Risk Factors for Hepatocellular Carcinoma Among Patients with Chronic Hepatitis B Infection in an Urban Hospital Setting

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Abstract

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Background: Risk factors for hepatocellular carcinoma (HCC) have not been well documented among immigrant populations with chronic hepatitis B virus (HBV) infection, and most data come from native Asian cohorts. We conducted a case-control study to determine the risk factors associated with HCC among immigrant patients with chronic HBV in a US-based academic urban hospital setting, with the goal of further clarifying HCC risk in this key subset of patients.

Methods: We identified a total of 278 patients with HCC and chronic HBV; these cases were age- and sex-matched in a 1:3 ratio with 823 non-cancer control subjects with chronic HBV. Logistic regression analyses were used to estimate the risk of HCC associated with race

(with black race stratified by foreign-born status), adjusted for patient demographics and clinical conditions.

Results: In the multivariate analysis, Asian race was the only risk factor associated with a statistically significant greater odds of HCC; adjusted odds ratio (aOR) 3.2 (95% CI [2.1 – 5.1]). Black patients comprised only 7% (19 of 278) of cases, and did not have increased odds of HCC. The crude OR was 0.6 (95% CI [0.3 – 1.1]) in African immigrants and 0.4 (95% CI [0.1 – 1.1]) in non-immigrant blacks. The aOR was 1.3 (95% CI [0.6 – 2.9]) in African immigrants and 0.6 (95% CI [0.2 – 1.8]) in non-immigrant blacks. Diabetes was associated with decreased HCC in the multivariate analysis aOR 0.6 (95% CI [0.4 – 0.9]). In a secondary multivariate analysis without cirrhosis in the model, alcohol was associated with HCC aOR 1.7 (95% CI [1.0 – 2.9]). We found no association between HCC and other risk factors including HCV coinfection and HIV coinfection.

Conclusions: Asian patients were the only racial subgroup with an increased odds of HCC in our cohort. Our African-immigrant patients, many of whom were from Ethiopia or Somalia, were not at increased risk of HCC, which questions our current guidelines for early screening in these patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh most common cancer in women, and is the second most common cause of cancer deaths worldwide.[1,2] Although there is regional variability, the global incidence of HCC continues to increase.[3] Three of the main risk factors known in the development of liver cancer are hepatitis B (HBV) infection, hepatitis C (HCV) infection, and alcohol.[4] The global prevalence of people with chronic hepatitis B is estimated to be almost 4%, with an estimated 360 million people living with HBV infection. Over half of hepatocellular carcinoma is attributable to chronic hepatitis B infection.[5,6] Up to 80% of people with HCC live in areas of high prevalence for hepatitis B surface antigen, the primary marker of chronic HBV infection.[7] In patients with chronic HBV infection, the incidence of HCC increases with increasing age and after a diagnosis of cirrhosis.[8]

Sub-Saharan Africa and Eastern Asia have the highest prevalence of HCC, likely due to the high prevalence of chronic HBV and exposure to aflatoxin b1 in these regions; both factors remain among the strongest epidemiologic risk factors for HCC.[4,9]African immigrant patients with chronic HBV infection appear to be at greatest risk of HCC at younger ages than other subgroups are, possibly due to aflatoxin exposure in their native countries or to genetic polymorphisms increasing susceptibility. These data, however, are based on older observational studies, largely from West Africa, and have not been replicated in the contemporary era.[10]

Current guidelines by the American Association for the Study of Liver Diseases recommend HCC screening of patients with chronic HBV infection in Africans older than 20 years, patients with cirrhosis, Asian females 50 years or older, Asian males 40 years or older, and patients with a family history of HCC. It remains unclear whether HBV-infected patients who emigrate from their country of origin remain at increased risk for HCC in the US, or whether other clinical factors play a greater role in HCC risk. Risk factors for HCC have not been well documented among immigrant-based populations with chronic HBV infection, and most data come from native Asian cohorts. [11] It is suggested that HBV carriers with cirrhosis be screened regardless of age in Asians because the HCC incidence in these patients is highest, at 2%-8% incidence/year.[11] Factors that increase the risk of HCC development in immigrant populations have not been well studied.

