Cancer Causes Control (2012) 23:455–462
DOI 10.1007/s10552-012-9895-z

ORIGINAL PAPER

Risk factors for hepatocellular carcinoma in patients with chronic liver disease: a case–control study

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Received: 3 August 2011 / Accepted: 6 January 2012 / Published online: 19 January 2012

Abstract The majority of data on risk factors (RFs) for hepatocellular carcinoma (HCC) comes from studies involving populations without underlying liver disease. It is important to evaluate RFs for HCC in patients with chronic liver disease since HCC rarely occurs in those without underlying liver disease. We conducted a hospital-based case–control study of 259 incident HCC cases and 781 controls by convenience sampling between 02/2001 and 12/2009 from the liver clinic at Stanford University Medical Center. The study population was 41% White, 14% Hispanic, 3% African American, 40% Asian American, and 2% other race/ethnicity. RFs were examined through medical records and an in-person questionnaire. Alcohol and tobacco use was calculated by cumulative grams of alcohol or cumulative pack(s) of cigarette consumed over one's lifetime. Diabetes mellitus (DM) was defined by random glucose level of $\geq$200 mg/dL. RFs were evaluated using multivariate logistic regression. Independent predictors of HCC risk, after mutual adjustment and additional control for alcohol use, etiology of liver diseases, and DM, included age >40 (OR = 8.5 [2.6–28.3]), male gender (OR = 3.5 [2.2–5.8]), presence of cirrhosis (OR = 2.8 [1.6–4.9]), Asian ethnicity (OR = 2.8 [1.8–4.6]), AFP > 50 (OR = 4.2 [2.6–6.8]), and cumulative lifetime tobacco use of >11,000 packs (OR = 1.7 [1.0–2.9]). Heavy prolonged cigarette smoking, but not alcohol use, was a significant independent predictor for HCC in patients with underlying liver disease. Besides older age, male gender, presence of cirrhosis, and elevated AFP, Asian ethnicity and heavy cumulative tobacco use are strong independent predictors of HCC.

Keywords Alcohol · Cigarette · Cirrhosis · Ethnicity · HCC

Abbreviation

RF	Risk factors
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
DM	Diabetes mellitus
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
MELD	Model for end-stage liver disease
CTP	Child-Turcotte-Pugh

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Introduction

Primary liver cancer is a global public health problem, based on it being the fifth most common cancer and third leading cause of cancer-related mortality worldwide [1]. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancer, constituting 85–90% of cases, and results in more than 650,000 deaths per year globally [2, 3]. Although the incidence of HCC is higher in regions such as sub-Saharan Africa and Asia, its incidence has also been rising in the last few decades in developed countries such as the United States, Western Europe, and Japan [2, 4, 5]. The age-adjusted incidence of HCC in the United States has doubled in the last few decades, with an increase from 1.3 cases per 100,000 persons between 1978 and 1980 to 3.3 cases per 100,000 persons between 1999 and 2001 [3]. Identification of risk factors associated with HCC may help identify high-risk patients for surveillance as well as intervention of modifiable high-risk behaviors.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are two established risk factors for the development of HCC [3, 6]. Both HBV and HCV increase the risk of HCC through their promotion of cirrhosis, although HBV carriers are at risk of HCC even in the absence of cirrhosis [3]. A cross-sectional study of several liver transplantation centers in the United States that examined etiologies of HCC reported that 47% of their HCC cohort had HCV, 15% had HBV, 5% had both HBV and HCV, and 33% had neither virus [7]. Among Asians, HBV accounts for at least 60% of HCC [8].

Age, sex, and ethnicity are also risk factors of HCC. The incidence of HCC increases progressively after 40 years of age in the United States, with a mean age at the time of diagnosis of 65 years and highest incidences in those between the ages of 70–75 [9, 10]. Men are 3–4 times more likely to have HCC than women in almost all populations with HCC [3, 9]. Asians and African Americans are 4 and 2 times, respectively, more likely than Caucasians to have HCC [3]. A similar trend was observed when risk for HCC was evaluated in patients with chronic hepatitis C and cirrhosis with risk of liver cancer being 4 times greater in Asians and 2 times greater in African American men when compared to Caucasians [11]. The most common etiology of HCC in Asian patients is HBV infection [12].

