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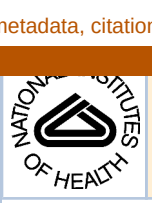

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Racial/ethnic variation in EBV-positive classical Hodgkin lymphoma in California populations

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Abstract

Epstein-Barr virus (EBV) is detected in the tumor cells of some but not all Hodgkin lymphoma (HL) patients, and evidence indicates that EBV-positive and –negative HL are distinct entities. Racial/ethnic variation in EBV-positive HL in international comparisons suggests etiologic roles for environmental and genetic factors, but these studies used clinical series and evaluated EBV presence by differing protocols. Therefore, we evaluated EBV presence in the tumors of a large (n=1,032), racially and sociodemographically diverse series of California incident classical HL cases with uniform pathology re-review and EBV detection methods. Tumor EBV-positivity was associated with Hispanic and Asian/Pacific Islander (API) but not black race/ethnicity, irrespective of demographic and clinical factors. Complex race-specific associations were observed between EBV-positive HL and age, sex, histology, stage, neighborhood socioeconomic status (SES), and birth place. In Hispanics, EBV-positive HL was associated not only with young and older age, male sex, and mixed cellularity histology, but also with foreign birth and lower SES in females, suggesting immune function responses to correlates of early childhood experience and later environmental exposures, respectively, as well as of pregnancy. For APIs, a lack of association with birth place may reflect the higher SES of API than Hispanic immigrants. In blacks, EBV-positive HL was associated with later-stage disease, consistent with racial/ethnic variation in certain cytokine polymorphisms. The racial/ethnic variation in our findings suggests that EBV-positive HL results from an intricate interplay of early- and later-life environmental, hormonal, and genetic factors leading to depressed immune function and poorly controlled EBV infection.

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Novelty: This paper is the first to describe epidemiologic patterns of EBV-positive Hodgkin lymphoma by racial/ethnic group in data uniformly collected for a large, ethnically diverse, and sociodemographically heterogeneous case series from a population-based cancer registry.

Impact: In this representative series of Hodgkin lymphoma patients, racial/ethnic variation in EBV-positive tumor status provides evidence for complex associations with socioeconomic/cultural exposures and suggested genetic predispositions supporting an intricate interplay of factors in the etiology of this lymphoma subtype.

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Keywords

Hodgkin lymphoma; Epstein-Barr virus; racial/ethnic variation; epidemiology

Introduction

Hodgkin lymphoma (HL) is a malignancy characterized by clinical, histopathologic and epidemiologic heterogeneity. Epstein-Barr virus (EBV) has been strongly implicated in the etiology of some HL based on the biological plausibility of EBV-mediated B-cell transformation[1, 2]; epidemiologic associations with infectious mononucleosis (IM), representing symptomatic primary EBV infection[3–8]; distinctive EBV antibody titer profiles[9–12] and viral loads[13, 14] both pre- and post-HL diagnosis; the presence of clonal EBV genomes within HL tumor cells, which implies that infection occurred before malignant transformation[15, 16]; and differing demographic, clinical, and epidemiologic characteristics of EBV-positive and EBV-negative HL[6, 8, 10, 12, 17–28]. Together this evidence strongly suggests that these virally defined variants of HL are distinct entities and that their pathogenesis should be considered separately.

Among the apparent epidemiologic differences between EBV-positive and –negative HL are their variable associations with patient race/ethnicity. This variation raises questions about the etiologic contributions to EBV-defined HL of socioeconomic and cultural exposures[29], and of genetic predisposition. The latter is of interest given the association of EBV-positive HL with the highly polymorphic human leukocyte antigen (HLA) genes[1, 10, 27, 28, 30, 31], which vary by racial/ethnic group[32–34]. However, as racial/ethnic variation in EBV-defined HL has been noted primarily in international data[17, 19, 35–47], understanding its etiologic implications is difficult because of the varying sociocultural exposures inherent in these comparisons and the challenges in distinguishing them from genetic characteristics of the populations. This difficulty could be lessened by examining racial/ethnic patterns in the distributions of EBV-defined HL in a single population. However, such research has been hampered by the requirement for a racially diverse case series of adequate size to accommodate the low incidence of HL in nonwhite racial/ethnic groups[15, 48–53] as well as the low proportion of EBV-positive HL in many patient subcategories[17, 19].

The population-based California Cancer Registry (CCR) covers a large, racially and ethnically varied and socio-economically diverse population in which racial/ethnic variation in HL (figure 1) has been described previously[15, 51]. Therefore, to better understand racial/ethnic variation in EBV-defined HL, we took advantage of the CCR resource to assemble a large series of classical HL cases for which we conducted uniform pathology re-review and detection for EBV using standard methods. In 1,032 non-Hispanic white, Hispanic, black, and Asian/Pacific Islander (API) cases, we then described the proportions of patients with EBV-positive disease by demographic and clinical characteristics, and estimated the independent effects of these variables on the presence of EBV in HL tumors.

Materials and methods

Patient population and data

The study, approved by the Northern California Cancer Center Internal Review Board, was based on all HL (ICD-O-2 histology codes 9650–9667) newly diagnosed in 1,553 northern Californians living in the nine-county Greater Bay Area in 7/1/88–12/31/97 and in 756 non-white southern Californians living in Los Angeles County in 1/1/92–12/31/96 or in Orange, San Diego or Imperial counties in 1/1/92–12/31/97. Greater Bay Area cases were included over a longer period to build on existing data for adult female patients from an earlier study[26, 54].

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With information routinely collected by the CCR pertaining to diagnosis, we classified HL patients by age group (10-year, and ages 0–14, 15–54, 55–69 and 70+ years based on the distribution of EBV-positive tumors in this case series), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic API, hereafter referred to as white, black, Hispanic, and API), birth place (US, not US), extent of disease (Ann Arbor stage summarized as earlier (stages I and II) and later (stages III and IV)), and presence of B symptoms (weight loss, night sweats, fever). We estimated neighborhood SES at diagnosis using a census block-group-based index[55] collapsed into tertiles reflecting the SES distribution of all HL cases (38 cases with unknown address were given the SES value of a randomly assigned block-group within their county of diagnosis). We assigned patient HIV status using information from SEER extent of disease information, cause of death, and/or manual review of the registry abstract[56].

