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Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma

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***Background/Aims*: Alcohol has been shown to be an important risk factor for hepatocellular carcinoma (HCC). The role of tobacco as a risk factor for HCC is controversial. Recently, obesity has been reported to be a risk factor for HCC. We investigated whether these factors increase the risk of HCC in American patients.**

***Methods*: Consecutive patients with HCC, cirrhosis without HCC and, control patients without liver disease were enrolled and exposure to risk factors was assessed.**

***Results*: When HCC cases were compared to cirrhotic controls, the risk of HCC increased 6-fold for alcohol (OR 5.7; 95% CI: 2.4–13.7), 5-fold for tobacco (OR 4.9; 95% CI: 2.2–10.6), and 4-fold with obesity (OR 4.3; 95% CI: 2.1–8.4). Using spline regression, a dose-dependent relationship between alcohol and tobacco exposure with risk of HCC was noted. There was significant interaction between alcohol, tobacco and obesity, with synergistic indices greater than 1.**

***Conclusions*: Alcohol, tobacco and obesity are independent risk factors for HCC in our patient population, and they interact synergistically to increase the risk of HCC. Data from this study may allow us to stratify cirrhotics into low- and high-risk groups for the development of HCC surveillance strategies.**

***Keywords*: Alcohol; Tobacco; Obesity; Hepatocellular carcinoma; Risk factors**

1. Introduction

In the recent 2001 Annual Report to the Nation on the Status of Cancer in the USA, primary liver cancer had the highest increase in incidence of all tumors during the past decade [1]. It is projected that the incidence of HCC in the US will continue to increase over the next 2 decades partially as a result of the hepatitis C (HCV) epidemic [2]. The most important and consistently identified risk factor for HCC is cirrhosis [3]. Worldwide, chronic HCV and hepatitis B (HBV) infection are the most important etiologic factors for the development of HCC [4]. It has been estimated that the lifetime risk of patients with HCV and HBV cirrhosis is between 10 and 37% [5,6]. Therefore, not all cirrhotics and not all patients with chronic HCV or HBV infection will develop HCC. It is possible that environmental factors may play a role in determining which patients with cirrhosis develop HCC.

Alcohol has been previously studied as a risk factor for HCC. Heavy alcohol consumption has been shown to increase the risk of HCC compared to controls without liver disease [7]. The results of studies on tobacco as a risk factor for HCC have been conflicting, varying from no significant risk to a 3-fold increase compared to non-smokers [8,9]. Obesity has been recently shown to be an important risk factor for liver cancer [10]. Diabetes has also been reported to be associated with an increase in risk of HCC [11].

There are significant limitations with available literature on the effects of alcohol and tobacco on the risk of HCC. First, the choice of controls is critical and should include individuals at risk of developing HCC [12]. Most studies evaluating risk factors for HCC employed controls without liver disease, who are at extremely low risk of developing HCC, and may have overestimated the impact of the risk factors studied. Secondly, most studies have been performed outside the US in which the cultural acceptance of tobacco and alcohol intake and the predominant etiology of the underlying liver disease may differ. Therefore, we

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performed a case-controlled study to test the hypothesis that tobacco, alcohol, and obesity independently increase the risk of HCC among Americans with cirrhosis.