We conducted a hospital-based case-control study using the Harborview Medical Center (HMC) and University of Washington Medical Center (UWMC) medical databases. The purpose of this study was to identify sociodemographic and medical factors associated with HCC among immigrant patients with chronic HBV in a US-based academic urban hospital setting. We also wanted to further characterize the burden of HCC in African immigrants.

METHODS

Data Source and Study Population

Our data source was a de-identified clinical data repository of all laboratory and clinical diagnoses extracted from electronic medical record system of two academic hospitals, University of Washington (UWMC) and Harborview Medical Center (HMC). We selected all

patients at UWMC or HMC with a diagnosis of chronic hepatitis B and HCC from January 2002 to December 2015. Chronic HBV was defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes 070.3X, 070.2X and confirmed by chart review for all cases. Cases were defined by ICD-9 CM 155.0 for HCC. We identified 296 cases that were seen at UWMC or HMC during the specified time period. Eighteen cases were excluded from the study after chart review showed they did not have HCC, leaving a total of 278 confirmed cases.

Non-cancer controls with chronic HBV were matched by age and sex in a 3:1 ratio to patients with HCC. Age was matched in controls to within 3 years of the case's age. A total of 859 controls were identified using ICD-9 codes. After chart review to confirm chronic HBV status, 36 controls were excluded, leaving a total of 823 controls. This research was approved by the Human Subjects division of the University of Washington.

Key Covariates

We collected data on age (categorized as 20-39, 40-59 and ≥60 years), sex and race/ethnicity (categorized as white, African immigrant, non-immigrant black, Asian, other). Asian immigrant origin was not broken down by country because they were not the main focus of our inquiry and the majority of the non-English speaking patients older than 40 years were assumed to be immigrants. Race/ethnicity was otherwise determined using the documented race field in the patient charts. All black and "other" races were confirmed by chart review for cases and controls. African immigrant versus non-immigrant status was confirmed by chart review for all black patients. We identified HIV, chronic hepatitis C

(HCV), diabetes mellitus, alcohol use disorder, and severity of liver disease as follows. HIV diagnosis was identified by ICD-9CM diagnosis codes 042, V08 and then confirmed by chart review and laboratory results. We defined HCV infection as the presence of hepatitis C virus antibody. We identified diabetes mellitus by ICD-9 CM code 250.X and alcohol use disorder by ICD-9 CM codes: 291.x, 303.x and 305.0. Patients were considered to have cirrhosis if they met any of the following criteria: (1) Fibrosis-4 (FIB-4) score greater than 3.25 based on serum aspartate aminotransferase (AST), platelet count, and alanine aminotransferase (ALT) closest to the time of diagnosis, (2) chronic liver disease and cirrhosis (ICD-9 CM 571) or (3) cirrhosis of liver without mention of alcohol (ICD-9 CM 571.5).[12] For additional information on disease severity, we collected diagnoses on complications of liver disease including ascites (ICD-9 CM 789.5), esophageal varices (ICD-9 CM 456.9, 456.1, 456.2), and spontaneous bacterial peritonitis (ICD-9 CM 567.23).

Statistical analysis

Descriptive statistics were calculated by determining the percent of cases or controls with each demographic characteristic; we compared distributions of categorical variables between cases and controls by performing Pearson chi squared tests. We compared ages between cases and controls using a two-sample Wilcoxon rank-sun (Mann-Whitney) test. Our primary objective was to examine the association between race/ethnicity and the risk of HCC in chronic hepatitis B, adjusting for several known risk factors including HIV coinfection, HCV coinfection, alcohol use disorder, cirrhosis, and diabetes. We opted for a standard logistic regression rather than a conditional or “matched” analysis since the resulting strata from matching were sufficiently large and a standard analysis has been

shown to offer more statistical precision than conditional analysis under these conditions.[13] A multivariate logistic regression was conducted to evaluate adjusted associations between the risk factors measured and the risk of HCC in chronic HBV patients, controlling for age and sex, our matching variables. Cirrhosis was included in the primary multivariate analysis to determine the extent to which associations between risk factors and HCC were mediated by this condition. A secondary multivariate analysis was conducted without cirrhosis in the model.

