Impact of Country of Birth on Age at the Time of Diagnosis of Hepatocellular Carcinoma in the United States

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BACKGROUND: There is global variation in the onset of hepatocellular carcinoma (HCC). The objective of the current study was to investigate the impact of country of birth on age at the time of HCC diagnosis in the United States. METHODS: Incident HCC cases diagnosed between 2000 and 2012 in the Surveillance, Epidemiology, and End Results program 18 registry were included. Factors associated with very early onset (age at diagnosis < 40 years) and early onset (age at diagnosis < 50 years) were identified by logistic regression. RESULTS: A total of 59,907 patients were included. The median age at the time of diagnosis of HCC was 62 years and 76% of the patients were male. Of the 75% of patients for whom information regarding birth country was available, 29% were foreign born. In multivariate logistic regression, birth in West Africa (adjusted odds ratio [AOR], 16.3; 95% confidence interval [95% CI], 9.2-27.9 [P < .01]), Central/South/other Africa (AOR, 11.0; 95% CI, 4.5-23.7 [P < .01]), Oceania (AOR, 4.9; 95% CI, 2.9-8.0 [P < .01]), and East Africa (AOR, 3.5; 95% CI, 1.5-6.8 [P < .01]) was found to have the strongest association with very early-onset HCC after adjusting for sex and race/ethnicity. Birth in West Africa, Central/South/other Africa, Oceania, or East Africa also was found to be strongly associated with early-onset HCC. CONCLUSIONS: Birth country was found to be independently associated with age at the time of HCC diagnosis in the United States. Birth in Africa (except for North Africa) and Oceania was strongly associated with very early-onset HCC. These findings have implications for the design of comprehensive HCC surveillance programs in the United States. Cancer 2017;123:81-9.

KEYWORDS: Africa, age, early onset, liver cancer, Oceania.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death in the world.1 Over the past 4 decades, there have been marked increases in the incidence of HCC in the United States.2 Viral hepatitis is the leading cause of HCC, accounting for >90% of all HCC cases, particularly in developing countries.3 There are racial and regional variations in the risk factors for HCC, which result in different demographic and clinical characteristics among patients with HCC across the United States and the world.4 Hepatitis C virus (HCV) is the leading etiology of HCC in North America, Europe, Japan, and South America, whereas hepatitis B virus (HBV) is the major cause of HCC in the majority of Asia and Sub-Saharan Africa.5 It is well known that HBV-associated HCC tends to occur earlier than HCC arising from HCV or other etiologies because HBV infection is acquired during birth or early childhood in HBV-endemic areas. Aflatoxin exposure, which is quite common in some HBV-endemic areas, also can contribute to genetic instability, causing early-onset HCC.6 For this reason, the American Association for the Study of Liver Diseases recommends initiating HCC surveillance after the age of 20 years for African/North American black individuals with HBV, age 40 years for Asian men, and age 50 years for Asian women with HBV.7 However, data to support these recommendations are scarce in the literature because to our knowledge there are few data regarding HCC epidemiology in HCC-endemic areas, particularly in Africa, in which HCC is highly endemic. Indeed, in the recent GLOBOCAN 2012 report, cancer incidence data were not available for approximately one-third of the countries, the majority of which are developing/underdeveloped countries.8
Our recent publication demonstrated that HCC tends to occur at a younger age in Africa, with a median age at diagnosis of HBV-associated HCC of only 42 years. This raises an important question regarding the optimal strategy for reducing the burden of morbidity and mortality from HCC among immigrants in the United States, and by extension in regions in which HCC is highly endemic but epidemiologic data are lacking. We hypothesized that the country of birth affects the onset of HCC in the United States. To test our hypothesis, we investigated the impact of country of birth on age at the time of HCC diagnosis in the US general population using the most current Surveillance, Epidemiology, and End Results (SEER) program 18 registry.

MATERIALS AND METHODS

Database and Case Identification
Incident HCC cases, diagnosed between January 1, 2000 and December 31, 2012, were extracted from the SEER 18 registry using the International Classification of Diseases for Oncology, 3rd Edition topography codes (C22) and morphology codes (8170-8175). The SEER 18 registries include Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose and Monterrey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia and covers approximately 28% of the US population.