2. Methods

2.1. Subjects

We conducted a prospective case-control study of 210 subjects enrolled from the Liver or General Medicine Clinics at our hospital. This study was approved by the University of Michigan Institutional Review Board, and informed consent was obtained from all participants. Treatment-naïve HCC patients were recruited between June 2002 and August 2003, only 7 HCC patients seen during this period refused enrollment. The diagnosis of HCC was made by histopathology ($n=57$), and if histopathology was not available by two imaging modalities (ultrasound [US], magnetic resonance imaging [MRI], or computed tomography [CT]) showing a vascular enhancing mass >2 cm ($n=10$); or an alpha-fetoprotein (AFP) >400 ng/ml plus one imaging modality showing a vascular mass in the liver ($n=3$) [13]. For each HCC patient enrolled, 2 controls matched for age (± 5 years) and gender were recruited (1 matched control with cirrhosis and 1 matched control with no liver disease were randomly selected for each case). Diagnosis of cirrhosis in the first group of controls was based on liver histology ($n=56$) or clinical, laboratory and imaging evidence of hepatic decompensation or portal hypertension ($n=14$) [14]; all but 5 of the eligible cirrhotic controls were enrolled. All cirrhotics had no evidence of HCC based on normal AFP and ultrasound or other imaging within 3 months of enrollment. All cirrhotic controls had at least one normal AFP and hepatic imaging 6 months after enrollment. The cirrhotic controls have been followed for a median of 12 months (range 7–18 months) after enrollment, and no one has developed HCC. The control group of patients without liver disease had normal liver chemistry tests consecutively seen at the primary care clinics of our hospital, and 91% of the eligible patients approached were enrolled.

2.2. Measurement of exposure to tobacco, alcohol and obesity

To obtain data on lifetime exposures to tobacco and alcohol, all patients were interviewed using validated questionnaires at the time of enrollment by a single trained interviewer. For alcohol, we utilized the Skinner Alcohol Use Inventory [15]. This instrument divides the patient's lifetime into different periods for easier recall, and the average daily intake of alcohol (beer, wine or hard liquor) during each period was recorded. Patients were classified as none, former and current drinkers. Former drinkers were defined as those who have not had a drink for more than 6 months before the interview. Because the duration and amount of alcohol consumption varies from person to person and in a single person's lifetime, lifetime alcohol exposure was expressed in gram-years: average daily consumption (grams) times the total duration of alcohol exposure (years). For example, a person who drank an average of 40 g a day between ages 20 and 30, 20 g a day between ages 30 and 40, and 80 g a day between ages 40 and 50, would have a total lifetime alcohol consumption of $[(0.04\times365\times10)+(0.02\times365\times10)+(0.08\times365\times10)]$ 511 kg. The total gram-years would be $[(40\times10)+(20\times10)+(80\times10)]$ 1400 gram-years and the average daily alcohol consumption would be $[(40+20+80)/3]$ 47 g/day. We categorized alcohol exposure as none (defined as a patient who consumed <100 servings of alcohol during his/her lifetime [16]), <1500 gram-years (mild-to-moderate) or $\geqq 1500$ gram-years (heavy), which is equivalent to $>$ or <60 g/day over a 25 year period [17].

Lifetime tobacco exposure was determined by a validated instrument similar to the Skinner alcohol inventory in that it divides a person's lifetime into different periods [18]. Only inhaled cigarette exposure was recorded. Patients were classified as none, former and current smokers. Smokers were classified as former smokers if their last cigarette was more than 6 months before the interview. Lifetime tobacco exposure was expressed as pack-years because it takes into account duration and quantity [19]. Tobacco exposure was characterized as none (<100 cigarettes during their lifetime [16]), <20 pack years or $\geqq 20$ pack-years. 20 pack-years were selected as the cutoff of tobacco exposure because 1 pack (20 cigarettes)/day has been shown to be a risk for HCC [20] over a 20-year period [21].

Height and weight were measured by a clinic nurse at the time of enrollment. Each patient was classified as lean (BMI <25 kg/m^2), overweight (BMI 25.1–30 kg/m^2) or obese (BMI >30 kg/m^2) [22]. Diabetes mellitus was defined by use of insulin or oral diabetic medication.

2.2.1. Statistical considerations

This study was planned to identify a difference alcohol exposure. We identified a proportion of patients with alcohol exposure >1500 gram-years (48% cases and 32% controls), the minimal detectable odds ratio is 0.61 (95% CI: 0.3–1.2). A sample size of 70 patients per group will have greater than 80% power when using McNemar's test at 5% level of significance. Continuous variables were transformed by taking the square root before analysis. The data were analyzed using a repeated measures analysis of variance, where the repeated factor was the matching and the grouping factor was the disease group. Categorical variables were compared by Fisher's exact test.

