

Hodgkin lymphoma incidence in California Hispanics: Influence of nativity and tumor Epstein–Barr virus

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Abstract

Purpose For classical Hodgkin lymphoma (HL), migrant studies could elucidate contributions of environmental factors (including Epstein–Barr virus (EBV)) to the lower rates in non-whites. Given the well-described etiologic complexity of HL, this research requires a large, immigrant population, such as California Hispanics.

Methods With 1988–2004 California Cancer Registry data (2,595 Hispanic, 8,637 white HL cases) and tumor cell EBV status on a subset (218 Hispanics, 656 whites), we calculated ethnicity- and nativity-specific HL incidence rates simultaneously by age, sex, and histologic subtype, and tumor cell EBV prevalence.

Results Compared with white rates, Hispanic HL rates were lower overall (70 %) and for nodular sclerosis HL, particularly among young adults (60–65 % for females). However, they were higher among children (200 %) and older adults, and for mixed cellularity HL. Compared with rates in foreign-born Hispanics, rates in US-born Hispanics were higher among young adults (>threefold in females), lower for children and adults over age 70, and consistently

intermediate compared with rates in whites. EBV tumor prevalence was 67, 32, and 23 % among foreign-born Hispanics, US-born Hispanics, and whites, respectively, although with variation by age, sex, and histology.

Conclusions Findings strongly implicate environmental influences, such as nativity-related sociodemographic differences, on HL occurrence. In addition, lower young adult rates and higher EBV prevalence in US-born Hispanics than in whites raise questions about the duration/extent of environmental change for affecting HL rates and also point to ethnic differences in genetic susceptibility. Lesser variation in mixed cellularity HL rates and greater variation in rates for females across groups suggest less modifiable factors interacting with environmental influences.

Keywords Hodgkin lymphoma · Epstein–Barr virus · Hispanics · Immigration · Nativity · Adolescents and young adults · Cancer epidemiology

Introduction

Hodgkin lymphoma (HL) is an uncommon B-cell malignancy with marked epidemiologic heterogeneity across histologic subtypes and patient age, sex, and race/ethnicity. Studies have long supported socioeconomic influences on disease etiology for children and young adults [1–11]; risk factors include characteristics describing intensity and timing of childhood social exposure, and management of infection [12], notably Epstein–Barr virus (EBV), which is present in monoclonal form in tumor cells of an epidemiologically distinctive proportion of cases [13–16]. Yet, racial/ethnic differences in HL occurrence persist regardless of socioeconomic status (SES) [4, 17], with higher rates [18] and lower tumor EBV prevalence [13, 16] in

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whites. This variation suggests additional environmental [17, 19] and/or genetic influences [20–23].

These contributions to HL etiology could be explored efficiently through migrant studies, but the paucity of large immigrant cohorts for evaluating this rare and complex disease has limited such research [11, 17, 19–21]. US Hispanics represent an ideal study population: This is a large group with a substantial foreign-born subset, and US- and foreign-born Hispanics likely differ in relevant childhood infectious exposures and other immune system influences [22]. However, migrant studies of HL in US Hispanics have been impeded by methodologic challenges, including cultural and genetic heterogeneity [23–28], which can dilute study findings, and missing cancer registry information on birthplace for a sizeable, non-random segment of cases, which may introduce bias into estimated rates [29–34].

To advance understanding of how environment affects HL incidence variation, we examined the effect of nativity on HL rates in US Hispanics in comparison with non-Hispanic whites, addressing the aforementioned challenges using California Cancer Registry (CCR) data, and nativity-specific numerators and denominators [35, 36] associated with the California Neighborhoods Data System [37]. This approach provided access to a Hispanic population that is large, relatively homogeneous culturally and ethnically (approximately 80 % of Mexican origin in 2001 [38]), and for which missing registry birthplace information for cases was imputed by a validated method [36, 39, 40]. In addition, as the association of tumor cell EBV with HL is strong in Hispanics [13, 41, 42] but not well studied by birthplace, we examined variation in its prevalence across a subset of study cases [16].

Materials and methods

Patient data

We identified all California residents newly diagnosed with primary classical HL (International Classification of Diseases for Oncology, 3rd Edition, morphology codes 9663–9665, 9667 (nodular sclerosis (NS)); 9652 (mixed cellularity (MC)); 9651 (lymphocyte rich); 9653–9655 (lymphocyte depletion), or 9650 (not otherwise specified)) during the period 1988 through 2004 and reported to the CCR. We obtained data (routinely abstracted from the medical record) on patient age, sex, race/ethnicity, social security number (SSN), birthplace, and tumor histology at diagnosis for all 2,754 HLs in Hispanics and 8,971 HLs in non-Hispanic whites (hereafter called whites). Hispanic status, based on patient medical records and death certificates, was enhanced using the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification Algorithm [43]. Because HIV-related HL

has unusual epidemiologic profiles and had increased rates in California Hispanics during the study period [44], we excluded 159 Hispanic (5.8 %) and 334 white (3.7 %) HL cases with evidence of HIV or AIDS in registry diagnostic or death certificate data [45]. These exclusions left 2,595 Hispanic and 8,637 white HL cases for analysis.

Nativity

Of the 2,595 Hispanic cases, the CCR listed 1,054 (41 %) as US-born and 849 (33 %) as having a foreign birthplace (Mexico ($n = 571$), Central America ($n = 119$), South America ($n = 51$), Cuba ($n = 21$), Puerto Rico ($n = 14$), other North America ($n = 6$), Europe ($n = 8$), Asia ($n = 4$), not US ($n = 5$), and unspecified ($n = 50$ with data from the death certificate)). Among the 692 cases (27 %) without a recorded birthplace, we applied a previously validated method using patient SSN (and presumed year of issuance) to impute nativity for 591 cases [36], and, for 101 cases with missing or invalid SSNs, assigned nativity based on its distribution within matched strata of race/ethnicity, sex, and age in the overall CCR Hispanic patient population. Ultimately, we categorized 531 Hispanic HL cases without registry birthplace as US-born, for a total of 1,585 (61 %), and 161 as foreign-born, for a total of 1,010 (39 %).

EBV tumor status

For all incident HL cases diagnosed in 1988–1997 in selected California counties (non-whites only from southern California), we previously linked CCR data to results of tumor cell EBV assays applied to diagnostic specimens [16]. Reflecting regional variation in specimen-releasing practices, specimens were available from 86 % of Greater Bay Area cases and 43 % of southern California cases, and thus for 73 % of whites and 38 % of Hispanics. For these 219 Hispanic cases with EBV results, birthplace had not been recorded for 54 (25 %). For the current study, we determined nativity for 53 of these cases using the methods described above, thus enabling reanalysis in 218 Hispanic cases by nativity compared with 656 whites.

Population data

To compute incidence rates, we obtained California population counts from the 1990 and 2000 Census Summary File 3 by sex, race/ethnicity, nativity, and 5-year age group. To estimate age- and nativity-specific population counts for Hispanics, we used the 5 % Integrated Public Use Microdata Series sample of the Census; for intercensal years, we estimated the percentages of the population that were US- or foreign-born using cohort component methods [36, 46].

Statistical analysis

Incidence rates and rate ratios

For the period 1988–2004, we computed average annual age-adjusted (standardized to the 2000 US standard million population) and age-specific incidence rates per 100,000 population and associated 95 % confidence intervals (CI). To accommodate HL incidence patterns [47], we examined age-specific rates for 5-year age groups (presented only in study figures), for 10-year age groups, and for age ranges 0–14, 15–39, 40–54, and ≥ 55 years (hereafter called “children,” “adolescents/young adults (AYAs),” “middle-aged adults” and “older adults”). We calculated rates for classical HL overall and, based on sample size, for the two most common histology subtypes (NS and MC). For comparisons of pairs of incidence rates, we calculated incidence rate ratios (IRRs), considering as significant any difference for which the IRR 95 % CI did not include 1.

EBV prevalence by race/ethnicity and nativity

We examined the associations of age group, sex, and histologic subtype (NS, MC, and other) with EBV-positive and EBV-negative HL in foreign-born Hispanics, US-born Hispanics, and whites using descriptive statistics. As EBV prevalence in HL varies markedly by these variables [13], we undertook multivariate analyses to determine whether they were independently associated with EBV-positive HL by calculating prevalence ratios (PRs) and 95 % CIs, controlling for additional cofactors (census block group SES, Ann Arbor stage, and California residential region), as used previously [16].

Analyses were conducted using SEER*Stat software for incidence rates [48] and SAS version 9.3 for EBV prevalence [49]. This study had approval from the institutional review boards of the Cancer Prevention Institute of California and institutions collaborating on the previous study of HL and EBV [16].

Results

Incidence rates

Hispanics

Among California Hispanics, the 1988–2004 age-adjusted HL incidence rate per 100,000 was 2.02 overall (Table 1). Figure 1a and b showed bimodal curves comprising modest modes in AYA males and females but considerably higher rate peaks in adults, particularly males, over age 70–74.

