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Childhood Leukemia Incidence in California: High and Rising in the Hispanic Population

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Abstract

Background—High rates of childhood leukemia incidence have been reported in Latin America and among Hispanic children in the United States. California's large Hispanic population affords an important opportunity to perform a detailed analysis of the leukemia burden among Hispanic children.

Methods—Leukemias diagnosed among non-Hispanic white (NHW), Hispanic, African American (AA), and Asian/Pacific Islander (API) children, aged 0 to 19 years, between January 1, 1990 and December 31, 2012 were obtained from the California Cancer Registry (n=11,084). Age-adjusted incidence rates (AAIR), standardized rate ratios (SRR), and secular trends in incidence (annual percent change [APC]) were analyzed by subtype, race/ethnicity, sex, and age.

Results—Compared to NHWs, acute lymphoblastic leukemia (ALL) incidence was higher among Hispanics (SRR=1.32) and lower among AAs (SRR=0.55) and APIs (SRR=0.91). From 1990 to 2012, ALL incidence increased overall (APC=1.1%), among males (APC=1.0%), females

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(APC=1.3%), Hispanics (APC=1.1%), AAs (APC=1.9%), AA males (APC=2.8%), API males (APC=1.9%), and Hispanic females (APC=1.5%). ALL increased among Hispanic males aged 15 to 19 years (APC=2.5%) and Hispanic females aged 0 to 4 and 15 to 19 years (APC=2.2% and 1.9%, respectively). Acute myeloid leukemia (AML) incidence did not differ among racial/ethnic groups. From 1990 to 2012, overall AML incidence remained stable but increased among Hispanics (APC=1.2%), females (APC=1.0%), Hispanic females (APC=2.3%), and Hispanic females aged 15 to 19 years (APC=3.4%).

Conclusions—Notable differences in childhood leukemia incidence among four racial/ethnic groups in California were observed. Factors which may contribute to these differences include differential exposure to carcinogens and/or genetic susceptibility.

Keywords

leukemia; children; Hispanic; incidence; trends; epidemiology

INTRODUCTION

Worldwide, leukemia is the most common cancer diagnosed among children with acute lymphoblastic leukemia (ALL) occurring most frequently followed by acute myeloid leukemia (AML).[1, 2] Childhood leukemia incidence differs with respect to subtype, race/ethnicity, sex, age, and geographic region.[1–9] Males have a higher risk of developing ALL than females and children aged 0 to 4 years have a higher risk than children aged 5 to 19 years. For AML, males have a slightly higher risk of developing the disease than females and incidence peaks in infancy. The highest incidence rates of childhood ALL have been observed in Costa Rica, Ecuador, Mexico City, and among Hispanics in the United States, and the lowest incidence rates observed in Africa and among African Americans in the United States. The highest incidence rates of childhood AML have been observed in the Philippines and Korea, and the lowest incidence rates observed in Africa.[2, 6, 7, 10–13]

In the United States, approximately 3,800 children are diagnosed with ALL or AML each year.[14] From 1975 to 2012, the incidence of ALL and AML among children aged 0 to 19 years increased significantly by 0.8% per year and 1.1% per year, respectively. During this time period, the percent change in the age-adjusted incidence rate was 54.9% for ALL and 55.9% for AML.[15]

Our study examined incidence rates and trends of leukemia among children aged 0 to 19 years in California by subtype, race/ethnicity, sex, and age. Given that high rates of childhood leukemia have been reported among Hispanics in the United States and internationally, California's large Hispanic population affords an important opportunity to examine the leukemia burden among Hispanic children.