Conditional logistic regression modeling was used to generate odds ratio (OR) with 95% confidence intervals (CI) to estimate the risk of HCC. The maximum likelihood ratio test was used to assess the significance of alcohol, tobacco and obesity in the model [23]. To depict the dose–response relation of alcohol and tobacco and the risk of HCC, we used a multivariable restricted regression spline analysis [24]. A spline analysis fits separate curves for segments of the dose distribution, which allows the overall curve to reflect more accurately the shape of a dose–response trend. The interactions between risk factors comparing cirrhotics and HCC patients were evaluated by including them in the additive regression model using an interaction term with levels of exposure as present or absent. To assess whether the interactions between the risk factors were additive or synergistic, the Synergism index and its 95% CI was calculated to assess deviation from an additive model. Synergism $(S)=[OR_{1+2}-1]/[OR_1+OR_2]$ [25]. OR_1 is the estimated odds ratio for the presence of one risk factor, OR_2 the odds ratio for the presence of another risk factor, and OR_{1+2} is the combined estimated odds ratio for the 2 risk factors. A value greater than the reference unit (1.0) suggests that the effect of the joint exposures of 2 risk factors is greater than the sum of the separate effects. All analysis was performed using SAS 8.2 (Cary, NC, USA).

3. Results

3.1. Patient characteristics

There was no difference in age or gender among the three groups (Table 1). In addition, the patients with cirrhosis and HCC were comparable with regards to etiology of underlying liver disease and race. All HCC patients had cirrhosis based on histological ($n=54$) or laboratory and radiological ($n=16$) criteria. The mean Child-Turcotte-Pugh (CTP) and Model for Endstage Liver Disease (MELD) scores were similar among HCC and cirrhotic patients. There was no difference in the presence of ascites between patients with cirrhosis (8%) and HCC (6%) ($P=0.842$).

3.2. Exposure history

Table 2 summarizes data on the various HCC risk factors across the three groups. HCC patients had a significantly longer total duration of alcohol consumption, higher average daily consumption and greater lifetime alcohol

Table 1
Characteristics of the HCC patients, cirrhosis controls and controls with no liver disease

Variables	HCC ($n=70$)	Cirrhosis ($n=70$)	No liver disease ($n=70$)	P value
Age	56±10	54±9	54±5	0.169
Gender	44:26	44:26	44:26	0.915
Race (*n*) NHW/AA/Asian/Hispanic	57/6/5/2	64/1/1/4	58/10/1/1	0.401
Etiology (*n*) HCV/Crypto/Alc/HBV/Other	37/13/9/5/6	32/17/12/6/3	NA	0.143
CTP score	7.3±3	7.9±2	NA	0.387
Child class (*n*) A/B/C	28/21/21	23/32/15	NA	0.235
MELD score	7.9±3.8	9±5	NA	0.305
AFP (median) ng/ml	17.6	4	2.1	<0.0001[a]
% AFP <20	52	100	100	0.122
% AFP 20–200	25	0	0	<0.001
% AFP >200	23	0	0	<0.001
Tumor staging % I/II/III/IV	18/37/29/16	NA	NA	

Continuous variables presented as mean±SD. NA, not applicable; NHW, non-Hispanic white; AA, African American; HCV, hepatitis C; Crypto, cryptogenic; Alc, alcohol; HBV, hepatitis B; CTP, Child-Turcotte-Pugh score; MELD, model for endstage liver disease; AFP, alpha-fetoprotein.
[a] HCC vs. cirrhosis controls and controls with no-liver disease.