Demographic and Country of Birth Data
Age at the time of HCC diagnosis, sex, and country of birth were extracted from the SEER registry. Because data regarding country of birth were not publicly available, the data were obtained after SEER scientific review of the study protocol. Reported country of birth was classified according to the World Population Prospects, 2015 Revision, from the United Nations. Other North or Central America/Caribbean include Bahamas; Belize; Bermuda; Canada; Central America, NOS; Costa Rica; Cuba; Dominican Republic; El Salvador; Guatemala; Haiti; Honduras; Jamaica; Mexico; Nicaragua; North America, NOS; other Caribbean islands, NOS; Panama; Puerto Rico; and Virgin Islands, US. South America includes Argentina; Bolivarian Republic of Venezuela; Bolivia; Brazil; Chile; Colombia; Ecuador; Guyana; Peru; South America, NOS; and Uruguay.

East Asia includes China; China, NOS; Hong Kong; Democratic People’s Republic of Korea (North Korea); Japan; Mongolia; Province of China; Republic of Korea (South Korea); and Taiwan. South East Asia includes Brunei, NOS; Cambodia; Indonesia; Lao People’s Democratic Republic (Laos); Macao; Malaysia; Myanmar; Philippines; Singapore; Southeast Asia, NOS; Thailand; and Vietnam. Other Asia includes Afghanistan; Arabian Peninsula, NOS; Armenia; Asia, NOS; Bangladesh; India; Iran; Islamic Republic of Iraq; Israel and Palestine, NOS; Jordan; Lebanon; Maldives; Nepal; other Asian Republics of the former Union of Soviet Socialist Republics, NOS; Pakistan; Sri Lanka; Syrian Arab Republic; Turkey; and Yemen. Oceania includes American Samoa; Australia; Federated States of Micronesia Islands, NOS; Guam; Kiribati; Marshall Islands; Melanesian Islands, NOS; Micronesia; New Zealand; Northern Mariana Islands; Pacific, NOS; Palau; Polynesian Islands, NOS; and Tonga.

West Africa includes Nigeria and West Africa, NOS. East Africa includes Burundi; East Africa, NOS; Ethiopia; Ethiopia and Eritrea, NOS; Kenya; Mauritius; Rwanda; Somalia; and Uganda. Central/South/other Africa includes Africa, NOS; African Islands, NOS; Angola; Congo; and Republic of South Africa, NOS. North Africa includes Egypt; Morocco; North Africa, NOS; Sudanese countries, NOS; and Tunisia.

Statistical Analysis
The chi-square test was used to compare categorical variables and the analysis of variance test was used for continuous variables. Factors associated with very early-onset HCC (age at diagnosis of HCC <40 years), early-onset HCC (age at diagnosis of HCC <50 years) or age <60 years at diagnosis were identified by multivariate logistic regression analysis. The main independent variables were sex, race/ethnicity (non-Hispanic white, non-Hispanic black, non-Hispanic Asian/Pacific Islander [API], and Hispanic), and country of birth. Statistical analyses were performed using JMP statistical software (version 10; SAS.
Institute Inc, Cary, NC). Joinpoint regression analysis for annual percent change was performed using SAS statistical software (SAS Institute, Inc). All P values presented are 2-sided and differences were considered statistically significant when \( P < .05 \). Two sensitivity analyses were performed. First, logistic analysis was performed after excluding patients aged <20 years to minimize the potential misdiagnosis of HCC because HCC rarely develops before age 20 years. Second, logistic regression analysis was repeated after excluding HCC cases with recent diagnosis years (2010-2012) due to the higher rate of missing data regarding country of birth.