MATERIALS & METHODS

Cases were identified using the California Cancer Registry (CCR). The CCR is a population-based registry which has been collecting information on new cancers diagnosed among California residents since 1988. The CCR follows standardized data collection and quality

control procedures and has consistently met the standards for data quality and completeness set by the North American Association of Central Cancer Registries.[16–23]

Cases of leukemia diagnosed among non-Hispanic white (NHW), Hispanic, non-Hispanic black (hereafter referred to as African American [AA]), and Asian/Pacific Islander (API) children aged 0 to 19 years during the time period January 1, 1990 to December 31, 2012 were included in this study. Subtypes of leukemia were defined according to the Surveillance, Epidemiology, and End Results program's International Classification of Childhood Cancer (ICCC) Recode ICD-O-3/WHO 2008 definition.[15] This definition groups acute lymphoblastic leukemia (ALL) into a single group with other lymphoid leukemias; however, ALL makes up the vast majority (approximately 99 percent) of lymphoid leukemias diagnosed in children.[4] Therefore, the term ALL is used throughout this paper. Cases that were not microscopically confirmed (n=68, 0.6%) or were not the first primary tumor (n=161, 1.4%) were excluded.

Information on the race/ethnicity of patients in the CCR is based primarily on information obtained from the medical record. This information may be based on self-report or by assumptions made by medical personnel. Additionally, the CCR utilizes various methods to enhance the identification of a patient's race/ethnicity and may infer this information based on birthplace, maiden name, surname, or the parents' race/ethnicity.[16] If more than one race was reported for a patient, only the primary race was used. In this study, patients with Hispanic ethnicity were not further categorized by race, whereas non-Hispanic patients were categorized as white, African American, or Asian/Pacific Islander.

The distribution of leukemia cases by subtype, sex, and age among the four racial/ethnic groups was compared by use of chi-square tests. SEER*Stat software from the National Cancer Institute was used to calculate incidence rates and rate ratios.[24] Population estimates for California by race/ethnicity, sex, and age were obtained from the National Center for Health Statistics.[25–27] All rates were age-adjusted to the 2000 U.S. Standard Population using the direct method of standardization and were calculated per 1,000,000 persons.

Trends in the age-adjusted incidence rates (AAIR) were analyzed using JoinPoint Regression Program software from the National Cancer Institute.[28] The JoinPoint regression model fits a series of joined straight lines (i.e., trends) to the AAIR on a logarithmic scale. The slope of each line segment describes the annual percentage change (APC) in the AAIR (and 95% confidence interval [CI]), and line segments are connected by "joinpoints" that denote a statistically significant change in trend ($p < 0.05$).[15] We allowed a minimum of zero joinpoints for each model. The maximum number of joinpoints for each model was based on the Joinpoint software's algorithmic recommendations based on the number of data points. If the model had 23 data points the maximum number of joinpoints allowed was four. If the model had 11 data points the maximum number of joinpoints allowed was one. In most instances, the optimal model had zero joinpoints. Due to the small number of AML cases in race/ethnicity, sex, and age strata, APCs were calculated by combining cases diagnosed in two-year periods (except for the three-year period from 1990 to 1992) in order to provide stable estimates.

RESULTS

From 1990 to 2012, a total of 11,084 incident cases of leukemia were diagnosed among NHW (n=3,699), Hispanic (n=5,803), AA (n=497) and API (n=1,085) children. In each racial/ethnic group, ALL was the most frequent. However, AA children had a larger proportion of AML cases (27.0%) compared to the other groups. Overall, each racial/ethnic group had a larger proportion of cases diagnosed among males and, with the exception of AAs, cases were more frequently diagnosed among 0 to 4 year olds (Table 1).

Compared to NHW children, the annual average age-adjusted incidence rate (AAIR) of all leukemias combined was significantly higher among Hispanic children (43.5 and 55.0, respectively; SRR=1.26, p≤0.01) and significantly lower among AA children (43.5 and 28.5 respectively; SRR=0.65, p≤0.01) (Table 2). The incidence among API children was close to that of NHW children. Similarly, compared to NHWs, childhood ALL was higher among Hispanics (33.7 and 44.5, respectively; SRR=1.32, p≤0.01) and lower among AAs (33.7 and 18.5, respectively; SRR=0.55, p≤0.01) and APIs (33.7 and 30.6, respectively; SRR=0.91, p=0.02). Results for all leukemias combined and ALL were similar for males and females (Table 2).

For AML, the AAIR did not significantly differ by race/ethnicity and sex. For other leukemia subtypes, API children had a significantly higher incidence compared to NHW children (3.0 versus 2.1; SRR=1.42, p≤0.01), especially for males (4.1 versus 2.4; SRR=1.72, p≤0.01; see Table 2).