Behavioral factors such as heavy alcohol intake and cigarette smoking are other possible risk factors for HCC [3, 13]. However, data on alcohol and/or cigarette use as risk factors for HCC have been conflicting and inconclusive. Many of these studies included general or healthy populations as control rather than patients with chronic liver disease. It is not clear whether alcohol is a risk factor for HCC or cirrhosis, which in turn is a risk factor for HCC [3]. Cigarette use as a risk factor for HCC has been reported by some previous studies but not in others [14–19].

A systematic review of association between diabetes mellitus (DM) and HCC reported a positive correlation between DM and HCC, with an approximately 2.5-fold increase in the risk of HCC [20]. However, DM is associated with both HCV and non-alcoholic fatty liver disease, which are associated with cirrhosis, an established risk factor for HCC [10, 20–22]. A study reported that DM in the presence of HCV infection increases the risk for HCC and DM mortality, with little evidence linking the increase in risk for HCC in diabetic patients with HBV infection [21].

Currently, there are few studies to examine specific risk factors for HCC in the United States, especially in patients with chronic liver diseases. Unlike other risk factor studies that have examined risk factors for HCC in the general population inclusive of healthy subjects, we restricted our study to subjects with chronic liver disease so that our data are more generalizable to this population since HCC rarely occurs in those without underlying liver disease. Thus, we examined various risk factors associated with HCC in a large case–control study of patients with underlying liver diseases using risk factor data collected via a detailed questionnaire.

Methods

Study design

We conducted a case–control study of patients prospectively enrolled between February 2001 and December 2009 at the liver clinic at Stanford University Medical Center, Palo Alto, California. Patients were identified from a daily encounter list at a tertiary liver clinic. Risk factors data was collected through personal face-to-face interviews conducted by study coordinators using a 12-page risk factor questionnaire. Participants' clinical characteristics were obtained by chart review using a case report form designed specifically for this study, which included data from clinical notes, laboratory results, serological results, and pathology and radiology reports.

Study population

We enrolled 1,037 eligible patients through convenient sampling, with selection based on availability of study staff. Approximately 95% of those invited to participate in this study agreed to participate. Of those, 259 patients were identified as cases and 778 as controls. Cases were patients with HCC, and criteria included hypervascular lesion $\geq$2 cm on two imaging tests, hypervascular lesion $\geq$2 cm on one

imaging test and alpha-fetoprotein (AFP) > 200 ng/mL, or an enlarging hypervascular lesion in patients with known cirrhosis or chronic HBV or HCV infection. Controls were patients with chronic liver disease but without HCC as evidenced by normal AFP levels and absence of a focal hepatic mass on imaging studies at least 6 months after the initial encounter. Controls were enrolled in the same manner as cases. All 1,037 patients gave written inform consent and completed the risk factor questionnaire. This study was approved by the Institutional Review Board at Stanford University.

Definitions and risk exposures

HCV infection was defined in patients with confirmed positive hepatitis C antibody and positive HCV RNA. CHB was defined in patients with confirmed positive hepatitis B surface antigen and negative hepatitis B surface antibody. Cirrhosis was defined in patients with nodular livers, ascites, encephalopathy, splenomegaly, esophageal varices, other varices, and/or platelet count of <120,000/μL.

Alcohol consumption and cigarette use were self-reported by patients. Patients were asked to report their lifetime history of alcohol consumption through questions regarding average number of alcohol serving consumed per day and the total number of years of alcohol consumption. One serving of alcohol was defined as 1.5 oz of hard liquor, 12 oz of beer, or 5 oz of wine, all of which were considered to have an equivalent ethanol content of 14 grams. Average grams/day was later calculated by study coordinators. Total alcohol use was calculated by cumulative grams of alcohol consumed up to the time of the interview.