We sought archival diagnostic tumor specimens for all 2,309 eligible cases. The 1,295 (56%) for whom specimens could be obtained were more likely ($p<=0.05$) than the other patients to be from the Greater Bay Area (86% vs 43%), because of regional variation in hospital practices for releasing specimens, and accordingly to be white (62% vs 30%) and female (48% vs 38%), because of the earlier study of Greater Bay Area women[25, 26]. They were more likely to be in the lowest tertile of neighborhood SES (43% vs 21%) and to show some differences in histologic subtype distributions (with 66% vs 57% nodular sclerosis (NS), 6% vs 15% not otherwise specified (NOS)), but not to differ in age (5% vs 8% under age 14, 56% vs 55% age 15–39, and 40% vs 37% age 40 and older).

Pathology re-review and EBV testing

Pathology re-review was undertaken by three hematopathologists, one (RFD) classifying 1988–94 adult female cases for the earlier Greater Bay Area study according to ICD-O-2[57], and the other two (MLG, FEC) working together on all other study cases using ICD-O-3. For 73 patients (6%), pathology materials were unsuitable for review. From the 1,222 remaining patients, we excluded 27 (2%) determined not to have HL, and 59 (5%) with the nodular lymphocyte predominance subtype, considered a separate histopathologic entity. All ICD-O-2 histologic subtypes were converted to ICD-O-3 classification. For the 1,136 confirmed classical HL specimens, paraffin sections were prepared and stained for EBV in the laboratory of RFA[58, 59]. *EBER* in situ hybridization was performed on paraffin sections using digoxigenin-labeled (Boehringer-Mannheim, Indianapolis, IN) riboprobes complementary to *EBER1* and *U6* control transcripts followed by anti-digoxigenin antibody detection (Boehringer-Mannheim) and alkaline phosphatase-catalyzed color reaction. LMP1 immunostains were performed on paraffin sections using a peroxidase-labeled streptavidin-biotin detection system and a commercial cocktail of antibodies to LMP1 (CS1-4; Dako, Carpinteria, CA) after antigen retrieval using 1mg/ml pronase E in phosphate-buffered saline for five minutes at 37°C. A negative control of each tissue section was treated identically except for omission of the primary antibody. Interpretation was facilitated by parallel hematoxylin and eosin (H & E) stain to guide the identification of Reed-Sternberg cells and variants.

Stained slides were interpreted for EBV presence by two study pathologists (RBM, JAD) for women diagnosed in 1988–94 and by two others (MLG, FEC) for the remaining cases. Tumors were considered EBV-positive if both assays were positive (or, if only one assay was successful, and it was positive) and as EBV-negative if both assays were negative (or if the single successful assay was negative)[59]. For 21 cases, assays could not be completed for technical reasons. Thus, a definitive finding as EBV-positive or EBV-negative was obtained for 1,115 patients.

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Statistical analyses

After excluding 18 subjects with unknown race/ethnicity and 65 HIV-positive cases (reported elsewhere[60]) because of distinctive epidemiologic patterns for HIV-associated HL, we described EBV-positive HL by calculating the proportion of cases with EBV-positive tumors (hereafter referred to as EBV prevalence) in each demographic and clinical subgroup, stratifying by race/ethnicity and using chi-squared statistics to test for differences. To measure associations of the study variables with EBV-positive HL, we first calculated unadjusted prevalence ratios (PR) and 95% confidence intervals (CI) and then computed multivariate PRs and 95% CI to evaluate independent effects of the variables, excluding the small number of cases (n=39) missing stage at diagnosis. Models to test for interactions included all variables significant in the overall models. All analyses used SAS version 9 software.

Results

HL overall

Of the 1,032 cases with successful EBV classification (table 1), the majority were under age 40 at diagnosis; Hispanics had a lower mean diagnostic age in years (34.0) than whites (38.7), blacks (38.6) or APIs (37.6). The majority of cases had a NS histologic subtype (75% of whites, 63% of blacks, 62% of Hispanics, 62% of APIs), no B symptoms (except in Hispanics), and earlier-stage disease (63% of whites, 61% of blacks, 56% of Hispanics, 67% of APIs). A slight male excess was apparent for Hispanics and APIs. Among the 165 Hispanic cases for whom birth place was recorded, 40% were foreign-born, including 54 in Mexico or Central America; of the 49 APIs with recorded birthplace, 67% were foreign-born, including 14 in the Philippines. 50% of whites, 12% of blacks, 15% of Hispanics, and 25% of APIs lived in neighborhoods with the highest SES level.

EBV-defined HL incidence

HL tumors were EBV-positive for 23% of white, 28% of black, 46% of Hispanic, and 40% of API patients ($p<0.0001$). After control for study variables, race/ethnicity remained independently associated with EBV prevalence for Hispanics (adjusted PR=1.5 (1.2–2.0)) and marginally for APIs (adjusted PR=1.3 (1.0–1.8)) but not for blacks (adjusted PR=1.1 (0.7–1.6)), compared to whites.

Age—EBV-positive tumors were most common in children under age 10 and adults over age 50 in all racial/ethnic groups except blacks, but EBV prevalences were lower in whites than in Hispanics and Asians in almost every age group. Unadjusted PRs (table 2) were elevated for both children and adults over 55, compared to adults 15–54, in all groups except blacks. After multivariate adjustment, EBV was twice as prevalent in tumors of children as of adults for Hispanics, whereas for blacks and APIs, young age was not related to EBV prevalence.

