Original Article

Disparities in Hepatocellular Carcinoma Incidence by Race/Ethnicity and Geographic Area in California: Implications for Prevention

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BACKGROUND: The incidence of hepatocellular carcinoma (HCC) has been rising rapidly in the United States. California is an ethnically diverse state with the largest number of incident HCC cases in the country. Characterizing HCC disparities in California may inform priorities for HCC prevention. METHODS: By using data from the Surveillance, Epidemiology, and End Results 18-Registry Database and the California Cancer Registry, age-adjusted HCC incidence in California from 2009 through 2013 was calculated by race/ethnicity and neighborhood ethnic enclave status. A geographic analysis was conducted using Medical Service Study Areas (MSSAs) as the geographic unit, and race/ethnicity-specific standardized incidence ratios (SIRs) were calculated to identify MSSAs with higher-than-expected HCC incidence compared with the statewide average. RESULTS: During 2009 through 2013, the age-adjusted incidence of HCC in California was the highest in Asians/Pacific Islanders (APIs) and Hispanics (>100% higher than whites), especially those living in more ethnic neighborhoods (20%-30% higher than less ethnic neighborhoods). Of the 542 MSSAs statewide, 42 had elevated HCC incidence (SIR > 1.5, lower bound of 95% confidence interval > 1) for whites, 14 for blacks, 24 for APIs, and 36 for Hispanics. These MSSAs have 24% to 52% higher proportions of individuals below the 100% federal poverty line than other MSSAs. CONCLUSIONS: API and Hispanics residing in more ethnic neighborhoods and individuals residing in lower income neighborhoods require more extensive preventive efforts tailored toward their unique risk factor profiles. The current race/ethnicity-specific geographic analysis can be extended to other states to inform priorities for HCC targeted prevention at the subcounty level, eventually reducing HCC burden in the country. Cancer 2018;124:3551-59. © 2018 American Cancer Society.

KEYWORDS: cancer registry, geographic analysis, hepatocellular carcinoma, racial disparity, targeted prevention.

INTRODUCTION

Liver cancer, which is the second most common cause of cancer death worldwide,1 is relatively rare in the United States. However, the incidence and mortality of liver cancer, specifically hepatocellular carcinoma (HCC), the most predominant histological type that accounts for >85% of all liver cancers, have tripled in the United States since the 1980s.2 A recent analysis based on US national statistics reported that, from 2003 to 2012, liver cancer mortality increased at the highest rate of all cancer sites, and its incidence increased at the second highest rate, although the incidence and mortality for most other cancers are on a decline.3 There is substantial racial/ethnic variation in HCC rates and temporal patterns, likely reflecting differences in the distribution of risk factors4; whereas hepatitis B virus (HBV) infection is the most common underlying cause of HCC among Asians, hepatitis C virus (HCV) infection, alcohol consumption, as well as obesity and related metabolic disorders are important risk factors for HCC among non-Asian groups.5 Historically, Asian Americans have had the highest liver cancer incidence and mortality rates in the United States; however, HCC incidence

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in Asian Americans plateaued around 2007 and has started to decline since then. In contrast, HCC rates for non-Asian groups have been rising; and, in 2014, Hispanics surpassed Asian Americans to have the highest HCC rates in the United States, likely attributable to the growing epidemic of metabolic disorders and the cohort effect of the hepatitis C epidemic. One recent analysis has projected that, by 2030, Hispanics will have the highest HCC rates, whereas Asian Americans will have the lowest HCC rates nationwide.

