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Journal of Cancer Prevention & Current Research

Research Article

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Acute leukemia in adult Hispanic Americans: differences in incidence rates by nativity

Abstract

The incidence pattern of adult acute leukemia (AL) in Hispanics is distinct, with increased B-cell acute lymphoblastic leukemia (ALL) and acute promyelocytic leukemia (APL) and decreased non-APL acute myeloid leukemia (AML). To better understand genetic versus environmental contributors, we assessed AL incidence rates in a population of adult California Hispanics according to birthplace. Using data from California AL patients ≥20 diagnosed between 2000-2009, incidence rate ratios (IRR) were employed to compare incidence rates of AL in foreign- versus United States (US)-born Hispanics. Compared to whites, Hispanics had increased incidence rates of B-cell ALL and APL, IRR2.13 (1.93-2.35) and 1.33 (1.12-1.57), respectively. No nativity differences in B-cell ALL were noted. Foreign-born Hispanics had a higher incidence rate of APL versus US-born Hispanics (IRR 1.79, 1.11-2.94). For adult Hispanics, increased B-cell ALL incidence rates may be due to heritable genetic factors; increased APL incidence rates may be due to as yet unknown environmental exposures.

Keywords: acute leukemia, Hispanic, nativity, incidence, racial/ethnic differences

Volume 1 Issue 1 - 2014

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Received: May 22, 2014 | **Published:** May 28, 2014

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; IRR, incidence rate ratios; CCR, california cancer registry; CIs, confidence intervals; IRR, incidence rate ratios

Introduction

Acute leukemia (AL) encompasses a heterogeneous spectrum of diseases with divergent etiologies, prognoses and treatments. Broadly classified into the two main sub types acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), AL afflicts approximately 20,000 patients each year in the United States (US), and is the cause of about 10,000 annual deaths.[1] At the direction of the consensus recommendations of the World Health Organization, clinical, morphologic, molecular, genetic and immune phenotypic data is required to classify and risk stratify AL. This reproducible framework affords the opportunity to correlate detailed diagnostic information with descriptive epidemiologic observations, with the expectation that this will elucidate potential causal factors as well as identify high-risk populations on which further research should be focused. These efforts are crucial, as the etiology of AL is for the most part unknown.[2]

Incidence patterns of AL by ethnicity suggest differences in host susceptibility, and while modified by age and sex, remain significant. In the US, blacks and Asians typically have the lowest incidence rates of B-cell ALL;[3] these groups, along with Asian-Pacific Islanders, also have lower incidence rates of AML compared with whites.[3] In contrast, across all age groups, Hispanics have the highest incidence rates of B-cell ALL.[3,4] In addition, while AML incidence rates in Hispanics, like blacks, are lower than whites, the incidence rate of acute promyelocytic leukemia (APL) is higher, irrespective of age.[1,3,4]

The degree to which these ethnic incidence variations could be due to environmental exposures, differences in inherited genetic susceptibility, or a combination of these factors remains unknown. Therefore, investigations of incidence patterns in patients with variable environmental exposures and homogenous genetic backgrounds could help to ascertain the degree to which environmental or genetic factors contribute to the observed differences in incidences between ethnicities, ultimately enriching the understanding of AL. However, although valuable, studies such as these evaluating AL incidence differentials between foreign- and US-born populations are few. One such study evaluating an Asian population did not show incidence differences based on nativity,[5] and another involving Puerto Rican patient was significantly limited by a small sample size and other factors.[6]

Hispanics comprise 38% of the California population, and 40% of California Hispanics are born outside the US.[7,8] Therefore, we utilized population-based California Cancer Registry (CCR) data enhanced with nativity data.[9] to assess incidence rates of AL in Hispanic Californians by nativity, with a hypothesis that this would inform the relevance of genetic or environmental factors on the etiology of AL.