Hispanics versus whites

Compared with whites, Hispanics had overall HL rates that were approximately 30 % lower and showed a larger male excess (male–female (M–F) IRRs with 95 % CI: Hispanics, 1.39 (1.27–1.53); whites, 1.18 (1.13–1.23)), reflecting relatively lower female than male rates (Table 1). For NS, rates in Hispanics were half those in whites; for MC, they were slightly higher than in whites. Age-specific data (Fig. 1a–f) show that AYA incidence peaks were markedly lower in Hispanics than in whites for HL overall; for NS, peak rates (at ages 20–29) were higher in females than in males for both Hispanics (M–F IRR: 0.70 (0.58–0.84)) and whites (M–F IRR: 0.84 (0.76–0.93)). For children and older adults, HL rates were higher for Hispanics than for whites, notably in males. For NS, similar patterns occurred, with higher rates in Hispanic than in white males, but not in females, under age 10 (M–F IRRs: Hispanics, 2.77 (1.64–4.87); whites, 1.21 (0.57–2.62)) and at ages 80 and over. For MC, Hispanics had higher rates than whites in children and older adults of both genders.

Hispanics by nativity

HL incidence rates were higher in US- than in foreign-born Hispanics, 55 % for females and 22 % for males (Table 2). AYA rates were substantially higher in the US-born than in the foreign-born (Fig. 2a, b), approximately two times among males and more than three times among females. For NS (Fig. 2c, d), rates across age groups 10–19 through 50–59 were up to 2.7 times higher in the US- than in the foreign-born for males and three to nearly five times higher for females, due to a female rate excess among the US-born. For MC (Fig. 2e, f), AYA rates were substantially higher in US- than in foreign-born Hispanics (fourfold for females at ages 20–29), although higher in males than in females in both the US-born (M–F IRR: 1.84 (1.21–2.87)) and foreign-born (M–F IRR: 2.94 (1.65–5.56)). Among children ages 5–9, rates per 100,000 were lower in US- than in foreign-born Hispanics overall and for MC (0.14 and 0.58, respectively), while for NS, they were higher for US- than for foreign-born boys (0.52 and 0.26) and similar for girls (0.15 and 0.19).

Whites, US-born and Foreign-born Hispanics

Overall HL rates were lower among both US-born and foreign-born Hispanics than whites (Table 3), although less so for the US-born, notably females, for whom rates in US- and foreign-born Hispanics were approximately 80 and 50 % those of whites. In contrast, for children, HL rates were twofold higher among US-born Hispanics and fourfold higher among foreign-born Hispanics than whites;

Table 1 Incidence rates of classical Hodgkin lymphoma (HL) overall and by selected histologic subtype, for Hispanics and whites, and race/ethnicity incidence rate ratios (IRR) and 95 % confidence intervals (CI), by gender and age, 1988–2004, California

	All HL						Nodular sclerosis HL						Mixed cellularity HL												
	Hispanics			Hispanic vs. White			Hispanics			Whites			Hispanics vs. White			Hispanics			Whites			Hispanic vs. White			
	N	Rate*	95% CI	IRR	95% CI	N	Rate*	95% CI	N	Rate*	95% CI	N	Rate*	95% CI	IRR	95% CI	N	Rate*	95% CI	N	Rate*	95% CI	IRR	95% CI	
TOTAL																									
Age (10-year groups)																									
00-09	134	0.38	0.32-0.45	2.24	1.64-3.05	77	0.22	0.17-0.27	32	0.10	0.07-0.14	2.20	1.46-3.32	44	0.13	0.09-0.17	13	0.04	0.02-0.07	3.25	1.75-6.03				
10-19	465	1.54	1.40-1.69	0.63	0.56-0.71	360	1.19	1.07-1.32	632	1.97	1.82-2.13	0.60	0.53-0.69	54	0.18	0.13-0.23	67	0.21	0.16-0.27	0.86	0.60-1.23				
20-29	648	1.98	1.83-2.14	2.071	1.83-2.36	474	1.45	1.32-1.59	1,650	4.51	4.29-4.73	0.32	0.29-0.36	93	0.29	0.22-0.35	192	0.52	0.45-0.60	0.56	0.44-0.71				
30-39	415	1.44	1.31-1.59	1,842	3.89	3.72-4.07	0.37	0.33-0.41	278	0.96	0.85-1.08	1,429	3.01	2.86-3.17	0.32	0.28-0.36	79	0.28	0.22-0.35	203	0.43	0.38-0.50	0.65	0.50-0.84	
40-49	254	1.45	1.28-1.64	1,133	2.56	2.42-2.72	0.57	0.49-0.65	127	0.72	0.60-0.86	769	1.74	1.62-1.87	0.41	0.34-0.50	69	0.40	0.31-0.51	176	0.40	0.34-0.46	1.00	0.76-1.32	
50-59	222	2.33	2.03-2.66	759	2.34	2.18-2.52	1.00	0.86-1.16	86	0.90	0.72-1.11	415	1.28	1.16-1.41	0.70	0.56-0.89	72	0.75	0.59-0.95	188	0.58	0.50-0.67	1.29	0.99-1.70	
60-69	207	3.65	3.17-4.18	792	3.23	3.01-3.46	1.13	0.97-1.32	62	1.09	0.84-1.40	334	1.36	1.22-1.52	0.80	0.61-1.05	85	1.50	1.20-1.86	226	0.92	0.80-1.05	1.63	1.27-2.09	
70-79	171	5.46	4.67-6.35	774	3.94	3.66-4.22	1.39	1.17-1.64	54	1.74	1.30-2.27	270	1.37	1.21-1.55	1.27	0.95-1.70	56	1.75	1.32-2.28	246	1.25	1.10-1.42	1.40	1.05-1.87	
80+	79	5.76	4.56-7.19	432	3.84	3.48-4.22	1.50	1.18-1.91	30	2.20	1.48-3.14	156	1.39	1.18-1.62	1.58	1.07-2.34	29	2.10	1.40-3.01	120	1.06	0.88-1.27	1.98	1.32-2.97	
Age groups																									
00-14	298	0.61	0.54-0.69	268	0.54	0.48-0.61	1.13	0.96-1.33	195	0.40	0.35-0.46	202	0.41	0.36-0.47	0.98	0.80-1.19	75	0.15	0.12-0.19	34	0.07	0.05-0.10	2.14	1.43-3.21	
15-39	1,364	1.76	1.67-1.86	4,479	4.48	4.35-4.62	0.39	0.37-0.42	994	1.28	1.20-1.36	3,541	3.55	3.43-3.67	0.36	0.34-0.39	195	0.26	0.22-0.29	441	0.44	0.40-0.48	0.59	0.50-0.70	
40-54	360	1.59	1.43-1.76	1,531	2.47	2.35-2.60	0.64	0.57-0.72	170	0.74	0.63-0.86	990	1.60	1.50-1.70	0.46	0.39-0.54	105	0.48	0.39-0.58	272	0.44	0.39-0.49	1.09	0.87-1.37	
55+	573	4.30	3.94-4.68	2,359	3.35	3.21-3.49	1.28	1.17-1.41	189	1.43	1.23-1.66	954	1.36	1.28-1.45	1.05	0.90-1.23	206	1.52	1.32-1.76	684	0.97	0.90-1.04	1.57	1.34-1.83	
TOTAL	2,595	2.02	1.93-2.11	8,637	2.96	2.90-3.02	0.68	0.65-0.71	1,548	1.01	0.95-1.07	5,687	1.99	1.93-2.04	0.51	0.48-0.54	581	0.55	0.50-0.61	1,431	0.47	0.45-0.50	1.17	1.06-1.29	
MALES																									
Age (10-year groups)																									
00-09	100	0.56	0.45-0.68	38	0.22	0.16-0.30	2.55	1.75-3.70	57	0.32	0.24-0.41	18	0.10	0.06-0.17	3.20	1.88-5.44	36	0.20	0.14-0.28	10	0.06	0.03-0.11	3.33	1.65-6.72	
10-19	243	1.54	1.35-1.75	376	2.27	2.05-2.52	0.68	0.58-0.80	175	1.11	0.95-1.29	282	1.71	1.51-1.92	0.65	0.54-0.78	37	0.23	0.17-0.32	46	0.28	0.20-0.37	0.82	0.53-1.27	
20-29	343	1.92	1.72-2.13	1,045	5.52	5.19-5.87	0.35	0.31-0.39	217	1.22	1.06-1.39	779	4.13	3.85-4.43	0.30	0.25-0.43	75	0.42	0.33-0.53	129	0.68	0.57-0.81	0.62	0.46-0.82	
30-39	219	1.45	1.26-1.65	982	4.07	3.82-4.33	0.36	0.31-0.41	131	0.86	0.72-1.03	696	2.88	2.67-3.10	0.30	0.25-0.36	51	0.33	0.25-0.44	149	0.62	0.53-0.73	0.53	0.39-0.73	
40-49	151	1.72	1.45-2.02	663	2.97	2.75-3.20	0.58	0.49-0.69	69	0.78	0.61-0.99	398	1.78	1.61-1.97	0.44	0.34-0.57	48	0.56	0.41-0.75	128	0.57	0.48-0.68	0.98	0.71-1.37	
50-59	130	2.84	2.37-3.37	477	2.97	2.71-3.25	0.96	0.79-1.16	43	0.94	0.68-1.26	236	1.47	1.29-1.67	0.64	0.46-0.89	38	0.83	0.59-1.14	128	0.80	0.67-0.95	1.04	0.72-1.49	
60-69	123	4.75	3.94-5.67	464	4.01	3.66-4.39	1.18	0.97-1.45	39	1.50	1.06-2.05	192	1.66	1.43-1.91	0.90	0.64-1.27	44	1.72	1.25-2.30	138	1.19	1.00-1.41	1.45	1.03-2.03	
70-79	96	7.33	5.93-8.97	387	4.54	4.10-5.02	1.61	1.29-2.02	27	2.06	1.35-3.01	134	1.58	1.32-1.87	1.30	0.86-1.97	34	2.55	1.76-3.57	120	1.41	1.17-1.68	1.81	1.24-2.65	
80+	40	8.01	5.71-10.93	198	5.13	4.43-5.90	1.56	1.11-2.19	15	3.07	1.71-5.07	65	1.68	1.29-2.15	1.83	1.04-3.20	17	3.30	1.91-5.30	61	1.57	1.19-2.02	2.10	1.23-3.60	
Age groups																									
00-14	195	0.78	0.67-0.89	150	0.59	0.50-0.69	1.32	1.07-1.64	120	0.48	0.40-0.57	96	0.38	0.31-0.46	1.26	0.97-1.65	57	0.22	0.17-0.29	28	0.11	0.07-0.16	2.00	1.27-3.14	
15-39	710	1.71	1.58-1.84	2,291	4.44	4.26-4.63	0.39	0.35-0.42	460	1.11	1.01-1.22	1,679	3.27	3.11-3.43	0.34	0.31-0.38	142	0.34	0.28-0.40	306	0.59	0.52-0.66	0.58	0.47-0.70	
40-54	213	1.89	1.64-2.16	913	2.93	2.74-3.12	0.65	0.56-0.75	89	0.77	0.62-0.95	518	1.66	1.52-1.81	0.46	0.37-0.58	67	0.60	0.47-0.77	197	0.63	0.55-0.73	0.95	0.72-1.26	
55+	327	5.69	5.05-6.39	1,276	4.14	3.91-4.37	1.37	1.22-1.55	104	1.83	1.47-2.25	507	1.63	1.49-1.78	1.12	0.91-1.39	114	2.02	1.65-2.46	378	1.23	1.10-1.36	1.64	1.33-2.02	
TOTAL	1,445	2.40	2.24-2.56	4,630	3.22	3.13-3.32	0.75	0.70-0.79	773	1.05	0.96-1.16	2,800	1.95	1.88-2.02	0.54	0.50-0.58	380	0.73	0.64-0.83	909	0.63	0.59-0.67	1.16	1.03-1.31	

