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Research Article

Disparities in Liver Cancer Incidence by Nativity, Acculturation, and Socioeconomic Status in California Hispanics and Asians

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Abstract

Background: Asians and Hispanics have the highest incidence rates of liver cancer in the United States, but little is known about how incidence patterns in these largely immigrant populations vary by nativity, acculturation, and socioeconomic status (SES). Such variations can identify high-priority subgroups for prevention and monitoring.

Methods: Incidence rates and rate ratios (IRR) by nativity among 5,400 Hispanics and 5,809 Asians diagnosed with liver cancer in 1988–2004 were calculated in the California Cancer Registry. Neighborhood ethnic enclave status and SES were classified using 2000 U.S. Census data for cases diagnosed in 1998–2002.

Results: Foreign-born Hispanic males had significantly lower liver cancer incidence rates than U.S.-born Hispanic males in 1988–2004 (e.g., IRR = 0.54, 95% confidence interval [CI] = 0.50–0.59 in 1997–2004), whereas foreign-born Hispanic females had significantly higher rates in 1988–1996 (IRR = 1.42, 95% CI = 1.18–1.71), but not 1997–2004. Foreign-born Asian males and females had up to 5-fold higher rates than the U.S.-born. Among Hispanic females, incidence rates were elevated by 21% in higher-enclave versus lower-enclave neighborhoods, and by 24% in lower- versus higher-SES neighborhoods. Among Asian males, incidence rates were elevated by 23% in higher-enclave neighborhoods and by 21% in lower-SES neighborhoods. In both racial/ethnic populations, males and females in higher-enclave, lower-SES neighborhoods had higher incidence rates.

Conclusions: Nativity, residential enclave status, and neighborhood SES characterize Hispanics and Asians with significantly unequal incidence rates of liver cancer, implicating behavioral or environmental risk factors and revealing opportunities for prevention.

Impact: Liver cancer control efforts should especially target foreign-born Asians, U.S.-born Hispanic men, and residents of lower-SES ethnic enclaves. *Cancer Epidemiol Biomarkers Prev; 19(12); 3106–18. ©2010 AACR.*

Introduction

Liver cancer incidence and mortality rates have been increasing in the United States since the 1970s (1–3). At present, U.S. Asians and Hispanics (the latter of whom are tied with American Indians/Alaska Natives) have the highest incidence rates, at 3-fold and 2-fold higher, respectively, than rates among non-Hispanic whites (4). Thus, these 2 fastest-growing U.S. minority groups (5) are also the groups with the greatest burdens of liver cancer. Counteracting this mounting public health problem requires appropriate planning of prevention and screening efforts. Several causes of liver cancer, such as chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse, and obesity, can be prevented or effectively treated (6, 7), thereby reducing the risk of liver cancer. Furthermore, early disease detection by routine liver screening may reduce liver cancer mortality (8). Targeting these prevention efforts toward high-risk groups could help to reduce the heavy burden of liver cancer among Asians and Hispanics, and reverse the escalating trends in liver cancer incidence and mortality nationwide.

However, the identification of high-risk groups remains incomplete. In U.S. Asian and Hispanic populations, which include large immigrant subsets, factors that may delineate groups at unequal risk include nativity, acculturation, and socioeconomic status (SES). Health in immigrant populations tends to differ from that of non-immigrants due to the maintenance of traditional cultural behaviors, the immigration experience itself, and the

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characteristics of individuals who choose to migrate (9). At the neighborhood level, the percentages of immigrant residents and non-English language usage patterns, which approximate acculturation and together can delineate "ethnic enclaves," may influence health behaviors and risks through the availability of cultural goods and services, social networks, means of communication, access to health care, and other channels (10–12). Similarly, neighborhood-level SES, in addition to reflecting the SES of its residents, may affect health status through community attitudes about health and health-related behaviors, the accessibility and availability of health-promoting infrastructure and services, and direct exposure to environmental agents (13, 14). Thus, all of these factors may be important for identifying high-priority groups for liver cancer prevention and monitoring in contemporary Asian and Hispanic populations. In addition, given the cultural, linguistic, and behavioral differences among groups defined by these characteristics, it may be critical to account for these factors when designing liver cancer control strategies.

To date, the influence of nativity on liver cancer incidence in Hispanics and Asians has not been widely studied, and the influence of ethnic enclave status and neighborhood SES has not, to our knowledge, been examined at all. Therefore, to learn whether these characteristics may help identify high-risk groups for targeted liver cancer control, we assessed the relationships of these factors with liver cancer incidence in California, home to approximately one-third of the nation's Asian and Hispanic population (15).

Methods

Cancer patient data

From the California Cancer Registry (CCR), we obtained information regarding all state residents newly diagnosed with a primary invasive liver cancer (International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site code 22.0, histology codes 8000–8999) from January 1, 1988, through December 31, 2004. All primary liver cancers were included because 31% of Hispanic and Asian liver cancer cases in the CCR lack microscopic confirmation, and cancer registries lack detailed data on diagnostic criteria. We performed secondary analyses limited to hepatocellular carcinoma, the single most common liver cancer type (ICD-O-3 histology codes 8170–8175). The CCR, comprising 3 of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program registries (16), is estimated to be 99% complete in its ascertainment of cancer cases (17).