RESULTS

We identified 278 patients who were seen at HMC and UWMC between January 2002 and December 2015 with chronic HBV and HCC. We identified 823 controls with chronic HBV but without HCC who were seen at HMC and UWMC in the same timeframe.

Table 1: Demographic characteristics of HCC cases and controls

		HCC Cases = 278		Controls = 823		p value
		Total	%	Total	%	
Age	< 40	4	1.4	12	1.5	
	40-59	88	31.7	286	34.8	0.356
	≥ 60	186	66.9	525	63.8	
Sex	Female	60	21.6	179	21.7	0.953
	Male	218	78.4	644	78.3	
Race	White	52	18.7	235	28.6	
	Black	19	6.8	166	20.2	
	African immigrant	14	5.0	110	13.4	<0.001
	Non-immigrant	5	1.8	56	6.8	
	Asian	199	71.6	394	47.9	
	Other	8	2.9	26	3.2	
Comorbidities						
	Alcohol abuse	27	9.7	73	8.9	0.673
	Cirrhosis	242	87.1	253	30.7	<0.001
	Hepatic encephalopathy	37	13.3	26	3.2	<0.001
	Ascites	37	13.3	47	5.7	<0.001
	Esophageal varices	58	20.9	24	2.9	<0.001
	Spontaneous bacterial peritonitis	12	4.3	10	1.2	0.001
	HIV coinfection	16	5.8	87	10.6	0.017
	DM diagnosis	62	22.3	188	22.8	0.852
	HCV coinfection	38	13.7	126	15.3	0.506

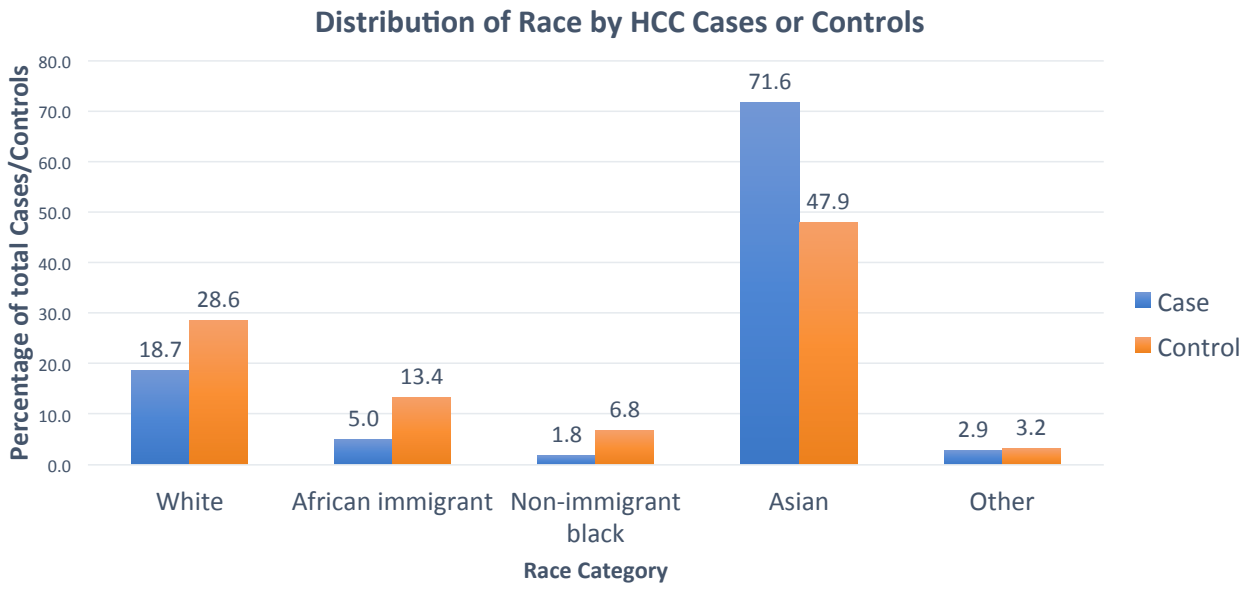
Footnote: All values represent total numbers followed by percentages. HCV: hepatitis C virus. DM: Diabetes Mellitus. HIV: human immunodeficiency virus. Cirrhosis: FIB4>3.25 or ICD-9 codes for cirrhosis