Sex—Males had a higher prevalence of EBV-positive tumors than females (table 1), and PRs (table 2) were elevated for whites, blacks and APIs. Figure 2 shows that the male excess varied by both age and race/ethnicity. In Hispanics, EBV prevalence was high for both males (67%) and females (89%) under age 14 but at ages 15–54 was higher for males (41%) than females (23%). As a result, unadjusted PRs for Hispanics ages 0–14 and 55+ vs 15–54 were somewhat more elevated for females (3.8 (2.4–6.1) and 3.1 (1.9–5.2)) than for males (1.6 (1.1–2.5) and 2.2 (1.6–3.0)). In multivariate models for Hispanics, an interaction was detected for sex and age, with a marginally significant male excess in adults ages 15–54 (adjusted PR for males vs females of 1.6 (1.0–2.6)) but not other age groups (data not shown).

Histology—EBV prevalence was highest for the mixed cellularity (MC) subtype in all racial/ethnic groups except blacks and appeared elevated for HL NOS in whites, for inter-follicular

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HL in blacks and Hispanics, and for NS cellular phase in all nonwhites (Table 1). For each subtype, EBV prevalence was lower in whites than Hispanics. For the two most common subtypes, this racial/ethnic difference was more marked for NS than for MC across age groups in all racial/ethnic categories (figure 3). In multivariate models, MC was a strong predictor of EBV prevalence except in blacks, and NOS predicted EBV prevalence in whites, compared to NS.

Clinical characteristics—EBV prevalence appeared to vary by the presence of B symptoms for APIs (p=0.07 among persons with known B-symptoms) but not after multivariate adjustment. EBV prevalence was higher for later- than earlier-stage disease marginally for whites (27% vs 21%, p=0.07) and significantly for blacks (44% vs 17%, p=0.01), for whom the adjusted PR for later vs earlier stage was elevated.

Birth place—EBV prevalence was associated with birth place only for Hispanics (tables 1 and 2), in whom it was higher in the foreign- than US-born, particularly for ages 10–19 and for late-stage disease (table 3). Birth place no longer predicted EBV tumor presence for Hispanics in multivariate analyses (table 2). However, a significant interaction occurred with age, such that adjusted PRs were elevated suggestively for foreign-born vs US-born cases at ages 15–54 (1.7 (1.0–3.0)), more so in women (2.5 (1.0–6.0)) than men (1.3 (0.7–2.4)). The more elevated PRs described above for younger and older age in Hispanic females than males appeared more pronounced for US- than foreign-born cases (table 4), but small sample sizes did not permit a formal test of interaction.

Neighborhood SES—In Hispanics, EBV prevalence increased with decreasing neighborhood SES (table 1, p for trend=0.01). However, this effect was confined to females (EBV prevalences for high, intermediate and low SES levels in females of 6%, 38%, 48% and in males of 47%, 48%, 57%). An interaction of SES and sex was suggested, with adjusted PRs for low vs high SES of 6.4 (0.9–46.3) and mid vs high SES of 5.2 (0.7–38.1) for females, and 1.2 (0.7–2.0) and 1.2 (0.7–2.0) for males. A much more modest gender-specific SES association was suggested in whites (females: 14%, 18%, 24%, males: 31%, 28%, 32% for high, intermediate and low SES levels), but PRs were not elevated, and no interaction was apparent. For Hispanics, there also was a suggested interaction of SES and birth place, with adjusted PRs for low vs high SES of 1.9 (0.9–4.3) in US-born and 0.9 (0.4–2.0) in foreign-born; these data were too sparse for stratification by gender.

Discussion

EBV-positive classical HL was associated with Hispanic and API but not black race/ethnicity irrespective of other demographic and clinical factors in a large case series from California, a US state in which racial/ethnic diversity implies substantial variation in SES, even for the age group at highest HL risk (table 5), in cultural experience, and in genetic composition. Moreover, complex race/ethnicity-specific associations were observed between EBV-positive HL and age, sex, histology, stage, neighborhood SES, and birth place. In addition to confirming previously noted associations of young and older age, male sex, and MC histology with EBV-positive HL, the observed patterns also identified associations with birth place and SES that varied with age and gender, as well as suggested that genetic factors may be protective against EBV-positive HL for blacks and Hispanics. Together, our findings imply an interplay of environmental and genetic factors for the etiology of EBV-positive HL that is intricate but ultimately consistent with the hypothesis that this form of HL may reflect an aberrant immune response to EBV infection[13, 14] secondary to depressed immune function[12].

Prior descriptions of racial/ethnic variation in EBV-associated HL have come from international comparisons[17, 19, 35–47] that generally were not based in common protocols for

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data collection, pathologic review, or EBV assays, and did not involve case series that were population-based[17, 35–39, 41, 43, 44, 46]. In a large combined international data set, we previously found the prevalence of EBV in HL tumors to be higher in non-white populations and those from economically less-developed countries, but the racial/ethnic variation in these cases was limited, and socioeconomic measures were indirect[17]. The few population-based studies of EBV prevalence with uniformly collected data have primarily involved white populations. In the UK, EBV-positive disease was observed in 33% of the 461 patients ages 16–74 with classical HL, with higher proportions in older than young adults, males than females, MC than NS subtypes[19], and, in young adults, later- rather than earlier-stage disease[20], but not with a measure of SES[20]. Similar associations with older age, male gender, and MC histology were observed in 398 US patients (prevalence of EBV=24%)[12] and 499 Scandinavian patients (prevalence of EBV=29%)[8], and an association with lower SES was also detected in the US series[12]. For the 656 white patients in our study, EBV prevalence was quite close to those in the other US series, overall and within subgroups, and was only slightly lower than prevalences in the UK and Scandinavia, despite the varying proportions of cases in these studies on whom specimens were obtained (i.e., 73%, 54%[12], 86%[19], 77%[8], respectively). Our results also are consistent with prior observations in the US of higher EBV prevalences for Hispanics (n=16) than whites (44% vs 23%)[12].