Patients were asked to estimate their tobacco use in number of cigarette or number of pack of cigarette smoked/day and total of number of month or year that they have been smoking. Tobacco use was calculated by cumulative packs of cigarette consumed up to the time of the interview. Smokers were defined as patients who have used ≥5 packs or ≥100 cigarettes during their lifetime. Smokers were further stratified into the former smoker cohort, defined by smoking cessation of ≥1 year from time of interview, and current smoker cohort. One pack of cigarette is equivalent to 20 cigarettes. In order to account for the time factor in heavy smoker, a prolonged heavy smoker definition was generated to define patients who have smoked 1 pack/day for 30 years or those who have smoked an equivalent cumulative amount of cigarettes of approximately 11,000 packs lifetime.

Diabetes mellitus was also evaluated as a risk factor for HCC. Patients with DM were defined by random glucose level >200 mg/dL [23].

Statistical analysis

Descriptive statistics were reported as proportion (%) for categorical variables, and mean ± standard deviation (SD) or median (range) for continuous variables depending on data distribution. Categorical variables were evaluated using the chi-square (χ^2) test. Normally distributed continuous variables were evaluated using the student t test. Continuous variables that were not normally distributed were evaluated using Wilcoxon Mann–Whitney test. We estimated odd ratios (OR) with 95% confident intervals (CI) for potential risk factors for HCC using univariate and multivariate logistic regression. Statistical significance was defined with a two-tailed p value ≤0.05. All statistical analyses were performed using Stata 9.1 (Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics

Overall, cases were significantly older than controls (60.2 ± 11.3 vs. 52.1 ± 11.3, $p < 0.0001$) and were predominantly male (81.5% vs. 61.3%, $p < 0.0001$). The racial/ethnic distribution of cases and controls was also significantly different with a higher proportion of Asian Americans in the HCC group than in controls. Etiologies of primary liver disease among cases and controls were similar with HCV (56 and 50%) being the dominant etiology followed by HBV (29 and 30%). However, the distributions of the primary etiologies of HCC were significantly different among the different ethnic groups included in this study, particularly among Asian versus non-Asian groups. HCV is the primary etiology of HCC in non-Asian patients accounting for 71.4% in non-Hispanic Whites, 75.9% in Hispanics, and 85.7% in African Americans compared to 38.7% in Asian Americans. HBV is the primary etiology of HCC in Asian American patients accounting for 52.2% among this group versus 5.5% in non-Hispanic Whites, 3.5% in Hispanics, and 14.3% in African Americans.

Baseline demographic characteristics for both cases and controls by gender are summarized in Table 1. There were significantly more Asians among male cases than controls with a similar trend also seen for female cases.

Baseline laboratory results for HCC cases and controls by gender are summarized in Table 2. Other than serum AFP, there were no major consistent laboratory differences between cases and controls.

Overall, the proportion of cirrhosis in HCC patients by different etiologies of liver diseases also varies significantly with a higher proportion of cirrhosis in patients with HCV (96%), HBV/HCV coinfection (100%), and other etiologies

Table 1 Patient demographic characteristics

Baseline characteristics	Female		*p* value	Male		*p* value
	Controls ($n = 301$)	Cases ($n = 48$)		Controls ($n = 477$)	Cases ($n = 211$)	
Age (years)	53.2 ± 12	63.5 ± 9.9	<0.0001	51.4 ± 10.8	59.5 ± 11.5	<0.0001
Race			0.30			0.02
White	121 (40.2)	16 (33.3)		219 (45.9)	75 (35.6)	
Hispanic	41 (13.6)	3 (6.25)		73 (15.3)	26 (12.3)	
African	11 (3.7)	1 (2.1)		8 (1.7)	6 (2.8)	
Asian	123 (40.9)	27 (56.3)		168 (35.2)	97 (46.0)	
Others	5 (1.7)	1 (2.1)		9 (1.9)	7 (3.3)	

Value expressed as mean ± SD, median (range), or number of patients (%)