On the basis of the major risk factors identified to date, HCC can be considered a preventable cancer. For example, universal HBV immunization at birth, which started in the United States in 1991, has resulted in a dramatic decrease in the prevalence of chronic HBV infection; and for those who are already infected (including infections in immigrants from HBV-endemic countries), lifetime antiviral treatment can effectively inhibit HBV replication, reducing HCC risk. For HCV, although there is no vaccination, treatment with a highly effective and safe, direct-acting antiviral agent can eradicate HCV infection and consequently reduce HCC occurrence. With regard to nonviral risk factors, there is no direct evidence yet that the treatment of metabolic disorders reduces HCC risk, but emerging data suggest that taking statin, metformin, or aspirin (agents to treat high cholesterol, diabetes, and chronic inflammation, respectively) may be associated with lower HCC risk. However, despite the large amount of literature on HCC etiology, few studies have provided empirical data that guide the targeted efforts of HCC prevention at subcounty levels. Effective preventive strategies depend on the etiologies of HCC, which may vary by race/ethnicity and geographic area. Thus, characterizing patterns of HCC incidence at a local level for each racial/ethnic group has strong public health relevance, because it will help identify high-risk subgroups and inform priorities in racial/ethnic-specific efforts for HCC prevention and control.

California has 1 of the highest incidence and mortality rates of HCC in the United States, ranked only after Texas, Hawaii, and New Mexico. It is also the most populous state in the United States (39.5 million as of July 2017). Because of its large population, California had the largest HCC burden (number of incident cases) in the United States in 2012. Notably, California accounts for 1 of 3 of the Asian population and 1 of 4 of the Hispanic population in the United States, and these 2 groups currently have the highest HCC incidence rates in the country. The objective of the current study was to describe the pattern of HCC incidence in California during 2009 through 2013, which were the most recent 5 years that had complete data available at the time of this analysis. Specifically, we examined disparities of HCC incidence in California by race/ethnicity (including various Asian ethnic groups) and Asian/Hispanic neighborhood ethnic enclave status. We also conducted a geographic analysis to identify HCC subcounty hot spots (areas with at least 50% higher HCC incidence than that expected in the average California population) overall and by race/ethnicity.

MATERIALS AND METHODS

Surveillance, Epidemiology and End Results Incidence Data
We defined patients with HCC using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography code C22.0 (liver) and histology codes 8170 through 8175. Five-year incidence data from 2009 through 2013 were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18-registry database (2000-2013). During this period, 48% of patients with HCC and 43% of the population in the SEER 18 database were from registries in California. We calculated race/ethnicity-specific, age-adjusted HCC incidence overall and stratified by sex, age at diagnosis, and stage at diagnosis. Four major racial/ethnic groups were included: non-Hispanic whites (hereafter referred to as “whites”), non-Hispanic blacks (hereafter referred to as “blacks”), non-Hispanic Asians and Pacific Islanders (hereafter referred to as “APIs”), and Hispanics. The incidence was age-adjusted to the 2000 US standard population.

California Cancer Registry Incidence Data
To examine HCC incidence rates by attributes that are not publicly available in the SEER data (eg, detailed Asian ethnicity and subcounty geographic designations), we obtained additional HCC data from the California Cancer Registry (CCR), comprising 3 registries in the SEER program. Patient information, such as age at diagnosis and race/ethnicity, is routinely collected by the registry. In addition, in the CCR data, patients’ residential address information was geocoded by a third-party vendor and assigned to latitude/longitude coordinates, which identify a census block group and tract that allows for the computation of cancer incidence rates at different geographic aggregations and for an examination of associations with specific neighborhood characteristics. The 3 analyses described below were performed using CCR data:
Incidence by Detailed Asian Ethnic Groups
In addition to the main racial/ethnic groupings, Asian Americans were further classified into several ethnic groups, including Chinese, Japanese, Korean, Filipino, Vietnamese, Asian Indians and Pakistanis (combined as South Asians), Cambodians, Laotians, Hmong, and Thai. Annual population counts for each group were estimated using linear interpolation and extrapolation of 1990, 2000, and 2010 Census counts. HCC incidence for the period from 2009 through 2013 was calculated for each Asian ethnic group.