In this study, the persistence across racial/ethnic groups of associations of young and older ages, male gender, and MC histologic subtype with EBV-positive HL[61] suggests etiologic involvement of certain relatively unvarying biologic characteristics, such as the host immune response to early childhood infection, immune senescence in older persons, or reproductive hormone interactions with immune function[62]. However, even for these factors, additional observed variation implies further modifying effects. For example, some part of the male excess of EBV prevalence by age and race/ethnicity may be due to the heightened immune response in women to pregnancy-related EBV reactivation[63]; this hypothesis is supported by the more pronounced male excess at young adult (and thus child-bearing) ages overall and particularly in Hispanics, who had a higher mean number of children born to women ages 15–44 than whites, blacks or APIs in California in 1990 (1.55 vs 1.12, 1.32, and 1.10, respectively)[63, 64].

Racial/ethnic differences in associations with socioeconomic situations in early life (suggested by birth place) and later life (suggested by neighborhood SES at diagnosis) also support a variety of environmental influences in the etiology of EBV-positive HL. The higher prevalence of EBV in tumors of foreign- than US-born Hispanics suggests the importance of early-life exposures, perhaps very early childhood infection with EBV and other chronic infections, that are consistent with a depressed-immunity etiologic model of EBV-positive HL. Of interest, EBV tumor prevalences were more elevated in foreign-born than US-born Hispanic young adults despite their lower likelihood of having had IM, a risk factor reported for EBV-positive HL in young adults in mostly white populations[6–8, 65]. In foreign-born Hispanic young adults, it is possible that EBV reactivation occurs from exposure to newly infected young offspring, as a larger mean number of children was born to foreign- than US-born California Hispanic women in 1990 (0.83 vs 0.66, ages 20–24; 1.60 vs 1.32, ages 25–29; 2.36 vs 1.85, ages 30–34)[64]. As stress has been shown to affect control of latent EBV infection in adults[66], the chronic challenges of immigrant life also may contribute to an aberrant immune response to EBV in susceptible individuals, increasing risk of EBV-positive HL. The association of low neighborhood SES with EBV prevalence particularly in US-born Hispanic females could reflect replacement of the relevant early-life exposures in non-US countries of origin with exposures related to poverty in the US. Similarly, the somewhat stronger effect of age on EBV prevalence in US- than foreign-born Hispanic females may reflect the US-born group's relatively diminished exposure to common infections in offspring due to their lower parity. Although most API HL cases also were foreign-born, the absence of a birth place effect on EBV presence in their tumors may be due to the higher SES of Asian than Hispanic immigrants

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to California (e.g., 64.2% of foreign-born Asians vs 27.6% of foreign-born Hispanics with a high school education or more in 1990)[64].

Genetic effects in the etiology of EBV-positive HL also are suggested by our findings. For most California Hispanic young adults during the study period, the prevalence of IM presumably was low, and thus IM is unlikely to be a strong contributor to the observed EBV-positive HL. Alternatively, as the risk of EBV-positive HL in young adults may be stronger in those with HLA DPB1-0301[10], and as the frequencies of DPB1-0301 are ten-fold lower in Mexican Indian than northern European populations[67], other gene-environment interactions may be relevant to EBV-positive HL in Hispanic young adults. In black patients, genetic predisposition may be suggested by the low EBV prevalence and the lack of other study predictors of EBV-positive HL, including neighborhood SES, despite some population similarities with Hispanics in SES distributions (table 5). For example, lower frequencies of DPB1-0301 alleles in various African than northern European populations[67] may contribute in part to the lower prevalence of EBV-positive HL in black than white Californians irrespective of SES. EBV-positive HL has been linked with specific HLA class I regions[27], but the racial/ethnic distribution of these variants has not been described. The limitation to blacks of an association of later-stage HL with EBV prevalence could reflect the demonstrated racial/ethnic differences in cytokine polymorphisms, particularly for interleukin (IL)-6 and IL-10[68], which perturb cellular immune responses and allow HL cells to thrive[69, 70], and whose expression may be induced by the EBV LMP1 protein.

Our results have the strength of being based on uniformly collected and coded data from a large, population-based resource in which HL tumors were subjected to expert histopathologic re-review and uniform EBV detection. Nevertheless, they should be interpreted in light of some limitations. The cases for whom tumor specimens could be obtained differed from the remainder in being more likely to be white, female, with the NS histologic subtype, and of higher neighborhood SES. Nevertheless, the similarity of our findings in whites to reports from others based on more complete case ascertainment suggests that our findings in this group are not strongly biased. As no significant differences occurred in the characteristics of black, Hispanic, and API cases for whom we did and did not obtain specimens, the primary impact of our incomplete specimen retrieval for these groups would be to reduce statistical power; the absence of EBV-positive HL in black children and older adults may be a chance effect based on the extremely small numbers of cases in these groups. Because of small sample sizes, we could not stratify data for blacks by SES; evaluate the joint contributions of birth place and neighborhood SES, which were strongly correlated in our cases; study specific API ethnic groups, despite differences in HL incidence across these groups[71]; or generate meaningful race-specific analyses stratified by the broad age groups postulated to reflect etiologically distinct HL entities[72]. We lacked data to examine the effect of socio-cultural background at an individual level or prior to diagnosis. Our racial/ethnic and birth place classifications were taken from cancer registry data, in which they may be recorded with some error[73]; the availability of birth place data is biased in the registry such that Hispanics without this information tend to be younger, better educated, and US-born[74–76].