We included all 3,737 male Hispanic/Latino (hereafter referred to as "Hispanic," in accordance with U.S. Census categorization) liver cancer cases, 1,663 female Hispanic cases, 4,115 male Asian cases, and 1,694 female Asian cases. Hispanics were not further disaggregated by national origin due to a high proportion of missing data, although approximately 77% of California Hispanics are of Mexican origin (18), followed by 9% of Central American origin (19), indicating a relatively homogeneous study population. Among the 5,809 Asian patients, 2,105 (36%) were Chinese, 552 (10%) were Japanese, 1,009 (17%) were Filipino, 873 (15%) were Korean, and 1,270 (22%) were Vietnamese (Table 1); together, they comprised 89% of all Asian CCR patients diagnosed with liver cancer during the study period. Asians of other ethnic backgrounds were not included in the nativity analysis due to insufficient case numbers. Classifications of Hispanic ethnicity and specific Asian ethnic group (20) were improved by application of the North American Association of Central Cancer Registries Hispanic Identification Algorithm (21) and Asian/Pacific Islander Identification Algorithm (22).

Nativity classification

Registry data on birthplace were available for 91% of Hispanic cases and 92% of Asian cases. As cancer registry cases with unknown birthplace data are more likely to be U.S.-born than those with available data (15, 23, 24), we estimated nativity for the remaining 9% of patients with unknown birthplace with minimal bias through statistical imputation (25). This approach used the patient's social security number (SSN), which is indicative of the state and year of issuance (26–28). Hispanic patients who received an SSN before age 20 years were classified as U.S.-born, and those who received an SSN at or after age 20 years were classified as foreign-born. Asian patients who received an SSN before age 25 years were classified as U.S.-born, and those who received an SSN at or after age 25 years were classified as foreign-born. These age cut-points were determined by comparisons with self-reported nativity from interviews with patients [N = 1,227 Hispanics and N = 1,836 Asians (29, 30)], and maximization of the area under the receiver-operating characteristic curve. The optimal positive predictive values of the age cut-points were confirmed by using logistic regression models with age at SSN issue as a continuous predictor of foreign-born status. The selected cut-points resulted in immigrant status classifications associated with 81% sensitivity and 80% specificity for detecting foreign-born status in Hispanics, and with 84% sensitivity and 80% specificity for detecting foreign-born status in Asians, with similar results across the Asian ethnic populations. The less than 1% of cases with missing or invalid SSNs were assigned a nativity status based on the known distribution of nativity within matched strata of race/ethnicity, sex, and age in the overall CCR patient population.

Neighborhood ethnic enclave status and socioeconomic status

We defined a neighborhood ethnic enclave as a geographic unit with a higher concentration of a foreign-born race/ethnicity-specific population and language(s) than other geographic units. As described previously (31, 32), in a CCR database separate from the nativity data, we

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Table 1. Demographic and disease characteristics of Hispanic and Asian patients with incident primary liver cancer in California, 1988–2004

Characteristic	Hispanics *N* = 5,400		Chinese *N* = 2,105		Japanese *N* = 552		Filipinos *N* = 1,009		Koreans *N* = 873		Vietnamese *N* = 1,270		Totals *N* = 11,209	
Age at diagnosis, y														
0–29	195	4%	30	1%	2	0%	13	1%	7	1%	23	2%	270	2%
30–39	105	2%	85	4%	1	0%	45	4%	24	3%	57	4%	317	3%
40–49	642	12%	224	11%	25	5%	113	11%	117	13%	155	12%	1,276	11%
50–59	1,232	23%	362	17%	80	14%	183	18%	210	24%	281	22%	2,348	21%
60–69	1,482	27%	595	28%	217	39%	220	22%	272	31%	377	30%	3,163	28%
70–79	1,239	23%	569	27%	159	29%	287	28%	179	21%	284	22%	2,717	24%
80+	505	9%	240	11%	68	12%	148	15%	64	7%	93	7%	1,118	10%
Median	63		66		67		66		62		63			
Sex														
Male	3,737	69%	1,579	75%	230	42%	735	73%	584	67%	987	78%	7,852	70%
Female	1,663	31%	526	25%	322	58%	274	27%	289	33%	283	22%	3,357	30%
Nativity														
U.S.-born	2,927	54%	181	9%	195	35%	54	5%	22	3%	19	1%	3,398	30%
Foreign-born	2,473	46%	1924	91%	357	65%	955	95%	851	97%	1251	99%	7,811	70%
Tumor stage at diagnosis														
Localized	1,609	30%	660	31%	171	31%	305	30%	269	31%	420	33%	3,434	31%
Regional	738	14%	318	15%	84	15%	174	17%	125	14%	218	17%	1,657	15%
Distant	1,406	26%	602	29%	158	29%	302	30%	224	26%	347	27%	3,039	27%
Unspecified	1,647	31%	525	25%	139	25%	228	23%	255	29%	285	22%	3,078	27%

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assigned a measure of enclave status to each of the 99.7% of cases with a residential address at diagnosis geocoded to a census tract. Cases whose address could not be precisely geocoded were randomly assigned to a census tract within their county of residence. To characterize residence in an ethnic enclave, we applied principal components analysis (33) to selected 2000 U.S. Census variables at the block-group level, then averaged these values across census tracts. For Hispanics, we included data on linguistic isolation, English fluency, Spanish language use, Hispanic ethnicity, immigration history, and nativity. For Asians, we included data on linguistic isolation, English fluency, Asian language use, Asian race, and immigration history. Each case was assigned to a neighborhood enclave status quintile based on the distribution of each enclave index across all census tracts in California. For statistical analysis, we combined quintiles 1–3 (lower enclave status, as the reference group) and quintiles 4–5 (higher enclave status).