Table 1 continued

	All HL						Nodular sclerosis HL						Mixed cellularity HL											
	Hispanics		Whites		Hispanic vs. White		Hispanics		Whites		Hispanic vs. White		Hispanics		Whites		Hispanic vs. White							
	N	Rate* 95% CI	N	Rate* 95% CI	IRR	95% CI	N	Rate* 95% CI	N	Rate* 95% CI	IRR	95% CI	N	Rate* 95% CI	N	Rate* 95% CI	IRR	95% CI						
FEMALES																								
Age (10-year groups)																								
00-09	34	0.20	0.14-0.28	18	0.11	0.07-0.18	1.82	1.03-3.22	20	0.12	0.07-0.18	14	0.09	0.05-0.14	1.33	0.67-2.64	8	0.05	0.02-0.09	<5	0.02	0.00-0.05	2.50	0.66-9.42
10-19	222	1.54	1.35-1.76	402	2.60	2.35-2.86	0.59	0.50-0.70	185	1.29	1.11-1.49	350	2.26	2.03-2.51	0.57	0.48-0.68	17	0.12	0.07-0.19	21	0.14	0.08-0.21	0.86	0.45-1.62
20-29	305	2.06	1.83-2.30	1,026	5.78	5.43-6.15	0.36	0.31-0.40	257	1.74	1.53-1.96	871	4.91	4.59-5.25	0.35	0.31-0.41	18	0.12	0.07-0.19	63	0.36	0.27-0.46	0.33	0.20-0.56
30-39	196	1.44	1.24-1.66	860	3.71	3.46-3.96	0.39	0.33-0.45	147	1.07	0.90-1.26	733	3.16	2.93-3.39	0.34	0.28-0.40	28	0.22	0.14-0.31	54	0.23	0.18-0.31	0.96	0.61-1.51
40-49	103	1.18	0.96-1.44	470	2.15	1.96-2.35	0.55	0.44-0.68	58	0.66	0.50-0.85	371	1.70	1.53-1.88	0.39	0.29-0.51	21	0.25	0.15-0.38	48	0.22	0.16-0.29	1.14	0.68-1.90
50-59	92	1.86	1.50-2.28	282	1.73	1.53-1.94	1.08	0.85-1.36	43	0.87	0.63-1.17	179	1.10	0.95-1.28	0.79	0.57-1.10	34	0.69	0.48-0.96	60	0.37	0.28-0.47	1.86	1.22-2.88
60-69	84	2.73	2.18-3.38	328	2.52	2.25-2.81	1.08	0.85-1.38	23	0.75	0.47-1.12	142	1.10	0.93-1.30	0.68	0.44-1.06	41	1.33	0.95-1.80	88	0.67	0.54-0.83	1.99	1.37-2.88
70-79	75	4.12	3.24-5.17	387	3.46	3.13-3.83	1.19	0.93-1.52	27	1.50	0.99-2.19	136	1.22	1.02-1.44	1.23	0.81-1.86	22	1.18	0.74-1.79	126	1.13	0.94-1.34	1.04	0.66-1.64
80+	39	4.48	3.19-6.13	234	3.20	2.80-3.64	1.40	1.00-1.96	15	1.72	0.96-2.84	91	1.24	1.00-1.52	1.39	0.80-2.40	12	1.38	0.71-2.41	59	0.81	0.62-1.04	1.70	0.92-3.17
Age groups																								
00-14	103	0.44	0.36-0.53	118	0.49	0.41-0.59	0.90	0.69-1.17	75	0.32	0.25-0.40	106	0.44	0.36-0.54	0.73	0.54-0.98	18	0.08	0.05-0.12	6	0.02	0.01-0.05	4.00	1.59-10.08
15-39	654	1.82	1.68-1.97	2,188	4.53	4.34-4.72	0.40	0.37-0.44	534	1.47	1.35-1.61	1,862	3.85	3.68-4.03	0.38	0.35-0.42	53	0.16	0.12-0.21	135	0.28	0.23-0.33	0.57	0.42-0.79
40-54	147	1.29	1.09-1.52	618	2.01	1.85-2.17	0.64	0.54-0.77	81	0.70	0.56-0.88	472	1.53	1.40-1.68	0.46	0.36-0.58	38	0.35	0.25-0.48	75	0.24	0.19-0.31	1.46	0.99-2.15
55+	246	3.28	2.87-3.72	1,083	2.73	2.57-2.90	1.20	1.05-1.38	85	1.15	0.91-1.43	447	1.14	1.04-1.26	1.01	0.80-1.27	92	1.18	0.94-1.45	306	0.77	0.68-0.86	1.53	1.21-1.93
TOTAL	1,150	1.72	1.61-1.84	4,007	2.73	2.65-2.82	0.63	0.59-0.67	775	0.99	0.91-1.07	2,887	2.04	1.96-2.12	0.49	0.45-0.53	201	0.40	0.34-0.46	522	0.32	0.29-0.35	1.25	1.06-1.47

* Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups–Census P25-1130); confidence intervals (Tiwari modification) are 95 % for rates

Bolded IRR and 95 % CI are statistically significant

To comply with California Cancer Registry confidentiality regulations, case counts fewer than 5 are not presented

