Hepatitis B Core Antibody Positivity Associated with Increased Risk of Liver Cancer in Patients with Chronic Hepatitis C: Analysis of a Large Patient Cohort in Hawai‘i

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Abstract

Chronic hepatitis C infection is a major cause of liver cancer in the United States. Hawai'i's incidence of liver cancer consistently ranks among the highest in the US, due in part to the high prevalence of hepatitis B in the state. To better understand the factors associated with liver cancer among patients in Hawai'i with hepatitis C virus (HCV) infection, the patient database of Kaiser Permanente's Hawai'i region was used to identify a cohort of 3198 patients with a history of chronic HCV infection, of whom 159 (5%) were diagnosed with liver cancer between the years 2004-2020. Multiple logistic regression was used to identify factors independently associated with liver cancer. Male sex (AOR 2.02, 95% CI 1.34-3.06), Asian race (AOR 1.78, 1.16 - 2.74) and hepatitis B core antibody (HBCAB) positivity (AOR 1.76, 95% CI 1.25 - 2.49) emerged as independent predictors of liver cancer among patients with chronic HCV infection. A history of diabetes (AOR 1.56, 1.07 - 2.27) and older age at the time of HCV diagnosis (AOR 1.19, 1.09-1.29) also emerged as significant associations. HBCAB-positive individuals did not differ significantly from those who were HBCAB-negative in regards to demographics or 5-year survival rate. In this cohort of patients with chronic HCV, a positive HBCAB without evidence of active hepatitis B infection was associated with 1.76 increased odds of liver cancer compared to those with negative HBCAB. This finding may have important implications for screening algorithms among individuals with hepatitis C infection.

Keywords

Liver cancer, chronic hepatitis C, hepatitis B, occult hepatitis B

Abbreviations and Acronyms

HBCAB = hepatitis B core antibody
HCV = hepatitis C virus
HBsAg = hepatitis B surface antigen
KP = Kaiser Permanente
OBI = occult hepatitis B infection
US = United States

Introduction

Liver cancer is currently the third leading cause of cancer-related death worldwide,[1] and its incidence in the United States (US) has more than tripled since 1980.[2] Despite recent treatment advances, liver cancer remains a particularly lethal malignancy with a 5-year relative survival rate in the US of 18%.[2] Deaths in the US from liver cancer increased 56% between 2003 and 2012,[3] largely due to the tide of maturing liver disease among Baby Boomers with chronic hepatitis C virus (HCV) infections.[4] It is estimated that approximately 50% of US liver cancer cases are related to underlying HCV infection; in contrast, only 15% of US cases are attributable to chronic hepatitis B infection.[3,5] In much of the world outside of the US and Europe, however — and especially in regions of Asia, the Pacific, and Africa where the penetrance of childhood immunization against hepatitis B is low — chronic hepatitis B infection is the predominant risk factor for liver cancer.[5] Although chronic hepatitis B and HCV infections rarely co-exist,[6] occult hepatitis B infection (OBI) (ie, detectable hepatitis B DNA in the blood or liver without detectable serum hepatitis B surface antigen (HBsAg)) is common in HCV-infected cohorts,[7-9] reflecting both the overlapping modes of transmission of the 2 viruses as well as the tendency of 1 virus to predominate as an active infection in any given individual. Whether OBI plays a significant role in the development of liver cancer among HCV-infected patients is a matter of active debate.

Although the prevalence of chronic HCV infection in Hawai‘i appears broadly similar to that of other states — estimated at 0.84 % in males and 0.64 % in females in recent modeling,[10] and higher among selected cohorts within the state[11,12] — Hawai‘i has an especially high incidence of liver cancer. For several decades, age-adjusted death rates for liver cancer in Hawai‘i have ranked among the highest 3 states in the country.[4,13] Hawai‘i's heavy burden of liver cancer is poorly understood, but likely reflects at least in part a high prevalence of chronic hepatitis B infection in the state, estimated at 3.6% overall[14] and particularly elevated among Asians and Pacific Islanders.[15-18] Other factors may also contribute to Hawai‘i's increased liver cancer incidence, including: historical immigration patterns to Hawai‘i from countries and regions with widely varying prevalences of hepatitis B, C, and smoking (eg, the Philippines, Polynesia, Micronesia, Japan, and Taiwan); steatohepatitis and diabetes prevalence in subsets of the population; and genetic/environmental factors.