Incidence by Tract-Level Ethnic Enclave Status
In our analysis, we assessed HCC incidence rates by tract-level ethnic enclave indices among Hispanics and APIs. An ethnic enclave is generally defined as a geographic unit that maintains more cultural mores and is distinct from the larger surrounding areas in cultural/ethnic attributes. Composite measures of ethnic enclave were previously developed by principal component analysis of tract-level indicator variables from the American Community Survey data (2007-2011). For the Hispanic enclave index, the indicator variables included percentages of Hispanics, foreign-born individuals, recent immigrants, households that are linguistically isolated, Spanish language-speaking households that are linguistically isolated, all language speakers with limited English proficiency, and Spanish language speakers with limited English proficiency. For the API enclave index, the indicator variables included percentages of APIs, recent immigrants, API language-speaking households that are linguistically isolated, and API language-speakers with limited English proficiency. The composite measures were grouped into quartiles based on statewide distributions, with a higher quartile denoting neighborhoods that are more ethnic. To be contemporaneous with the period for which the enclave measures were based using American Community Survey data, we chose to examine incidence by enclave status during 2008 through 2012 (rather than 2009-2013 as in other analyses). Population counts were estimated using 2010 US Census population estimates by race/ethnicity and sex at the census-tract level. To examine the linear relation between ethnic enclave status and HCC incidence, we performed the Kendall τ correlation test.

Geographic Analyses
We used Medical Service Study Areas (MSSAs) as the subcounty unit for the geographic analyses. The MSSAs, defined by the California Office of Statewide Health Planning and Development, are aggregations of census tracts that provide a good basis for needs assessment analysis, health care planning, and health care policy development. In total, there are 542 MSSAs in California, with a mean population of approximately 70,000 in each MSSA. The boundaries of each MSSA were nested within the corresponding county. We also retrieved important attributes of each MSSA, such as population size, distribution of race/ethnicity, and poverty rates.

To identify MSSAs with elevated HCC incidence, we calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for each California MSSA during 2009 through 2013, both overall and by race/ethnicity, adjusted for age (5-year age groups) and sex. The 2010 Census population counts were multiplied by 5 to estimate the total population at risk for the 5-year study period. For each MSSA, expected case counts were calculated by multiplying the age-specific and sex-specific population counts by the age-specific and sex-specific HCC incidence in all of California (the reference population) from 2009 through 2013, then summing up across age group and sex. The overall SIR was then calculated as the ratio of observed HCC case counts versus expected HCC case counts. Race/ethnicity-specific SIRs were calculated using the same method, except that the observed case counts, population counts, and reference rates were specific to that racial/ethnic group. The 95% CIs were calculated using the exact method. An MSSA was considered to have elevated HCC incidence if: 1) the SIR was statistically significantly greater than 1 (the lower bound of the 95% CI > 1); and 2) the point estimate of the SIR was ≥1.5. We set the cutoff point of 1.5 for SIR to reduce the possibility of identifying large MSSAs with moderately elevated risk (eg, SIR = 1.3 but statistically significant because of the large sample size). We excluded MSSAs with an observed case count ≤5, because the small sample size could result in unstable estimates and wide 95% CIs. We acknowledge that calculating the SIR for 542 MSSAs could result in a proportion of false-positive findings, but we chose not to account for multiple comparisons to avoid missing any areas with truly elevated HCC incidence. Furthermore, we compared the mean proportion of population under the 100% federal poverty level between MSSAs with elevated HCC incidence and other MSSAs; for this comparison, we also performed a sensitivity analysis by adjusting for the MSSA-specific proportion of elderly residents (age 65 years or older), because the elderly may be more vulnerable to poverty.
using SAS version 9.3 (SAS Institute, Inc, Cary, NC). Statistical tests were 2-sided, and \( P \) values < .05 were considered statistically significant. We created maps depicting MSSAs with elevated HCC incidence overall and by race/ethnicity using ArcGIS software from ESRI (Redlands, CA). This analysis was covered under the Greater Bay Area Cancer Registry Institutional Review Board protocol from the Cancer Prevention Institute of California.

