.05 - 1.15	<.01
Birth order			
1st	Referent		
2nd	0.98	0.87 - 1.09	0.67
≥ 3rd	0.89	0.78 - 1.02	0.10
Continuous	0.96	0.92 - 1.01	0.09
Mode of delivery			
Vaginal	Referent		
Cesarean	1.11	0.99 - 1.25	0.07
Maternal age (years)			
<20	0.65	0.48 - 0.86	<.01
20-24	0.88	0.76 - 1.02	0.09
25-29	Referent		
30-34	1.02	0.89 - 1.18	0.74
≥ 35	1.04	0.86 - 1.25	0.71
Ever 5-year	1.11	1.04 - 1.18	<.01
Paternal age (years)			
<20	1.01	0.66 - 1.55	0.95
20-24	0.84	0.70 - 1.01	0.06
25-29	Referent		
30-34	0.97	0.84 - 1.12	0.66
≥ 35	1.20	1.03 - 1.41	0.02
Unknown	0.70	0.50 - 0.99	0.04
Ever 5-year	1.07	1.02 - 1.13	0.01
Percentage of population below 150% poverty at census block group level			
1st quartile (lowest)	Referent		
2nd quartile	1.05	0.91 - 1.22	0.83
3rd quartile	1.06	0.91 - 1.24	0.46

Characteristic	Odds Ratio	95% Confidence interval	*P*
4th quartile (highest)	1.02	0.84 - 1.24	0.49
Unknown	1.08	0.94 - 1.24	0.28

All variables in the table were mutually adjusted.

Table 3.

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

Characteristic	Odds Ratio	95% Confidence interval	p
Maternal birthplace			
United States	Referent		
Foreign	0.78	0.69 - 0.88	<.01
Sex			
Female	Referent		
Male	1.26	1.12 - 1.42	<.01
Birth weight			
Low	1.09	0.85 - 1.40	0.48
Normal	Referent		
High	1.11	0.93 - 1.33	0.24
Per 500 grams	1.09	1.03 - 1.15	<.01
Birth order			
1st	Referent		
2nd	0.98	0.84 - 1.14	0.80
≥ 3rd	0.88	0.75 - 1.04	0.12
Continuous	0.96	0.92 - 1.01	0.10
Mode of delivery			
Vaginal	Referent		
Cesarean	1.07	0.93 - 1.24	0.34
Maternal age (years)			
<20	0.62	0.49 - 0.79	<.01
20-24	0.76	0.64 - 0.89	<.01
25-29	Referent		
30-34	0.97	0.81 - 1.16	0.72
≥ 35	1.05	0.82 - 1.35	0.68
Every 5-year	1.15	1.07 - 1.24	<.01
Paternal age (years)			
<20	0.98	0.71 - 1.36	0.91
20-24	1.00	0.84 - 1.18	0.95
25-29	Referent		
30-34	0.93	0.78 - 1.11	0.41
≥ 35	0.94	0.76 - 1.15	0.54
Unknown	0.94	0.70 - 1.25	0.67
Every 5-year	0.99	0.93 - 1.05	0.74
Percentage of population below 150% poverty at census block group level			
1st quartile (lowest)	Referent		
2nd quartile	0.89	0.72 - 1.09	0.29
3rd quartile	0.84	0.69 - 1.02	0.08

Characteristic	Odds Ratio	95% Confidence interval	p
4th quartile (highest)	0.91	0.75 - 1.09	0.26
Unknown	0.88	0.72 - 1.08	0.23

All variables in the table were mutually adjusted.