Table 2 Patient baseline laboratory characteristics

Laboratory results at baseline	Female		*p* value	Male		*p* value
	Controls	Cases		Controls	Cases	
White blood cell ($\times 10^3/\mu L$)	4.7 (0.8–14.3)	4.6 (1.8–27.7)	0.63	5.2 (1.6–15.3)	5 (1.3–12.4)	0.26
Hemoglobin (g/dL)	13.5 ± 2.3	13.9 ± 1.5	0.50	14.3 ± 1.8	13.9 ± 1.6	0.35
Platelet ($\times 10^3/\mu L$)	152 ± 86.2	131.0 ± 78.4	0.13	144.1 ± 84.7	138.8 ± 80.7	0.13
Prothrombin time (INR)	1.3 ± 0.3	1.3 ± 0.3	0.26	1.4 ± 0.7	1.3 ± 0.5	0.20
Creatinine (mg/dL)	0.8 (0.3–7.6)	0.8 (0.5–11)	0.003	1 (0.4–11.9)	1 (0.5–8.8)	0.63
	0.9 ± 0.7	1.4 ± 2.1		1.1 ± 1.0	1.1 ± 0.9	
Sodium (mEq/L)	138.2 ± 3.2	138.3 ± 3.9	0.83	137.9 ± 3.8	137.6 ± 3.7	0.41
Glucose (mg/dL)	98 (62–399)	126 (67–306)	0.03	100 (57–566)	110 (48–528)	0.03
AST (U/L)	49 (15–1,772)	79.5 (3–810)	0.33	51 (7–889)	70 (14–659)	0.02
ALT (U/L)	45 (6–1,190)	64 (15–753)	0.33	51 (6–744)	62.5 (6–650)	0.23
Albumin (g/dL)	3.4 ± 0.7	3.3 ± 0.6	0.24	3.5 ± 1.2	3.3 ± 0.7	0.09
Total bilirubin (mg/dL)	0.8 (0.2–20)	1.2 (0.5–8.2)	0.29	1.1 (0.2–41.6)	1.2 (0.3–30)	0.64
Alkaline phosphatase (U/L)	93 (15–659)	128 (48–942)	<0.0001	95 (15–931)	108 (37–685)	0.02
AFP (ng/mL)	4.7 (1.0–251)	37.2 (1.9–942)	<0.0001	4.5 (1.6–251)	14.6 (9–942)	0.006
AFP > 50 ng/mL	50 (16.6)	22 (45.8)	<0.0001	58 (12.2)	72 (34.1)	<0.0001
MELD scores	10.3 ± 4.6	11.2 ± 4.4	0.26	12.1 ± 5.6	10.9 ± 3.9	0.01
CTP scores	6.7 ± 1.9	7.3 ± 2.1	0.08	7.0 ± 2.1	6.8 ± 1.9	0.26

Value expressed as mean ± SD, median (range), or number of patients (%)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *MELD* model for end-stage liver disease score, *CTP* Child-Turcotte-Pugh score

(88%) when compared to patients with HBV (64%). Presence of anti-HBc was examined among patients with HCV, and similar proportions were observed among cases versus controls (44.1% vs. 45.7%). Anti-HBc was not a significant risk factor for HCC when it was evaluated among HCV patients using univariate and multivariate analyses inclusive of age, sex, and ethnicity. The rate of prior treatment with interferon was similar among cases and controls, 27.3% versus 27.2%. Cases and controls had similar proportions of patients with a family history of cancer, a family history of liver disease, exposure to vinyl chloride, and exposure to hormonal therapy or contraceptives.

Potential risk factors for HCC by gender are summarized in Table 3. There was a significant difference in the distribution of cirrhosis between cases and controls and for both men (82.9% vs. 70.9%, $p = 0.001$) and women (93.8% vs. 70.4%, $p = 0.001$).

Detailed data on alcohol consumption in both cases and controls are summarized in Table 4. Alcohol consumption frequency (never, occasional, and daily drinker) was similar between cases and controls. There were no significant differences in the proportion of patients who have had heavy alcohol consumption when evaluated at ≥50 or ≥80 g/day for both cases and controls. Average alcohol use duration was also similar in both groups. There was no significant difference in the cumulative amount of alcohol consumed among the cases and controls. There was no significant dose–response correlation between cumulative