Trends in ALL

From 1990 to 2012, the incidence of childhood ALL increased significantly overall (APC=1.1%, p≤0.01), among males (APC=1.0%, p≤0.01) and females (APC=1.3%, p≤0.01), as well as among Hispanics (APC=1.1%, p≤0.01) and AAs (APC=1.9%, p=0.03). ALL also increased significantly from 1990 to 2012 among AA males (APC=2.8%, p≤0.01), API males (APC=1.9%, p=0.04), and Hispanic females (APC=1.5%, p≤0.01) (Table 3).

In analyses further stratified by age, ALL incidence increased significantly from 1990 to 2012 among Hispanic males aged 15 to 19 years (APC=2.5%, p≤0.01) as well as among Hispanic females aged 0 to 4 years (APC=2.2%, p≤0.01) and 15 to 19 years (APC=1.9%, p=0.05). On the contrary, ALL incidence remained stable among NHW males and females in all age groups except for NHW females aged 15 to 19 years for whom ALL incidence decreased significantly from 2007 to 2012 (APC= −27.3%, p=0.02) (Table 4). Sex- and age-stratified trends could not be calculated for AA and API children due to small sample size.

Trends in AML

From 1990 to 2012, the overall incidence of AML remained stable (APC=0.6%, p=0.09). However, AML incidence increased significantly among females (APC=1.0%, p≤0.01) and Hispanics (APC=1.2%, p≤0.01), particularly among Hispanic females (APC=2.3%, p≤0.01).

In analyses further stratified by age, AML incidence among Hispanic female children aged 0 to 4 years increased significantly between 1990 and 2004 (APC=7.0%, p≤0.01) and then

decreased between 2004 and 2012 (APC= −2.9%, p=0.33). However, this decrease was not statistically significant. From 1990 to 2012, AML incidence significantly increased among Hispanic female children aged 15 to 19 years (APC=3.4%, p=0.03) and also increased among NHW females aged 0 to 4 years from 1998 to 2012 (APC=6.3%, p=0.03) (Table 4).

DISCUSSION

In this study, Hispanic children had significantly higher incidence of ALL than NHW children, whereas AA and API children had significantly lower incidence. These findings are consistent with previously published studies of children in the United States.[8, 9, 29–32] The observed differences in childhood ALL incidence by race/ethnicity may reflect underlying differences in genetic susceptibility by race/ethnicity. Genome-wide association studies have identified several single nucleotide polymorphisms associated with ALL, which have higher risk allele frequencies in Hispanics compared to NHWs and AAs, partially explaining the higher risk of ALL in Hispanic children.[33, 34] Similarly, candidate gene studies have identified ethnic differences in risk associated with gene variants in several pathways.[35–38] However, only a handful of genetic risk factors for childhood ALL have been discovered, and the proportion of leukemia risk attributable to these known genetic variants is low.[34, 39–43] Moreover, while risk allele frequencies could change within the Hispanic population over long periods of time, genetic susceptibility is unlikely to explain the upward trends in childhood leukemia we observed over an evolutionarily short time period. A recent analysis of California Cancer Registry records from 1988 to 2012 found higher rates of leukemia in children of Hispanic mothers born in the U.S. (and mostly from Mexican descent), compared to children of non-U.S. born Hispanic mothers or children of NHW mothers.[44] While this finding suggests a role for environmental factors in the observed elevated rates of leukemia for Hispanic children in California, characterizing the relative contribution of environmental, sociodemographic, and genetic factors to the racial/ethnic differences in childhood leukemia rates is complex and requires studies with detailed information on these factors.