Three prior studies have investigated the characteristics of patients with liver cancer in Hawai‘i;[16-18] however, none of these focused exclusively on patients with HCV infection who developed liver cancer. The current study explored the possible role of OBI and other potential risk factors in the development of liver cancer in patients in Hawai‘i with a history of chronic HCV infection.

Methods

Kaiser Permanente (KP) currently provides medical care for approximately 250 000 individuals in Hawai‘i. Since 2004, any KP-insured patient in the state referred by their primary care physician for HCV-related care has been evaluated at a single clinic in Honolulu (KP's Viral Hepatitis Clinic). The demographic, clinical, and outcomes data for all patients seen at the clinic are maintained and updated in an electronic database, allowing for long-term, longitudinal study of a large HCV-infected population. In addition, KP's electronic medical record system — which is called Health Connect and was adopted by KP's Hawai‘i region in 2004 — enabled the inclusion of KP-insured patients with HCV infection who were not referred to the clinic.

For the current study, a retrospective analysis of patient demographics and outcomes data for all patients with chronic HCV infection evaluated at the Viral Hepatitis Clinic from January 1, 2004 to December 31, 2019 was performed. This included analysis of patients diagnosed with liver cancer during follow-up care. In addition, queries were run in Health Connect for the same 16-year period to identify additional patients who had not been referred to the clinic but had HCV infection. These queries pulled lab data (eg, results from hepatitis C antibody tests, genotypes, and viral loads), diagnostic codes, and problem lists. Lastly, a separate registry of patients with liver cancer maintained by KP's multi-disciplinary Liver Cancer Tumor Board was also used to help identify and verify the status of liver cancer patients in the HCV-infected patient cohort. These 3 sources of patient information formed a cohort of patients with HCV infection and liver cancer during this 16-year timespan. The subset of patients with liver cancer and HCV infection included both patients who were diagnosed initially with liver cancer and had chronic HCV infection discovered during their cancer evaluation, as well as patients with chronic HCV infection who developed liver cancer during follow-up care for their HCV. For patients with liver cancer, clinical data (eg, age, BMI, diabetes mellitus type 1 or 2, smoking history) at the time of cancer diagnosis were collected from the clinic's database and cross-checked in Health Connect. The remaining HCV-infected patients in the cohort who did not develop liver cancer and for whom there were sufficient evaluable data were used for comparison.

Liver cancer was defined by standard radiographic and clinical criteria, and by biopsy data when available. Cancers in the liver of non-hepatic or indeterminate origin were excluded from the analysis.

Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC). Comparisons of the demographic and clinical characteristics of patients with and without liver cancer were conducted using chi-square and t-tests as appropriate. Multiple logistic regression was used to identify factors independently associated with liver cancer. Factors that were statistically significant at alpha level .05 were retained in the final models. Interaction terms were tested, but none were statistically significant. A number of patients did not have hepatitis C genotype or hepatitis B core antibody results. For these, the missing data were treated as separate indicator variables (eg, unknown genotype vs. known) to achieve maximum sample size and statistical power. Sensitivity analyses were conducted, including complete case analysis where patients with missing data were not included in the model, to confirm that this categorization of missing data did not bias the results.

This study was granted exempt status from IRB approval by the Resource Determination Committee for the Kaiser Permanente Hawaii Region (RDO-KPH-06-18).