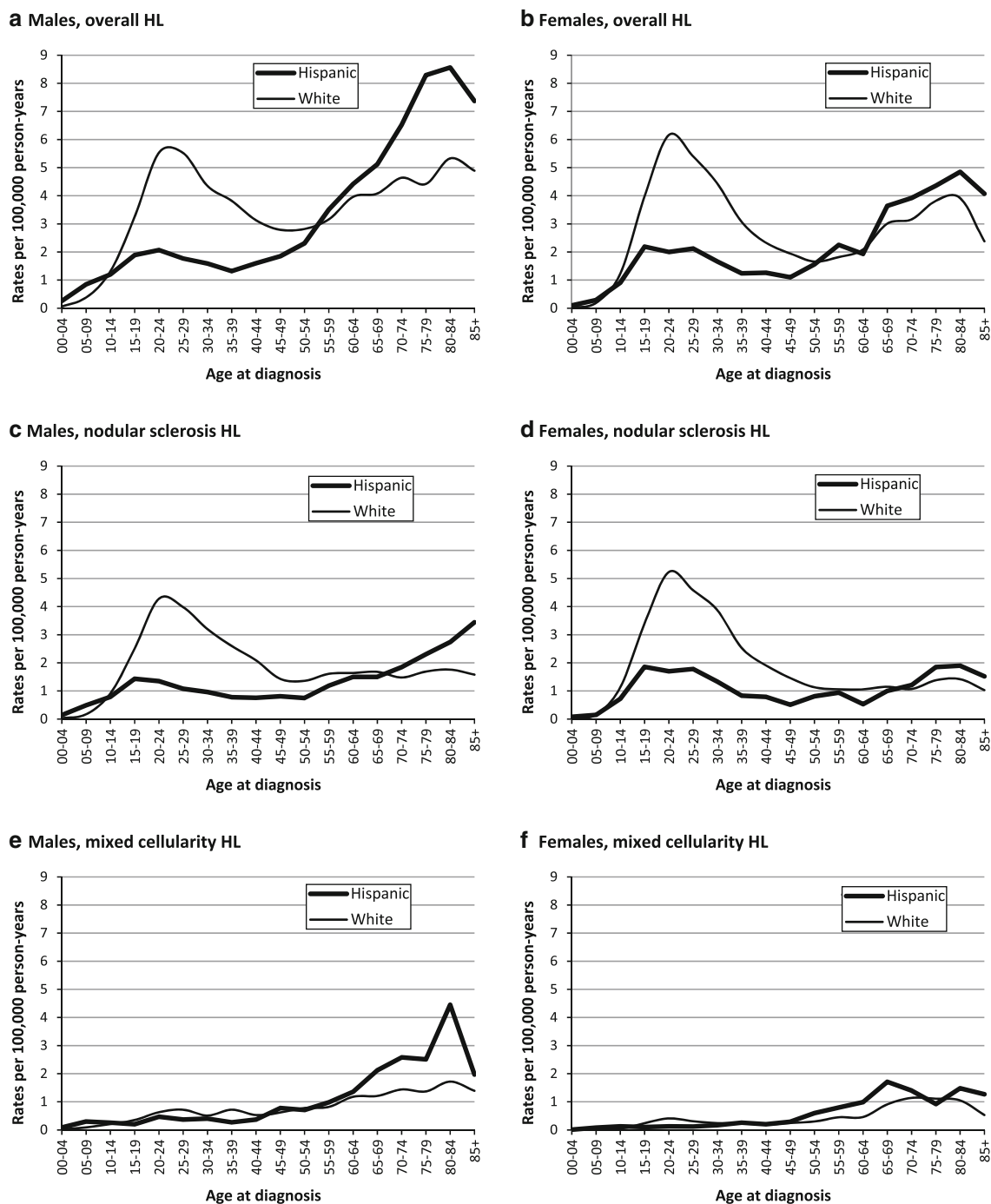


Fig. 1 Age- and sex-specific incidence rates of classical Hodgkin lymphoma (HL) overall and for selected histologic subtypes in Hispanics and whites, 1988–2004, California

similar, but smaller, differences occurred for adults over age 70. For MC, rates were higher in Hispanics, irrespective of nativity, than in whites overall, although these differences were smaller for US-born than for foreign-born Hispanics. Among children, MC rates in Hispanics were eightfold higher in the foreign-born and about 2.5-fold higher in the US-born than in whites.

EBV associations

Tumor cell EBV prevalences were highest in foreign-born Hispanics, followed by US-born Hispanics and whites, in almost every age, sex, and histology subtype group (Table 4). For children and older adults, EBV prevalences were relatively similar for foreign- and US-born Hispanics

Table 2 Incidence rates of classical Hodgkin lymphoma (HL) overall and by selected histologic subtype, for US- and foreign-born Hispanics, and nativity incidence rate ratios (IRR) and 95 % confidence intervals (CI), by gender and age, 1988–2004, California

	All HL						Nodular sclerosis HL						Mixed cellularity HL											
	US-born Hispanics		Foreign-born Hispanics		US-born vs. Foreign-born		US-born Hispanics		Foreign-born Hispanics		US-born vs. Foreign-born		US-born Hispanics		Foreign-born Hispanics		US-born vs. Foreign-born							
	N	Rate*	95% CI	N	Rate*	95% CI	IRR	95% CI	N	Rate*	95% CI	IRR	95% CI	N	Rate*	95% CI	IRR	95% CI						
TOTALS																								
Age (10-year groups)																								
00-09	105	0.34	0.28-0.41	29	0.71	0.48-1.04	0.47	0.31-0.74	67	0.22	0.17-0.28	10	0.27	0.13-0.51	0.81	0.40-1.77	30	0.10	0.06-0.14	14	0.33	0.18-0.57	0.29	0.15-0.59
10-19	356	1.73	1.55-1.92	109	1.26	1.03-1.53	1.37	1.10-1.72	280	1.37	1.21-1.54	80	0.92	0.73-1.15	1.48	1.15-1.94	41	0.19	0.14-0.26	13	0.17	0.09-0.29	1.12	0.59-2.32
20-29	439	3.16	2.87-3.47	209	1.12	0.97-1.28	2.83	2.40-3.36	326	2.35	2.10-2.62	148	0.79	0.67-0.93	2.96	2.43-3.62	56	0.40	0.30-0.51	37	0.19	0.14-0.27	2.04	1.32-3.19
30-39	250	2.57	2.26-2.92	165	0.87	0.74-1.01	2.98	2.41-3.63	177	1.81	1.55-2.10	101	0.53	0.43-0.64	3.43	2.67-4.45	43	0.44	0.32-0.60	36	0.19	0.14-0.27	2.27	1.41-3.66
40-49	140	2.29	1.93-2.70	114	1.00	0.83-1.21	2.28	1.77-2.95	166	1.24	0.97-1.55	51	0.44	0.33-0.58	2.79	1.93-4.06	34	0.57	0.39-0.80	35	0.31	0.22-0.44	1.81	1.10-3.00
50-59	95	2.60	2.10-3.18	127	2.17	1.81-2.58	1.20	0.91-1.58	43	1.18	0.85-1.59	43	0.73	0.53-0.99	1.60	1.03-2.51	25	0.68	0.44-1.01	47	0.80	0.59-1.06	0.85	0.50-1.42
60-69	104	3.98	3.25-4.83	103	3.38	2.76-4.10	1.18	0.89-1.56	26	1.00	0.65-1.46	36	1.17	0.82-1.63	0.85	0.49-1.45	42	1.61	1.16-2.18	43	1.42	1.03-1.92	1.13	0.72-1.78
70-79	72	4.67	3.65-5.90	99	6.17	5.01-7.52	0.76	0.55-1.04	25	1.64	1.06-2.43	29	1.82	1.22-2.62	0.90	0.50-1.60	23	1.42	0.90-2.14	33	2.05	1.41-2.88	0.69	0.39-1.22
80+	24	4.22	2.69-6.32	55	6.65	5.01-8.65	0.64	0.37-1.05	20	1.75	0.83-3.27	20	2.41	1.47-3.73	0.73	0.30-1.65	10	1.75	0.83-3.27	19	2.30	1.41-3.73	0.76	0.31-1.75
Age groups																								
00-14	227	0.56	0.49-0.64	71	0.90	0.70-1.15	0.62	0.47-0.83	155	0.39	0.33-0.45	40	0.49	0.34-0.68	0.80	0.55-1.18	53	0.13	0.10-0.17	22	0.30	0.19-0.46	0.43	0.25-0.74
15-39	923	2.77	2.58-2.96	441	1.04	0.94-1.15	2.66	2.36-3.01	695	2.05	1.90-2.22	299	0.71	0.63-0.80	2.89	2.51-3.35	117	0.37	0.31-0.45	78	0.17	0.14-0.22	2.15	1.58-2.93
40-54	189	2.32	2.00-2.68	171	1.19	1.02-1.38	1.96	1.58-2.42	99	1.21	0.98-1.47	71	0.48	0.38-0.61	2.50	1.82-3.46	47	0.59	0.43-0.79	58	0.42	0.31-0.54	1.42	0.94-2.13
55+	246	3.95	3.46-4.50	327	4.54	4.04-5.08	0.87	0.73-1.04	81	1.35	1.06-1.69	108	1.49	1.21-1.82	0.90	0.66-1.23	87	1.38	1.10-1.72	119	1.63	1.34-1.97	0.85	0.63-1.14
TOTAL	#####	2.45	2.31-2.60	#####	1.79	1.66-1.92	1.37	1.25-1.51	1,030	1.36	1.26-1.47	518	0.78	0.70-0.86	1.75	1.53-1.99	304	0.58	0.51-0.67	277	0.56	0.49-0.65	1.03	0.85-1.25
MALES																								
Age (10-year groups)																								
00-09	81	0.51	0.41-0.64	19	0.91	0.54-1.44	0.57	0.34-0.99	51	0.33	0.24-0.43	6	0.31	0.11-0.69	1.05	0.44-3.03	25	0.16	0.10-0.23	11	0.51	0.25-0.93	0.31	0.14-0.70
10-19	184	1.73	1.48-1.99	59	1.29	0.97-1.68	1.34	0.98-1.85	136	1.28	1.07-1.52	39	0.83	0.58-1.15	1.55	1.06-2.30	26	0.24	0.15-0.35	11	0.27	0.13-0.49	0.87	0.41-1.99
20-29	210	2.90	2.52-3.33	133	1.24	1.04-1.47	2.34	1.87-2.93	135	1.87	1.56-2.21	82	0.77	0.61-0.96	2.41	1.82-3.22	42	0.57	0.41-0.77	33	0.30	0.21-0.43	1.88	1.16-3.07
30-39	115	2.35	1.94-2.83	104	1.02	0.83-1.24	2.31	1.75-3.06	70	1.43	1.11-1.82	61	0.60	0.45-0.77	2.40	1.67-3.46	26	0.51	0.33-0.76	25	0.25	0.16-0.36	2.09	1.15-3.81
40-49	80	2.67	2.12-3.33	71	1.23	0.96-1.55	2.17	1.55-3.03	40	1.33	0.95-1.81	29	0.50	0.34-0.72	2.65	1.60-4.44	24	0.82	0.53-1.22	24	0.43	0.27-0.64	1.92	1.04-3.53
50-59	56	3.17	2.40-4.12	74	2.64	2.07-3.32	1.20	0.83-1.72	23	1.30	0.82-1.95	20	0.71	0.43-1.10	1.83	0.96-3.52	15	0.85	0.48-1.40	23	0.82	0.52-1.23	1.04	0.50-2.07
60-69	64	5.24	4.04-6.70	59	4.32	3.28-5.58	1.21	0.84-1.76	17	1.39	0.81-2.22	22	1.60	1.00-2.44	0.87	0.43-1.71	23	1.89	1.20-2.84	21	1.56	0.96-2.38	1.22	0.64-2.32
70-79	44	6.58	4.76-8.88	52	8.03	5.98-10.55	0.82	0.53-1.26	13	1.96	1.03-3.38	14	2.15	1.17-3.62	0.91	0.39-2.11	16	2.25	1.28-3.69	18	2.80	1.65-4.44	0.80	0.38-1.69
80+	9	4.37	1.96-8.51	31	10.22	6.94-14.51	0.43	0.18-0.94	5	2.65	0.83-6.33	10	3.32	1.59-6.10	0.80	0.21-2.62	<5	1.29	0.27-4.08	14	4.57	2.50-7.67	0.28	0.05-1.09
Age groups																								
00-14	152	0.73	0.62-0.85	43	1.07	0.77-1.47	0.68	0.47-0.99	100	0.48	0.39-0.59	20	0.48	0.29-0.77	1.00	0.60-1.75	39	0.18	0.13-0.25	18	0.47	0.28-0.77	0.38	0.21-0.72
15-39	438	2.55	2.30-2.82	272	1.13	1.00-1.28	2.25	1.91-2.64	292	1.66	1.47-1.88	168	0.71	0.60-0.83	2.34	1.91-2.87	80	0.48	0.38-0.60	62	0.24	0.19-0.32	1.96	1.37-2.82
40-54	109	2.75	2.25-3.32	104	1.44	1.17-1.75	1.91	1.44-2.53	50	1.24	0.92-1.64	39	0.53	0.37-0.72	2.35	1.51-3.69	33	0.85	0.58-1.19	34	0.47	0.33-0.67	1.78	1.07-2.98
55+	144	5.08	4.23-6.05	183	6.09	5.18-7.10	0.83	0.66-1.06	48	1.81	1.29-2.48	56	1.85	1.37-2.45	0.98	0.62-1.52	48	1.64	1.19-2.22	66	2.27	1.73-2.93	0.72	0.48-1.10
TOTAL	843	2.74	2.51-2.99	602	2.24	2.02-2.48	1.22	1.07-1.40	490	1.35	1.19-1.52	283	0.87	0.74-1.01	1.56	1.28-1.90	200	0.74	0.62-0.88	180	0.78	0.64-0.93	0.96	0.74-1.24