Overall, in a diverse US population, we found race/ethnicity to be a significant predictor of EBV-positive HL even after accounting for sociodemographic and clinical differences. In addition, complex variation in racial/ethnic patterns of this form of HL suggests that environmental exposures related to foreign birth place and lower neighborhood SES are associated with a higher prevalence of EBV-positive disease, consistent with a role for early and later-life influences in currently hypothesized etiologic pathways. Further variability with gender may point to the effects of reproduction and the timing of EBV exposure on immune response. For black patients, the lack of apparent predictors of EBV-positive HL, despite an overall lower-SES profile for this group, could indicate a role of genetic factors in disease

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development. For MC, the strong association with EBV irrespective of race/ethnicity suggests a larger component of shared biological influences, although variation in EBV prevalence between US- and foreign-born Hispanics with MC HL demonstrates a role for environmental etiologic factors. Although racial/ethnic variation occurred in both HL incidence rates and EBV prevalences in the study period, the respective race-specific and age-specific patterns in rates and in EBV prevalences were not correlated. Thus, the relative contributions of environmental exposures and genetics to the etiologies of EBV-positive and EBV-negative HL likely differ. Fuller understanding of the implication of racial/ethnic variation to the etiology of EBV-defined HL subtypes could come from examination of EBV-associated incidence rates by race/ethnicity, although the complete series of tumor specimens from racially diverse, population-based cases required for this research has proven daunting to compile.

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Abbreviations

API	Asian/Pacific Islander
CCR	California Cancer Registry
CI	confidence interval
EBV	Epstein-Barr virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
IM	infectious mononucleosis
MC	mixed cellularity
NOS	not otherwise specified
NS	nodular sclerosis
PR	prevalence ratio
SEER	Surveillance, Epidemiology and End Results
SES	socioeconomic status

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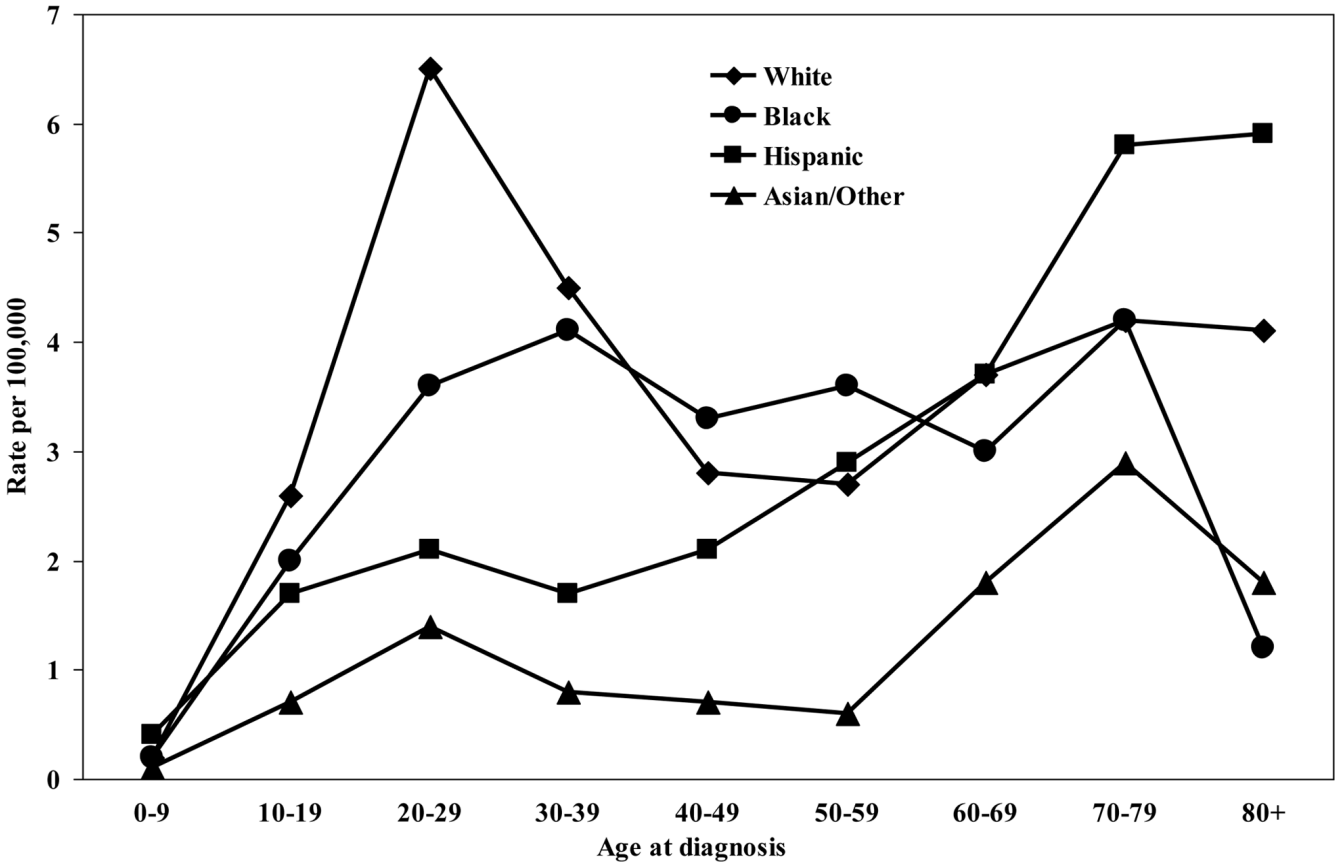

Figure 1.
Age-specific incidence rates of Hodgkin lymphoma by race/ethnicity, California, 1992–97