Table 2
Comparison of alcohol and tobacco exposure, diabetes mellitus and BMI between HCC patients and the two control groups

	HCC ($n=70$)	Cirrhosis ($n=70$)	P value[a]	No liver disease ($n=70$)	P value[b]
Alcohol					
Consumption *n* (%)			0.216		0.0001
None	11 (16)	9 (13)		23 (33)	
Former	48 (68)	56 (80)		22 (31)	
Current	11 (16)	5 (7)		25 (36)	
Total duration of drinking (yr)	27±16	22±13	0.0006	16±12	<0.0001
Total alcohol intake (kg ethanol)	730±482	347±307	0.0005	93±44	<0.0001
Avg. consumption g/day *n* (%)			0.0003		<0.0001
<40	8 (11)	27 (38)		39 (56)	
≧40	51 (73)	34 (49)		8 (11)	
Lifetime consumption gram-years *n* (%)			<0.0001		<0.0001
None	11 (16)	9 (13)		23 (33)	
<1500	11 (16)	35 (50)		44 (63)	
≧1500	48 (68)	26 (37)		3 (4)	
Tobacco					
Consumption *n* (%)			0.04		<0.0001
None	5 (7)	13 (19)		34 (49)	
Prior	41 (59)	28 (40)		21 (30)	
Current	24 (34)	29 (41)		15 (21)	
Total duration of smoking (yr)	26±14	20±14	0.002	13±10	<0.0001
Lifetime exposure pack-years *n* (%)	33±22	16±17	0.001[c]	10±7	<0.0001[c]
None	5 (7)	13 (19)	0.04	34 (49)	<0.0001
<20	16 (23)	23 (33)		32 (46)	
≧20	49 (70)	34 (49)		4 (5)	
Obesity					
n (%) BMI (kg/m^2) *n* (%)	32±5	28±5	0.01[c]	26±4	0.004[c]
<25	16 (23)	21 (30)	0.23	23 (33)	0.01
25.1–30	19 (27)	24 (34)		29 (41)	
≧30	35 (50)	25 (36)		18 (26)	
Diabetes %	26	23	0.291	21	0.134

All continuous variables expressed as mean±SD. BMI, body mass index.
[a] Comparison of HCC versus cirrhosis.
[b] Comparison of HCC versus controls without liver disease.
[c] Comparison of continuous variable by ANOVA, and chi-square for categorical variables. No exposure to alcohol was defined as less than 100 drinks per lifetime. No exposure to tobacco was defined as less than 100 cigarettes.

Table 3
Adjusted odds ratio for the risk of HCC

Variables	Odds ratio (95% CI)	
	HCC versus cirrhotics	HCC versus no liver disease
Alcohol (gram-years)[a]		
None	1.0[a]	1.0[a]
<1500	0.5 (0.1–0.7)	1.4 (0.8–1.9)
≧1500	5.7 (2.4–13.7)	23.8 (7.3–79)
Tobacco (pack-years)[a]		
None	1.0[a]	1.0[a]
<20	0.7 (0.4–1.2)	1.2 (0.7–1.5)
≧20	4.9 (2.2–10.6)	63.7 (16.7–144.2)
Obesity (BMI)[a]		
Lean	1.0[a]	1.0[a]
25.1–30	0.3 (0.09–0.5)	0.4 (0.04–0.6)
≧30	4.3 (2.1–8.4)	47.8 (9.6–74.5)

[a] Reference value for no exposure is set at 1.0. Multivariate analysis adjusted for obesity, alcohol and tobacco consumption. Lean = BMI <25. No exposure to alcohol was defined as less than 100 drinks per lifetime. No exposure to tobacco was defined as less than 100 cigarettes. Multivariate analysis adjusted for etiology and race.

exposure compared to controls ($P<0.05$). A total of 33 patients with HCC and 23 controls (20 cirrhotics and 3 without liver disease) had an alcohol exposure of >1500 gram-years. Patients with HCC had significantly longer duration of tobacco smoking and lifetime tobacco exposure compared to both control groups ($P<0.05$). A total of 38 patients with HCC and 24 controls (19 cirrhotics and 5 without liver disease) had a tobacco exposure of >20 pack-years. Twenty-one HCC patients (15%) had an exposure to alcohol of >1500 gram-years and tobacco of >20 pack-years. Patients with HCC also had significantly higher BMI compared to both control groups ($P<0.001$).