Table 2 continued

	All HL						Nodular sclerosis HL						Mixed cellularity HL											
	US-born Hispanics			Foreign-born Hispanics			US-born Hispanics			Foreign-born Hispanics			US-born Hispanics			Foreign-born Hispanics								
	N	Rate*	95% CI	IRR	95% CI	IRR	95% CI	N	Rate*	95% CI	IRR	95% CI	N	Rate*	95% CI	IRR	95% CI							
FEMALES																								
Age (10-year groups)																								
00-09	24	0.16	0.10-0.23	10	0.51	0.24-0.97	0.31	0.14-0.73	16	0.10	0.06-0.17	<5	0.23	0.06-0.60	0.46	0.14-1.94	5	0.03	0.01-0.08	<5	0.14	0.03-0.46	0.23	0.04-1.48
10-19	172	1.73	1.48-2.01	50	1.24	0.91-1.64	1.39	1.01-1.96	144	1.46	1.23-1.72	41	1.03	0.73-1.41	1.41	0.99-2.07	15	0.14	0.08-0.23	<5	0.05	0.01-0.19	2.66	0.61-25.61
20-29	229	3.43	3.00-3.91	76	0.95	0.74-1.19	3.63	2.78-4.78	191	2.86	2.47-3.30	66	0.82	0.63-1.05	3.49	2.62-4.70	14	0.21	0.11-0.35	<5	0.05	0.01-0.12	4.41	1.36-18.67
30-39	135	2.79	2.34-3.31	61	0.70	0.53-0.90	4.02	2.94-5.55	107	2.19	1.79-2.65	40	0.45	0.32-0.61	4.90	3.36-7.27	17	0.37	0.21-0.59	11	0.13	0.07-0.24	2.74	1.21-6.53
40-49	60	1.92	1.47-2.48	43	0.77	0.56-1.04	2.50	1.66-3.80	36	1.15	0.80-1.59	22	0.39	0.24-0.59	2.98	1.70-5.32	10	0.33	0.16-0.61	11	0.20	0.10-0.36	1.66	0.63-4.31
50-59	39	2.07	1.47-2.82	53	1.74	1.30-2.28	1.19	0.76-1.83	20	1.06	0.65-1.64	23	0.76	0.48-1.13	1.41	0.73-2.68	10	0.53	0.25-0.97	24	0.78	0.50-1.17	0.67	0.29-1.46
60-69	40	2.87	2.05-3.91	44	2.62	1.90-3.51	1.10	0.70-1.73	9	0.65	0.30-1.23	14	0.83	0.45-1.39	0.78	0.30-1.94	19	1.36	0.82-2.13	22	1.31	0.82-1.99	1.04	0.53-2.01
70-79	28	3.21	2.13-4.65	47	4.91	3.61-6.54	0.65	0.39-1.07	12	1.39	0.72-2.44	15	1.60	0.89-2.63	0.87	0.37-2.01	7	0.77	0.31-1.60	15	1.55	0.86-2.55	0.50	0.17-1.31
80+	15	4.16	2.32-6.91	24	4.56	2.92-6.78	0.91	0.44-1.82	5	1.32	0.43-3.15	10	1.89	0.91-3.48	0.70	0.19-2.29	7	1.98	0.79-4.12	5	0.95	0.31-2.21	2.09	0.57-8.44
Age groups																								
00-14	75	0.39	0.31-0.49	28	0.72	0.47-1.07	0.54	0.34-0.88	55	0.29	0.22-0.38	20	0.49	0.29-0.79	0.59	0.33-1.06	14	0.07	0.04-0.12	<5	0.12	0.03-0.32	0.63	0.18-2.66
15-39	485	2.99	2.72-3.29	169	0.92	0.78-1.08	3.25	2.70-3.93	403	2.46	2.21-2.72	131	0.71	0.59-0.85	3.47	2.82-4.30	37	0.26	0.18-0.36	16	0.08	0.05-0.14	3.13	1.66-6.13
40-54	80	1.92	1.52-2.39	67	0.94	0.72-1.19	2.05	1.46-2.89	49	1.18	0.87-1.56	32	0.44	0.30-0.62	2.69	1.68-4.36	14	0.34	0.19-0.58	24	0.35	0.23-0.53	0.98	0.47-1.97
55+	102	3.03	2.46-3.70	144	3.47	2.91-4.10	0.87	0.67-1.14	33	1.00	0.68-1.42	52	1.25	0.92-1.64	0.80	0.50-1.28	39	1.15	0.81-1.59	53	1.21	0.90-1.60	0.95	0.60-1.48
TOTAL	742	2.21	2.03-2.41	408	1.43	1.28-1.59	1.55	1.35-1.79	540	1.40	1.27-1.55	235	0.72	0.62-0.83	1.95	1.63-2.34	104	0.43	0.34-0.53	97	0.39	0.31-0.48	1.10	0.80-1.50

* Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups–Census P25-1130); confidence intervals (Tiwari modification) are 95 % for rates

Bolded IRR and 95 % CI are statistically significant

To comply with California Cancer Registry confidentiality regulations, case counts fewer than 5 are not presented

(albeit higher in the former), but much lower for whites. For AYAs, EBV prevalences were higher for foreign-born than for US-born Hispanics but similar for US-born Hispanics and whites; however, this latter pattern was limited to females (EBV prevalences for males and females, respectively: 48 and 27 % in foreign-born Hispanics ($n = 25$ male and 11 female HL cases), 35 and 11 % in US-born Hispanics ($n = 37$ and 38), and 26 and 13 % in whites ($n = 174$ and 220)). Adjusted EBV PRs were increased for older adults versus AYAs and for MC versus NS in all three Hispanic/white groups, and for children versus AYAs in US- and foreign-born Hispanics. Adjusted EBV PRs for males versus females were higher for whites than for foreign-born and US-born Hispanics, reflecting the relatively low EBV prevalence in white women.