As a neighborhood SES measure, we assigned each case a previously described index that incorporates 2000 U.S. Census data on education, occupation, unemployment, household income, poverty, rent, and house values (34). Again, each patient was assigned to a neighborhood SES quintile based on the statewide distribution of the SES index, and we combined quintiles 1–3 (lower neighborhood SES) and quintiles 4–5 (higher neighborhood SES, as the reference group) for statistical analysis. Cancer registries do not collect data on individual-level SES.

Analyses of residential ethnic enclave status and neighborhood SES were limited to the pericensal period January 1, 1998, through December 31, 2002. In these analyses, which included 1,771 male Hispanic cases, 728 female Hispanic cases, 1,554 male Asian cases, and 680 female Asian cases, all Asian ethnic groups were included and combined into a single group due to the lack of subgroup-specific population estimates for census tracts.

General population data

From the 1990 and 2000 Census Summary File 3, we obtained population counts by sex, race/ethnicity, immigrant status, and five-year age group for California. We used data from the 20% Integrated Public-Use Microdata Sample of the Census to estimate age- and nativity-specific population counts for each ethnic group (35) by smoothing with a spline-based function (36). For intercensal years, we estimated the foreign-born population using cohort component interpolation and extrapolation methods, adjusting estimates to the populations by age and year provided by the California Department of Finance for years 1988–1989 and by the U.S. Census for years 1990–2004, based on data availability. Incidence rates for U.S.-born Filipinos, Koreans, and Vietnamese were not stable enough to report because 1) the U.S.-born populations are significantly smaller than the foreign-born, and 2) they have considerably younger age distributions, reducing stability of age-adjusted rates for cancers, which predominantly occur at older ages. Therefore, we combined Filipinos, Koreans, and Vietnamese into a single group of "other Asians" for the nativity analysis. For the analyses of ethnic enclave status and neighborhood SES, we used 2000 U.S. Census population estimates by race/ethnicity and sex at the census-tract level.

Statistical analysis

We used SEER*Stat software (37) to compute age-adjusted incidence rates (standardized to the 2000 U.S. standard million population) and 95% confidence intervals (CIs). We calculated incidence rate ratios (IRRs) to compare incidence rates between U.S.-born and foreign-born populations (Chinese, Japanese, other Asian, or Hispanic) for 1988–1996 and 1997–2004, and by neighborhood ethnic enclave status or SES within census tracts for 1998–2002. The lack of census-tract-level population data by nativity precluded joint analyses by nativity and neighborhood enclave status or SES. For comparisons of incidence rates among U.S.-born and foreign-born populations in the United States and other countries based on estimations published by the International Agency for Research on Cancer (GLOBOCAN; refs. 38, 39), we standardized rates to the age distribution of the world standard population.

Results

In our study population, 41% of the Hispanic males and 56% of the Hispanic females diagnosed with incident liver cancer were foreign-born. Among Asians with incident liver cancer, 92% of the males and 92% of the females were foreign-born. Koreans, Vietnamese, and Hispanics were younger at diagnosis, on average, than Japanese, Chinese, and Filipinos (Table 1). From 1988–1996 to 1997–2004, the incidence rate of liver cancer increased in Hispanics by 87% and 83% among U.S.-born males and females, respectively, and 31% and 29% among foreign-born males and females, respectively (Tables 2 and 3). By contrast, the incidence rate was stable among most Asians. However, among Filipino, Korean, and Vietnamese ("other Asian") males and Japanese females born outside the United States, the liver cancer incidence rates increased by 19% and 32%, respectively, while among foreign-born Chinese males, the rate decreased by 8%.

In males, the incidence rate of liver cancer was 22% lower in 1988–1996 and 46% lower in 1997–2004 in foreign-born than U.S.-born Hispanics (Table 2). By contrast, the rate was 42% higher in foreign-born than U.S.-born Hispanic females in 1988–1996, with no difference by nativity in 1997–2004 (Table 3). Among Chinese, Japanese, and other Asians, the incidence rate of liver cancer was consistently higher in the foreign-born than the U.S.-born. The nativity gap was especially pronounced among Japanese men and women, among whom incidence rates were 3.5 to 5 times higher in the foreign-born than the U.S.-born. In analyses of nativity excluding those with imputed birthplace, results were unchanged (data not shown).