A growing body of literature has linked numerous environmental hazards to an increased risk of developing childhood leukemia.[1, 45–51] For example, investigators from the California Childhood Leukemia Study (CCLS) have reported that dust concentrations of certain persistent organic pollutants (POPs), including congeners of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs), were associated with an increased risk of ALL.[52, 53] At the same time, the CCLS found that dust levels of certain POPs, including PBDEs, were higher in the homes of Hispanic children than in the homes of NHW children.[52, 54] Interestingly, time trends in PBDE body burdens roughly parallel the observed increases in childhood leukemia incidence rates during the study period (1990–2012), as longitudinal studies suggest that levels of BDEs 47, 99, and 153 in blood from U.S. adults increased from the 1970s to the early 2000s, plateauing in the mid-2000s.[55, 56]

Investigators from the CCLS have also observed ethnic disparities in occupational exposures to putative childhood ALL risk factors, including pesticides and organic solvents. For example, among the fathers participating in the CCLS who were exposed to pesticides at the workplace, the vast majority was Hispanic (87%). Moreover, fathers occupationally exposed

to pesticides were more likely to have a child diagnosed with ALL.[57] Similarly, associations were observed between paternal exposure to organic solvents and childhood ALL for Hispanic fathers, but not for NHW fathers.[58] Ethnic disparities in children's exposure to chemicals at home, as well as ethnic disparities in their parents' exposures to chemicals at work, may contribute to the higher burden of childhood leukemia in Hispanic children. A more complete evaluation of the role of specific environmental factors that disproportionally affect the Hispanic community in the increased risk of leukemia in Hispanic children is warranted.

To our knowledge, our study demonstrated for the first time that increasing trends in ALL and AML incidence among female children overall and among Hispanic children specifically, were primarily due to significant increases in Hispanic female incidence. There is not current literature to explain the trends for Hispanic female children identified here. In fact, though gender difference for childhood leukemia incidence has long been noted, with predominance among males, the basis for this remains largely unexplained.

When analyses were further stratified by age, significant increases in ALL incidence were observed among Hispanic males and females in the highest age group of 15 to 19 years. This could be due in part to prolonged and cumulative exposure to environmental carcinogens.

Despite having lower incidence, a significant increase in ALL was observed among AA children, particularly among males. The published literature regarding trends in ALL incidence among AA children in the United States provides inconsistent findings. A recent study by Siegel et al. reported an APC of 2.0% for lymphoid leukemia among non-Hispanic black children aged 0 to 19 years in the United States during the time period from 2001 to 2009, but this increase was not statistically significant.[59] Similarly, Xie et al. reported a statistically significant APC of 2.2% for black males and a non-significant APC of 1.8% for black females, aged 0 to 19 years, from 1973 to 1998 in the SEER 9 regions of the United States.[60] On the contrary, Linabery and Ross reported an APC of −2.1% for ALL among black children aged 0 to 19 years in the SEER 13 regions of the United States from 1992–2004 but this decrease was not statistically significant.[61] Given the small number of cases of ALL diagnosed among AA children in California each year, our finding of an increasing trend in this population should be interpreted with caution, especially in the context of the inconsistent findings reported in the literature. Future studies should evaluate the trend of ALL incidence among AA children to see if a significant increase is replicated.

This study has some limitations that should be considered. Although California has a very large Hispanic population, mostly from Mexican origin (83%), Hispanics residing in California may not be representative of those living throughout the United States and thus our findings are not generalizable to all Hispanics.

Race/ethnicity of patients in the CCR is based primarily on information contained in the medical record. This information may be based on self-report by the patient (or the patient's family), by assumptions made by medical personnel, or inferred by cancer registry personnel based on the patient's birthplace or the race/ethnicity of the patient's parents. How often race/ethnicity in the CCR is determined by self-report versus other means is unknown. As

such, misclassification of race/ethnicity is known to exist in the CCR and can impact the accuracy of incidence rates.[62] Several studies evaluating the quality of race and ethnicity in cancer registry data indicate high agreement for race and moderate agreement for Hispanic ethnicity between cancer registry and self-reported data.[62, 63] Overall, the effect of such misclassification in this study was likely an underreporting of Hispanic ethnicity in the cancer registry, suggesting an underestimation of incidence rates among Hispanic children.

Imprecise population estimates also impact the accuracy of incidence rates. The Census strives to count every person living in the United States, regardless of immigration status; however, the estimated undercount of Hispanic children aged less than 18 years was 5.0% in 1990 and 2.1% in 2010.[64, 65] An undercount of the Hispanic population would result in artificially high incidence rates for this group. However, given that the incidence of childhood leukemia among Hispanics has increased while the undercount of Hispanic children by the Census has decreased, it is unlikely that the observed increase in incidence among Hispanics can be explained by the undercount in the population estimates.