Table 3 Risk factors for hepatocellular carcinoma

Risk factor	Female		*p* value	Male		*p* value
	Controls	Cases		Controls	Cases	
Family history of cancer	120 (40.3)	22 (46.8)	0.40	240 (43.0)	90 (43.7)	0.86
Family history of liver disease	80 (31.0)	13 (36.1)	0.54	124 (29.7)	43 (24.6)	0.21
Occupational exposure: vinyl chloride	84 (28.4)	7 (15.2)	0.06	141 (29.7)	58 (27.9)	0.63
Cirrhosis	212 (70.4)	45 (93.8)	0.001	338 (70.9)	58 (82.9)	0.001
Diabetes mellitus						
Serum glucose level (glucose >200 mg/dL)	12 (5.6)	2 (6.7)	0.82	22 (6.7)	16 (12.0)	0.06
Birth control and estrogen use						
Female	145 (56.9)	17 (48.8)	0.35	–	–	–

Value expressed as mean ± SD, median (range), or number of patients (%)

alcohol consumption and HCC. When alcohol use was evaluated by the presence of cirrhosis, patients with cirrhosis had a significantly higher amount of cumulative alcohol consumption than patients without cirrhosis (5.5 ± 5.8 vs. 4.9 ± 5.5 g ($\log_{10}$), $p < 0.0001$). Upon controlling for age, sex, etiology of liver diseases, and cumulative tobacco use, there was a 5.7-fold increase in odds of cirrhosis in patients with heavy alcohol consumption (≥50 g/day).

Quantitative results of cigarette use are summarized in Table 5. A higher proportion of tobacco use (in duration in years) was only seen in male cases compared to controls but not in female cases. When all cases and controls were considered, there was a dose-dependent correlation between the amount of cumulative cigarette use and HCC, in that 16.6% of cases versus 10.3% of controls smoked >10,000 packs lifetime. There was a significant difference in the proportion of those who have quit smoking for >30 years at the time of interview in cases versus controls (6.4% vs. 15.3%, $p = 0.02$). Cumulative smoking amount was calculated for 10, 20, and 30 years from the time of interview, and there were no significant differences in cumulative smoking amount between cases and controls. There was no significant difference in the proportion of patients who were classified as non-smoker, former smoker, or current smoker between cases and controls or proportion of heavy smoker (≥1 pack/day).

Predictors for HCC in patients with chronic liver diseases

Results of univariate and multivariate analyses relating various risk predictors to HCC are summarized in Table 6. On multivariate analysis following adjustment for alcohol

Table 4 Risk factor: alcohol consumption

Baseline characteristics	Female		*p* value	Male		*p* value
	Controls	Cases		Controls	Cases	
Alcohol			0.37			0.43
Never	133 (44.2)	26 (54.2)		127 (26.6)	59 (28.0)	
Occasionally	72 (23.9)	11 (22.9)		186 (39.0)	90 (42.6)	
Daily	96 (31.9)	11 (22.9)		164 (34.4)	62 (29.4)	
Alcohol consumption						
≥50 g/day	54 (20.1)	5 (11.4)	0.36	163 (36.9)	63 (33.5)	0.42
≥80 g/day	40 (14.8)	3 (6.8)	0.15	122 (27.6)	47 (25)	0.50
Average alcohol use duration (years)	7.4 ± 10.5	7.7 ± 12.8	0.86	4.5 ± 9.1	5.1 ± 11.0	0.68
Amount of cumulative alcohol consumed (g)			0.93			0.40
1,000–250,000	200 (90.9%)	34 (89.5%)		248 (76.3%)	98 (81.0%)	
250,001–500,000	7 (3.2%)	2 (5.3%)		29 (8.9%)	6 (5.0%)	
500,001–750,000	6 (2.7%)	1 (2.6%)		9 (2.7%)	5 (4.1%)	
750,001–1,000,000	0 (0%)	0 (0%)		7 (2.2%)	4 (3.3%)	
>1,000,001	7 (3.2%)	1 (2.6%)		32 (9.9%)	8 (6.6%)	
Cumulative alcohol consumed in grams ($\log_{10}$)	5.2 ± 5.9	4.99 ± 5.5	0.65	5.6 ± 6.2	5.4 ± 5.9	0.32

Value expressed as mean ± SD, median (range), or number of patients (%)