Discussion

This study is the first to examine HL incidence rates using a case series of US Hispanics whose large size, relative ethnic homogeneity, fully characterized birthplace, and tumor cell EBV status for a subset, permitted detailed insights into immigration-related differences in occurrence. Overall, the lower HL rates in Hispanics than in whites among AYAs, but higher rates in children and older adults (notably males), varied by nativity. Ethnic differences were quite marked in foreign-born Hispanics, particularly younger children, but attenuated for US-born Hispanics, especially for women and for the NS subtype. EBV prevalence in HL tumors declined from foreign-born Hispanics to US-born Hispanics to whites, more dramatically in AYA women than in other age–sex groups. Together, these patterns extend evidence for strong socioeconomically associated environmental influences on HL incidence and on its EBV-defined subtypes. They also support the hypothesis that HL results from age-differing challenges to immune function [12], with higher risk in children exposed to intense, early infection, consistent with their larger family sizes [50]; higher risk in AYAs with delayed exposures to infection related to fewer childhood social contacts (e.g., fewer older siblings [51], less nursery school attendance [52]); and higher risk in older adults linked with more social contacts, likely because control of infection, especially with chronic herpesviruses, diminishes with immunosenescence. Beyond that, HL rate differences between US-born Hispanics and whites raise questions about the timing, duration, and/or extent of environmental change required to reduce ethnic variation in rates. Differences in nativity-specific variation for NS and MC underscore distinct etiologies. The markedly larger nativity effect on NS rates in AYA females than in males, but the lesser effect on rates for girls than for boys, illustrates the strong, age-varying influence of gender on NS HL occurrence.

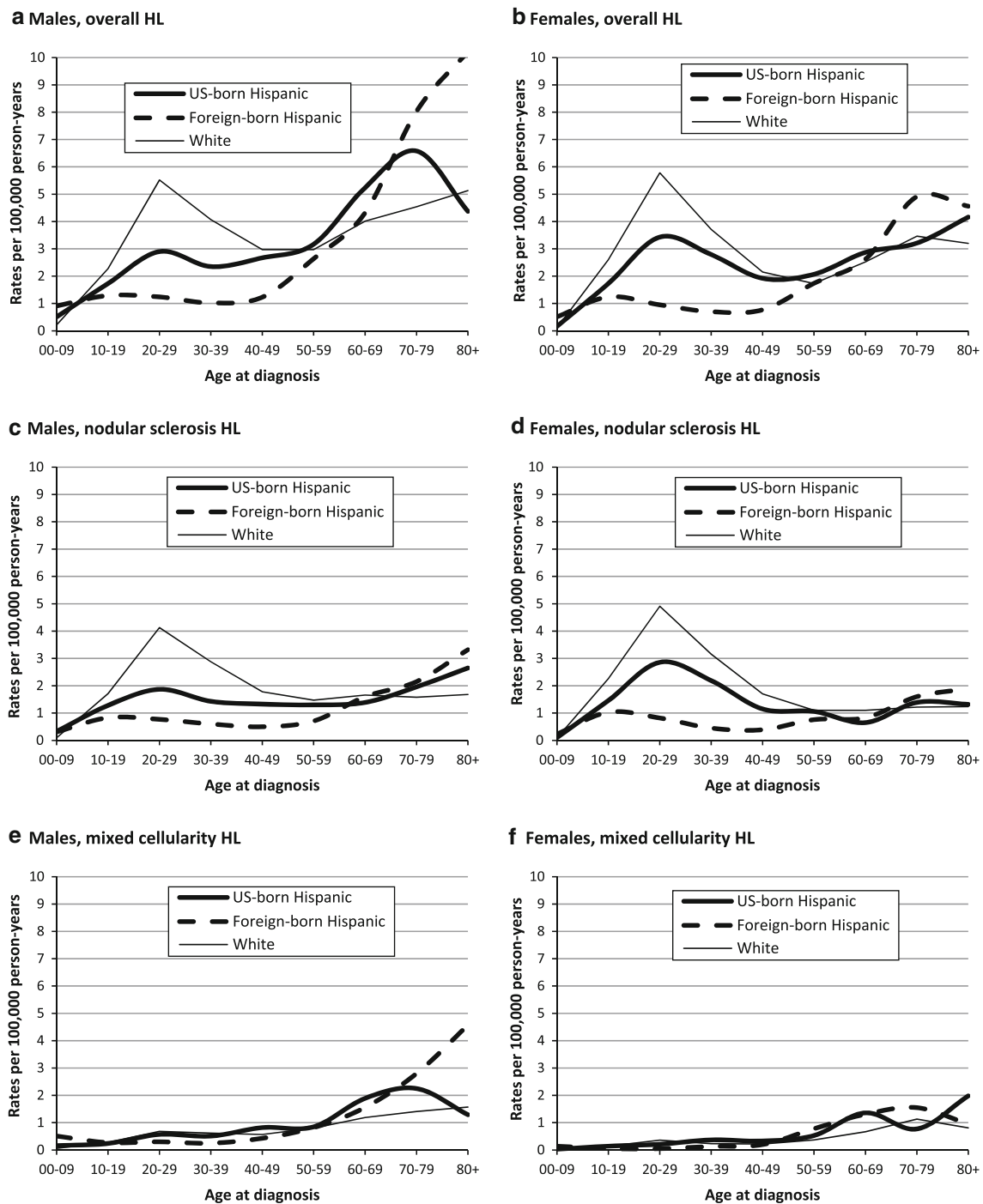


Fig. 2 Age- and sex-specific incidence rates of classical Hodgkin lymphoma (HL) overall and for selected histologic subtypes in US-born and foreign-born Hispanics and whites, 1988–2004, California

Previous studies reported lower overall HL rates in US Hispanics, especially in AYAs, but higher rates for children and older adults, although most studies did not have adequate sample sizes to calculate rates simultaneously by age, sex, and histologic subtype [3, 4, 11, 17, 19, 53–55]. The three prior studies evaluating the effect of nativity on HL in

Hispanics [11, 17, 19] lacked either the numbers of cases to stratify data by age, sex, and histologic subtype [17, 19], or nativity for all cases [11]; none included EBV information. In our study, nativity results generally resembled the prior findings. However, whereas Cozen et al. [17] showed higher NS rates in foreign- than in US-born Latinos under age 14 in

Table 3 Incidence rate* ratios (IRR) and 95 % confidence intervals (CI) for classical HL overall and by histologic subtype for US-born Hispanics versus whites and foreign-born Hispanics versus whites, by age and gender, 1988–2004, California