Socioeconomic status (SES) is associated with both childhood leukemia incidence and race/ethnicity. This study did not include information on SES because population estimates by SES are only available for Census years. Future studies should include information on SES to evaluate the effect modification on risk factors for childhood leukemia, particularly race/ethnicity.

In conclusion, ALL incidence was significantly higher among Hispanic children and significantly lower among AA and API children compared to NHWs. Furthermore, ALL and AML incidence significantly increased among Hispanic children, predominantly among Hispanic females, and remained stable among NHW children. There is some evidence to suggest that racial/ethnic differences in childhood ALL incidence reflect differences in genetic susceptibility as well as differences in patterns of carcinogenic exposure between populations. However, more research on the underlying causes (environmental or others) of the disproportionate burden of leukemia in Hispanic children is warranted.

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Table 1

Characteristics of childhood leukemia cases by race/ethnicity, California, 1990–2012 (n=11,084)

Variable	NHW (n=3,699)		Hispanic (n=5,803)		AA (n=497)		API (n=1,085)	
	n	%	n	%	n	%	n	%
Subtype[*]								
ALL	2,861	77.3	4,711	81.2	324	65.2	780	71.9
AML	657	17.8	852	14.7	134	27.0	227	20.9
Other	181	4.9	240	4.1	39	7.8	78	7.2
Sex								
Male	2,110	57.0	3,269	56.3	280	56.3	620	57.1
Female	1,589	43.0	2,534	43.7	217	43.7	465	42.9
Age at Diagnosis[*]								
0 to 4 years	1,707	46.1	2,574	44.4	172	34.6	516	47.6
5 to 9 years	861	23.3	1,325	22.8	128	25.8	236	21.8
10 to 14 years	560	15.1	971	16.7	116	23.3	165	15.2
15 to 19 years	571	15.4	933	16.1	81	16.3	168	15.5

[*] p is ≤ 0.01

Table 2

AAIRs and SRRs for leukemias diagnosed among Hispanic, AA, and API children compared to NHW children, California, 1990 to 2012

Subtype and Racial/Ethnic Group	Both Sexes			Male			Female		
	AAIR	SRR (95% CI)	Ratio P-Value	AAIR	SRR (95% CI)	Ratio P-Value	AAIR	SRR (95% CI)	Ratio P-Value
Leukemias (all combined)									
NHW	43.5			48.3			38.5		
Hispanic	**55.0**	**1.26 (1.21 – 1.32)**	**≤ 0.01**	**60.6**	**1.25 (1.19 – 1.32)**	**≤ 0.01**	**49.1**	**1.28 (1.20 – 1.36)**	**≤ 0.01**
AA	**28.5**	**0.65 (0.60 – 0.72)**	**≤ 0.01**	**31.5**	**0.65 (0.57 – 0.74)**	**≤ 0.01**	**25.4**	**0.66 (0.57 – 0.76)**	**≤ 0.01**
API	42.4	0.97 (0.91 – 1.04)	0.46	47.1	0.97 (0.89 – 1.07)	0.59	37.5	0.97 (0.88 – 1.08)	0.64
ALL									
NHW	33.7			38.0			29.1		
Hispanic	**44.5**	**1.32 (1.26 – 1.39)**	**≤ 0.01**	**49.5**	**1.30 (1.23 – 1.39)**	**≤ 0.01**	**39.2**	**1.35 (1.25 – 1.45)**	**≤ 0.01**
AA	**18.5**	**0.55 (0.49 – 0.62)**	**≤ 0.01**	**20.7**	**0.54 (0.46 – 0.63)**	**≤ 0.01**	**16.4**	**0.56 (0.47 – 0.67)**	**≤ 0.01**
API	**30.6**	**0.91 (0.84 – 0.98)**	**0.02**	34.2	0.90 (0.81 – 1.00)	0.05	26.7	0.92 (0.81 – 1.04)	0.17
AML									
NHW	7.7			8.0			7.4		
Hispanic	8.2	1.06 (0.95 – 1.17)	0.29	8.5	1.06 (0.92 – 1.22)	0.43	7.9	1.05 (0.91 – 1.23)	0.51
AA	7.7	1.00 (0.82 – 1.20)	> 0.99	7.8	0.97 (0.74 – 1.26)	0.89	7.7	1.03 (0.77 – 1.35)	0.89
API	8.8	1.14 (0.98 – 1.33)	0.10	8.8	1.10 (0.89 – 1.36)	0.39	8.8	1.18 (0.94 – 1.48)	0.14
Other Subtypes									
NHW	2.1			2.4			1.9		
Hispanic	2.3	1.08 (0.89 – 1.32)	0.46	2.6	1.09 (0.84 – 1.42)	0.55	2.0	1.07 (0.79 – 1.45)	0.72
AA	2.3	1.06 (0.73 – 1.50)	0.81	3.1	1.29 (0.81 – 1.99)	0.28	1.4	0.75 (0.37 – 1.38)	0.43
API	**3.0**	**1.42 (1.07 – 1.86)**	**≤ 0.01**	**4.1**	**1.72 (1.21 – 2.41)**	**≤ 0.01**	1.9	1.02 (0.62 – 1.64)	> 0.99