RESULTS

Table 1 indicates that the age-adjusted incidence of HCC in California was 7.6 per 100,000 person-years during 2009 through 2013, which is 17% higher than the overall estimates in the SEER 18-registries database. Compared with SEER 18, California has a slightly higher incidence for each of the racial/ethnic groups. In California, age-adjusted HCC incidence (per 100,000 person-years) was the highest in APIs (11.7 per 100,000 person-years), followed by Hispanics (10.6 per 100,000 person-years), blacks (9.6 per 100,000 person-years), and whites (5.2 per 100,000 person-years). Among Asian ethnic groups, the highest rates were observed among Vietnamese (27.2 per 100,000 person-years), Cambodians (26.6 per 100,000 person-years), and Laotian (25.3 per 100,000 person-years), whereas the highest number of cases were observed among Chinese, Vietnamese, Filipinos, and Koreans (Supporting Table 1). For each racial/ethnic group, approximately 50% of the cases were diagnosed at the localized stage (Supporting Table 2). HCC incidence generally increased with age, especially starting from age 55 years (Supporting Table 3). In addition, age-adjusted HCC incidence was higher among men than among women, with the male/female incidence ratio ranging from 3.1 to 4.2 for each racial/ethnic group in either SEER or California (data not shown).

Fig. 1 illustrates the age-adjusted incidence of HCC by neighborhood ethnic enclave status from 2008 through 2012 in California. Among APIs, there was a positive association between HCC incidence and the API enclave index \( (P_{\text{trend}} = .04) \), with an HCC incidence that was 30% higher in the most ethnic versus least ethnic neighborhood (top vs bottom quartile of the ethnic enclave index). Among Hispanics, HCC incidence appeared to be higher for individuals living in neighborhoods with a higher Hispanic enclave index; however, no significant linear trend was observed \( (P_{\text{trend}} = .17) \).

Of the 542 MSSAs in California, 66 had elevated HCC incidence (SIR ≥ 1.5; lower bound of the 95% CI > 1) for all racial/ethnic groups combined after adjusting for age and sex (Supporting Table 4). The maximum SIR in these 66 MSSAs was 3.0. The Greater Bay Area had a disproportionally high number of MSSAs with elevated HCC incidence (21 of the 66 MSSAs), and ≥50% of all MSSAs in San Francisco and Monterey counties had elevated HCC incidence (Table 2). When stratified by race/ethnicity, 42 of 542 MSSAs (8%) had elevated HCC incidence for whites (maximum SIR = 4.0), 14 MSSAs (3%) had elevated incidence for blacks (maximum SIR = 9.3), 24 MSSAs (4%) had elevated incidence for APIs (maximum SIR = 3.7), and 36 MSSAs (7%) had elevated incidence for Hispanics (maximum SIR = 4.9) (Supporting Table 5, Fig. 2). Two MSSAs (1 in San Diego County and 1 in San Francisco County) had elevated HCC incidence for all 4 racial/ethnic groups, 9 had elevated HCC incidence for 3 groups, 9 had elevated HCC incidence for 2

### TABLE 1. Age-Adjusted Incidence Rates and Case Counts of Hepatocellular Carcinoma by Race/Ethnicity, 2009 to 2013

| Race/Ethnicity                      | SEER 18a Rateb | SEER 18a Count | California Rateb | California Count |
|-------------------------------------|----------------|---------------|------------------|-----------------|
| All races                           | 6.5            | 31,071        | 7.6              | 15,056          |
| Non-Hispanic white                  | 4.8            | 15,547        | 5.2              | 5893            |
| Non-Hispanic black                  | 8.4            | 4237          | 9.6              | 1202            |
| Non-Hispanic Asian/Pacific Islander | 11.2           | 4756          | 11.7             | 3250            |
| Hispanic                            | 10.3           | 6065          | 10.6             | 4511            |

Abbreviation: SEER 18, Surveillance, Epidemiology, and End Results 18-registry database.

*The SEER 18-registry database contains data from 18 registries from 2000 through 2013, including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey.