RESULTS

Patients
A total of 59,907 patients diagnosed with HCC between 2000 and 2012 and included in the SEER registry were analyzed in the current study. Demographic characteristics of the patients are summarized in Table 1. Information regarding country of birth was available for 75% of patients, and 29% of the patients for whom this information was available were foreign born (Fig. 1). Overall, the percentage of foreign-born patients remained stable over time in all race/ethnicity subgroups. Due to the variations in the percentages of foreign-born individuals in each race/ethnicity subgroup,

TABLE 1. Number of HCC Diagnoses and Median Patient Age in the US SEER 18 Registries Between 2000 and 2012, Stratified By Race/Ethnicity, Sex, and Birth Country

|                    | US Born |                  | Non-US Born |                  | Place of Birth Unknown | Total |
|--------------------|---------|------------------|------------|------------------|------------------------|-------|
|                    | No. of Cases | Median Age (IQR, y) | No. of Cases | Median Age (IQR, y) | No. of Cases | Median Age (IQR, y) | No. of Cases | Median Age (IQR, y) |
| White              |         |                  |            |                  |                        |       |
| Total              | 20,335  | 63 (56-74)       | 1789       | 69 (59-77)       | 7808       | 62 (55-72)       | 29,932      | 63 (56-74)       |
| Men                | 16,023  | 62 (55-73)       | 1303       | 68 (58-76)       | 5942       | 61 (55-70)       | 23,268      | 62 (55-72)       |
| Women              | 4312    | 70 (58-79)       | 486        | 73 (63-80)       | 1866       | 67 (57-77)       | 6664        | 69 (58-78)       |
| Black              |         |                  |            |                  |                        |       |
| Total              | 5708    | 59 (54-66)       | 352        | 56 (46-69)       | 1614       | 59 (54-66)       | 7674        | 59 (54-66)       |
| Men                | 4485    | 59 (54-65)       | 267        | 53 (43-66)       | 1184       | 59 (54-65)       | 5936        | 59 (54-65)       |
| Women              | 1223    | 61 (55-71)       | 85         | 67 (54-76)       | 430        | 60 (54-70)       | 1738        | 61 (55-71)       |
| Asian/Pacific Islander |          |                  |            |                  |                        |       |
| Total              | 1525    | 64 (55-75)       | 7178       | 64 (55-73)       | 2469       | 65 (55-74)       | 11,172      | 64 (55-73)       |
| Men                | 1111    | 62 (54-73)       | 5164       | 62 (53-71)       | 1761       | 62 (54-71)       | 8036        | 62 (54-72)       |
| Women              | 414     | 70 (59-79)       | 2014       | 69 (60-76)       | 708        | 71.5 (62-78)     | 3136        | 70 (61-77)       |
| Hispanic           |         |                  |            |                  |                        |       |
| Total              | 4047    | 60 (53-70)       | 3798       | 62 (54-72)       | 3093       | 61 (54-71)       | 10,938      | 61 (53-71)       |
| Men                | 3208    | 59 (53-68)       | 2678       | 60 (53-69)       | 2387       | 59 (53-68)       | 8273        | 59 (53-68)       |
| Women              | 839     | 67 (57-76)       | 1120       | 68 (60-76)       | 706        | 68 (58-76)       | 2665        | 67 (58-76)       |
| Unknown race       |         |                  |            |                  |                        |       |
| Total              | 47      | 59 (55-67)       | 26         | 64.5 (57-73)     | 118        | 60 (53-68)       | 191         | 60 (54-68)       |
| Men                | 39      | 58 (56-66)       | 20         | 64.5 (57-71)     | 97         | 60 (54-66.5)     | 156         | 60 (56-67)       |
| Women              | 8       | 61.5 (19-83)     | 6          | 64.5 (53-79)     | 21         | 59 (50-75.5)     | 35          | 59 (50-76)       |
| Total              | 31,662  | 62 (55-73)       | 13,143     | 64 (55-73)       | 15,102     | 62 (55-72)       | 59,907      | 62 (55-73)       |
| Men                | 24,866  | 61 (55-71)       | 9432       | 62 (53-72)       | 11,371     | 60 (54-69)       | 45,669      | 61 (54-71)       |
| Women              | 6796    | 68 (57-77)       | 3711       | 69 (60-77)       | 3731       | 67 (57-76)       | 14,238      | 68 (58-77)       |

Abbreviations: HCC, hepatocellular carcinoma; IQR, interquartile range, SEER, Surveillance, Epidemiology, and End Results.