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Table 2. Age-adjusted incidence rates (per 100,000 person-years) of liver cancer and incidence rate ratios (IRRs) by nativity among Hispanic and Asian males in California, 1988–2004

Ethnic group	Years of diagnosis	Nativity	Cases (*N*)	Population	Incidence rate[a]	95% CI	IRR	95% CI
Hispanics		U.S.-born	691	21,071,875	9.9	(9.0–10.8)	1.00	reference
	1988–1996	Foreign-born	510	18,095,886	7.7	(7.0–8.4)	**0.78**	**(0.68–0.88)**
		U.S.-born	1,506	25,534,575	18.5	(17.6–19.5)	1.00	reference
	1997–2004	Foreign-born	1,030	20,466,825	10.1	(9.4–10.8)	**0.54**	**(0.50–0.59)**
Chinese		U.S.-born	56	1,109,824	15.4	(11.0–20.8)	1.00	reference
	1988–1996	Foreign-born	628	2,315,169	27.3	(25.1–29.7)	**1.77**	**(1.30–2.50)**
		U.S.-born	79	1,380,593	16.2	(12.6–20.4)	1.00	reference
	1997–2004	Foreign-born	816	2,697,457	25.0	(23.3–27.0)	**1.55**	**(1.22–2.02)**
Japanese		U.S.-born	61	951,274	5.6	(4.1–7.5)	1.00	reference
	1988–1996	Foreign-born	38	372,960	21.6	(14.5–30.5)	**3.85**	**(2.33–6.21)**
		U.S.-born	72	872,647	6.8	(5.3–8.6)	1.00	reference
	1997–2004	Foreign-born	59	391,684	23.8	(17.2–32.0)	**3.51**	**(2.33–5.21)**
Filipinos, Koreans, and Vietnamese		U.S.-born	28	1,611,348	16.4	(8.5–27.7)	1.00	reference
	1988–1996	Foreign-born	820	4,220,104	23.9	(22.2–25.7)	1.46	(0.86–2.83)
		U.S.-born	40	2,170,383	12.7	(8.6–18.0)	1.00	reference
	1997–2004	Foreign-born	1,418	4,802,922	28.5	(26.9–30.2)	**2.23**	**(1.57–3.32)**

[a]Standardized to the 2000 U.S. population age standard. Incidence rates with numerator <15 are not computed. CI: Confidence interval.

Table 3. Age-adjusted incidence rates (per 100,000 person-years) of liver cancer and incidence rate ratios (IRRs) by nativity among Hispanic and Asian females in California, 1988–2004

Ethnic group	Years of diagnosis	Nativity	Cases (*N*)	Population	Incidence rate[a]	95% CI	IRR	95% CI
Hispanics		U.S.-born	241	20,639,600	2.9	(2.5–3.3)	1.00	reference
	1988–1996	Foreign-born	331	15,721,107	4.1	(3.6–4.5)	**1.42**	**(1.18–1.71)**
		U.S.-born	489	25,116,383	5.3	(4.8–5.8)	1.00	reference
	1997–2004	Foreign-born	602	18,538,762	5.3	(4.9–5.8)	1.00	(0.88–1.13)
Chinese		U.S.-born	12	1,045,316	—		1.00	reference
	1988–1996	Foreign-born	192	2,533,953	7.6	(6.6–8.9)	**2.18**	**(1.20–4.64)**
		U.S.-born	34	1,314,287	5.5	(3.7–7.7)	1.00	reference
	1997–2004	Foreign-born	288	3,092,306	7.9	(6.9–8.9)	1.44	(0.99–2.19)
Japanese		U.S.-born	24	958,160	2.2	(1.4–3.5)	1.00	reference
	1988–1996	Foreign-born	105	596,184	11.1	(8.7–14.3)	**5.02**	**(2.99–8.81)**
		U.S.-born	38	871,207	2.7	(1.9–3.8)	1.00	reference
	1997–2004	Foreign-born	155	640,558	14.7	(12.3–17.7)	**5.43**	**(3.67–8.17)**
Filipinos, Koreans, and Vietnamese		U.S.-born	6	1,525,876	—		1.00	reference
	1988–1996	Foreign-born	303	4,762,158	7.8	(6.9–8.9)	**3.67**	**(1.31–12.31)**
		U.S.-born	21	2,053,269	5.4	(3.0–8.8)	1.00	reference
	1997–2004	Foreign-born	516	5,646,961	8.5	(7.8–9.4)	1.57	(0.96–2.84)

[a]Standardized to the 2000 U.S. population age standard. Incidence rates with numerator <15 are not computed.
CI: Confidence interval.

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Table 4. Age-adjusted incidence rates (per 100,000 person-years) of liver cancer among Hispanics in California and Central America, and among Asians in California and Asia[a]

		Males		Females	
Ethnic group	**Nativity and residence**	**Rate[b]**	**95% CI**	**Rate[b]**	**95% CI**
Hispanics					
	U.S.-born, living in United States	13.7	(13.0–14.4)	3.6	(3.3–4.0)
	Foreign-born, living in United States	6.6	(6.2–7.1)	3.2	(2.9–3.5)
	Living in Central America	4.9	—	4.9	—
Chinese					
	U.S.-born, living in United States	11.6	(9.0–14.7)	3.9	(2.6–5.5)
	Foreign-born, living in United States	17.7	(16.4–19.3)	5.0	(4.4–5.9)
	Living in China	37.9	—	14.2	—
Japanese					
	U.S.-born, living in United States	4.5	(3.4–5.9)	1.6	(1.0–2.4)
	Foreign-born, living in United States	14.7	(11.0–19.3)	10.1	(8.5–12.4)
	Living in Japan	23.1	—	7.6	—
Filipinos, Koreans, and Vietnamese					
	U.S.-born, living in United States	9.0	(6.1–12.5)	3.4	(1.9–5.6)
	Foreign-born, living in United States	20.0	(18.6–21.5)	5.3	(4.8–5.9)
	Living in Philippines, Korea, or Vietnam	30.9	—	11.4	—

[a]California rates from 1997–2004; international rates from GLOBOCAN 2002 (38) or GLOBOCAN 2008 for Philippines, Korea, and Vietnam (39).
[b]Standardized to the world population age standard. CI, confidence interval.