Demographic characteristics

Demographic characteristics of HCC cases and non-cancer controls are presented in Table 1. Over sixty percent of cases and controls were ≥60 years of age, with very few patients <40. A majority of HCC cases and non-cancer controls were males (78.4% and 78.3%, respectively). As expected, 87.1% of the cases had cirrhosis, as defined above, compared

with only 30.7% of the non-cancer controls. Other signs of advanced liver disease including spontaneous bacterial peritonitis, esophageal varices, ascites or hepatic encephalopathy were noted more frequently in cases than controls (details in Table 1). The cases were less likely to have HIV coinfection (5.8% versus 10.6%) than controls. There was no statistically significant difference between cases and controls in the percentage of patients with alcohol use diagnoses, DM diagnosis, and HCV coinfection.

Figure 1: Distribution of Race by HCC Cases or Controls



Race and HCC

When assessing race as a risk factor for HCC, a large proportion of the cases and controls were Asian, almost three quarters of the cases and half of the controls (Figure 1). Black patients comprised a very small proportion of all cases of HCC in the 15-year period of the study, only 19 out of 275 patients (6.8% of the cases) but made up 20.2% of the controls.

Table 2 summarizes the basic characteristics of the fourteen African immigrant cases with HCC in our study: the age, sex, country of origin as confirmed by chart review and whether or not they have cirrhosis, as defined above. Eleven of the African immigrants are from Ethiopia and Somalia, consistent with the predominantly East African origin of African immigrants in the Seattle region.

The "other" category for race included American Indian, Alaska Native, Guamanian or Chamorro, Hispanic, Mexican, Mexican-American, Chicano, Middle Eastern, Native Hawaiian, Pacific Islander or unknown.

Table 2: Hepatocellular Carcinoma Cases among African-Immigrant Patients, 2002-2015

Age	Sex	Country of Origin	Cirrhosis (Y/N)
45	M	Chad	No
41	M	Ethiopia	No
50	M	Ethiopia	Yes
56	M	Ethiopia	Yes
47	M	Liberia	Yes
56	M	Senegal	Yes
56	M	Somalia	No
49	M	Somalia	Yes
61	M	Somalia	No
54	M	Somalia	Yes
33	M	Sudan	Yes
77	F	Eritrea	No
51	F	Ethiopia	Yes
67	F	Kenya	Yes

Cirrhosis: FIB4>3.25 or ICD-9 codes for cirrhosis

Risk Factors associated with HCC

The primary univariate and multivariate analysis results are presented in Table 3. Age and sex as risk factors had odds ratios of OR 0.9 (95% CI [0.3- 2.9]) for age 40-59, OR 1.1 (95% CI [0.3 – 3.3]) in ≥60 and OR 1.0 (95% CI [0.7 – 1.4]) for male sex in the univariate analysis, as expected due to matching on these factors. The aOR in the multivariate analysis decreased to 0.5 (95% CI [0.1 – 2.2]) in age 40-59, and aOR 0.4 (95% CI [0.1 – 1.6]) for ≥60, while the aOR for sex did not change. In univariate analysis, Asian race was the only statistically significant race subgroup associated with HCC and it remained associated with HCC in the multivariate analysis aOR 3.2 (95% CI [2.1 – 5.1]). The crude OR for African immigrants was 0.6 and crude OR for non-immigrant blacks was 0.4 in the univariate analysis. Adjusted ORs were 1.3 (95% CI [0.6 – 2.9]) in African immigrants and 0.6 (95% CI [0.2 – 1.8]) in the non-immigrant black patient population in multivariate analysis.