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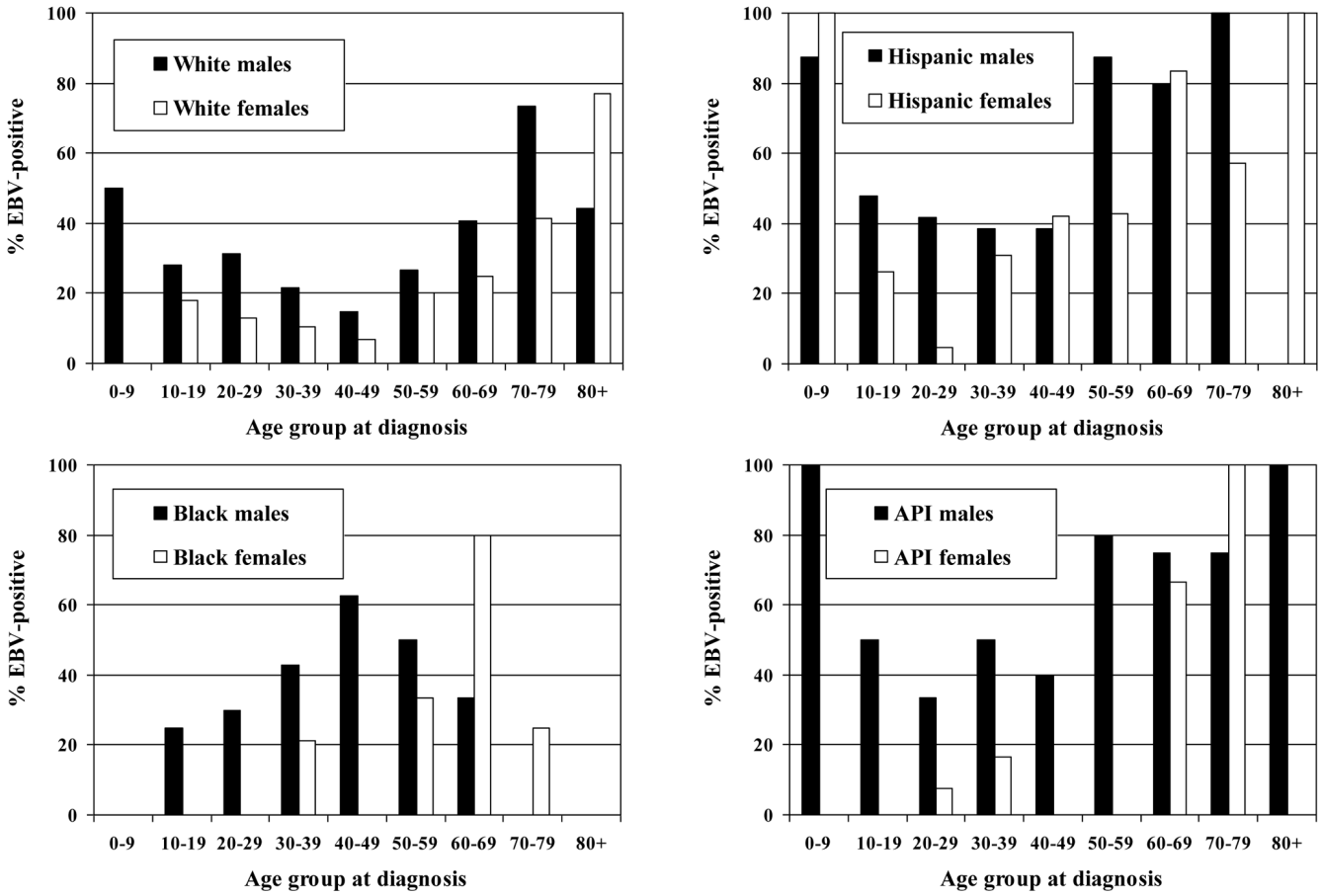

Figure 2.
Percent of Hodgkin lymphoma cases EBV-positive by race/ethnicity, sex and age, California regions, 1988–97

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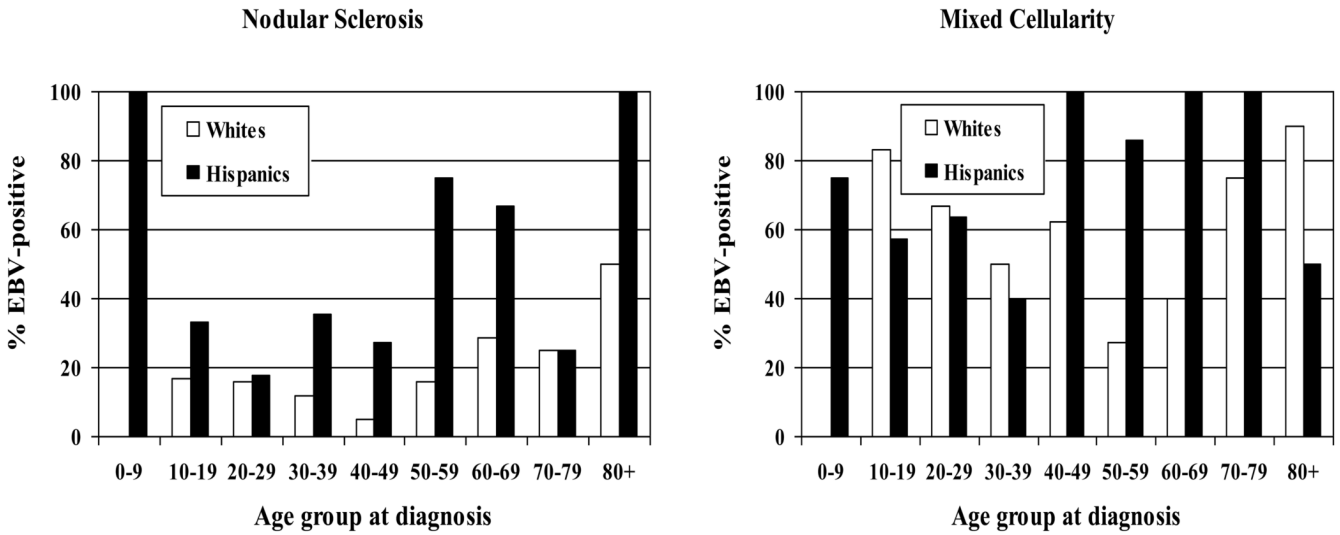

Figure 3.
Percent of Hodgkin lymphoma cases EBV-positive by histologic subtype and age, whites and Hispanics, California regions, 1988–97

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Table 1

Number of Hodgkin lymphoma cases and percentages with EBV-positive tumors in patient demographic and tumor subgroups, by race/ethnicity, California regions, 1988–97