Results

Table 1 shows the clinical characteristics of HCV-infected patients with (n=159) and without (n=3039) liver cancer in the patient cohort. Patients with HCV infection and liver cancer were more likely to be male (odds ratio [OR] 2.18, 95% confidence interval [CI] 1.48-3.22), to be Asian (OR 2.40, 95% CI 1.65-3.51), to have diabetes (OR 2.01, 95% CI 1.41-2.87), to have a positive HBCAB (OR 1.89, 95% CI 1.37-2.62), and to have a history of smoking (OR 1.74, 95% CI 1.19-2.55) than those without liver cancer. Patients with liver cancer were, on average, approximately 5 years older at time of diagnosis of HCV than those without liver cancer ($P<.001$). Among those with known hepatitis C genotypes, Genotype 1 infection was less common and Genotype 3 infection more common among patients with liver cancer ($P<.01$). The percentage of patients treated successfully for hepatitis C (as defined by a 12-week sustained virologic response) did not differ between the 2 groups ($P=.16$), and neither the prevalence of obesity nor mean body mass index (BMI).

Table 2 presents the results of multiple logistic regression analysis and the adjusted odds ratios of clinical and demographic variables associated with liver cancer among patients with chronic HCV infection. In this analysis, male sex (adjusted odds ratio [AOR] 2.02, 95% CI 1.34-3.06), HBCAB positivity (AOR 1.76, 95% CI 1.25-2.49), and Asian race as compared to Caucasian (AOR 1.78, 95% CI 1.16-2.74) emerged as independent predictors of liver cancer. A history of diabetes (AOR 1.56, 95% CI 1.07-2.27) and older age at the time of HCV diagnosis (AOR 1.19, 95% CI 1.09-1.29) also emerged as risks for liver cancer. Neither a history of smoking nor HCV genotype emerged as independent predictors of liver cancer. Sensitivity analyses using complete cases yielded similar results (data not shown).

Table 3 compares the characteristics of patients with HCV infection and liver cancer who were HBCAB-positive (n = 79) with those of HCV-infected patients with liver cancer whose HBCAB were negative (n = 76); 4 patients in the liver cancer cohort had

unknown HBCAB status. The 2 groups did not differ significantly in regards to ethnicity, age at the time of the diagnosis of liver cancer, smoking history, sex distribution, obesity prevalence, or HCV genotype. Diabetes was less common among those with HBCAB positivity than in those who were HBCAB-negative (*P*=.02). Five-year survival did not differ between those with and without HBCAB. Of the 79 patients with liver cancer and HBCAB positivity, only 1 patient had detectable HBsAg, which was only transiently positive; this patient's hepatitis B DNA viral load was very low at 119 IU/ml (reference range, <20 HBV DNA IU/ml). The remaining 78 HBCAB-positive patients with liver cancer had persistently negative HBsAg; of these patients, 14 had serum hepatitis B DNA assays sent, and all were negative. No patient with liver cancer had tissue hepatitis B DNA assayed in liver biopsy specimens.

Table 1. Clinical Characteristics of Hepatitis C-infected Patients With and Without Liver Cancer

	No liver cancer n =3039	Liver cancer n = 159	*P*-value*	OR (95% CI)#
Age at HCV diagnosis: mean (sd)	50.7 (10.9)	55.3 (8.6)	< .001	1.22 (1.13 – 1.32)
Sex: n (%)				
Male	1934 (63.6)	126 (79.3)	<.001	2.18 (1.48 - 3.22)
Female	1105 (36.4)	33 (20.8)		
Ever Smoker: n (%)	2039 (67.1)	124 (78.0)	.004	1.74 (1.19 - 2.55)
Race: n (%)				
Native Hawaiian/Other Pacific Islander	445 (14.6)	28 (17.6)	<.001	1.25 (0.81 - 1.90)
Asian	362 (11.9)	39 (24.5)		2.40 (1.65 - 3.51)
Caucasian	1337 (44.0)	75 (47.2)		1.14 (0.83 - 1.56)
Other	240 (7.9)	9 (5.7)		0.70 (0.35 - 1.39)
Unknown	655 (21.6)	8 (5.0)		
Diabetes: n (%)	512 (16.9)	46 (28.9)	<.001	2.01 (1.41 - 2.87)
BMI >30: n (%)	626 (25.4)	32 (21.6)	.306	0.81 (0.54 - 1.21)
BMI: mean (sd)	27.0 (5.8)	26.4 (5.8)	.178	
Genotype 1: n (%)				
Yes	1185 (72.1)	82 (61.2)	.007	0.61 (0.42 - 0.88)
No	458 (27.9)	52 (38.8)		
Unknown%	1396	25		
Genotype 2: n (%)				
Yes	248 (15.1)	22 (16.4)	.682	1.10 (0.69 - 1.78)
No	1395 (84.9)	112 (83.6)		
Unknown%	1396	25		
Genotype 3: n (%)				
Yes	193 (11.8)	27 (20.2)	.005	1.90 (1.21 - 2.97)
No	1450 (88.3)	107 (79.9)		
Unknown%	1396	25		
HBCAB positive: n(%)				
Yes	851 (28.0)	79 (49.7)	<.001	1.89 (1.37 - 2.62)
No	1548 (50.9)	76 (47.8)		
Unknown	640 (21.1)	4 (2.5)		
Successfully treated for HCV: n (%)	761 (25.0)	32 (20.1)	.162	0.75 (0.51 – 1.12)