*aRates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups; Census P25-1130) standard.*
groups, and 63 had elevated HCC incidence for 1 group. For each race/ethnicity, MSSAs with elevated HCC incidence had 24% to 52% higher proportion of individuals living below the 100% federal poverty line compared with other MSSAs; the proportion of individuals living below the 100% federal poverty line also was higher in

Figure 2. Hepatocellular carcinoma (HCC) hot spots in California are illustrated overall and by race/ethnicity for (A) all racial/ethnic groups combined, (B) non-Hispanic whites, (C) non-Hispanic blacks, (D) non-Hispanic Asians/Pacific Islanders, and (E) Hispanics. Note that the geographic unit in this analysis is the Medical Service Study Area (MSSA); these areas are aggregations of census tracts (typically 20-30) that provide a good basis for needs assessment analysis, health care planning, and health care policy development. Hot spots are MSSAs with at least 50% higher HCC incidence than that expected in the average California population. Each map shows the 58 counties in California, and dark areas indicate MSSA hot spots within counties, with some MSSAs bordering others.
areas that had elevated HCC incidence for multiple race/ethnic groups (Fig. 3). This pattern persisted after also adjusting for the proportion of elderly residents in each MSSA (data not shown).

DISCUSSION

In this study, we examined the race/ethnicity-specific patterns of HCC incidence in California and identified areas with elevated HCC incidence that may require targeted HCC prevention efforts. Currently, HCC incidence in California is highest among APIs and Hispanics, especially those living in high ethnic enclave neighborhoods. Targeted preventive efforts focused on particular geographic regions are especially needed in the Greater Bay Area and in neighborhoods with higher poverty rates. To our knowledge, our geographic analysis is the first to identify subcounty areas with elevated HCC incidence within a state, and this method could be extended to other states with high HCC rates to identify neighborhoods that need targeted efforts and eventually reduce the burden of HCC in the United States.

Our analysis examined disparity of HCC incidence by race/ethnicity in California, including a detailed investigation by various Asian ethnic groups, as well as the degree of ethnic composition of Asian and Hispanic neighborhoods. In California, the incidence of HCC during 2009 through 2013 was highest among APIs, followed by Hispanics and blacks, with the lowest rates among whites. This pattern is consistent with that observed nationwide.7 The overall HCC incidence in California is 17% higher than that in the entire SEER, which is likely related to the population structure in California (higher concentrations of Hispanics and Asians, which are high-risk populations for HCC); however, because the race/ethnicity-specific rates are consistently higher in California than in the SEER data (by 3%-14%), it is also possible that certain risk factors may be more prevalent in California, such as alcohol consumption.25 Among Asians, the highest burden of HCC (ie, the

### TABLE 2. Distribution of Medical Service Study Areas Identified as Hot Spots for Hepatocellular Carcinoma in All Races/Ethnicities Combined by County: California, 2009 to 2013

| County                    | Total No. of MSSAs | Total No. of MSSAs Identified as Hot Spots | Percentage of MSSAs Identified as Hot Spots |
|---------------------------|-------------------|---------------------------------------------|---------------------------------------------|
| Greater Bay Area          |                   |                                             |                                             |
| San Francisco             | 8                 | 6                                           | 75.0                                        |
| Monterey                  | 8                 | 4                                           | 50.0                                        |
| Santa Clara               | 16                | 5                                           | 31.3                                        |
| San Mateo                 | 10                | 2                                           | 20.0                                        |
| Alameda                   | 16                | 3                                           | 18.8                                        |
| Contra Costa              | 11                | 1                                           | 9.1                                         |
| Marin                     | 4                 | 0                                           | 0.0                                         |
| San Benito                | 1                 | 0                                           | 0.0                                         |
| Santa Cruz                | 6                 | 0                                           | 0.0                                         |
| Greater Los Angeles Area  |                   |                                             |                                             |
| Los Angeles               | 99                | 15                                          | 15.2                                        |
| Orange                    | 27                | 3                                           | 11.1                                        |
| San Bernardino           | 26                | 2                                           | 7.7                                         |
| Ventura                   | 9                 | 0                                           | 0.0                                         |
| Riverside                 | 23                | 0                                           | 0.0                                         |
| Other areas (30 counties with no hot spots are not shown below) |                   |                                             |                                             |
| Kings                     | 3                 | 1                                           | 33.3                                        |
| Madera                    | 3                 | 1                                           | 33.3                                        |
| Fresno                    | 14                | 4                                           | 28.6                                        |
| Tuolumne                  | 4                 | 1                                           | 25.0                                        |
| Humboldt                  | 5                 | 1                                           | 20.0                                        |
| Imperial                  | 5                 | 1                                           | 20.0                                        |
| Lake                      | 5                 | 1                                           | 20.0                                        |
| San Joaquin               | 10                | 2                                           | 20.0                                        |
| Sacramento                | 16                | 3                                           | 18.8                                        |
| Solano                    | 6                 | 1                                           | 16.7                                        |
| Yolo                      | 6                 | 1                                           | 16.7                                        |
| San Diego                 | 38                | 6                                           | 15.8                                        |
| Butte                     | 8                 | 1                                           | 12.5                                        |
| Kern                      | 15                | 1                                           | 6.7                                         |