Characteristics	White		Black		Hispanic		Asian/Pacific Is.	
	N	% *EBV*+	N	% *EBV*+	N	% *EBV*+	N	% *EBV*+
Age at diagnosis (years)								
0–9	4	*25.0*	1	*0.0*	13	*92.3*	1	*100.0*
10–19	53	*22.6*	8	*12.5*	44	*38.6*	7	*28.6*
20–29	206	*20.4*	22	*13.6*	58	*27.6*	25	*20.0*
30–39	152	*15.8*	21	*28.6*	26	*34.6*	10	*30.0*
40–49	77	*10.4*	15	*33.3*	32	*40.6*	6	*33.3*
50–59	50	*24.0*	10	*40.0*	15	*66.7*	6	*66.7*
60–69	60	*33.3*	8	*62.5*	16	*81.3*	7	*71.4*
70–79	32	*56.3*	4	*25.0*	11	*72.7*	5	*80.0*
80+	22	*63.6*	0	-	4	*75.0*	1	*100.0*
Sex								
Male	304	*29.9*	36	*41.7*	118	*53.4*	40	*55.0*
Female	352	*17.1*	53	*18.9*	101	*37.6*	28	*17.9*
Histologic subtype								
NS NOS	268	*16.8*	42	*26.2*	83	*30.1*	23	*13.0*
NS grade1	122	*13.1*	7	*0.0*	23	*39.1*	11	*9.1*
NS grade 2	70	*12.9*	5	*20.0*	13	*30.8*	4	*50.0*
NS cellular phase	33	*15.2*	2	*50.0*	17	*47.1*	4	*75.0*
Lymphocyte rich	17	*11.8*	4	*0.0*	6	*16.7*	0	-
Mixed cellularity	91	*59.3*	19	*42.1*	51	*74.5*	20	*80.0*
Inter-follicular	7	*28.6*	3	*100.0*	9	*66.7*	1	*0.0*
Lymphocyte depletion	2	*0.0*	0	-	4	*100.0*	0	-
Not otherwise specified	46	*39.1*	7	*14.3*	13	*46.2*	5	*40.0*
B symptoms								
No	305	*23.3*	33	*24.2*	80	*46.3*	35	*48.6*
Yes	250	*24.4*	27	*29.6*	95	*43.2*	21	*23.8*
Unknown	101	*18.8*	29	*31.0*	44	*52.3*	12	*41.7*
Ann Arbor stage								
I	121	*29.8*	13	*38.5*	35	*60.0*	16	*56.3*
II	281	*16.7*	39	*10.3*	82	*37.8*	28	*25.0*
III	134	*26.9*	24	*45.8*	57	*43.9*	14	*42.9*
IV	97	*26.8*	10	*40.0*	34	*50.0*	8	*37.5*
Unknown*	23	*26.1*	3	*33.3*	11	*63.6*	2	*100.0*
Birth place								
US	359	*24.5*	56	*32.1*	99	*36.4*	16	*37.5*
Not US	31	*29.0*	2	*50.0*	66	*57.6*	33	*39.4*
Unknown	266	*20.3*	31	*19.4*	54	*50.0*	19	*42.1*
Neighborhood SES level								
High	325	*22.2*	11	*45.5*	33	*24.2*	17	*47.1*
Intermediate	279	*23.3*	35	*25.7*	77	*42.9*	39	*35.9*
Low	52	*26.9*	43	*25.6*	109	*55.1*	12	*41.7*
California Region								
Greater Bay Area	656	*23.0*	55	*29.1*	116	*38.8*	58	*39.7*
Southern California	-		34	*26.5*	103	*54.4*	10	*40.0*
TOTAL	**656**		**89**		**219**		**68**	

* cases excluded from subsequent analyses

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Table 2

Prevalence ratios and 95% confidence intervals for EBV presence in Hodgkin lymphoma tumor cells in patient demographic and tumor subgroups, by race/ethnicity, California regions, 1988–97