Materials and methods

Cancer incidence data were obtained from the CCR, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

Patients were included if they were age 20 and older, living in California, and diagnosed between 2000-2009 with AL, as defined by International Classification of Diseases for Oncology 3rd Edition histology codes (B-cell ALL: 9727, 9728, 9835, 9836; T-cell ALL: 9729 and 9837; non-APL AML: 9840, 9861, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9930, 9931; APL: 9866). We limited our assessment to adults because of the well-recognized epidemiologic differences between adult and childhood leukemias.[10] Given previous reports of incidence differences between Hispanics and whites in adult APL and non-APL AML, these subtypes were considered independently;[1,3,4] B- and T-cell ALL were considered independently due to the differing clinical manifestations, incidence rates and prognosis of these conditions. Unclassified AL cases were excluded from this analysis because of limited numbers.

Registry data on race and ethnicity, categorized here as white non-Hispanic and Hispanic any race were abstracted from patients' medical

records. The North American Association of Central Cancer Registries Hispanic Identification Algorithm, based on surname, maiden name, and/or birthplace, was used to improve the classification of Hispanic ethnicity.[11] Among Hispanics in the present analysis, birthplace information was available for 80%. For those whose birthplace was not available, nativity was imputed using a validated method based on the first five digits of the Social Security number.[12]

Corresponding population estimates were obtained from the 2000 Census Summary Files 3, and estimates by nativity were derived from the 20% Integrated Public-Use Microdata Sample of the censuses.[13] SEER* Stat software (Version 7.0.8) was used to compute age-adjusted incidence rates per 100,000 people, standardized to the 2000 US standard million population, and 95% confidence intervals (CIs). Incidence rate ratios (IRR) and corresponding CIs were calculated to estimate the magnitude of differences between rates. We calculated incidence rates for two time periods: 2000-2009, the most recent, largest time period for which data were available from the CCR, and 2000-2004, the most recent time period for which nativity-specific population counts were available, due to uncertainties associated with extrapolating nativity-specific population counts from the 2000 Census. Multiple testing p-values were adjusted using Bonferroni correction.

Results

Table 1 summarizes the incidence rates and IRRs of B- and T-cell ALL, APL and non-APL AML in whites and Hispanics, as well as the incidence rates and IRRs of foreign and US-born Hispanics with respect to these AL subtypes. As previously described, compared to whites Hispanics have a higher incidence rate of B-cell ALL, a lower rate of non-APL AML, and a higher rate of APL. While the nativity analysis revealed no significant difference in the incidence rate of B-cell ALL between US- and foreign-born Hispanics, foreign-born Hispanics had a higher incidence rate of APL compared with those born in the US. T-cell ALL did not vary by ethnicity, and due to limited numbers, no conclusions regarding nativity could be made. Age-adjusted incidence rates of ALs were not different during the two periods assessed, 2000-2004 and 2000-2009 (Table 2). To determine the degree to which age impacted these findings, the age distribution by 15-year increments and associated incidence rates were calculated (Table 3). Comparisons were made based on race/ethnicity and, within the Hispanic population, nativity.

Table 1 Age-adjusted incidence rates (per 100,000 person-years) of adult acute leukemiasa and incidence rate ratios (IRR) by race/ethnicity (2000-2009) among whites and Hispanics and nativity among Hispanics (2000-2004)

Acute Leukemia Subtype	Race/Ethnicity[b] Or Nativity[c]	Cases	Incidence Rate* (95% CI)	IRR (95% CI)
B-Cell ALL[b]	White	784	0.60 (0.56-0.65)	1.00 (reference)
	Hispanic	956	1.35 (1.25-1.45)	2.24 (2.03-2.48)**
T-Cell ALL[b]	White	59	0.05 (0.04-0.07)	1.00 (reference)
	Hispanic	36	0.04 (003-0.06)	0.83 (0.52-1.33)
Non-APL AML[b]	White	5598	3.91 (3.81-4.02)	1.00 (reference)
	Hispanic	1540	3.13 (2.96-3.31)	0.80 (0.75-0.85)**
APL[b]	White	369	0.29 (0.26-0.32)	1.00 (reference)
	Hispanic	275	0.38 (0.33-0.43)	1.33 (1.12-1.57)**
B-Cell ALL[c]	US-Born	160	1.24 (1.04-1.48)	1.00 (reference)
	Foreign-Born	256	1.32 (1.15-1.52)	1.07 (0.85-1.34)
T-Cell ALL[c]	US-Born	6	§	§
	Foreign-Born	7	§	§
Non-APL AML[c]	US-Born	316	3.64 (3.22-4.10)	1.00 (reference)
	Foreign-Born	413	3.21 (2.86-3.58)	0.88 (0.75-1.04)
APL[c]	US-Born	33	0.23 (0.15-400.34)	1.00 (reference)
	Foreign-Born	82	0.41 (0.32-0.53)	1.79 (1.11-2.94)*