3.3. Risk of hepatocellular carcinoma

Conditional regression analysis controlling for the etiology of the underlying liver disease (presence or absence of Hepatitis C) and race (non-Hispanic white vs. others) showed that tobacco and alcohol exposure were independent risk factors for HCC, with a dose-dependent increase in the risk (Table 3). When HCC patients were compared to cirrhotic controls, the spline regression plots confirmed the dose-dependent effect of alcohol and tobacco exposure on the risk of HCC (Fig. 1). The risk of HCC increased 6-fold for patients with lifetime alcohol exposure >1500 gram-years, 5-fold with >20 pack-years of smoking, and 4-fold with BMI >30 (Table 3). The effects of alcohol, tobacco and obesity on the risk of HCC were elevated when the HCC patients were compared to normal controls with no liver disease (Table 3).

3.4. Interactions of risk factors

After evaluating the independent effects of each of the risk factors, the interactions of alcohol consumption, tobacco smoking, and obesity on the risk of HCC were evaluated by comparing the HCC patients with the cirrhotic controls. Pairs of risk factors were analyzed with adjustment for the third risk factor. Table 4 shows that compared to patients with exposure to tobacco or alcohol only, the risk of HCC was higher when both risk factors were present (OR 7.2; 95% CI: 2.2–14.1). An increase in risk of HCC was also observed when exposure to tobacco or alcohol was present with obesity.

To determine if the interactions between alcohol, tobacco and obesity on the risk of HCC were synergistic or additive, the synergistic indices were determined based on the estimated odds ratio. The synergistic indices for the interaction between alcohol and tobacco, tobacco and obesity, and alcohol and obesity were 3.3, 2.9 and 2.5, respectively. When all three variables were analyzed together, the synergistic index was 1.6. Thus, there is synergism between the effects of alcohol, tobacco and obesity on the risk of HCC in our cohort.

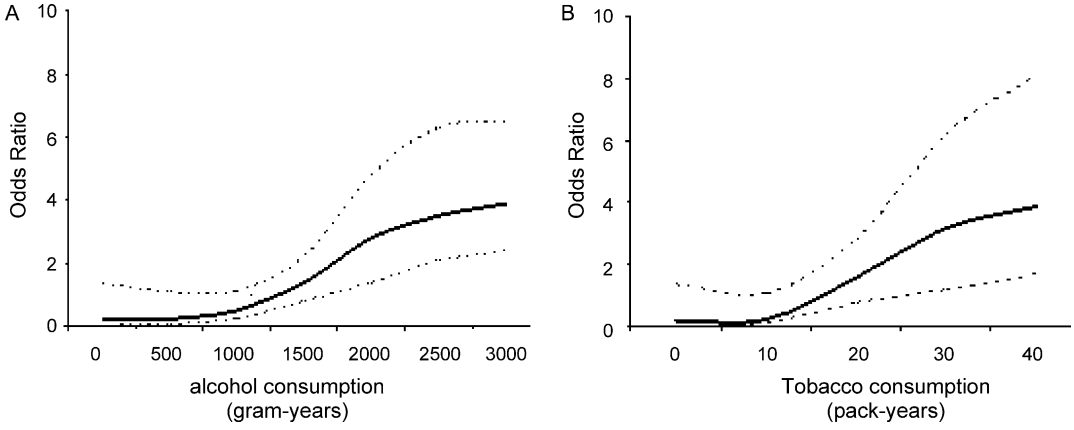

Fig. 1. Odds ratio and their 95% confidence intervals (dotted line) for the risk of HCC according to alcohol (A) and tobacco (B) exposure by fitting spline regression models.