Incidence rates among foreign-born Hispanics and Asians were consistently intermediate between rates for those born in the United States and those living (and predominantly born) abroad (Table 4). The sole exception was for Hispanic females, in whom the incidence rate among the foreign-born living in the United States was the lowest of the 3 groups.

In comparisons by neighborhood ethnic enclave status and SES, differences among Hispanic males were relatively small and not statistically significant (Table 5). By contrast, among Hispanic females, the incidence rate of liver cancer was 21% higher for those in areas with higher ethnic enclave status than those in areas with lower enclave status, and 24% higher among those in lower-SES than higher-SES neighborhoods (Table 6). Hispanic males and females living in neighborhoods with both higher enclave status and lower SES had significantly higher incidence rates, by 17% and 34%, respectively, than those in lower-enclave, higher-SES neighborhoods.

Among Asian males but not females, those in areas with higher ethnic enclave status had a 23% higher incidence rate of liver cancer than those in areas with lower enclave status, and those in lower-SES versus higher-SES neighborhoods had a 21% higher rate (Tables 5 and 6). When neighborhood enclave status and SES were combined, Asian males in higher-enclave, lower-SES neighborhoods had a 41% higher incidence rate of liver cancer than those in lower-enclave, higher-SES neighborhoods. Asian females in higher-enclave, lower-SES neighborhoods also had a 13% higher incidence rate, although this difference was not statistically significant.

We evaluated the effects of nativity, neighborhood ethnic enclave status, and neighborhood SES on incidence rates of hepatocellular carcinoma (which affected 86% of cases among Hispanic males, 76% among Hispanic females, 91% among Asian males, and 87% among Asian females) and of liver cancer presenting with regional or distant disease (which affected 41% of cases among Hispanic males, 36% among Hispanic females, 46% among Asian males, and 39% among Asian females, excluding localized and unstaged disease). These analyses yielded similar results (data not shown).

Discussion

In this population-based study in California, we found that foreign-born Asians had significantly and consistently higher incidence rates of liver cancer than U.S.-born Asians—as high as a 5-fold difference among Japanese women. By contrast, foreign-born Hispanic men had significantly lower liver cancer incidence rates than their U.S.-born counterparts, a disparity that widened as the incidence rate increased more among U.S.-born than foreign-born Hispanic men in recent years. A similar increase among U.S.-born Hispanic women, meanwhile, closed an earlier gap with

Table 5. Age-adjusted incidence rates (per 100,000 person-years) of liver cancer and incidence rate ratios (IRRs) by neighborhood immigrant enclave status and socioeconomic status (SES)[a] among Hispanic and Asian males in California, 1998–2002

Racial/ethnic group	Neighborhood characteristic	Cases (*N*)	Population	Incidence rate[b]	95% CI	IRR	95% CI
Hispanics							
	Low enclave status	486	7,603,625	13.7	(12.4–15.1)	1.00	reference
	High enclave status	1,068	20,409,605	14.5	(13.6–15.5)	1.06	(0.94–1.19)
	High SES	278	4,243,850	13.0	(11.4–14.8)	1.00	reference
	Low SES	1,276	23,774,865	14.5	(13.7–15.4)	1.12	(0.97–1.29)
	Low enclave status/high SES	226	3,552,400	12.3	(10.6–14.1)	1.00	reference
	High enclave status/high SES	52	688,845	17.3	(12.3–23.4)	1.41	(0.97–1.98)
	Low enclave status/low SES	260	4,051,225	15.3	(13.4–17.4)	**1.25**	**(1.03–1.52)**
	High enclave status/low SES	1,016	19,720,760	14.4	(13.4–15.4)	**1.17**	**(1.00–1.38)**
Asians							
	Low enclave status	320	1,924,885	21.0	(18.6–23.5)	1.00	reference
	High enclave status	1,451	7,099,465	25.7	(24.3–27.1)	**1.23**	**(1.08–1.39)**
	High SES	790	4,620,540	22.5	(20.8–24.2)	1.00	reference
	Low SES	981	4,404,810	27.2	(25.5–29.0)	**1.21**	**(1.10–1.34)**
	Low enclave status/high SES	139	890,150	20.4	(16.9–24.3)	1.00	reference
	High enclave status/high SES	651	3,730,100	23.0	(21.2–24.9)	1.13	(0.93–1.39)
	Low enclave status/low SES	181	1,034,735	22.0	(18.8–25.5)	1.08	(0.85–1.37)
	High enclave status/low SES	800	3,369,365	28.7	(26.7–30.8)	**1.41**	**(1.16–1.72)**

[a]Low, quintiles 1–3 of the statewide distribution; high, quintiles 4–5 of the statewide distribution.
[b]Standardized to the 2000 U.S. population age standard. CI: Confidence interval.