In univariate analysis, cirrhosis was associated with greatly increased odds of HCC OR 15.1 (95% CI [10.4 – 22.1]). In the multivariate analysis, cirrhosis remained strongly associated with HCC aOR 17.9 (95% CI [11.9 – 26.9]). Diabetes was associated with decreased odds of HCC aOR 0.6 (95% CI [0.4 – 0.9]). HCV, HIV and alcohol use were not associated with increased odds of HCC.

Table 3: Univariate and multivariate analysis assessing factors associated with HCC

	Crude OR	95% CI	p value	aOR	95% CI	p value
Age (Reference: 20-39 yr)						
40-59	0.9	0.3 - 2.9	0.892	0.5	0.1 - 2.2	0.392
≥ 60	1.1	0.3 - 3.3	0.917	0.4	0.1 - 1.6	0.193
Race (Reference: white)						
African immigrant	0.6	0.3 - 1.1	0.086	1.3	0.6 - 2.9	0.442
Non-immigrant black	0.4	0.1 - 1.1	0.065	0.6	0.2 - 1.8	0.419
Asian	2.3	1.6 - 3.2	< 0.001	3.2	2.1 - 5.1	< 0.001
Other	1.4	0.6 - 3.2	0.446	2.2	0.8 - 6.0	0.134
Sex	1.0	0.7 - 1.4	0.953	1.0	0.7 - 1.6	0.842
DM	1.0	0.7 - 1.3	0.852	0.6	0.4 - 0.9	0.017
HCV	0.9	0.6 - 1.3	0.507	0.9	0.5 - 1.4	0.64
HIV	0.5	0.3 - 0.9	0.019	0.9	0.4 - 1.8	0.761
EtOH	1.1	0.7 - 1.8	0.673	1.2	0.6 - 2.1	0.593
Cirrhosis	15.1	10.4 - 22.1	< 0.001	17.9	11.9 - 26.9	< 0.001

DM: diabetes mellitus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. EtOH: alcohol use disorder diagnosis. Cirrhosis: FIB4>3.25 or ICD-9 codes for cirrhosis

In the secondary multivariate analysis that did not include cirrhosis, Asian race remained associated with HCC with aOR 2.6 (95% CI [1.8 – 3.9]) and the rest of the race categories remained unchanged. Unlike in the primary analysis, diabetes was not associated with lower odds of HCC aOR 0.9 (95% CI [0.7 – 1.3]). Having HCV coinfection or HIV coinfection was not associated with an increased risk of HCC. The aOR for alcohol use disorder diagnosis was greater and statistically significant in this analysis, aOR 1.7 (95% CI [1.0 – 2.9]), p value 0.049.

DISCUSSION

We assessed risk factors associated with HCC in patients with chronic HBV infection seen in a large academic center. Asian race was a strong and independent predictor of HCC in our patient population.

Globally, Asia and Africa have the highest incidence and prevalence of HCC, likely due to both high rates of HBV surface antigen carriage and poor access to effective treatment in these regions.[14–16] As an example, it is estimated that almost half of the liver cancer cases worldwide occur in China.[2] In our study, individuals of Asian race had 3-fold greater odds of HCC in the multivariate analysis. In contrast, African immigrant and non-immigrant black patients comprised a very small proportion (6.8%) of all cases of HCC in the 15-year period of our study, while they made up 20.2% of controls. In multivariable analyses, black race, African immigrant status, and non-immigrant black race were not associated with HCC. The adjusted OR for African immigrants was 1.3, which is greater than the OR of 0.6 in non-immigrant black patients, but neither was statistically significant.