HCV=Hepatitis C virus, BMI=body mass index, HBCAB = hepatitis B core antibody. OR = odds ratio and 95% CI=95% confidence interval.
* *P*-values for age and BMI means were calculated using the t-test. P-values for all other factors were based on chi-square test.
# Odds ratio for age using a 5-year interval. Odds ratio for BMI using 1 kg/m2 interval.
% Unknown category is not included in calculation of P-values and odds ratios for genotype 1, genotype 2 and genotype 3.

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Risk of Liver Cancer (Multiple Logistic Regression, n=3,049*)		
	AOR#	**95% CI**
Age at HCV diagnosis (per 5 years)	**1.19**	**1.09 - 1.29**
Male vs Female	**2.02**	**1.34 - 3.06**
Race (reference is Caucasian)		
Native Hawaiian/Pacific Islander	1.06	0.66 - 1.71
Asian	**1.78**	**1.16 - 2.74**
Other Race	**0.66**	**0.32 - 1.35**
Unknown Race	0.30	0.14 - 0.67
Diabetes	**1.56**	**1.07 - 2.27**
Hep B Core Testing		
Positive vs Negative	**1.76**	**1.25 - 2.49**

AOR = adjusted odds ratio, 95% CI=95% confidence interval, and HCV=Hepatitis C virus.
* Excludes 149 patients with missing age at HCV diagnosis (141 without liver cancer, 8 with liver cancer).
# Odds ratios are adjusted for all other risk factors in the table (eg, AOR for age at HCV diagnosis is adjusted for sex, race, diabetes and Hep B core testing).

Table 3. Comparison of Patient Characteristics Among 155* Hepatitis C-positive Liver Cancer Patients, Stratified by Hepatitis B Core Antibody Status			
	Hepatitis B Core Antibody Status		***P*-value#**
	Negative n =76	**Positive n = 79**	
Age at diagnosis of liver cancer: mean (sd)	60.6 (8.7)	61.3 (6.2)	.602
Gender: n (%)			
Male	61 (80.3)	62 (78.5)	.784
Female	15 (19.7)	17 (21.5)	
Ever smoker: n (%)	58 (76.3)	63 (79.8)	.606
Race: n (%)			
Native Hawaiian/Other Pacific Islander	17 (22.4)	11 (13.9)	.744
Asian	17 (22.4)	20 (25.3)	
Caucasian	34 (44.7)	40 (50.6)	
Other	4 (5.3)	4 (5.1)	
Unknown	4 (5.3)	4 (5.1)	
Diabetes: n (%)	28 (36.8)	16 (20.3)	.022
BMI>30: n (%)	15 (19.7)	17 (21.5)	.784
Genotype 1: n (%)			
Yes	40 (63.5)	42 (59.2)	.607
No	23 (36.5)	29 (40.9)	
Unknown%	13	8	
Genotype 2: n (%)			
Yes	9 (14.3)	13 (18.3)	.530
No	54 (85.7)	58 (81.7)	
Unknown%	13	8	
Genotype 3: n (%)			
Yes	13 (20.6)	14 (19.7)	.895
No	50 (79.4)	57 (80.3)	
Unknown%	13	8	
Alive 5 years after liver cancer diagnosis: n (%)	19 (25.0)	29 (36.7)	.115