Table 4
Interaction between exposure to alcohol, tobacco and obesity and the risk of Hepatocellular Carcinoma

Interaction variables			Odds ratio (95% CI)	Synergistic index (95% CI)
Tobacco	Alcohol			
Present	None		2.5 (1.7–15)	
None	Present		1.4 (1.1–4)	
Present	Present		7.2 (2.2–14.1)	3.3 (1.8–5.7)
Tobacco	Obesity			
Present	None		2.8 (2.1–24.7)	
None	Present		1.3 (1.03–2.4)	
Present	Present		7.1 (2.4–18)	2.9 (1.8–3.5)
Alcohol	Obesity			
Present	None		2.6 (1.8–7.6)	
None	Present		1.2 (1.02–2.2)	
Present	Present		5.5 (1.8–20)	2.5 (1.6–4.9)
Alcohol+	Obesity+	Tobacco		
Present	None	Present	2.6 (1.2–8.1)	
None	Present	Present	2.1 (1.4–17.3)	
Present	Present	None	2.3 (1.1–9.2)	
Present	Present	Present	7.4 (2.1–14.6)	1.6 (1.1–4.3)

Cirrhotic controls and HCC patients were utilized in this analysis. Tobacco is measured in pack-years, obesity by BMI, and alcohol in gram-years. Alcohol = none when <100 drinks per lifetime. Tobacco = none when <100 cigarettes. Obesity = none when BMI <30.

4. Discussion

In this case-control study, we showed that alcohol consumption, tobacco smoking and obesity are independent risk factors of HCC. Compared to normal controls with no liver disease, alcohol, tobacco and obesity were associated with a 24-, 64-, and 48-fold increase in risk of HCC, respectively. The effects of these risk factors were less dramatic when HCC patients were compared to cirrhotic controls, but a statistically significant effect persisted indicating that these factors may play a role in determining which patients with chronic liver disease will develop HCC.

Our study confirmed that alcohol consumption had a dose-dependent effect on the risk of HCC, the risk increased after >1500 gram-years of alcohol exposure. The risk of HCC was not different when alcohol consumption was classified as none, former or active, because many of our patients had stopped drinking prior to or at the time of diagnosis. Our results are consistent with other studies indicating an estimated risk of HCC ranging from an odds ratio of 1.7–34 [26–30]. Most published studies expressed alcohol exposure as average daily consumption; we found that 72% of our patients drank intermittently, with a wide range in average daily consumption throughout their lifetime (data not shown). By measuring alcohol consumption in gram-years, we took into account average daily consumption as well as duration of regular drinking giving us a better estimate of lifetime alcohol exposure. We also showed that an exposure of <1500 gram-years was protective for development of HCC. It is unclear why, but likely there is a threshold of alcohol exposure that leads to cirrhosis, recently demonstrated to be >50 g a day [31], and another one for HCC (>80 g of ethanol) [29]. Therefore, if the alcohol threshold for developing HCC is not exceeded then it might not increase the risk of HCC or be protective as seen in coronary artery disease [32].

Tobacco exposure is the leading carcinogen associated with multiple solid tumors [33]. Our results indicate an important role of tobacco in the development of HCC in our patient population. Several investigators have previously reported an association between tobacco and HCC with odds ratios ranging from 1.5 to 6.8 [28,34,35]. However, other studies found no association between tobacco and HCC [13,36]. An effect of tobacco in the development of HCC is biologically plausible, due to the carcinogenic potential of several of the ingredients in tobacco that are metabolized in the liver [37].

We also showed that obesity at the time of diagnosis is an independent risk factor for HCC. Evidence indicating that obesity is an important risk factor for liver cancer came from a prospectively followed adult cohort in the US [38]. That study showed that obesity was associated with increased death rates for multiple solid tumors; the greatest impact of obesity was on liver cancer. The relative risk of death from liver cancer among adults with BMI >35 was 5.2 compared to those with BMI <30, the risk may be higher if weights prior to diagnosis of HCC were available. The mechanism by which obesity leads to cancer is unclear, though insulin growth factor-1 and estrogen have been implicated [39].

We showed a synergistic interaction between heavy alcohol consumption, heavy tobacco smoking and obesity on the risk of HCC. There have been no prior studies evaluating all three factors simultaneously. Three previous studies evaluating alcohol and tobacco as risk factors for HCC did not show tobacco exposure as an important risk factor [8,16,26], but 2 others showed that tobacco and alcohol had synergistic effect on the risk of HCC [9,28].