Studies have shown that African immigrant patients remain at increased risk of HCC and develop HCC at an earlier age than other populations, specifically among West African immigrants.[10,17–19] One study found country of birth to be an independent risk factor for age at diagnosis with HCC in the US-based Surveillance, Epidemiology, and End Results cancer registry program, and that patients from West African and to a lesser extent Central/South or East African had a strong association for onset of HCC at age <40 years.[18] Our study however did not find this excess risk. Our inability to find an association may

have been due to differences in engagement in care or screening for HCC in black patients compared with other races, although it is not clear a priori that African immigrant patients would be less likely to engage in care than Asian patients. HCC incidence can vary significantly by African region, and this may also have accounted for our not finding an association since our cohort of African immigrant patients mainly comprised individuals from Ethiopia and Somalia.[20] Additionally, the REVEAL study found that HBV DNA levels was a strong predictor of HCC risk, second only to liver cirrhosis and African patients with HBV infection have been shown to have on average lower HBV DNA levels than has been observed in the Asian cohorts[21,22].

Our study matched on age and sex; therefore we were unable to assess these variables as risk factors in our patient population. The literature shows that increased age is a strong predictor of increased HCC risk.[23–26] Almost 80% of total HCC cases develop in cirrhotic livers and cirrhosis is one of the strongest risk factors of HCC development.[27] The odds of HCC in our patient population in the univariate analysis was 15 times greater in those with cirrhosis compared to those without and 18 times higher in the multivariate analysis. Conducting the multivariate analysis without cirrhosis did not significantly change any of the results. Male sex has been shown in multiple studies to be a strong risk factor for development of HCC. Hypotheses for the gender disparity include that men have more risk factors associated with liver cancer than women or that the sex steroid differences play a role in HCC development.[14]

Alcohol use as a risk factor had increased odds of HCC in the multivariate analysis, although it did not meet statistical significance. The secondary multivariate analysis conducted without cirrhosis had a statistically significant aOR of 1.7 (95% CI [1.0 – 2.9]) for alcohol use, suggesting that the association of alcohol and HCC may be mediated by cirrhosis. The number of patients with alcohol use disorder is likely underrepresented and underreported because the use of ICD9 codes to identify the risk factor although specific, are not sensitive.[28,29] Diabetes and metabolic disorder have been shown to increase the risk of developing HCC, while adjusting for other factors.[30,31] In our study, diabetes was associated with decreased odds of HCC in the primary multivariate analysis. The relationship between chronic HBV and metabolic syndrome or diabetes is less well studied and there are conflicting reports describing the risk of HCC.[32] We found no association of HCC with HCV coinfection or HIV coinfection. HCV coinfection has also been shown to be associated with an increased risk of HCC development.[33,34] We had a small number of cases with HCV coinfection, so our study may have been underpowered to detect this association. Similarly, we had insufficient data to draw conclusions on any additional risk of HCC in patients with chronic HBV and HIV coinfection.[9,35,36]

Limitations of this study include the retrospective design and the inability of a cross-sectional, case-control design to provide an estimate of HCC incidence. We were not able to assess or adjust for the variability of screening practices, if they existed, between different subgroups of patients. Studies suggest that guidelines for screening are not consistently followed in clinical practice and differences in screening intervals or practices may have accounted for some of the differences we found in our cohort.[37] There is the possibility of

misclassification when relying on ICD-9 codes but we were able to confirm the accuracy of these diagnoses for chronic HBV infection and HCC by chart review.[28] We did not have HBV-specific data, e antigen status or more importantly HBV DNA levels, which have been shown to be associated with HCC risk.[21] This study was conducted in an urban hospital setting and our findings therefore may not be generalizable to other populations or settings. Despite these limitations, our study included a large heterogeneous population of foreign-born patients with chronic HBV infection and offered an examination of foreign-born status in black patients as a risk factor for HCC, independent of key clinical factors.

CONCLUSION:

We found that Asian race was associated with increased odds of HCC among patients with chronic HBV infection in a US-based academic urban medical center. We did not however find that African immigrant patients with chronic HBV had an excess risk of HCC when adjusting for other key clinical factors such as age and sex. The guidelines currently suggest screening for HCC starting at age 20 in this group compared to 40 or 50 in the other high-risk groups, specifically Asian women and men. Our results suggest that optimal screening strategies for African immigrants warrant further attention and study.

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