BMI=body mass index. * Four HCV-infected patients with liver cancer had unknown hepatitis B core antibody status.
# *P*-value for age and BMI means are calculated using the t-test. P-values for all other factors are based on chi-square analysis.
% Unknown category is not included in calculation of P-values for genotype 1, genotype 2 and genotype 3.

Discussion

In this study of more than 3000 patients with chronic hepatitis C infection in a single health care system, of whom 5% were diagnosed with liver cancer during the years under study, HBCAB positivity was associated with a 1.76 increased odds of liver cancer compared to those with negative HBCAB. The prevalence of a positive HBCAB among patients with chronic HCV infection and liver cancer was strikingly high at 49.7%, compared to 28% in the HCV-infected population without liver cancer; in multivariate analysis, HBCAB positivity emerged as a strong independent risk for liver cancer (AOR 1.76, 1.25-2.49, *P*=.0001), increasing the risk more than either older age at hepatitis C diagnosis or diabetes.

Of the 79 patients in the current study with liver cancer and a positive HBCAB, none had a persistently positive HBsAg. The serologic profile of HBCAB positivity with negative HBsAg is an increasingly accepted surrogate for OBI,[8,19,20] a term which refers to the presence of detectable hepatitis B DNA in individuals seronegative for surface antigen. The majority of patients with OBI have undetectable hepatitis B DNA in the serum, consistent with their serum HBsAg negativity, but have detectable hepatitis B DNA in liver tissue. However, the laboratory techniques for detecting hepatitis B DNA in hepatocytes are technically complex, non-standardized, not commercially available, and necessitate a liver biopsy. Because the majority of individuals with OBI are seropositive for HBCAB, and given the risks and logistics involved in assaying hepatitis B DNA in liver tissue to definitively establish OBI, in both epidemiologic studies and in clinical practice HBCAB positivity with negative HBsAg is commonly considered a surrogate for OBI.[8,19, 20]

OBI has been found to be common in patients with a history of chronic hepatitis C who develop liver cancer.[19-24] However, the question of whether OBI significantly increases the risk for cirrhosis or liver cancer among patients with HCV infection remains an open one,[8,20] with several studies from a variety of countries suggesting that OBI in patients with HCV infection significantly increases the risk of developing liver cancer,[21-26] and others finding no such association.[19,27] Several lines of evidence from the woodchuck model of hepatitis B infection[28-31] as well as tissue-based studies of HBV genomic integration in patients with liver cancer[32-34] provide mechanistic support for the oncogenic potential of OBI in promoting this malignancy. The discrepant findings in the literature as to whether OBI increases the risk of liver cancer in patients with chronic HCV infection raises the question of whether OBI may do so only in subsets of HCV-infected patients with other contributory behavioral, environmental, or genetic risk factors. The findings of the current study clearly suggest an oncogenic role for HBCAB positivity in this population of HCV-infected patients in Hawai'i.

Because many risk factors may impact the development of liver cancer, other aspects of the current patient cohort bear examination. As illustrated in Table 1, the 159 patients with a history of HCV infection and liver cancer were disproportionately male and more likely to have a history of diabetes than patients with chronic HCV infection who did not develop liver cancer; both male sex[35,36] and diabetes[35,37] have been previously described as risks for liver cancer in patients with chronic hepatitis C infection. Smoking has been identified as a risk factor for liver cancer in several studies;[35,36] in the current cohort, a history of ever having smoked was significantly more common among patients with liver cancer, but smoking did not emerge as an independent risk factor in multivariate analysis. The mean age at diagnosis of HCV infection was higher among patients with liver cancer than in those with chronic HCV without liver cancer, which may reflect longer-term exposure to hepatitis C and greater degrees of hepatic fibrosis.