B-Cell ALL, B-cell acute lymphoblastic leukemia; T-Cell ALL, T-cell acute lymphoblastic leukemia; non-APL AML, non-acute promyelocytic leukemia acute myeloid leukemia; APL, acute promyelocytic leukemia

[a]Standardized to the 2000 US population age standard

[b]Age-adjusted incidence rates (per 100,000 person-years) of acute leukemias and incidence rate ratios (IRR) by race/ethnicity among whites and Hispanics age ≥20 in California, 2000-2009

[c]Age-adjusted incidence rates (per 100,000 person-years) of hematological malignancies and incidence rate ratios by nativity among Hispanics age ≥20 in California, 2000-2004

[§]Insufficient case counts to calculate reliable rate. *= p<0.05; **= p <0.01

Citation: Pollyea DA, Kohrt HE, Yang J, et al. Acute leukemia in adult Hispanic Americans: differences in incidence rates by nativity. *J Cancer Prev Curr Res.* 2014;1(1):14–19. DOI: 10.15406/jcpcr.2014.01.00005

Table 2 Comparison of age-adjusted incidence rates (per 1000,000 person-years) of acute leukemias among Hispanics age ≥20 in California, 2000-2004 and 2000-2009[a]

Acute Leukemia	Database	Cases	Incidence Rate* (95% CI)
B-Cell ALL	2000-2004	416	1.27(1.13-1.41)
	2000-2009	956	1.35 (1.25-1.45)
T-Cell ALL	2000-2004	13	0.03 (0.02-0.06)
	2000-2009	37	0.04 (0.03-0.06)
Non-APL AML	2000-2004	729	3.37 (3.10-3.65)
	2000-2009	1540	3.13 (2.96-3.31)
APL	2000-2004	115	0.35 (0.28-0.42)
	2000-2009	275	0.38 (0.33-0.43)

B-Cell ALL, B-Cell acute lymphoblastic leukemia; T-Cell ALL, T-Cell acute lymphoblastic leukemia; non-APL AML, non-Acute promyelocytic leukemia acute myeloid leukemia; APL, acute promyelocytic leukemia
[a]Standardized to the 2000 US population age standard

Discussion

In the large Hispanic population of California, we confirm previous observations that the incidence rate of B-cell ALL and APL is higher in Hispanics than whites, while the incidence rate for non-APL AML is lower.[3,4] For the first time, we report that foreign-born status did not impact incidence rates of B-cell ALL, but was associated with a higher increased incidence rate of APL and a lower incidence rate of non-APL AML.

Despite observations suggesting a major pathogenic contribution from environmental factors to B-cell ALL,[14] the lack of a nativity difference reported here suggests heritable genetic traits may be additionally relevant. This is supported by observations that single nucleotide gene polymorphisms in genes such as *CYP1A1* and *GATA3* and gene rearrangements of *CRLF2* known to be associated with B-cell ALL are more commonly observed in Hispanic patients,[15–17] and that Hispanic children with increased genome-wide Native American ancestry have a higher incidence of this disease.[18]

The increased incidence rate of APL in Hispanics reported here and elsewhere,[1,3,4] suggests an underlying genetic propensity for this condition, supported by the observation that Hispanic APL patients have a disproportionate prevalence of one PML gene breakpoint site (bcr1) compared to non-Hispanics.[19] However, the lower incidence rate of APL in US versus foreign-born Hispanics reported here was unexpected. One retrospective cohort study suggested that US Hispanics do not have a greater lifetime incidence of APL, but instead have a significant difference in age distribution at diagnosis, and it is this variable that explains the higher disease incidence in Hispanics.[20] In this analysis, the incidence rates are age-adjusted, which accounts for the differences in the underlying population's age structures among the groups being compared, and therefore, our reported differential incidence rates between populations cannot be explained by differences in age composition.

