Early Age Hepatocellular Carcinoma Associated With Hepatitis B Infection in South America

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Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and is associated almost universally with chronic liver disease and cirrhosis. Risk factors for HCC generally vary by geographic region. To date, studies have focused on characterizing patients with HCC in Europe, North America, Asia, and, to a lesser extent, Africa.[1,2] However, little is known about the underlying demographic characteristics and risk factors for HCC in South America, particularly the association between viral hepatitis and HCC. In this study, we describe the early results of a multinational effort to characterize hepatitis B virus (HBV)-related HCC in South America.

Methods

We designed a retrospective cohort study that aimed to identify the demographics and risk factors associated with HCC in South America. Overall, 14 medical centers from 6 countries in South America participated. Each center was responsible for adhering to their respective institutional review policies. Participating centers completed a standardized retrospective chart review of patient characteristics at the time of HCC diagnosis. Data then were de-identified and placed into a composite database. The HCC diagnosis was made radiographically or histologically for all cases as defined by institutional standards. Continuous variables were summarized as means or as medians (interquartile range) according to their homogeneity. Statistical analysis was performed using the SPSS version 22.0 statistical package (Armonk, NY).

Results

Fourteen centers from 6 countries across South America contributed data for an aggregate of 1336 patients. Brazil accounted for 540 patients, Argentina accounted for 251 patients, Colombia accounted for 239 patients, Peru accounted for 220 patients, Ecuador accounted for 65 patients, and Uruguay accounted for 21 patients. Of the 1336 patients, 68% were male, and the overall median age of both males and females was 64 years. A total of 1153 (86%) patients had complete data on risk factors for HCC. HBV infection represented the main risk factor for HCC in 131 subjects (11% of those with complete data), of which 74% were males. Centers from Peru and Brazil contributed the majority of HBV patients (34% and 38%, respectively), followed by Argentina (16%), Colombia (7%), Ecuador (3%), and Uruguay (2%). The median α-fetoprotein level at diagnosis was 161 ng/mL, and 86% of HBV-infected individuals had evidence of cirrhosis (in patients who provided that information, N = 81). When evaluating HCC in individuals infected with HBV, we found that 38% (n = 48) of cases occurred before age 50, with a median age at

Abbreviations used in this paper: **HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.**

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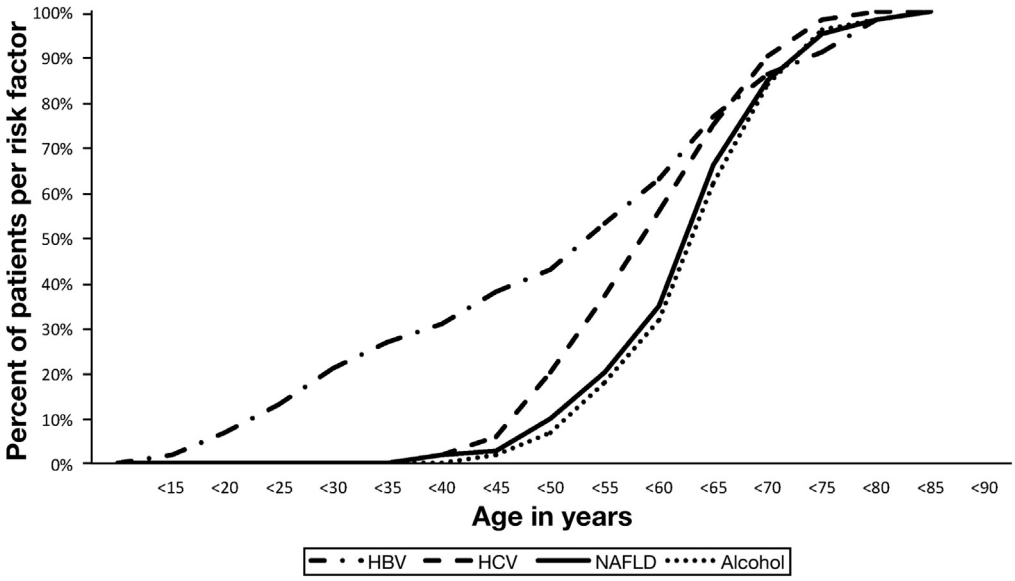

Figure 1. Cumulative percentage of HCC per independent risk factors based on age. There was a significant difference between age at diagnosis for HBV-related HCC vs others ($P < .001$). NAFLD, nonalcoholic fatty liver disease.

diagnosis of 58 years, whereas in patients infected with HCV, only 6% (n = 24) were diagnosed with HCC before age 50 ($P < .001$) and the median age at diagnosis was 63 years (Figure 1). Even larger differences were observed when HBV-induced HCC was compared with nonalcoholic fatty liver disease (median age at diagnosis, 67 y; $P < .001$) and alcohol-induced HCC (median age at diagnosis, 68 y; $P < .001$). We also analyzed intercountry variability for HBV-related HCC and age at HCC incidence and found a larger number of HCC diagnoses at younger than age 50 from Peru (43%) compared with other countries (25%), but the difference was not significant ($P = .09$).

Discussion

Our study unexpectedly found that nearly 40% of HCCs in HBV-infected individuals occurred before age 50. This finding raises the question of whether surveillance at earlier ages should be considered in this group. We did not obtain information about cirrhosis in all HBV-infected patients with HCC diagnosed before age 50, but fewer than half of those with such information had cirrhosis (15 of 34 patients). Peru contained the highest rate of HBV-related HCC (35%), making it the most common risk factor for HCC in the country. Of those individuals from Peru with specific information about the area of origin (N = 24), 45% were from the Amazonian region, which has a higher prevalence of HBV.[3] The mode of transmission also could play a role in early HCC, but this was not assessed in our study. Interestingly, the most frequent HBV genotype in South America is F, and a significant association between HBV genotype F and early HCC occurrence has been found in Alaska natives.[3,4] It is possible that the viral genotype had a role in early HBV-associated HCC in our cohort. However, our centers did not perform HBV genotype studies, and sequence-specific studies should be performed addressing this question.

The diagnosis of HCC at an early age in individuals infected with HBV in Africa has been attributed to a synergy between HBV and dietary aflatoxins, which is thought to induce mutations in the TP53 gene. However, aflatoxins have not been thought to play a role in South America, although 1 study found aflatoxin-associated p53 mutations in HBV-related HCCs.[5] Other factors such as insertional mutagenesis or family history could play a role in early HCC.[6] However, we could not assess for these variables in our study. A larger, more comprehensive study is needed to understand further the clinical implications of HBV infection in HCC development in South America.

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Conflicts of interest
The authors disclose no conflicts.