	All HL				Nodular sclerosis HL				Mixed cellularity HL			
	US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites		US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites		US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites	
	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
Total												
Age (10-year groups)												
00–09	2.00	1.45–2.77	4.18	2.67–6.54	2.20	1.44–3.35	2.70	1.33–5.49	2.50	1.30–4.79	8.25	3.88–17.55
10–19	0.71	0.63–0.81	0.52	0.42–0.63	0.70	0.60–0.80	0.47	0.37–0.59	0.90	0.61–1.33	0.81	0.45–1.47
20–29	0.56	0.50–0.62	0.20	0.17–0.23	0.52	0.46–0.59	0.18	0.15–0.21	0.77	0.57–1.04	0.37	0.26–0.52
30–39	0.66	0.58–0.75	0.22	0.19–0.26	0.60	0.51–0.70	0.18	0.14–0.22	1.02	0.74–1.42	0.44	0.31–0.63
40–49	0.89	0.75–1.07	0.39	0.32–0.47	0.71	0.56–0.90	0.25	0.19–0.34	1.43	0.99–2.06	0.78	0.54–1.11
50–59	1.11	0.90–1.38	0.93	0.77–1.12	0.92	0.67–1.26	0.57	0.42–0.78	1.17	0.77–1.78	1.38	1.00–1.90
60–69	1.23	1.00–1.51	1.05	0.85–1.28	0.74	0.49–1.10	0.86	0.61–1.21	1.75	1.26–2.43	1.54	1.11–2.14
70–79	1.19	0.93–1.51	1.57	1.27–1.93	1.20	0.79–1.80	1.33	0.91–1.95	1.14	0.74–1.74	1.64	1.14–2.36
80+	1.10	0.73–1.66	1.73	1.31–2.29	1.26	0.66–2.39	1.73	1.09–2.76	1.65	0.87–3.15	2.17	1.34–3.52
Age groups												
00–14	1.04	0.87–1.24	1.67	1.28–2.17	0.95	0.77–1.17	1.20	0.85–1.68	1.86	1.21–2.86	4.29	2.51–7.33
15–39	0.62	0.58–0.66	0.23	0.21–0.26	0.58	0.53–0.63	0.20	0.18–0.23	0.84	0.69–1.03	0.39	0.30–0.49
40–54	0.94	0.81–1.09	0.48	0.41–0.56	0.76	0.62–0.93	0.30	0.24–0.38	1.34	0.98–1.83	0.95	0.72–1.27
55+	1.18	1.03–1.34	1.36	1.21–1.52	0.99	0.79–1.25	1.10	0.90–1.34	1.42	1.14–1.78	1.68	1.38–2.04
Total	0.83	0.78–0.87	0.60	0.57–0.65	0.68	0.64–0.73	0.39	0.36–0.43	1.23	1.09–1.40	1.19	1.05–1.36
Males												
Age (10-year groups)												
00–09	2.32	1.58–3.41	4.14	2.38–7.17	3.30	1.93–5.65	3.10	1.23–7.81	2.67	1.28–5.55	8.50	3.61–20.01
10–19	0.76	0.64–0.91	0.57	0.43–0.75	0.75	0.61–0.92	0.49	0.35–0.68	0.86	0.53–1.39	0.96	0.50–1.86
20–29	0.53	0.45–0.61	0.22	0.19–0.27	0.45	0.38–0.54	0.19	0.15–0.23	0.84	0.59–1.19	0.44	0.30–0.65
30–39	0.58	0.48–0.70	0.25	0.20–0.31	0.50	0.39–0.63	0.21	0.16–0.27	0.82	0.54–1.25	0.40	0.26–0.62
40–49	0.90	0.71–1.13	0.41	0.32–0.53	0.75	0.54–1.03	0.28	0.19–0.41	1.44	0.93–2.22	0.75	0.49–1.17
50–59	1.07	0.81–1.41	0.89	0.70–1.14	0.88	0.58–1.36	0.48	0.31–0.76	1.06	0.62–1.81	1.03	0.66–1.60
60–69	1.31	1.01–1.70	1.08	0.82–1.41	0.84	0.51–1.37	0.96	0.62–1.50	1.59	1.02–2.47	1.31	0.83–2.07
70–79	1.45	1.06–1.98	1.77	1.32–2.36	1.24	0.70–2.19	1.36	0.78–2.36	1.60	0.95–2.69	1.99	1.21–3.26
80+	0.85	0.44–1.66	1.99	1.36–2.91	1.58	0.64–3.92	1.98	1.02–3.85	0.82	0.26–2.62	2.91	1.63–5.20
Age groups												
00–14	1.24	0.99–1.55	1.81	1.29–2.55	1.26	0.95–1.67	1.26	0.78–2.04	1.64	1.01–2.66	4.27	2.36–7.72
15–39	0.57	0.52–0.64	0.25	0.22–0.29	0.51	0.45–0.57	0.22	0.19–0.25	0.81	0.64–1.04	0.41	0.31–0.53
40–54	0.94	0.77–1.14	0.49	0.40–0.60	0.75	0.56–1.00	0.32	0.23–0.44	1.35	0.93–1.95	0.75	0.52–1.07
55+	1.23	1.03–1.46	1.47	1.26–1.72	1.11	0.83–1.49	1.13	0.86–1.50	1.33	0.99–1.80	1.85	1.42–2.40
Total	0.85	0.79–0.92	0.70	0.64–0.76	0.69	0.63–0.76	0.45	0.39–0.50	1.17	1.01–1.37	1.24	1.06–1.45
Females												
Age (10-year groups)												
00–09	1.45	0.79–2.68	4.64	2.14–10.04	1.11	0.54–2.28	2.56	0.84–7.76	1.50	0.36–6.28	7.00	1.41–34.68
10–19	0.67	0.56–0.80	0.48	0.36–0.64	0.65	0.53–0.78	0.46	0.33–0.63	1.00	0.52–1.94	0.36	0.08–1.52
20–29	0.59	0.51–0.68	0.16	0.13–0.21	0.58	0.50–0.68	0.17	0.13–0.21	0.58	0.33–1.04	0.14	0.05–0.38
30–39	0.75	0.63–0.90	0.19	0.15–0.24	0.69	0.57–0.85	0.14	0.10–0.20	1.61	0.93–2.77	0.57	0.30–1.08
40–49	0.89	0.68–1.17	0.36	0.26–0.49	0.68	0.48–0.95	0.23	0.15–0.35	1.50	0.76–2.96	0.91	0.47–1.75
50–59	1.20	0.86–1.67	1.01	0.75–1.35	0.96	0.61–1.53	0.69	0.45–1.07	1.43	0.73–2.80	2.11	1.31–3.38
60–69	1.14	0.82–1.58	1.04	0.76–1.42	0.59	0.30–1.16	0.75	0.44–1.31	2.03	1.24–3.33	1.96	1.23–3.12

Table 3 continued

	All HL				Nodular sclerosis HL				Mixed cellularity HL			
	US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites		US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites		US-born Hispanics versus Whites		Foreign-born Hispanics versus Whites	
	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI	IRR	95 % CI
70–79	0.93	0.63–1.36	1.42	1.05–1.92	1.14	0.63–2.06	1.31	0.77–2.24	0.68	0.32–1.46	1.37	0.80–2.34
80+	1.30	0.77–2.19	1.43	0.94–2.17	1.06	0.43–2.62	1.52	0.79–2.93	2.44	1.12–5.35	1.17	0.47–2.92
Age groups												
00–14	0.80	0.60–1.06	1.47	0.97–2.22	0.66	0.48–0.91	1.11	0.69–1.80	3.50	1.35–9.11	6.00	1.69–21.26
15–39	0.66	0.60–0.73	0.20	0.17–0.24	0.64	0.57–0.71	0.18	0.15–0.22	0.93	0.65–1.34	0.29	0.17–0.48
40–54	0.96	0.76–1.21	0.47	0.36–0.60	0.77	0.57–1.04	0.29	0.20–0.41	1.42	0.80–2.51	1.46	0.92–2.31
55+	1.11	0.91–1.36	1.27	1.07–1.51	0.88	0.62–1.25	1.10	0.82–1.46	1.49	1.07–2.08	1.57	1.17–2.10
Total	0.81	0.75–0.88	0.52	0.47–0.58	0.69	0.63–0.75	0.35	0.31–0.40	1.34	1.09–1.66	1.22	0.98–1.51

* Rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups–Census P25-1130)

Bolded IRR and 95 % CI are statistically significant

Los Angeles County in 1972–1985, we observed no significant nativity differences at these ages, suggesting possible temporal or cohort changes in NS incidence. In SEER-wide data (2,067 Hispanic cases from 1992–2007), Evens et al. [11] reported lower proportions of MC in the US- than in the foreign-born; in our study, the lack of difference in MC rates by nativity, likely reflecting adjustment for age differences between groups, indicates little impact of birthplace on overall incidence of this histologic subtype. Numerous studies of EBV-related HL have described higher tumor EBV prevalence in Hispanics than in whites [16, 41, 42, 56–59]. Although none considered nativity, prevalences in our foreign-born cases were similar to those reported from Mexico and Costa Rica [42, 58].

As HL rates vary with economic conditions [1, 2, 4, 5, 7, 10, 17], some of the ethnic and nativity variation in rates reported here likely reflects socioeconomic differences. In 2001, California Hispanics differed from whites in having less education (74 vs. 31 % completing high school or less), more poverty (35 vs. 6 % living at or below the federal poverty level), and larger households (86 vs. 56 % with 3 or more persons) [60]—all characteristics associated with lower HL risk [1–11]. Similarly, foreign-born Hispanics differed from US-born Hispanics in reporting less education (84 vs. 57 % completing high school or less) and more poverty (42 vs. 28 % living at or below the federal poverty level) [60]. These socioeconomic conditions likely reflect aspects of the timing and intensity of exposure to infection linked to HL risk [12]. In several studies, Mexican-Americans had higher seroprevalence and overall burdens of common, latent infections even after control for social class [61, 62], and earlier age at infection [63, 64] than whites, and foreign birthplace was an independent predictor of these

associations [61–66]. For children, these findings may describe the early and intense infections assumed to predict higher HL risk and may help explain the higher HL rates in foreign-born Hispanic children. For AYAs, they may speak to a well-primed childhood immune system, particularly in the foreign-born, consistent with their much lower young adult HL rates [67]. For older adults, greater infectious disease burdens among Mexican-Americans, particularly the foreign-born [68], may relate to the increased HL rates in Hispanics compared with whites; specifically, higher antibody titers against latent herpesviruses in Hispanics [69] may reflect diminished immune function and poorer control of latent infection due to stress [68, 70–72], lower SES [61, 69, 72, 73], or related aspects of immigration [74, 75] that could be related to HL development.