Figure 1. Trends in percentages of foreign-born patients with hepatocellular carcinoma (HCC) in the US Surveillance, Epidemiology, and End Results program 18 registries. Joinpoint regression annual percent change in foreign-born place of birth is shown by race and ethnicity. The overall trend was -1.12% (\( P < .05 \)), the trend for white patients was -1.65%, the trend for black patients was -2.64%, the trend for Asian/Pacific Islander patients was -0.34% (\( P < .05 \)), and the trend for Hispanic patients was 0.70%.
US-born patients with HCC were most commonly white (64%), whereas foreign-born patients with HCC were most often API (55%).

The median age at the time of diagnosis of HCC was 62 years, and 76% of patients were male. The median age at the time of HCC diagnosis was found to be younger among men compared with women (61 years vs 68 years; \(P < .01\)) and varied by race/ethnicity (59 years in black patients, 63 years in white patients, 54 years in API patients, and 61 years in Hispanic patients) (\(P < .01\)). The median age at the time of HCC diagnosis was higher in foreign-born compared with US-born white patients (\(P < .01\)). The median age at the time of HCC diagnosis was lower in foreign-born compared with US-born black patients (\(P < .01\)). The median age at the time of HCC diagnosis was similar between foreign-born and US-born API and Hispanic patients.

**Age at the Time of HCC Diagnosis in Individuals Born in Different Regions of the World**

The median age at time of diagnosis of HCC varied among individuals born in different regions of the world (Fig. 2). The cumulative percentage of HCC cases with increasing age in different regions of the world is shown in Table 2, and the percentage of cases of early-onset HCC per country or region is shown in Figure 3. The percentage of US-born patients with very early-onset HCC (age at HCC diagnosis < 40 years) was < 3% in each race/ethnicity subgroup. The percentage of individuals with very early-onset HCC was highest in those born in Africa, particularly West Africa (28%), followed by individuals born in Oceania (11%). The percentage of individuals with very early-onset HCC was 3% to 4% in those born in Asia, whereas it was <3% in individuals born in all other regions.

The percentage of US-born patients with early-onset HCC (age at HCC diagnosis < 50 years) was ≤ 15% in each race/ethnicity subgroup. The percentage of patients with early-onset HCC was again noted to be highest in patients born in West Africa (57%) followed by patients born in Oceania (24%). The percentage of early-onset HCC was between 10% and 15% in patients born in Asia, whereas it was <5% in patients born in Europe. With regard to the percentage of patients with an age at the time of diagnosis < 60 years, < 70 years, and < 80 years, the percentages remained highest in patients born in West Africa and lowest in patients born in Europe.

**Factors Associated With Very Early/Early Age at Onset of HCC**

Factors found to be associated with very early/early age at the onset of HCC in multivariate logistic regression are summarized in Table 3. Black race (AOR, 1.8; 95% CI, 1.5-2.2 [\(P < .01\)]) API race (AOR, 1.9; 95% CI, 1.6-2.4 [\(P < .01\)]), and country of birth were found to be associated with very early-onset of HCC (aged < 40 years). Birth in West Africa (AOR, 16.3; 95% CI, 9.2-27.9 [\(P < .01\)])

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**Table 2. Cumulative Percentages of HCC by Age of Onset in the US SEER 18 Registries Between 2000 and 2012, Classified by Country or Region of Birth**