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Table 6. Age-adjusted incidence rates (per 100,000 person-years) of liver cancer and incidence rate ratios (IRRs) by neighborhood immigrant enclave status and socioeconomic status (SES)[a] among Hispanic and Asian females in California, 1998—2002

Racial/ethnic group	Neighborhood characteristic	Cases (*N*)	Population	Incidence rate[b]	95% CI	IRR	95% CI
Hispanics							
	Low enclave status	186	7,450,545	4.9	(4.2–5.6)	1.00	reference
	High enclave status	494	19,303,670	5.9	(5.4–6.5)	**1.21**	**(1.02–1.45)**
	High SES	113	4,234,710	4.7	(3.8–5.6)	1.00	reference
	Low SES	567	22,520,645	5.8	(5.3–6.3)	**1.24**	**(1.01–1.54)**
	Low enclave status/high SES	91	3,591,880	4.4	(3.5–5.4)	1.00	reference
	High enclave status/high SES	22	642,320	6.2	(3.9–9.4)	1.42	(0.84–2.27)
	Low enclave status/low SES	95	3,858,665	5.4	(4.3–6.7)	1.23	(0.91–1.67)
	High enclave status/low SES	472	18,661,350	5.9	(5.3–6.5)	**1.34**	**(1.06–1.71)**
Asians							
	Low enclave status	154	2,174,195	8.1	(6.9–9.6)	1.00	reference
	High enclave status	574	7,555,760	8.7	(8.0–9.5)	1.07	(0.89–1.29)
	High SES	343	5,028,075	8.5	(7.6–9.5)	1.00	reference
	Low SES	386	4,702,390	8.7	(7.9–9.7)	1.03	(0.88–1.19)
	Low enclave status/high SES	65	1,038,520	7.8	(5.9–10.0)	1.00	reference
	High enclave status/high SES	277	3,989,405	8.7	(7.7–9.8)	1.11	(0.84–1.50)
	Low enclave status/low SES	89	1,135,675	8.5	(6.8–10.5)	1.09	(0.77–1.54)
	High enclave status/low SES	297	3,566,355	8.8	(7.8–9.9)	1.13	(0.86–1.52)

[a]Low, quintiles 1–3 of the statewide distribution; high, quintiles 4–5 of the statewide distribution.
[b]Standardized to the 2000 U.S. population age standard.

foreign-born Hispanic women. We also found that liver cancer incidence rates varied by neighborhood ethnic enclave status and SES, with increased rates among Hispanics and Asians living in neighborhoods with both higher enclave status and lower SES. In all subgroups, the markedly stronger IRRs by nativity than by neighborhood ethnic enclave status, SES, or both, suggest that individual-level nativity is a more important determinant of liver cancer risk than these residential neighborhood characteristics.

The observed disparities in liver cancer incidence by nativity and residential characteristics are likely explained in large part by differences in known and unknown environmental and behavioral (as opposed to genetic) risk factors for liver cancer. The rising prevalence of such risk factors, such as obesity and chronic HCV infection, in past decades may explain the increasing trend in liver cancer incidence among U.S.-born and, to a lesser extent, foreign-born Hispanics observed here and elsewhere (3, 40). The consistency of our results when the analysis was limited to regional and distant-stage disease argues against patterns of liver cancer screening as an explanation for the observed incidence rate patterns. Instead, perhaps the most prominent cause of the rising incidence rates of liver cancer in the United States, especially among Hispanics, is chronic HCV infection. The prevalence of HCV infection escalated from the 1960s through the 1980s, mostly as a result of intravenous drug use and contaminated blood transfusion, and is expected to drive a continued increase in liver cancer rates for several years to come following a latency period of 2 to 4 decades (41, 42). HCV is likely a leading cause of liver cancer among Hispanics; at a New York City medical center between 1994 and 2001, 60% of Hispanic liver cancer patients were infected with HCV, compared with 43% of non-Hispanic patients (43). However, further population-based studies are needed to determine the percentage of liver cancer due to HCV in Hispanics. The incidence rate patterns in our study may point to a higher prevalence of HCV infection among U.S.-born than foreign-born Hispanic males, and possibly a higher prevalence among less acculturated and lower-SES males and females, although data to support this conjecture are lacking. While separate studies suggest that the prevalence of HCV infection is higher among Mexicans in the United States than those in Mexico (44, 45), to our knowledge, no studies have directly compared the prevalence of HCV infection among Hispanics by nativity, acculturation, or SES. Alcohol abuse, another behavioral risk factor for liver cancer (46), may also help to explain some of the observed incidence patterns by nativity and neighborhood characteristics. In support of this hypothesis, population-based data from the 2001 California Health Interview Survey (CHIS) (47) showed that U.S.-born His-