Abbreviation: MSSAs, Medical Service Study Areas.

aMSSAs, defined by the California Office of Statewide Health Planning and Development, are aggregations of census tracts (typically 20-30) that provide a good basis for needs assessment analysis, health care planning, and health care policy development.

bHot spots are MSSAs with at least 50% higher HCC incidence than that expected in the average California population.
number of incident cases) is among Chinese, followed by Vietnamese, Filipinos, and Koreans, consistent with a previous report that used data in the Greater Bay Area from 1990 through 2004.\textsuperscript{26} The large HCC burden among Chinese, Vietnamese, Filipinos, and Koreans indicates that HCC prevention among Asians should target these groups, because this approach will most likely result in substantial reduction of HCC burden. In addition, we observed higher incidence of HCC among APIs and Hispanics living in neighborhoods with higher enclavification (more ethnic), consistent with a previous report using data from California during 1998 through 2002,\textsuperscript{20} indicating that APIs and Hispanics living in these ethnic neighborhoods should be prioritized for HCC prevention in California.

Our analysis to identify local areas with higher than expected incidence of HCC is novel and informative. To our knowledge, this is the first study to examine HCC incidence patterns at the subcounty level in the United States. The current analysis was not intended to identify new HCC risk factors, because its etiology is quite well established; instead, our objective was to identify priority populations that need targeted prevention efforts, which is especially useful when information on the prevalence of HCC risk factors is not always available at the subcounty level. In our analysis, we first identified MSSAs with elevated HCC incidence for all racial/ethnic groups combined to gain a general idea of neighborhoods with a high incidence of HCC in California. Given the different HCC risk-factor profiles by race/ethnicity (especially between Asians and non-Asians),\textsuperscript{5} we then examined race/ethnicity-specific MSSAs with elevated HCC incidence, which could provide further insights for race/ethnicity-specific prevention efforts. For example, if an area has elevated HCC incidence for Asians, it may indicate a higher prevalence of HBV infection among Asians in this area compared with Asians in other parts of California; thus, this area is likely to benefit from improved HBV screening (especially among the older immigrant population) and efforts to remove barriers to screening at the patient, provider, and the health care system levels, such as improving linkage to care and community outreach.\textsuperscript{27} Alternatively, if an area has an elevated HCC incidence for Hispanics, then this area may require better identification and treatment of HCV-infected individuals as well as management of metabolic disorders and nonalcoholic fatty liver diseases. If an area has elevated HCC incidence for multiple racial/ethnic groups, including both Asians and non-Asians, it may indicate the presence of community-level factors that are common to all racial/ethnic groups, such as low socioeconomic status (as we have shown in Fig. 3B), or coexistence of risk factors for different racial/ethnic groups (eg, high prevalence of both HBV and HCV), which requires a multipronged approach for HCC prevention.