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. Standard Population.

Note: Boldface indicates statistical significance ($p < 0.05$).

Table 3

Trend (APC) in the AAIR of childhood leukemia by subtype, race/ethnicity, and sex, California, 1990–2012

Sex	Race/Ethnicity	Time Period	APC	95% CI	P-Value
ALL					
Both Sexes	All Racial/Ethnic Groups*	1990–2012	**1.1**	0.8 – 1.5	≤ **0.01**
	NHW	1990–2012	0.5	−0.1 – 1.1	0.10
	Hispanic	1990–2012	**1.1**	0.5 – 1.7	≤ **0.01**
	AA	1990–2012	**1.9**	0.2 – 3.7	**0.03**
	API	1990–2012	1.2	−0.2 – 2.7	0.09
Male	All Racial/Ethnic Groups*	1990–2012	**1.0**	0.5 – 1.5	≤ **0.01**
	NHW	1990–2012	0.5	−0.4 – 1.4	0.26
	Hispanic	1990–1992	25.0	−2.7 – 60.5	0.08
		1992–2012	0.1	−0.6 – 0.8	0.72
	AA	1990–2012	**2.8**	0.8 – 5.0	≤ **0.01**
	API	1990–2012	**1.9**	0.1 – 3.7	**0.04**
Female	All Racial/Ethnic Groups*	1990–2012	**1.3**	0.7 – 1.8	≤ **0.01**
	NHW	1990–2012	0.5	−0.5 – 1.5	0.30
	Hispanic	1990–2012	**1.5**	0.9 – 2.2	≤ **0.01**
	AA	1990–2012	1.1	−2.1 – 4.4	0.48
	API	1990–2012	0.5	−1.6 – 2.7	0.61
AML					
Both Sexes	All Racial/Ethnic Groups*	1990–2012	0.6	−0.1 – 1.3	0.09
	NHW	1990–2012	0.5	−1.1 – 2.1	0.51
	Hispanic	1990–2012	**1.2**	0.6 – 1.8	≤ **0.01**
	AA	1990–2012	−0.7	−3.1 – 1.8	0.55
	API	1990–2012	−1.0	−3.2 – 1.2	0.31
Male	All Racial/Ethnic Groups*	1990–2012	0.2	−0.9 – 1.2	0.71
	NHW	1990–2012	0.4	−1.4 – 2.3	0.62
	Hispanic	1990–2012	0.3	−1.1 – 1.8	0.64
	AA	1990–2012	−0.5	−3.3 – 2.4	0.71
	API	1990–1996	−11.7	−23.4 – 1.7	0.07

Sex	Race/Ethnicity	Time Period	APC	95% CI	P-Value
		1996–2012	0.2	−2.1 – 2.5	0.84
Female	All Racial/Ethnic Groups*	1990–2012	**1.0**	0.3 – 1.8	**≤ 0.01**
	NHW	1990–2012	0.6	−1.6 – 2.9	0.55
	Hispanic	1990–2012	**2.3**	0.9 – 3.8	**≤ 0.01**
	AA	1990–2012	−0.7	−5.7 – 4.5	0.75
	API	1990–2012	0.1	−4.3 – 4.6	0.98

*Includes children of other and unknown races.