EBV-positive HL tumors appear to result from an aberrant immune response to EBV infection due to abnormal immune function [25, 76, 77]. The higher EBV prevalence in tumors of foreign-born than US-born Hispanics than whites in our study, which recalls the higher EBV prevalence in HL in populations from developing than developed economies [13, 42, 57, 78–80], and in some but not other European populations [13], suggests that foreign-born Hispanics have poorer immune control of EBV than US-born Hispanics and whites, particularly among children and older adults. For Hispanics, some data indirectly support this conjecture. In children and teenagers, adjusted PRs for EBV seroprevalence [81] and absolute antibody titers [81, 82] were higher in Mexican-Americans than whites, foreign- than US-born individuals, girls than boys, and children from lower versus the highest quartiles of household income [81]. In adults ages 24–32, EBV antibody titers were increased for Hispanics, females, and having lower SES during adolescence, suggesting long-lasting impacts of

Table 4 Number of classical Hodgkin lymphoma cases, percentages with EBV-positive tumors, and adjusted EBV prevalence ratios (PR) and 95 % confidence intervals (CI), in patient demographic and tumor subgroups, for foreign-born and US-born Hispanics and whites, 1988–1997, California regions

Characteristic	Foreign-born Hispanics				US-born Hispanics				Whites			
	N	% EBV+	PR*	95 % CI	N	% EBV+	PR†	95 % CI	N	% EBV+	PR‡	95 % CI
Age groups												
0–14	7	85.7	1.7	1.03–2.7	22	72.7	2.8	1.7–4.5	21	28.6	1.4	0.8–2.6
15–39	36	41.7	1.0		75	22.7	1.0		394	18.5	1.0	
40–54	14	64.3	1.4	0.7–2.6	27	29.6	1.5	0.8–3.2	104	11.5	0.6	0.3–0.97
55+	24	83.3	1.6	1.03–2.6	13	76.9	3.4	2.0–5.7	137	43.8	1.6	1.2–2.2
<i>p</i> **		0.005					<.0001				<.0001	
Sex												
Male	48	66.7	1.1	0.7–1.6	70	44.3	1.3	0.9–2.1	304	29.9	1.6	1.2–2.0
Female	33	54.6	1.0		67	29.9	1.0		352	17.1	1.0	
<i>p</i> **		0.36					0.07				<.0001	
Histologic subtype												
NS	40	42.5	1.0		95	30.5	1.0		493	15.2	1.0	
MC	28	85.7	1.7	1.1–2.5	23	60.8	1.9	1.2–2.9	91	59.3	3.0	2.2–4.0
Other	13	69.3	1.2	0.7–2.0	19	42.1	1.1	0.6–1.8	72	30.6	1.4	0.9–2.1
<i>p</i> **		0.001					0.02				<.0001	
Census block group SES [16]												
Low	50	60.0	0.9	0.6–1.4	59	50.9	1.5	0.97–2.4	52	26.9	1.0	0.7–1.6
Mid–high	31	64.5	1.0		78	26.9	1.0		604	22.7	1.0	
<i>p</i> **		0.68					0.004				0.49	
Ann Arbor stage [16]												
I/II	45	51.1	1.0		72	40.3	1.0		402	20.7	1.0	
III/IV	31	71.0	1.3	0.9–1.9	59	33.9	0.8	0.5–1.2	231	26.8	1.1	0.9–1.5
Unknown	5	100.0	1.5	1.02–2.3	6	33.3	0.5	0.2–1.1	23	26.1	1.1	0.6–1.8
<i>p</i> **		0.03					0.75				0.18	
California region [16]												
Greater Bay area	36	58.3	1.0		79	30.4			656	23.0		
Southern CA	45	64.4	1.1	0.7–1.5	58	46.6	1.2	0.8–1.8	–			
<i>p</i> **		0.57					0.05					
Total	81	61.7			137	37.2			656	23.0		

*Adjusted for age (4 groups), gender, histologic group (3 groups), Ann Arbor stage (3 groups), SES (2 groups), California region

†Adjusted for age (4 groups), gender, histologic group (3 groups), Ann Arbor stage (3 groups), SES (2 groups), California region

‡Adjusted for age (4 groups), gender, histologic group (3 groups), Ann Arbor stage (3 groups), SES (2 groups)

***p* value for Chi-square statistic

early environment on immune control of EBV [71]. EBV seroprevalence and antibody titers against lytic and latent antigens were higher in Mexicans than in Italians, Dutch, Israelis, Columbians, or Papua New Guineans [83], although a Texas community study found lower antibody titers against EBV lytic antigens in Hispanics than in whites [72]. Our finding of a lower EBV prevalence in HL tumors among US-than foreign-born Hispanics thus may reflect improved immune function as related to EBV control. However, given their higher HL rates, it also may reflect increased exposure to, or greater prevalence of, other environmental causes.

The deficit of AYA HL rates even in US-born Hispanics compared with whites in these data may diminish with increasing acculturation. In 2001, the California Hispanic population was still relatively recently immigrated (46 % foreign-born, 30 % residing in the US for under 10 years [60]). Nevertheless, to date, no study of HL incidence has observed an equivalence of rates in immigrants to those in the host country or of rates in young adult non-whites with those in whites over time [10, 11, 20, 21, 84]. For Hispanics, young adult HL rates did not change over the 1990s and 2000s in either the US- or foreign-born [11]. Thus,

persistent differences in HL rates between US-born Hispanics and whites may in part also reflect less modifiable aspects of HL etiology, such as HLA genotype [85–88], which manifests racial/ethnic variation in its association with HL overall [89] and by tumor cell EBV status [87]. Prevalence of the HLA-A2 allele, protective against EBV-positive HL [87, 90], varies across racial/ethnic groups, including Hispanics [87, 91, 92], and Mexican-Americans have specific HLA region determinants of immune response to EBV infection, including SNPs associated with HL [93].

The greater rate stability with immigration for the MC than for the NS subtypes in our data and the stronger association of EBV with MC irrespective of ethnicity and nativity support separate histology-specific etiologies [94] and, for MC, a larger component of invariable etiologic pathways across populations. Nevertheless, the nativity variation in MC rates also reveals environmental sensitivity in MC etiology, possibly through changes in immune function: Barros et al. [59] hypothesized that, as in HIV-related HL, EBV infection in children with poorer immune responses due to challenging environments may promote development of MC, while those with stronger immune function associated with healthier environments would develop NS. For NS, the higher rates in US- than in foreign-born AYAs, together with the lower EBV prevalences, confirm the view that EBV is not a dominant etiologic factor for this HL subtype [47]. However, as infectious mononucleosis, a strong risk factor for young adult EBV-associated HL [95, 96], seems less likely in US-born Hispanic AYAs than in whites in California, given their socioeconomic profiles [60], other pathways may lead to the observed higher EBV prevalences in HL in AYA US-born Hispanic males.

The larger immigration-related variation in HL rates in females than in males may reflect acculturation-related exposures together with biologic differences. If hormonal exposures related to reproduction interact with exposures to children to affect HL risk in women [97], the greater HL rate variation by ethnicity and nativity among AYA females than males may reflect protection to Hispanic women from earlier and more intense household exposure to infection. Among California women ages 15–39 in 2001, 41 % of foreign-born Hispanics, 17 % of US-born Hispanics, and 12 % of whites had had three or more children [60]. Among older men, the high HL rates in foreign-born than in US-born Hispanics might result in part from chronic inflammation from higher lifetime infection burdens [75].

Our findings are subject to some limitations. First, our inability to account for duration of US residence among foreign-born Hispanics, or degree of acculturation among US-born Hispanics, limits the precision of estimated rates

and may bias our nativity-specific findings [17]. Second, although SES is a predictor of racial/ethnic differences in HL incidence [4, 13, 16], we lacked the denominators to calculate nativity- and neighborhood-level SES-specific rates. Third, tumor cell EBV status was available only on a small proportion of cases, limiting statistical power. HL tumors not retrievable for EBV testing were more likely to be from cases that were non-white, male, and from southern California [16], potentially resulting in selection bias. However, for 704 Hispanic cases in that study, birthplace distributions (US, foreign, unknown) did not differ significantly between those with and without available specimens (data not shown). Fourth, estimated nativity via imputation could underestimate rates for the foreign-born to the extent that they were undocumented, and thus be counted in the cancer registry but not in the census. Fifth, registry-recorded Hispanic ethnicity is subject to some misclassification [32] and may undercount Hispanics, enhancing ethnic rate differentials [24].

Our study also has several notable strengths. First, the case series is both large enough for evaluating HL rates simultaneously by age group, sex, and histologic subtype and for allowing evaluation of the joint effects of race and nativity on HL by tumor cell EBV status [16]. Second, as cancer registry cases without recorded birthplace are younger, better educated, and more likely to be US-born [29–34], our imputation of nativity where missing, rather than exclusion or proportional assignment of such cases, eliminates underestimation of rates in US-born Hispanics and subsequent attenuation of nativity comparisons [11]. Third, use of population-based cancer registry and census data for a relatively ethnically homogeneous population of Hispanics assures more precise study findings, given genetic admixture among Hispanics [27, 28] and enhances representativeness and generalizability of study findings. Fourth, by calculating rates with annual nativity-specific denominators based on statistical modeling, we avoided the likely biases associated with applying single-year census estimates to a longer time period.

Summary

In the large California Hispanic and white populations, this study was able to detect complex variation in HL incidence rates and EBV associations consistent with strong but age-varying effects of socioeconomic and related factors on HL incidence. However, persistent rate deficits in AYA US-born Hispanics versus whites and higher tumor EBV prevalence for US-born Hispanic than for white children and older adults suggest less modifiable aspects of HL etiology. The lesser ethnic and nativity variability, and stronger and persistent association of EBV, for MC than for NS point to differing etiologies, with a larger component of invariable biological influences for the former. The much stronger impact of

nativity on HL rates for females than for males, particularly in AYAs, highlights underexplored age-varying influences of gender on HL occurrence. Together, these findings not only underscore the substantial etiologic heterogeneity of HL, but also point to the need for further investigation of genetic and hormonal factors that interact with environmental influences associated with HL occurrence.

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