	Whites						Blacks						Hispanics						Asians/Pacific Islanders					
	Unadjusted			Adjusted*			Unadjusted			Adjusted			Unadjusted			Adjusted			Unadjusted			Adjusted		
		CI			CI			CI			CI			CI			CI			CI			CI	
Characteristics	PR	Low	high	PR	low	high	PR	low	high	PR	low	high	PR	low	high	PR	low	high	PR	low	high	PR	low	high
Age at diagnosis (years)																								
0–14	1.8	0.9	3.6	**1.8**	**1.0**	**3.3**	1.5	0.3	8.1	1.1	0.2	5.8	2.3	1.7	3.2	**2.1**	**1.5**	**3.0**	3.6	2.3	5.6	1.5	0.6	3.7
15–54	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
55–69	2.0	1.4	2.9	**1.5**	**1.0**	**2.2**	2.4	1.3	4.7	**2.9**	**1.3**	**6.6**	2.8	2.1	3.7	**2.2**	**1.6**	**3.0**	2.2	1.1	4.5	1.4	0.6	3.2
70+	3.4	2.5	4.6	**2.3**	**1.6**	**3.2**	1.1	0.2	6.6	2.0	0.3	11.3	2.2	1.4	3.3	**2.0**	**1.2**	**3.2**	2.9	1.5	5.3	1.7	0.8	3.6
Sex																								
Female	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
Male	1.8	1.3	2.4	**1.6**	**1.2**	**2.1**	2.3	1.1	4.5	**2.2**	**1.0**	**4.7**	1.4	1.0	1.9	1.2	0.9	1.6	3.7	1.4	9.6	**3.2**	**1.4**	**7.2**
B symptoms																								
No	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
Yes	1.1	0.8	1.4	1.0	0.8	1.4	1.2	0.5	2.8	1.3	0.5	2.9	1.0	0.7	1.3	1.0	0.7	1.3	0.5	0.2	1.2	0.8	0.3	1.7
Unknown	0.8	0.5	1.3	0.8	0.5	1.2	1.3	0.6	2.9	1.6	0.7	3.5	1.2	0.8	1.8	1.0	0.7	1.4	0.6	0.2	1.7	1.2	0.4	3.9
Histologic subtype																								
NS	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
MC	3.7	2.8	4.9	**2.7**	**2.0**	**3.7**	1.9	0.9	3.8	1.3	0.6	3.0	2.3	1.7	3.1	**2.0**	**1.4**	**2.7**	4.1	2.1	7.9	**3.9**	**2.0**	**7.6**
NOS	2.6	1.7	3.9	**1.7**	**1.1**	**2.6**	0.6	0.1	4.1	0.4	0.1	3.5	1.4	0.8	2.7	1.1	0.6	1.9	2.1	0.6	7.1	1.5	0.4	6.2
Other	0.8	0.3	2.5	0.6	0.2	1.8	1.9	0.7	5.1	2.5	0.8	7.2	1.8	1.1	2.9	1.4	0.9	2.1						
Ann Arbor stage*																								
I–II	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
III–IV	1.3	1.00	1.7	1.1	0.8	1.5	2.6	1.3	5.2	**2.8**	**1.3**	**6.0**	1.0	0.8	1.4	1.0	0.8	1.3	1.1	0.6	2.1	0.8	0.3	1.9
Birth place																								
US	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
Not US	1.3	0.7	2.2	1.1	0.7	1.8	1.6	0.4	6.6	1.6	0.5	5.7	1.5	1.1	2.1	1.1	0.8	1.6	1.0	0.5	2.2	0.7	0.3	1.6
Unknown	0.9	0.6	1.2	1.0	0.7	1.3	0.6	0.2	1.3	0.7	0.3	1.7	1.3	0.9	2.0	**1.5**	**1.0**	**2.1**	1.0	0.4	2.4	0.7	0.3	1.8
Neighborhood SES level																								
High	1.0			1.0			1.0			1.0			1.0			1.0			1.0			1.0		
Intermediate	1.1	0.8	1.4	0.9	0.7	1.2	0.7	0.3	1.8	0.7	0.2	2.3	1.7	0.9	3.3	**1.7**	**1.0**	**2.9**	0.9	0.4	1.9	0.7	0.3	1.7
Low	1.3	0.8	2.0	1.0	0.6	1.6	0.6	0.3	1.6	0.8	0.3	2.3	2.1	1.1	4.0	1.7	0.9	2.9	1.0	0.4	2.6	0.6	0.3	1.7
Region																								
Greater Bay Area							1.0			1.0			1.0			1.0			1.0			1.0		
Southern California							0.8	0.4	1.8	0.6	0.3	1.3	1.5	1.1	2.0	1.3	0.9	1.7	0.9	0.3	2.3	1.5	0.5	4.8

*Missing stage excluded; multivariate models include all variables in table

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Table 3

Number of Hispanic Hodgkin lymphoma cases and percentages with EBV-positive tumors in patient demographic and tumor subgroups, by known birth place, California regions, 1988–97

	Birth place			
	US		Not US	
Characteristics	**N**	***% EBV+***	**N**	***% EBV+***
Age at diagnosis (years)*				
0–9	10	*100.0*	1	*0.0*
10–19	21	*9.5*	9	*77.8*
20–29	24	*20.8*	20	*35.0*
30–39	11	*36.4*	7	*42.9*
40–49	18	*33.3*	7	*57.1*
50–59	3	*33.3*	6	*66.7*
60–69	5	*80.0*	6	*80.0*
70–79	2	*100*	6	*83.3*
80+	1	*100*	1	*0.0*
Sex				
Male	48	*41.7*	35	*57.1*
Female	47	*31.9*	27	*51.9*
Histologic subtype				
NS	67	*26.9*	29	*31.0*
MC	16	*68.8*	24	*83.3*
Other	9	*55.6*	6	*66.7*
NOS	3	*33.3*	3	*33.3*
B symptoms				
No	39	*41.0*	22	*54.6*
Yes	44	*34.1*	26	*53.9*
Unknown	12	*33.3*	14	*57.1*
Ann Arbor Stage				
I–II	49	*42.9*	35	*45.7*
III–IV	45	*30.4*	27	*66.7*
Neighborhood SES level				
High	17	*23.5*	2	*100.0*
Intermediate	36	*30.6*	21	*52.4*
Low	42	*47.6*	39	*53.9*
California Region				
Greater Bay Area	57	*28.1*	29	*51.7*
Southern California	38	*50.0*	33	*57.6*
TOTAL	**95**		**62**	

* p=0.05

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Table 4

Number of Hispanic Hodgkin lymphoma cases and percentages with EBV-positive tumors by age group, sex and birth place, and associated unadjusted prevalence ratios and 95% confidence intervals, California regions, 1988–97

	Birth place															
	US								Not US							
	Males				Females				Males				Females			
Age	N	% EBV+	PR	95% CI	N	% EBV+	PR	95% CI	N	% EBV+	PR	95% CI	N	% EBV+	PR	95% CI
0–14	12	58.3	**2.0**	**1.0–4.2**	6	83.3	**5.1**	**2.3–11.6**	5	80.0	**1.8**	**1.0–3.5**	1	100	**2.4**	**1.4–4.0**
15–54	31	29.0	1.0		37	16.2	1.0		23	43.5	1.0		19	42.1	1.0	
55+	5	80.0	**2.8**	**1.4–5.6**	4	100	**6.2**	**3.0–12.8**	7	85.7	**2.0**	**1.1–3.4**	7	71.4	1.7	0.8–3.4
TOTAL	**48**				**47**				**35**				**27**			

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Table 5

Distribution of social class measures in persons ages 15–54, by race/ethnicity, California, US Census, 1990

Census variable	Whites	Blacks	Hispanics	API
% completing less than high school	14.5	24.7	55.9	23.3
Mean salary and wage income, US dollars	21,318.06	13,920.76	11,090.49	15,911.56
Mean number of children born to women ages 15–54	1.28	1.38	1.80	1.34
% foreign-born	7.9	7.2	60.3	79.8