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panic men had a higher prevalence of binge drinking in the past month (31.8%; 95% CI: 29.0–34.5%) than foreign-born Hispanic men (26.4%; 95% CI: 24.2–28.6%), whereas there was no difference in the prevalence of binge drinking between U.S.-born and foreign-born Asian men (14.0% and 14.5%, respectively). Of note, a study based in SEER-Medicare found the proportion of liver cancer attributable to alcoholic liver disease did not increase during the 1990s (42), and there is no consistent evidence of an increase in the prevalence of alcohol abuse in the United States over the last several decades (48, 49), indicating that alcohol abuse is unlikely to be responsible for the rising incidence of liver cancer. Instead, the more likely causes are HCV and nonalcoholic fatty liver disease or steatohepatitis; the latter is an underlying cause of cirrhosis that has become increasingly common in concert with the epidemics of type 2 diabetes and obesity (50, 51), and appears to be more common in Mexican Americans than in other racial/ethnic groups in the United States (52, 53). According to 2001 CHIS data, the prevalence of obesity among Hispanic adults generally coincided with liver cancer incidence patterns, with higher rates among U.S.-born Hispanic men (27.7%; 95% CI: 25.0–30.3%) than foreign-born Hispanic men (21.1%; 95% CI: 19.1–23.1%), and higher rates among foreign-born Hispanic women (29.0%; 95% CI: 26.9–31.0%) than U.S.-born Hispanic women (25.3%; 95% CI: 23.0–27.5%) (47). A higher prevalence of obesity among women and a lower prevalence among men in Mexico compared with those in California (54) may also contribute to international liver cancer incidence patterns in Hispanics. Among Asians, however, CHIS data on the prevalence of obesity did not correspond with liver cancer incidence patterns, with higher rates in U.S.-born (12.9%; 95% CI: 7.5–18.3%) than foreign-born Asian men (4.9%; 3.3–6.5%), and slightly higher rates in U.S.-born (5.4%; 2.9–8.0%) than foreign-born Asian women (3.7%; 2.6–4.8%) (47). These patterns, along with the fact that liver cancer incidence rates among Asians have not risen in concert with the rising prevalence of obesity and chronic HCV infection, suggest that nonalcoholic fatty liver disease and HCV may not be major contributing factors to liver cancer risk among U.S. Asians.

Instead, 60–80% of liver cancer among Asians in Asia, as well as foreign-born Asians in the U.S., is caused by chronic HBV infection (55–59), except in Japan, where up to 50–70% of liver cancer is attributable to HCV (59, 60). The predominant etiologic role of HBV in most of Asia likely explains why Asians, despite having markedly lower prevalences of binge drinking and obesity than Hispanics, nevertheless have higher incidence rates of liver cancer. HBV is endemic in most of East and Southeast Asia, where approximately 10% of the population is chronically infected (61). (Japan is an exception, with a 2–7% prevalence of chronic HBV infection (61).) By comparison, the prevalence of chronic HBV infection in the U.S. non-Asian population is less than 0.5% (61). Most chronic HBV infection in Asia is acquired at birth from infected mothers and during early childhood from close contact with infected adults or children (62). Due in part to the lower population-wide prevalence of chronic HBV infection in the United States, and perhaps to the widespread availability of an HBV vaccine since 1982, the prevalence of chronic HBV infection is substantially lower in U.S.-born than foreign-born Asians (61, 63, 64). The prevalence of HCV infection is also likely lower in U.S.-born than foreign-born Asians, given the higher population-wide prevalence of HCV infection in several Asian countries than in the US (60), although direct evidence is unavailable. In addition, aflatoxin B_1, a hepatocarcinogenic metabolite produced by *Aspergillus* fungi, is more prevalent and more commonly consumed with contaminated staple foods in Asia than in the United States (65). These differences most likely offer the primary explanation for the lower incidence rates of liver cancer among U.S.-born than foreign-born Asians in our study, as well as the lower rates among Asians in the United States than in Asia.

The nativity patterns we observed among Hispanics are consistent with those of El-Serag et al., who found that liver cancer mortality rates among U.S.-born Hispanic men in California and Texas in 1999–2001 were double those among foreign-born Hispanic men, whereas rates did not differ appreciably between U.S.-born and foreign-born Hispanic women (40). El-Serag et al. also found that liver cancer mortality rates increased substantially more among U.S.-born than foreign-born Hispanic men and women between 1979–1981 and 1999–2001. By using incidence instead of mortality data, we showed that these patterns were most likely due to differences in disease risk, rather than liver cancer treatment. Although they lacked the ability to compare U.S.-born with foreign-born Hispanics, Pinheiro et al. found that liver cancer incidence rates among (predominantly foreign-born) Mexican, Puerto Rican, and Cuban males in Florida in 1999–2001 were consistently higher than the GLOBOCAN 2002 incidence rates in their countries of origin, whereas rates were lower among Mexican, Puerto Rican, and Cuban females in Florida than in Central America (66). Similarly, Ho et al. reported higher liver cancer incidence rates in U.S. mainland than island Puerto Rican males, but not females (67). Taken together, these results reinforce the notion that behavioral or environmental risk factors related to migration or acculturation act rapidly to influence liver cancer incidence among Hispanic males within a single generation. In particular, Pinheiro et al. suggested that the diverging patterns by sex might be due to a tendency of male immigrants to adopt less healthy lifestyles, including increased alcohol consumption and intravenous drug use leading to viral hepatitis infection, compared with females (66).