Table 5 Risk factor: cigarette use

Baseline characteristics	Female		*p* value	Male		*p* value
	Controls	Cases		Controls	Cases	
Cigarette use			0.60			0.28
Non-smoker	184 (66.8)	35 (72.9)		228 (47.8)	92 (43.6)	
Former smoker	60 (20.0)	8 (16.7)		178 (37.3)	83 (39.3)	
Smoker	40 (13.2)	5 (10.4)		71 (14.9)	36 (17.1)	
Cigarette (≥1 pack/day)	47 (15.6)	7 (14.6)	0.85	157 (32.9)	75 (35.6)	0.50
Average cigarette per day	7.4 ± 10.2	11.4 ± 15.5	0.11	13.2 ± 14.2	15.6 ± 16.2	0.11
Average tobacco use duration (years)	7.2 ± 15.7	7.4 ± 13.9	0.92	9.9 ± 12.9	12.8 ± 14.9	0.01
Amount of cumulative cigarette use			0.08			0.447
Non-smoker	199 (66.1)	35 (72.9)		228 (47.8)	92 (43.6)	
5–5,000 packs	64 (21.3)	5 (10.4)		127 (26.6)	53 (25.1)	
5,001–10,000 packs	22 (7.3)	2 (4.2)		58 (12.2)	29 (13.7)	
>10,000 packs	16 (5.3)	6 (12.5)		64 (13.4)	37 (17.6)	
Cigarette (packs)—cumulative lifetime use	1,726 ± 4,483	2,519 ± 6,634	0.29	3,545 ± 6,279	4,312 ± 6,619	0.15

Value expressed as mean ± SD, median (range), or number of patients (%)

Table 6 Predictors for HCC

Risk factors	Univariate analysis		Multivariate analysis[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age >40 years	6.2 (2.9–13.5)	<0.0001	8.5 (2.6–28.3)	<0.0001
Male gender	2.8 (1.96–3.9)	<0.0001	3.5 (2.2–5.8)	<0.0001
Cirrhosis	2.3 (1.6–3.4)	<0.0001	2.8 (1.6–4.9)	0.002
Asian ethnicity	1.6 (1.2–2.2)	0.001	2.8 (1.8–4.6)	<0.0001
AFP >50 ng/mL	3.5 (2.5–4.9)	<0.0001	4.2 (2.6–6.8)	<0.0001
Diabetes mellitus	1.9 (1.0–3.4)	0.04	1.2 (0.6–2.4)	0.59
Cumulative cigarette use (>11,000 pack lifetime)	1.6 (1.1–2.4)	0.01	1.7 (1.0–2.9)	0.04
Heavy alcohol use (>50 g/day)	0.9 (0.6–1.2)	0.90	0.8 (0.5–1.3)	0.38
Etiology of liver diseases	1.2 (1.0–1.5)	0.02	1.0 (0.8–1.3)	0.88

[a] Multivariate model is inclusive of age, sex, cirrhosis status, Asian versus non-Asian, AFP ≥50 ng/mL, cumulative cigarette use, heavy alcohol consumption, etiology of liver diseases, and diabetes mellitus

use, DM status, and etiology of liver diseases, independent predictors for HCC included age >40 (OR = 8.5 [2.6–28.3], $p < 0.0001$), male gender (OR = 3.5 [2.2–5.8], $p < 0.0001$), presence of cirrhosis (OR = 2.8 [1.6–4.9], $p = 0.002$), Asian ethnicity (OR = 2.8 [1.8–4.6], $p < 0.0001$), AFP >50 (OR = 4.2 [2.6–6.8], $p < 0.0001$), and cumulative lifetime tobacco use of >11,000 packs (OR = 1.7 [1.0–2.9], $p = 0.040$).

Discussion

The goal of HCC surveillance is early detection to increase the number of treatment options that can be available to patients, including potential cures. Evaluation of risk factors for HCC among patients with chronic liver disease is especially crucial since patients with preexisting liver disease are at highest risk for developing HCC. In this study, besides older age, male genders, AFP level >50 ng/mL, and presence of cirrhosis, independent risk factors for HCC included Asian ethnicity and cumulative lifetime tobacco use, but not alcohol use or DM. Increasing age, male gender, elevated AFP, and cirrhosis are well-established risk factors for HCC, and our data is consistent with the previous findings [3, 9–11, 24]. In this study, patients with underlying liver disease over the age of 40 were 8.5 times more likely to have HCC than those under the age of 40 years, and male patients were 3.6 times more likely to have HCC than female patients. Patients with cirrhosis of any etiologies were 2.9 times more likely to have HCC than those without. In addition, the proportion of patients with cirrhosis was significantly higher in patients with HCV infection, HBV/HCV coinfection, and all other etiologies when compared to patients with HBV.