A case-control study from Japan evaluated tobacco and alcohol as risk factors for HCC compared to controls with chronic liver disease found that the estimated risk of developing HCC in subjects with exposure to both alcohol and tobacco was 17.9 [40]. The biological mechanism for the synergy between tobacco, alcohol and obesity is unknown. However, a similar synergistic effect has been observed in patients with esophageal and stomach cancer [41].

Our study is the first to simultaneously evaluate the relationship of alcohol, tobacco and obesity with HCC, but there are several limitations. Recruitment from a single tertiary center limits generalizability of results. We minimized selection bias by selecting cases and controls from clinics in the same institution to decrease potential differences such as access to care, referral patterns and socioeconomic status. Furthermore, lifetime assessment of exposure to alcohol and tobacco may be inaccurate due to recall bias, but we tried to address these concerns by using validated questionnaires administered by a trained interviewer. The interviewer was not blinded to case-control status; we do not eliminate the possibility that HCC patients may have been probed more thoroughly than the controls leading to recall bias. BMI was determined at the time of enrollment and may not reflect the usual weight of the HCC patients thus under-estimating the impact of obesity on the risk of HCC. Cirrhotic controls may harbor small HCC that are not detected at enrollment, however, all the cirrhotic controls had at least 6 months of follow up (with ultrasound and AFP) with no evidence of HCC. Our cirrhotic controls were age-matched to the HCC patients, indicating that they had less alcohol and tobacco exposure up to the same age. We did not find an association between HCC and diabetes likely due to the high prevalence of diabetics in the control groups (23% in cirrhotics and 21% in controls without liver disease) [42].

In conclusion, we have shown that alcohol, tobacco and obesity are independent risk factors for HCC with a dose-dependent effect. Moreover, these three risk factors appear to act synergistically in increasing the risk of HCC when compared with cirrhotic controls indicating that these factors may in part explain why some cirrhotics develop HCC and others do not. Our data need to be validated in large multicenter prospective studies. If confirmed, our data may help stratify patients with chronic liver disease into high and low risk groups and to design HCC surveillance algorithms tailored to the risk.

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References

[1] Howe HL, Wingo PA, Thun MJ, Ries LA, Rosenberg HM, Feigal EG, et al. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. J Natl Cancer Inst 2001;93:824–842.
[2] Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, et al. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci USA 2002;99:15584–15589.
[3] Befeler AS, DiBisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology 2002;122:1609–1619.
[4] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917.
[5] El-Serag HB. Hepatocellular carcinoma and Hepatitis C in the United States. Hepatology 2002;36:S74–S83.
[6] Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP study group on Hepatitis B virus and cirrhosis. Hepatology 1995;21:77–82.
[7] Donato F, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, et al. Hepatitis B and C virus infection, alcohol drinking and hepatocellular carcinoma: a case-control study in Italy. Hepatology 1997;26:579–584.
[8] Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Kukuoka, Japan. Int J Cancer 1992;51:509–514.
[9] Yu MC, Tong MJ, Govindarajan S, Henderson BE. Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles county, California. J Natl Cancer Inst 1991;83:1820–1826.
[10] Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? Hepatology 2002;36:150–155.
[11] El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460–468.
[12] Wacholder S, Silverman DT, McLaughlin JK, Manderl JS. Selection of controls in case-controlled studies. II. Types of controls. Am J Epidemiol 1992;135:1042–1050.
[13] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 2001;35:421–430.
[14] Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003;37:520–527.
[15] Skinner HA, Allen BA. Differential assessment of alcoholism. Evaluation of the alcohol use inventory. J Study Alcohol 1983;44:852–862.
[16] Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzesse JL, Beasley P, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–1213.
[17] Peters MG, Terrault NA. Alcohol use and Hepatitis C. Hepatology 2002;36:S220–S225.
[18] Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, Darby SC, et al. Lung cancer and cigarette smoking in women: a multicenter case-control study in Europe. Int J Cancer 2000;88:820–827.