| Age of Onset | Total |
|--------------|-------|
| < 40 Years   |       |
| < 50 Years   | US born White 247 (1.2%) 1665 (8.2%) 7754 (38.1%) 12,992 (63.9%) 17,613 (86.6%) 20,335|
| < 60 Years   | US born Black 101 (1.8%) 599 (10.5%) 2932 (51.4%) 4683 (82.0%) 5402 (94.6%) 5708|
| < 70 Years   | US born Asian/Pacific Islander 42 (2.8%) 163 (10.7%) 589 (38.6%) 955 (62.6%) 1288 (84.5%) 1525|
| < 80 Years   | US born Hispanic 63 (1.6%) 575 (14.2%) 1969 (48.7%) 2994 (74.0%) 3766 (93.1%) 4047|
| < 80 Years   | US born African born West Africa 18 (28.1%) 41 (66.9%) 56 (77.8%) 65 (90.3%) 72 (100%) 72|
| < 80 Years   | US born African born Non-West Africa 17 (5.7%) 51 (17.2%) 130 (43.8%) 215 (72.4%) 279 (93.9%) 297|
| < 80 Years   | US born Africa/Oceania born East Asia 98 (3.3%) 376 (12.5%) 1024 (34.0%) 1832 (60.8%) 2683 (89.0%) 3015|
| < 80 Years   | US born Africa/Oceania born South East Asia 134 (3.6%) 497 (14.0%) 1388 (39.1%) 2395 (67.5%) 3189 (89.9%) 3548|
| < 80 Years   | US born Africa/Oceania born Other Asia 14 (2.9%) 50 (10.5%) 155 (32.4%) 310 (64.9%) 432 (90.4%) 478|
| < 80 Years   | US born Africa/Oceania born Oceania born 19 (9.6%) 48 (24.2%) 114 (57.6%) 159 (80.3%) 186 (95.0%) 198|
| < 80 Years   | US born Africa/Oceania born European born 10 (1.1%) 42 (4.5%) 200 (21.2%) 424 (45.0%) 749 (79.4%) 943|
| < 80 Years   | US born Africa/Oceania born Other North America/Central/South America 90 (2.5%) 466 (12.9%) 1522 (42.1%) 2539 (70.3%) 3261 (90.3%) 3613|
| < 80 Years   | US born Africa/Oceania born Other regionsa 20 (2.6%) 82 (11.2%) 267 (35.2%) 460 (60.6%) 646 (85.1%) 759|
| < 80 Years   | US born Africa/Oceania born Unknown 287 (1.9%) 1601 (10.6%) 6443 (42.7%) 10,636 (70.4%) 13,629 (90.3%) 15,102|

Abbreviations: HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results.

a "Other regions" indicates 759 cases for which the country of birth was indicated as "non-United States/Canada, not otherwise specified."
Central/South/other Africa (AOR, 11.0; 95% CI, 4.5-23.7 [P < .01]), Oceania (AOR, 4.9; 95% CI, 2.9-8.0 [P < .01]), or East Africa (AOR, 3.5; 95% CI, 1.5-6.8 [P < .01]) was found to have the strongest associations with very early onset of HCC. Male sex appeared to be protective against very early onset of HCC (AOR, 0.8; 95% CI, 0.7-0.9 [P < .01]).

For early-onset HCC, independent predictors were male sex (AOR, 1.4; 95% CI, 1.3-1.5 [P < .01]); minority race/ethnicity, including black race (AOR, 1.4; 95% CI, 1.3-1.6 [P < .01]), API race (AOR, 1.4; 95% CI, 1.3-1.5 [P < .01]), and Hispanic ethnicity (AOR, 1.7; 95% CI, 1.6-1.8 [P < .01]); and country of birth. Birth in West Africa (AOR, 10.5; 95% CI, 6.6-16.9 [P < .01]), Central/South/other Africa (AOR, 4.0; 95% CI, 2.0-7.5 [P < .01]), Oceania (AOR, 2.5; 95% CI, 1.8-3.5 [P < .01]), or East Africa (AOR, 2.1; 95% CI, 1.3-3.3 [P < .01]) had the strongest associations with early-onset HCC. Birth in Japan (AOR, 0.2; 95% CI, 0.1-0.4 [P < .01]), Canada (AOR, 0.4; 95% CI, 0.1-0.9 [P = .04]), or Europe (AOR, 0.5; 95% CI, 0.4-0.7 [P < .01]) had the strongest inverse associations with early-onset HCC.

For age < 60 years at the time of HCC diagnosis, independent predictors were male sex (AOR, 2.0; 95% CI, 1.9-2.1 [P < .01]), black race (AOR, 1.7; 95% CI, 1.6-1.8 [P < .01]), Hispanic ethnicity (AOR, 1.4; 95% CI, 1.3-1.5 [P < .01]), and country of birth. Birth in West Africa (AOR, 3.3; 95% CI, 1.9-5.9 [P < .01]) or Oceania (AOR, 2.2; 95% CI, 1.7-3.0 [P < .01]) was found to have the strongest association with age < 60 years at HCC diagnosis. Birth in Canada (AOR, 0.4; 95% CI, 0.3-0.6 [P < .01]), Europe (AOR, 0.4; 95% CI, 0.4-0.5 [P < .01]), or Japan (AOR, 0.5; 95% CI, 0.4-0.6 [P < .01]) had the strongest inverse association with age < 60 years at the time of HCC diagnosis.