Note: Boldface indicates statistical significance ($p < 0.05$).

Table 4

Trend (APC) in the AAIR of childhood leukemia by subtype, race/ethnicity, sex, and age, California, 1990–2012

Race/Ethnicity	Sex	Age (years)	Time Period	APC	95% CI	P-Value
ALL						
Overall *	Both	0 to 19	1990–2012	**1.1**	0.8 – 1.5	≤ **0.01**
NHW	Male	0 to 4	1990–2012	1.2	−0.2 – 2.7	0.09
		5 to 9	1990–2012	0.9	−1.0 – 2.9	0.35
		10 to 14	1990–2012	−1.9	−4.0 – 0.2	0.07
		15 to 19	1990–2012	−0.6	−3.1 – 2.0	0.62
	Female	0 to 4	1990–2012	0.8	−0.5 – 2.1	0.23
		5 to 9	1990–2012	0.9	−1.0 – 2.9	0.35
		10 to 14	1990–2012	0.1	−2.9 – 3.1	0.96
		15 to 19	1990–2007	0.2	−3.9 – 4.5	0.92
			2007–2012	**−27.3**	−44.4 – −5.0	**0.02**
Hispanic	Male	0 to 4	1990–2012	−0.1	−0.9 – 0.7	0.87
		5 to 9	1990–2012	0.7	−0.3 – 1.7	0.15
		10 to 14	1990–1992	109.8	−2.7 – 352.6	0.06
			1992–2012	−0.2	−2.3 – 1.9	0.85
		15 to 19	1990–2012	**2.5**	0.7 – 4.2	≤ **0.01**
	Female	0 to 4	1990–2012	**2.2**	1.3 – 3.1	≤ **0.01**
		5 to 9	1990–2012	0.6	−1.0 – 2.1	0.46
		10 to 14	1990–2012	1.4	−0.2 – 3.0	0.09
		15 to 19	1990–2012	**1.9**	0.03 – 3.8	**0.05**
AML						
Overall *	Both	0 to 19	1990–2012	0.6	−0.1 – 1.3	0.09
NHW	Male	0 to 4	1990–2012	2.1	−1.4 – 5.8	0.21
		5 to 9	1990–2012	~	~	~
		10 to 14	1990–2012	−1.1	−5.2 – 3.1	0.56
		15 to 19	1990–2012	0.1	−2.5 – 2.8	0.91
	Female	0 to 4	1990–1998	−8.7	−22.0 – 6.9	0.21
			1998–2012	**6.3**	0.8 – 12.1	**0.03**

Race/Ethnicity	Sex	Age (years)	Time Period	APC	95% CI	P-Value
		5 to 9	1990–2012	1.0	−6.5 – 9.0	0.78
		10 to 14	1990–2012	~	~	~
		15 to 19	1990–2012	0.1	−4.1 – 4.5	0.94
Hispanic	Male	0 to 4	1990–2012	1.9	−0.4 – 4.2	0.10
		5 to 9	1990–2012	−3.1	−7.4 – 1.5	0.16
		10 to 14	1990–2012	2.1	−2.2 – 6.5	0.30
		15 to 19	1990–2012	−0.8	−3.2 – 1.7	0.50
	Female	0 to 4	1990–2004	**7.0**	3.4 – 10.7	**≤ 0.01**
			2004–2012	−2.9	−9.3 – 4.0	0.33
		5 to 9	1990–2012	0.8	−5.0 – 6.8	0.78
		10 to 14	1990–1996	24.8	−6.0 – 65.7	0.10
			1996–2012	−1.7	−6.2 – 2.9	0.39
		15 to 19	1990–2012	**3.4**	0.3 – 6.6	**0.03**

* Includes children of all racial/ethnic groups including unknown.

Note: Boldface indicates statistical significance ($p < 0.05$).

~ The APC could not be calculated due to zero counts in one or more cell.