Cirrhosis was present in 64% of HBV patients compared to 95% in HCV patients. This may be due to the direct carcinogenic properties of the HBV and its ability to cause HCC in the absence of cirrhosis [3]. Thus, it is important to screen HBV patients for HCC regardless of cirrhosis status.

As suggested by the previous studies of Asian ethnicity and chronic hepatitis C, Asian ethnicity was confirmed to be a significant predictor for HCC in this patient population with various underlying liver diseases. After accounting for etiology of liver disease, Asian patients are still 2.8 times more likely to have HCC than other patients.

Heavy and prolonged cigarette use was found to be a significant and independent risk factor for HCC even after adjusting for potential confounders such as age, gender, ethnicity, cirrhosis status, DM, AFP level >50 ng/mL, etiology of liver diseases, and cumulative alcohol consumption. These results are in agreement with some of the previous studies that examined tobacco use as a risk factor for HCC [15, 16, 25–29]. However, many of the previous studies examined tobacco use in the general population rather than in patients with underlying liver diseases. We used cumulative cigarette use to evaluate tobacco as a risk factor for HCC because it accounts for both intensity and duration of cigarette use. When cumulative cigarette use was evaluated as a discrete variable using the same multivariate model, there was a 1.7-fold increase in odds of patients who used ≥11,000 packs of cigarette in cases. A dose-dependent correlation was also observed, in that there were higher proportions of HCC cases in categories of greater cumulative cigarette use, particularly in those who have used >10,000 packs lifetime. A previous study has shown that smoking duration has a greater effect on HCC development than intensity of smoking [30].

Unlike cigarette use, alcohol use was not a significant risk factor for HCC in this study. This may be due to similar drinking habits, inclusive of intensity and duration of alcohol consumptions, among cases and controls in this study. Although alcohol was not a significant risk factor for HCC, it was a significant risk factor for cirrhosis. The association between alcohol use and HCC as shown by the previous studies involving general patient population without underlying liver disease or cirrhosis may be an indirect association via cirrhosis.

There are potential weaknesses of this study. This is a case–control study at a single referral center, and selection biases can be present because of referral patterns. In addition, results of this study may not be generalizable to the general population since it only involves those with chronic liver disease, many of whom also had advanced disease stages. However, the primary goal of this study was to identify risk factors for HCC in patients with chronic liver diseases and not for the general population since routine HCC surveillance and intervention should be targeted only at high-risk populations. Recall biases can also occur in our study since patients with HCC may be more likely to recall risk exposure than patients without HCC, especially when many of these risk factors occurred over prolonged periods of time. Both cases and controls were interviewed by the same coordinators as to minimize differences in the data collection process. The strength of this study is its large and ethnically diverse patient sample and the use of a high-risk control group since results from this study are more likely to be applicable to general populations of patients with chronic liver diseases. Patients were recruited over a span of 10 years, which may help mediate the effects of changes in referral patterns. The distributions of various etiologies of underlying liver diseases were also similar in cases and controls.

In conclusion, in this hospital-based case–control study, Asian ethnicity and heavy cumulative use of cigarette were significant independent predictors for HCC in patients with chronic liver diseases in addition to age greater than 40, male gender, presence of cirrhosis, and AFP level greater than 50 ng/mL. We did not find alcohol use or DM to be significant risk factor in patients with preexisting chronic liver disease. Since it is the cumulative and not recent use of cigarette that is a risk factor, patients with underlying liver disease should be advised to quit smoking early in the course of their liver disease [31]. Results of this study also help identify higher risk patients among those with chronic liver disease for future surveillance and intervention.

Conflict of interest None to disclose.

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