The percentage of patients with missing information regarding country of birth increased over time during the study period (see Supporting Information Fig. 1). Because the percentage of patients with missing information regarding country of birth increased steeply after 2010, we performed additional logistic regression analysis after excluding cases diagnosed between 2010 and 2012 (18,377 cases). The main results did not change significantly (see Supporting Information Table 1). Next, the analysis was
repeated after excluding patients aged <20 years (168 patients) to avoid potential misdiagnosis of HCC, considering that the development of HCC before age 20 years is extremely rare. Again, the main findings remained essentially the same (see Supporting Information Table 2).

**DISCUSSION**

In a US population-based study using the SEER registry, we found that country of birth was associated with age at the time of HCC diagnosis, after adjusting for sex and race/ethnicity. The median age at the time of HCC diagnosis was 7 years younger in men compared with women ($P<.01$). Nonwhite race and Hispanic ethnicity were found to be associated with earlier age at HCC diagnosis. The vast majority of white and black patients were born in the United States. Conversely, the majority of Asian and approximately 40% of Hispanic patients with HCC were foreign born. The percentage of foreign-born patients with HCC remained largely stable between 2000 and 2012. Logistic regression analysis demonstrated that country of birth had the largest impact on age at the time of HCC diagnosis. Birth in West Africa, Central/South/other Africa, Oceania, and East Africa was found to be associated with a 16.3-fold, 11.0-fold, 4.9-fold, and 3.5-fold, respectively, increased risk of very early onset of HCC (age at HCC diagnosis <40 years). Again, birth in West Africa, Central/South/other Africa, Oceania, and East Africa was found to be associated with a 10.5-fold, 4.0-fold, 2.5-fold, and 2.1-fold, respectively, increased risk of developing early-onset HCC (age at HCC diagnosis <50 years). Conversely, birth in Europe, Canada, or Japan was found to be inversely associated with early onset of HCC.

The data from the current study clearly demonstrate that country of birth, rather than race/ethnicity, had the largest impact on the age of the patient at the time of HCC diagnosis in the US general population. In particular, the high percentage of early-onset HCC diagnosed in individuals born in Africa is quite striking. This finding closely mirrors the local epidemiology of HCC in that region and is consistent with previous study findings regarding the epidemiology of HCC in different regions of the world.9,13 For example, we have developed a consortium of collaborating centers to establish a database of HCC.
cases to describe the clinical features of patients with HCC in Africa. In our initial analysis of 1552 patients with HCC from 14 different institutions in 7 African countries, the median age at the time of HCC diagnosis was 44 years in West Africa and approximately one-third of West African patients with HCC developed HCC before the age of 40 years. A nationwide Gambia Liver Cancer Study of 216 cases of HCC had similar results, with a median age at the time of onset of HCC of 47 years. The global cancer statistics database published by the International Agency for Research on Cancer, GLOBOCAN 2012, reported age-specific HCC incidence rates in individuals aged 15 to 39 years in West Africa and Sub-Saharan Africa that were 11-fold and 6-fold higher, respectively compared with the United States. Conversely, the age-specific HCC incidence rates in North Africa were the same as in those in the United States in individuals aged 15 to 39 years, whereas the age-standardized incidence rates of HCC were 2-fold higher in North Africa compared with United States. Thus, there are clear regional variations in HCC epidemiology in countries and regions within Africa. The SEER data also were consistent with previous studies of HCC diagnosed outside Africa. For example, the global HCC BRIDGE (‘Bridge to Better Outcomes in HCC’) study was a large multiregional longitudinal cohort study designed to describe the global epidemiology, practice patterns, and outcomes of 18,031 patients with HCC in North America, Europe, and Asia. The mean age at the time of HCC diagnosis was found to be significantly higher in Japan and Europe and lower in other Asian countries in comparison with the United States.