Some caution should be exercised when interpreting our geographic analysis results. We used the MSSAs as the geographic unit for analysis, a readily acceptable unit for analysis in local public health practice, because it was previously established by the California Office of Statewide Health Planning and Development. However, because the average population of each MSSA region is about 70,000, future studies should use smaller neighborhood aggregations, preferably those aggregated based on neighborhood socioeconomic status and racial/ethnic
composition, to allow for more granular identification of vulnerable geographic areas. It should be noted that the race/ethnicity-specific SIRs were calculated within each particular race/ethnicity and are not intended for comparison across races/ethnicities. The finding that we observed the highest number of areas with elevated HCC incidence among whites and relatively few among blacks and APIs could be largely explained by statistical power (ie, population size is the largest for whites), but does not suggest that whites have the highest incidence of HCC in California. Also, current cancer incidence rates may not reflect past and ongoing prevention efforts, as many of their effects can take years or decades to be observed. For example, the reduction in HCC from the universal newborn HBV vaccination in the United States starting from 1991 will not be evident, because the generation of newborns who received HBV vaccination at birth is only in the third decade of their lives, whereas HCC occurs more commonly after age 50 years. Thus, it will be another 2 decades before we see a significant reduction of HCC in the United States because of HBV newborn vaccination.

Our analysis focused on HCC incidence, which may inform priorities in primary prevention efforts. We did not examine mortality from HCC because histology codes were not available in mortality data. Furthermore, mortality data were not available by neighborhood enclave status. Historically, mortality of HCC is very close to its incidence because of the high fatality of this disease, so the pattern of incidence would reflect the pattern of mortality; however, HCC survival has improved over the past 3 decades, likely because of earlier stage at diagnosis and improved treatment. Therefore, a separate analysis on the pattern of HCC mortality in California will be required to provide insights into priorities in secondary and tertiary prevention efforts, such as early detection of HCC and access to cancer care.

This study has several strengths and limitations. To our knowledge, this is the most comprehensive evaluation of HCC incidence patterns in California, including data on neighborhood characteristics, Asian ethnic groups, and geographic locations. In particular, we demonstrated that the geographic analysis typically used to identify clusters of infectious disease or to identify occupational/environmental hazards could provide helpful insights for cancer prevention efforts in the general population. Such targeted efforts, tailored for each specific race/ethnicity and geographic area, will be more efficient than applying the same efforts across the entire country or entire state.

Several limitations should also be acknowledged. For Hispanic and Asian populations, HCC incidence may differ by nativity. A previous paper reported that, during 1988 through 2004, foreign-born Asians had higher HCC incidence than US-born Asians, whereas the pattern was the opposite for Hispanics. However, cancer registry data on birthplace have become increasingly incomplete and prior methods used to impute nativity for patients with unknown birthplace are less valid for recent cases; thus, we did not examine HCC incidence by nativity in the current analysis. We may have limited power to detect elevated HCC incidence among MSSA regions with small number of cases, especially for blacks (4 areas for whites, 10 for blacks, 3 for Hispanics, and 6 for APIs had elevated HCC incidence but could not be reported because of the small number of cases). We do not have MSSA-level prevalence of HCC risk factors or Census tract characteristics other than poverty (eg, education and income) to help us evaluate whether specific factors indeed account for the higher rate of HCC in this neighborhood (and thus these factors should be the target of prevention).

In conclusion, our study provides a comprehensive characterization of HCC patterns in California that will inform priorities in HCC prevention and control efforts. Our methodology could be extended to examine patterns of HCC in other states with a high HCC burden. Giving the rapidly changing landscape of HCC in the United States and the fact that HCC is largely preventable, this is a timely and critical investigation that could contribute to reducing the burden of HCC in the United States.

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**CONFLICT OF INTEREST DISCLOSURES**

The authors made no disclosures.

**AUTHOR CONTRIBUTIONS**

Baiyu Yang: Conceptualization, formal analysis, investigation, visualization, writing—original draft, and writing—review and
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