Previous studies of liver cancer patterns by nativity among U.S. Asians also found results similar to ours, although our data enhance prior findings in several ways. El-Serag et al. reported that liver cancer mortality

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rates among Asian men and women in California and Texas were nearly 3 times higher in the foreign-born than the U.S.-born, and increased modestly among foreign-born but not U.S.-born Asian men and women between 1979–1981 and 1999–2001 (40). Again, by analyzing incidence data, we ruled out the possibility that these patterns could have been due to differences in liver cancer treatment. Like us, Rosenblatt et al. found using SEER data that liver cancer incidence rates were highest among Asians in Asia, intermediate among foreign-born Asians in the United States, and lowest among U.S.-born Asians. However, they did not compute rate ratios to compare incidence rates directly between foreign-born and U.S.-born Asians, and they randomly imputed birthplace for all cases with unknown birthplace. Because birthplace is nonrandomly missing in cancer registry data (15, 23, 24), we strengthened these prior findings through imputation of missing birthplace using a validated SSN-based method. Lee et al. found similar results comparing liver cancer incidence rates between native South Koreans and Korean Americans, but they did not classify Korean Americans by nativity.

To our knowledge, no other study in the United States has examined differences in liver cancer incidence rates by neighborhood ethnic enclave status and SES. A Canadian study found that liver cancer incidence rates were geographically clustered according to the proportion of immigrants within provincial health regions (68). In that study, the regional prevalence of smoking, alcohol use, obesity, and diabetes, as well as the distribution of physical activity, fruit and vegetable consumption, education, and income, did not contribute significantly to geographic variation in liver cancer incidence, although the large geographic scale may have obscured true etiologic effects.

An important consideration in interpreting our results is the impact of misclassification of undocumented/unlawful immigrants as U.S.-born instead of foreign-born. In 2006, approximately 2.8 million undocumented immigrants lived in California, comprising about 8% of the state's inhabitants and 30% of all immigrants (69). Approximately 90% of undocumented immigrants in California are estimated to be from Latin America, including 65% from Mexico alone; most of the remaining 10% are from Asia (69). Undocumented immigrants may be more likely than documented immigrants to falsely report themselves as U.S.-born, as well as to provide false SSNs. A recent study by the Social Security Administration found that only 4% of U.S. employees overall had SSNs that did not match the name and number in the administration's records, although this figure is almost certainly an underestimate of the proportion of mismatched SSNs specifically among undocumented immigrants (70).

However, we believe that the bias due to misclassification of nativity among undocumented immigrants was limited in our study. False reporting of a U.S. birthplace would likely have affected both the numerators and denominators of incidence rates, producing little net change. Bias due to the use of false SSNs to impute nativity for patients with missing birthplace information, resulting in an overestimate of U.S.-born cases and a corresponding underestimate of foreign-born cases, was also limited, as nativity was imputed for only 9% of cases. Furthermore, even an individual using a false SSN would have been correctly classified as foreign-born if the SSN was issued after the individual reached age 25 years (if Asian) or 20 years (if Hispanic). For legally documented immigrants who had a true SSN issued early in life and missing birthplace in the CCR, the bias due to being misclassified by our algorithm as U.S.-born was tempered by the fact that those individuals would have spent the majority of their lives in the United States, like the U.S.-born population with whom they were grouped.

Other limitations of our study include the lack of cancer registry data on individual-level risk factors that may contribute to the observed incidence rate differences, as well as our inability to examine joint combinations of nativity and neighborhood enclave status or SES, due to the unavailability of nativity- and race/ethnicity-specific population data at the census-tract level. Counterbalancing these limitations are the notable strengths of this study, including its setting in the state with the nation's largest Hispanic and Asian populations; the generalizability of our results, due to the population-based design; and our use of high-quality cancer registry data. For the 91% of cases with known birthplace, we have previously demonstrated that cancer registry birthplace information is highly valid in comparison with self-reported birthplace (29, 30). Similarly, prior studies have shown excellent agreement between cancer registry data and self-reported data on race, and good agreement on Hispanic ethnicity and Asian subgroup (71, 72).

In summary, we found that liver cancer incidence rates among California Hispanics and Asians varied significantly by nativity, residential enclave status, and neighborhood SES, with U.S.-born Hispanic males, possibly foreign-born Hispanic females, foreign-born Asian males and females, and those living in lower-SES, higher-enclave-status neighborhoods having higher rates than their respective comparison groups. These geographic and environmental differences highlight the importance of behavioral and environmental risk factors in liver cancer development, and provide valuable new information to guide the prioritization of future liver cancer control strategies. In particular, our results indicate that cultural, linguistic, and socioeconomic considerations are likely critical in the design of programs to prevent, detect, and treat hepatitis B and C infection and reduce the prevalence of alcohol abuse, obesity, and diabetes in the high-risk Hispanic and Asian populations. For example, to be accessible to those at greatest risk, such programs may need to be

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located in dense ethnic enclaves and to offer hepatitis testing, antiviral and substance abuse treatment, liver cancer screening, and other preventive care for free or at a low cost. Better understanding of how behavioral risk factors for liver cancer vary by nativity, acculturation, and SES can enhance such programs to maximize their effectiveness and impact.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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