Alternatively, this observation may suggest etiological contributions from unstudied environmental exposures. Candidates may include viruses, ionizing radiation, benzene, herbicides, embalming fluids and ethylene oxides. Smoking is associated with an increased risk of AML,[21] and there is an increased prevalence of smoking in Latin America;[22] however, although the numbers are small, there does not appear to be an association between smoking and the incidence rate of APL.[23] Therapy-related causes may account for the increased incidence rate of APL in foreign versus US-born Hispanics. The incidence rate of therapy-related APL, which occurs after treatment for malignant and non-malignant conditions, is increasing,[24] and since different oncology practice patterns exist between the US and Latin America.[25] APL incidence rate differences between US and foreign-born Hispanics may be partially explained by previous treatments patients received in their native countries for malignancies diagnosed prior to moving to the US.

Table 3 Age-adjusted incidence rates (per 100,000 person-years) of adult acute leukemiasa and incidence rate ratios (IRR) by race/ethnicity (2000-2009)[b] among whites and Hispanics and nativity (2000-2004)[c] among Hispanics. All data are stratified by 15-year age groupings.

Acute Leukemia Subtype	Age Range	Race/Ethnicity or Nativity	Cases	Incidence Rate (95% CI)	IRR (95% CI)	Ratio P-Value
2000-2009 Data[b]						
B-Cell ALL	20-34	White	146	0.49 (0.42-0.58)		
		Hispanic	399	1.22 (1.11-1.35)	2.48 (2.04-3.01)**	0
	35-49	White	184	0.48 (0.41-0.56)		
		Hispanic	273	1.10 (0.97-1.24)	2.28 (1.89-2.77)**	0
	50-64	White	205	0.63 (0.55-0.72)		
		Hispanic	171	1.48 (1.27-1.72)	2.34 (1.90-2.89)**	0
	65-79	White	152	0.86 (0.73-1.01)		
		Hispanic	90	1.90 (1.53-2.34)	2.21 (1.68-2.88)**	0
	≥80	White	97	1.22 (0.99-1.49)		
		Hispanic	23	1.70 (1.08-2.55)	1.39 (0.84-2.21)	0.203
T-Cell ALL	20-34	White	23	0.08 (0.05-0.12)		
		Hispanic	24	0.07 (0.05-0.11)	0.94 (0.51-1.74)	0.937
	35-49	White	19	0.05 (0.03-0.08)		
		Hispanic	7	0.03 (0.01-0.06)	0.54 (0.19-1.34)	0.219
	50-64	White	7	0.02 (0.01-0.04)		
		Hispanic	<5	§	§	§
	65-79	White	8	0.05 (0.02-0.09)		
		Hispanic	<5	§	§	§
	≥80	White	<5	§		
		Hispanic	0	0.00 (0.00-0.28)	§	§

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Table continued...