[19] Krall EA, Valadian I, Dwyer JT, Gardner J. Accuracy of recalled smoking data. Am J Pub Health 1998;79:200–206.
[20] Chen ZM, Liu BQ, Boreham J, Wu YP, Chen JS, Peto R. Smoking and liver cancer in China: case-control comparison of 36,000 liver cancer deaths vs. 17,000 cirrhosis deaths. Int J Cancer 2003;107:106–112.
[21] Liaw KM, Chen CJ. Mortality attributed to cigarette smoking in Taiwan: a 12-year follow-up study. Tob Control 1998;7:141–148.
[22] NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Obes Res 1998;6:51S–2209.
[23] Breslow NE, Day NE. The analysis of case-control studies. In: International agency for research on cancer. Statistical methods in cancer research, vol. 1. Lyon, France: IARC; 1980 p. 42–81.
[24] Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analyses. Epidemiology 1995;6:356–365.
[25] Rothman KJ. Interactions between causes. In: Modern epidemiology. Boston: Little Brown and Company; 1986 p. 311–326.
[26] Vall Mayans M, Calvet X, Bruix J, Brugera M, Costa J, Esteve J, et al. Risk factors for hepatocellular carcinoma in Catalonia, Spain. Int J Cancer 1990;46:378–381.
[27] Tagger A, Donato F, Ribero ML, Chiesa R, Portera G, Gelatti U, et al. Case-control study on Hepatitis C virus as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with Hepatitis B virus and alcohol. Int J Cancer 1999;81: 695–699.
[28] Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami ZH, et al. Tobacco, smoking, alcohol consumption and their interaction in the causation of heaptocellular carcinoma. Int J Cancer 2000;85: 408–502.
[29] Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323–331.
[30] Adami HO, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekbom A, et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992;51:898–902.
[31] Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchinson JG, et al. Risk of a range of alcohol intake on hepatitis C-related fibrosis. Hepatology 2004;39:826–834.
[32] Agarwal DP. Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms. Alcohol Alcoholism 2002;37:409–415.
[33] Stein CJ, Colditz GA. Modifiable risk factors for cancer. Br J Cancer 2004;90:299–303.
[34] Hadziyannis S, Tabor E, Kaklamani E, Stuver S, Tassopoulos N, Mueller N, et al. A case-control study of hepatitis B and C virus infections in the etiology of hepatocellular carcinoma. Int J Cancer 1995;60:627–631.
[35] Tzonou A, Trichopoulos D, Kaklamani E, Zavitsanos X, Koumantaki Y, Hsieh CC. Epidemiologic assessment of interactions of hepatitis-C virus with seromarkers of hepatitis-B and -D viruses, cirrhosis and tobacco smoking in hepatocellular carcinoma. Int J Cancer 1991;49:377–380.
[36] Austin H, Delzell E, Grufferman S, Levine R, Morrison AS, Stolley PD, et al. A case-control study of hepatocellular carcinoma and the hepatitis B virus, cigarette smoking and alcohol consumption. Cancer Res 1986;46:962–966.
[37] Starez ME, Murphy SE, Patten CJ, Nunes MG, Keohl W, Amin S, et al. Comparative metabolism of the tobacco-related carcinogens benzo(a)pyrene, 4-(methylnitrosamino)-1-(3-pyridil)-1-butanone, 4-(methylnitrosamino)-1-1(3-pyridyl)-1-butanol and N'nitrosonornicotine in human hepatic microsomes. Drug Metab Dispos 1997;25:154–162.
[38] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity and mortality from cancer in a prospective studied cohort of US adults. N Engl J Med 2003;348:1625–1638.
[39] Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4: 579–591.
[40] Mukaiya M, Nishi M, Miyake H, Hirata K. Chronic liver disease for the risk of hepatocellular carcinoma: a case-control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver disease. Hepatogastroenterology 1998;45:2328–2332.
[41] Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinoma of the stomach and esophagus (United States). Cancer Causes Control 2001; 12:721–732.
[42] Center for Disease Control. Prevalence of diabetes and impaired fasting glucose in adults—United States, 1999–2000. Morb Mortal Wkly Rep 2003;52:833–837.