### TABLE 3. Demographic Factors Associated With Earlier Age of Onset of HCC in the US SEER 18 Registries Between 2000 and 2012

| Sex          | Outcome: Age of Onset < 40 Years | Outcome: Age of Onset < 50 Years | Outcome: Age of Onset < 60 Years |
|--------------|----------------------------------|----------------------------------|----------------------------------|
|              | AOR 95% CI P                      | AOR 95% CI P                      | AOR 95% CI P                      |
| Women (reference) |                                |                                  |                                  |
| Men           | 0.76 0.67-0.86 .01               | 1.39 1.30-1.48 .01               | 2.01 1.93-2.10 .01               |
| Race          |                                  |                                  |                                  |
| Black         | 1.84 1.53-2.20 .01               | 1.38 1.27-1.50 .01               | 1.71 1.62-1.80 .01               |
| Asian/Pacific Islander | 1.92 1.55-2.37 .01 | 1.43 1.29-1.58 .01               | 0.97 0.90-1.03 .32               |
| Hispanic      | 1.15 0.92-1.41 .21              | 1.69 1.56-1.82 .01               | 1.38 1.31-1.45 .01               |
| Country of birth |                                   |                                  |                                  |
| United States (reference) |                                |                                  |                                  |
| Europe        | 0.86 0.42-1.53 .63              | 0.52 0.37-0.70 .01               | 0.44 0.37-0.51 .01               |
| Canada        | 0.53 0.03-2.39 .53              | 0.40 0.14-0.87 .04               | 0.41 0.27-0.61 .01               |
| Mexico        | 1.62 1.14-2.27 .01              | 1.11 0.96-1.28 .15               | 0.94 0.85-1.04 .22               |
| Other North or Central America/Caribbean | 2.27 1.56-3.23 .01 | 0.93 0.77-1.12 .46               | 0.88 0.77-0.99 .03               |
| South America | 3.06 1.42-5.78 .01              | 0.88 0.55-1.33 .56               | 0.64 0.47-0.85 .01               |
| East Asia     | 1.66 1.24-2.21 .01              | 1.29 1.11-1.50 .01               | 0.99 0.89-1.10 .82               |
| South East Asia | 1.70 1.30-2.23 .01           | 1.29 1.12-1.48 .01               | 1.08 0.98-1.18 .13               |
| Japan         | - - .97                        | 0.24 0.13-0.40 .01               | 0.48 0.37-0.63 .01               |
| Other Asia    | 1.73 0.95-2.88 .05              | 1.10 0.80-1.47 .55               | 0.78 0.64-0.95 .02               |
| Oceania       | 4.92 2.86-8.02 .01              | 2.51 1.77-3.50 .01               | 2.20 1.85-2.05 .01               |
| West Africa   | 16.3 9.15-27.9 .01              | 10.5 6.55-16.9 .01               | 3.28 1.92-5.94 .01               |
| East Africa   | 3.48 1.54-6.32 .01              | 2.08 1.27-3.27 .01               | 0.68 0.46-1.00 .05               |
| Central/South and Other Africa | 11.0 4.45-23.7 .01 | 3.97 1.99-7.52 .01               | 1.30 0.70-2.43 .41               |
| North Africa  | 1.15 0.19-3.62 .85              | 1.39 0.79-2.27 .22               | 1.21 0.86-1.71 .27               |
| Other regionsa | 1.53 0.94-2.37 .07           | 1.08 0.85-1.35 .53               | 0.81 0.70-0.94 .01               |
| Unknown       | 1.25 1.07-1.45 .01              | 1.07 1.00-1.14 .04               | 1.07 1.03-1.12 .01               |

Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio; HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results.

*a "Other regions" indicates 759 cases for which the country of birth was indicated as “non-United States/Canada, not otherwise specified.”
because the median age of the US-born population is not substantially different from the median ages of the African-born or Oceania-born individuals, it appears unlikely that differences in the age distributions of the populations would completely account for the observed differences in age at the time of HCC diagnosis. In addition, we were able to obtain data regarding the percentages of individuals aged <45 years in the different groups from the 2000 US Census; this percentage was 66% for the US-born population, whereas it was 75% for African-born, 67% for Oceania-born, 64% for Asian-born, 74% for Latin American-born, 42% for European-born, and 44% for other non-US North American-born individuals. Although the higher percentage of young individuals among African-born patients may have affected the results to some extent, it again is highly unlikely that adjusting for population structure would substantially reduce the AORs of the incidence of early-onset HCC in African-born and Oceania-born individuals compared with those born in the United States.