Acute Leukemia Subtype	Age Range	Race/Ethnicity or Nativity	Cases	Incidence Rate (95% CI)	IRR (95% CI)	Ratio P-Value
Non-APL AML	20-34	White	222	0.76 (0.66-0.86)		
		Hispanic	261	0.80 (0.71-0.91)	1.06 (0.88-1.28)	0.538
	35-49	White	570	1.46 (1.34-1.59)		
		Hispanic	347	1.41 (1.27-1.57)	0.97 (0.84-1.11)	0.642
	50-64	White	1,345	4.13 (3.91-4.35)		
		Hispanic	344	3.04 (2.73-3.38)	0.74 (0.65-0.83)**	0
	65-79	White	2,038	11.55 (11.05-12.06)		
		Hispanic	407	8.92 (8.07-9.83)	0.77 (0.69-0.86)**	0
	≥80	White	1,423	18.02 (17.09-18.98)		
		Hispanic	181	13.57 (11.66-15.70)	0.75 (0.64-0.88)**	0
APL	20-34	White	49	0.17 (0.12-0.22)		
		Hispanic	109	0.34 (0.28-0.41)	2.02 (1.43-2.90)**	0
	35-49	White	109	0.29 (0.24-0.35)		
		Hispanic	96	0.38 (0.31-0.47)	1.32 (0.99-1.76)	0.055
	50-64	White	114	0.35 (0.29-0.42)		
		Hispanic	43	0.38 (0.28-0.51)	1.08 (0.74-1.55)	0.718
	65-79	White	74	0.42 (0.33-0.53)		
		Hispanic	25	0.54 (0.35-0.79)	1.28 (0.78-2.05)	0.344
	≥80	White	23	0.29 (0.19-0.44)		
		Hispanic	<5	§	§	§
2000-2004 Data[c]						
B-Cell ALL	20-34	US-born	82	1.19 (0.94-1.49)		
		Foreign-born	92	1.02 (0.82-1.26)	0.86 (0.62-1.18)	0.356
	35-49	US-born	36	0.98 (0.68-1.36)		
		Foreign-born	91	1.14 (0.92-1.41)	1.17 (0.79-1.78)	0.489
	50-64	US-born	20	1.12 (0.68-1.73)		
		Foreign-born	46	1.45 (1.06-1.94)	1.30 (0.75-2.32)	0.398
	65-79	US-born	19	1.98 (1.19-3.10)		
		Foreign-born	21	1.74 (1.07-2.69)	0.88 (0.45-1.74)	0.812
	≥80	US-born	<5	§		
		Foreign-born	6	1.93 (0.71-4.20)	§	§
T-Cell ALL	20-34	US-born	<5	§		
		Foreign-born	5	0.06 (0.02-0.13)	§	§
	35-49	US-born	<5	§		
		Foreign-born	0	0.00 (0.00-0.05)	§	§
	50-64	US-born	0	0.00 (0.00-0.21)		
		Foreign-born	<5	§	§	§
	65-79	US-born	0	0.00 (0.00-0.39)		
		Foreign-born	<5	§	§	§
	≥80	US-born	0	0.00 (0.00-1.55)		
		Foreign-born	0	0.00 (0.00-1.20)	§	§
Non-APL AML	20-34	US-born	56	0.84 (0.63-1.10)		
		Foreign-born	68	0.75 (0.58-0.96)	0.90 (0.62-1.32)	0.621
	35-49	US-born	54	1.52 (1.14-1.99)		
		Foreign-born	102	1.29 (1.05-1.57)	0.85 (0.60-1.21)	0.375
	50-64	US-born	72	4.18 (3.27-5.26)		
		Foreign-born	87	2.74 (2.19-3.38)	0.66 (0.47-0.91)*	0.011
	65-79	US-born	98	10.31 (8.37-12.57)		
		Foreign-born	107	9.57 (7.82-11.60)	0.93 (0.70-1.24)	0.648
	≥80	US-born	36	14.53 (10.13-20.19)		
		Foreign-born	49	15.87 (11.74-20.99)	1.09 (0.69-1.74)	0.775

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Table continued...

Acute Leukemia Subtype	Age Range	Race/Ethnicity or Nativity	Cases	Incidence Rate (95% CI)	IRR (95% CI)	Ratio P-Value
APL	20-34	US-born	19	0.30 (0.18-0.47)		
		Foreign-born	19	0.20 (0.12-0.31)	0.68 (0.33-1.38)	0.31
	35-49	US-born	7	0.19 (0.08-0.39)		
		Foreign-born	41	0.51 (0.36-0.69)	2.70 (1.19-7.20)*	0.013
	50-64	US-born	5	0.28 (0.09-0.65)		
		Foreign-born	14	0.47 (0.26-0.79)	1.70 (0.58-6.03)	0.438
	65-79	US-born	<5	§		
		Foreign-born	8	0.69 (0.29-1.38)	§	§
	≥80	US-born	0	0.00 (0.00-1.55)		
		Foreign-born	0	0.00 (0.00-1.20)	§	§

B-Cell ALL, B-cell acute lymphoblastic leukemia; T-Cell ALL, T-cell acute lymphoblastic leukemia; non-APL AML, non-acute promyelocytic leukemia acute myeloid leukemia; APL, acute promyelocytic leukemia

[a]Standardized to the 2000 US population age standard.

[b]Age-adjusted incidence rates (per 100,000 person-years) of acute leukemias and incidence rate ratios (IRR) by race/ethnicity among whites and Hispanics age ≥20 in California, 2000-2009.