The current patient cohort was strikingly multi-racial (Table 1), reflecting Hawai'i's mixed ethnic and racial composition. In the current study, Asian race emerged as a strong risk factor for liver cancer (AOR 1.78, 95% CI 1.16-2.74), independent of smoking history, HBCAB positivity, diabetes, or hepatitis C genotype. Whether this reflects a genetic predisposition for liver cancer among Asians, or whether environmental exposures among immigrant groups, dietary aflatoxin intake, prior *Fasciola hepatica* infection, or other factors are involved is unclear.

The current study has several strengths: the data are derived primarily from a single comprehensive database maintained since 2004 by a large referral clinic serving the entirety of KP's Hawai'i membership, and were augmented by careful review of a unified electronic health record system used across the health care organization. In addition, the findings are strengthened by the ability to link any patient's hepatitis C and liver cancer status to clinical and demographic variables via a unique medical record number assigned at enrollment in the health plan.

The study also has several important limitations. A detailed evaluation of ethnicity, race, and birthplace/immigration history was not performed in all patients. In addition, grouping patients into categories such as "Asian" or "Pacific Islander" is an overly broad classification in regards to patterns of viral hepatitis; within these categories lie significant differences in regards to hepatitis B and C epidemiology and risk factors for liver cancer. For example, Micronesians in Hawai'i with liver cancer have been noted to have much higher rates of hepatitis B infection and lower rates of HCV infection as compared with non-Micronesian Pacific Islanders;[18] similarly, the prevalence of hepatitis B and C infections differ markedly in sub-regions within Asia.[39] Place of birth—not effectively captured in ethnic or racial groupings--is also of direct relevance to viral epidemiology. Immigrants to Hawai'i have patterns of hepatitis B and C infection primarily reflective of their countries of origin,[15] whereas individuals born in Hawai'i or elsewhere in the US are much more likely to have patterns of hepatitis B and C infection similar to the general US population. The current study employed

the commonly used surrogate of serum HBCAB positivity and negative HBSAG to infer OBI. Only a minority of the HBsAg-negative patients in the study had their serum hepatitis B virus DNA levels tested, and hepatitis B DNA in the liver (the gold standard for occult hepatitis B detection) was not assayed in liver biopsies. The assessment of alcohol intake, an established risk factor for liver cancer, was not reliably quantifiable in this retrospective review; differential alcohol intake by sex could account, in part, for the strength of the association of male sex with liver cancer in our study. Lastly, the study did not include estimates of the degree of liver fibrosis given wide variability in the timing of and approaches to assessing liver fibrosis/cirrhosis during the 16-year period under study.

Conclusions

Efforts to better understand the epidemiology of liver cancer at the state level are increasingly relevant in the US, given the sharp differences in liver cancer incidence between states[4,13] and the complex interplay of risk factors for liver cancer in different communities. A recent analysis of the National Cancer Institute's large Surveillance, Epidemiology, and End Results (SEER) cancer registry[38] projected a steady increase in liver cancer burden in the US through 2030. In this evolving landscape, region-specific evaluations of the risk factors associated with this lethal malignancy may prove crucial to future public health efforts.

In Hawai'i, shifting demographics and the aging of different ethnic cohorts have been suggested as important co-factors in observed patterns of liver cancer incidence.[17] The findings of the current retrospective study add to the understanding of liver cancer in Hawai'i, clarifying the associations of several clinical and demographic variables associated with liver cancer in a large cohort of patients with chronic HCV infection. In particular, the current findings underscore the potential importance of OBI, independent of Asian ethnicity, as a risk for liver cancer among patients with a history of hepatitis C infection. If the strong association between HBCAB positivity and liver cancer among HCV-infected patients observed in this patient cohort is borne out in future investigations, HBCAB serostatus may prove important in tailoring screening approaches for liver cancer among those chronically infected with hepatitis C.

Conflict of Interest

None of the authors identify any conflict of interest.

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