Regional variation in the age of onset of HCC could be explained by different degrees of exposure to risk factors. For example, the age at which HCC develops in individuals infected with HBV or HCV is closely related to their age at acquisition of infection. HBV infection is acquired before age 5 years in the majority of cases in many Asian and African countries, which could lead to earlier onset of HCC. The synergistic interaction between HBV infection and environmental exposures such as aflatoxin, which is widely prevalent in these regions, may be a major contributor to the earlier onset of HCC noted in these regions. Co-infections with HBV/hepatitis D virus and HBV/HCV also are more common in some of these endemic areas, potentially further contributing to the earlier onset of HCC. Geographic variations in the HBV genotype and integration patterns also may contribute to early-onset HCC in specific HCC-endemic regions. Conversely, HCV is acquired in adulthood, leading to a later onset of HCC in most European and American countries.

The results of the current study have important clinical implications. First, they have implications for HCC surveillance strategies in the United States. It is important to recognize that place of birth rather than race/ethnicity per se has a major impact on the age of onset of HCC. Identifying high-risk, foreign-born individuals and enrolling them into HCC surveillance programs at appropriate earlier ages should be strongly considered in the development of national guidelines. Conversely, the risk of early-onset HCC does not appear to be as high in US-born black or API individuals compared with their foreign-born counterparts.

The current study has several limitations. First, approximately 25% of patients did not have information regarding their country of birth, which may introduce bias. The main data source for country of birth is death certificates. Therefore, information regarding country of birth was preferentially obtained from decedents. For this reason, a higher percentage of patients had missing information regarding country of birth among persons diagnosed with HCC after 2010 (see Supporting Information Fig. 1). Our sensitivity analysis demonstrated a minimal impact of excluding HCC cases diagnosed after 2010 on the AOR. Furthermore, the AORs of individuals with an unknown country of birth were between 1.07 and 1.25, suggesting a minimal impact of having an unknown country of birth on age at HCC diagnosis. In addition, the SEER registry does not have information regarding the etiology of liver disease, severity of any underlying liver disease, or aflatoxin exposure. Thus, the current study was not able to objectively adjust for the impact of etiology and aflatoxin or other environmental exposures on age at the time of HCC diagnosis. Overall, compared with those born in other regions, the number of US patients with HCC born in Africa was relatively small: approximately 1% of all US patients with HCC had a known country of birth. Furthermore, the findings of the current study reflect attributes of cases in the US immigrant population and should not be viewed as a proxy for age at diagnosis in a specific country of origin. Due to the privacy protection rule of SEER, the numbers of cases in some regions (non-West Africa, other North America, and Central and South America) were combined in Table 2. The age at the time of immigration or the duration of stay in the United States was not available and also might introduce a potential bias.

Race/ethnicity, sex, and country of birth were found to be independently associated with age at the time of HCC diagnosis in the US general population. Birth in Africa (except for North Africa) and Oceania was found to be strongly associated with very early onset of HCC, mirroring the HCC epidemiology in these countries. These findings have implications for the design of comprehensive HCC surveillance programs in the United States and potentially for strategies to minimize the burden of morbidity and mortality from HCC in regions such as Africa and Oceania, in which HCC is highly endemic but where robust epidemiologic data are lacking.
FUNDING SUPPORT
Supported by grant T32 DK07198 from the National Institute of Diabetes and Digestive and Kidney Diseases (to Ju Dong Yang) and grant CA165076 from the National Cancer Institute (to Lewis R. Roberts). The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosures.

AUTHOR CONTRIBUTIONS
Contributed to study design, acquisition of data, analysis and interpretation of data, and drafting of the article: Ju Dong Yang. Contributed to study concept and design, interpretation of data, and drafting of the article: Lewis R. Roberts.

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