[c]Age-adjusted incidence rates (per 100,000 person-years) of hematological malignancies and incidence rate ratios by nativity among Hispanics age ≥20 in California, 2000-2004.

[§]Insufficient case counts to calculate reliable rate

*= p<0.05; **= p <0.01

Our observation that foreign birth was associated with a reduced incidence rate of AML was also unexpected, and suggests a protective environmental exposure may occur in those who spend their childhood in third-world countries. It has previously been hypothesized that early infectious exposures may contribute to normal maturation of the immune system and a decreased incidence rate of cancers derived from these progenitor cells.[26] While the association between early common infections, as measured by variables such as day-care attendance and birth order, have been associated with a decreased incidence of ALL, similar findings have not been shown in AML.[27] However, if this "hygiene hypothesis," extrapolated from a theory that Western populations have higher rates of allergic and inflammatory diseases due to a decreased exposure to bacteria or endotoxins from soil is relevant to AL, one would expect the nativity analysis to have shown that the incidence of ALL is lower in foreign-born Hispanic leukemics. Because this was not observed, one must question whether alternative hypotheses may explain the decreased incidence of ALL in those with early infectious exposures, as well as our observation suggesting a protective effect on AML conferred by foreign birth.

There are a number of potential limitations to our analysis. The relative under-representation of T-cell ALL in our analysis is likely due to the younger age distribution of this disease. However, consistent with our limited findings, T-cell ALL has not been shown to vary by ethnicity.[4] The heterogeneity of ALs may have resulted in misclassification of certain subtypes in this report, and although this is to our knowledge the first assessment of nativity differences in the incidence rates of these rare diseases using a robust database, we are nonetheless limited by small numbers. The paucity of population-based studies involving AL is due in large part to the relative rarity of these tumors and the lack of nativity information in most cancer registries. Although foreign-born Hispanics are not a homogenous group, hailing from many different countries, approximately 84% of California Hispanics are of Mexican origin, providing some uniformity to this analysis.[28] The age at immigration would impact the duration of exposure to non-American environmental exposures; unfortunately, this information is not available for our analysis. Finally, AL incidence patterns vary widely by age, with the majority of B-cell ALL cases occurring in the pediatric population and the majority of AML cases occurring in the adult population. Because prognosis, treatment and outcomes differ significantly between pediatric and adult AL, and because nativity analyses that include young children have the potential for age-related bias, we restricted our analysis to the adult population, with the understanding that these observations may not apply to pediatric data sets. Table 3 details the age distribution of AL in our adult population, and compares the incidence within 15-year age groups by race/ethnicity and for Hispanics, nativity. These age distribution trends reflect what is commonly known about incidence patterns for adult acute leukemias, and suggest our major nativity findings are driven by disease comparisons of the most commonly affected age groups for each respective leukemia.

In conclusion, we confirm the higher incidence rate of B-cell ALL and APL in Hispanics in California. In addition, a nativity analysis shows foreign birth does not impact the incidence rate of B-cell ALL, suggesting a heritable genetic component for the higher incidence. Foreign birth is associated with a higher incidence rate of APL in Hispanics, suggesting unknown environmental factors contribute to the increased incidence rate of this disease in this population.

Acknowledgements

DAP was supported by a fellowship from the Leukemia and Lymphoma Society. HEK was supported by fellowships from the Leukemia and Lymphoma Society, Department of Defense and the American Society of Hematology. This research was supported by the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California. Collection of cancer incidence data in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the NCI's SEER Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 awarded to the Public Health Institute.

Author's contributions

Conception and Design: DAP, HEK, SLG, CAC Acquisition of Data: JY, ETC, SLG, CAC Analysis and Data Interpretation: DAP, HEK, JY, ETC, SLG, CAC Writing, Reviewing and Revising the Manuscript: DAP, HEK, SLG, CAC.

Conflicts of interest

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Citation: Pollyea DA, Kohrt HE, Yang J, et al. Acute leukemia in adult Hispanic Americans: differences in incidence rates by nativity. *J Cancer Prev Curr Res*. 2014;1(1):14–19. DOI: 10.15406/jcpcr.2014.01.00005