

Is Obesity an Independent Risk Factor for Hepatocellular Carcinoma in Cirrhosis?

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Recently, several epidemiologic observations have suggested that obesity might be an independent risk factor for certain malignancies such as breast cancer, colon cancer, renal cell carcinoma, and esophageal adenocarcinoma. However, there are no studies examining the risk of hepatocellular carcinoma (HCC) in obesity. The aim of the present study was to determine whether obesity is an independent risk factor for HCC in patients with cirrhosis. Explanted liver specimens from a national database on patients undergoing liver transplantation were examined for HCC, and the incidence was compared among patients with varying body mass indices according to the etiology of cirrhosis. A multivariate analysis was used for controlling other potentially confounding variables such as age and sex. Among 19,271 evaluable patients, the overall incidence of HCC was 3.4% (n = 659) with a slightly higher prevalence among obese patients compared with lean patients. Obesity was an independent predictor for HCC in patients with alcoholic cirrhosis (odds ratio [OR], 3.2; 95% CI, 1.5-6.6; *P* = .002) and cryptogenic cirrhosis (OR, 11.1; 95% CI, 1.5-87.4; *P* = .02). Obesity was not an independent predictor in patients with hepatitis C, hepatitis B, primary biliary cirrhosis, and autoimmune hepatitis. The higher risk of HCC in obese patients is confined to alcoholic liver disease and cryptogenic cirrhosis. In conclusion, more frequent surveillance for HCC may be warranted in obese patients with alcoholic and cryptogenic cirrhosis. However, as this study is based on patients with advanced cirrhosis, our findings need to be confirmed in a broader population of individuals with cirrhosis. (HEPATOLOGY 2002;36:150-155.)

Hepatocellular carcinoma (HCC) is a serious and relatively frequent complication of cirrhosis. Incidental HCC is observed in at least 3% to 6% of explanted livers.¹ Although the regenerative activity inherent to cirrhosis predisposes to HCC,² malignant transformation is also influenced by the specific disease state that led to cirrhosis. Other factors can also increase the susceptibility to HCC. Several studies, especially in viral hepatitis, have suggested that male sex and age are additional risk factors for HCC in patients with chronic liver diseases.^{3,4} Recently, several epidemiologic observations have implicated obesity as an independent risk factor for certain malignancies such as breast cancer, colon

cancer, renal cell carcinoma, and esophageal adenocarcinoma.⁵⁻⁸ However, it is unclear whether obesity increases the risk of HCC in patients with cirrhosis. The aim of the current study was to determine whether the incidence of HCC is increased in obese cirrhotic patients compared with nonobese cirrhotic patients.

Patients and Methods

The United Network of Organ Sharing (UNOS) maintains a database on all liver transplantations performed in the United States. After liver transplantation, UNOS collects data on the presence of HCC in the explants from each transplant center. These data are collected as a binary response (yes or no). For the present study, we used the UNOS database on all liver transplantations from 1991 to 2000. We excluded all transplantations in which definite information was not obtained from the respective transplant center. Body mass index (BMI) was calculated from the height and weight recorded at the time of listing. The recipients were divided into 3 groups based on BMI as follows: nonobese, BMI less than 25 kg/m²; overweight, BMI 25.1 to 30 kg/m²; obese, BMI greater than 30 kg/m². The obese recipients

Abbreviations: HCC, hepatocellular carcinoma; UNOS, United Network for Organ Sharing; BMI, body mass index; OR, odds ratio.

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Received January 10, 2002; accepted March 25, 2002.

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0270-9139/02/3601-0019\$35.00/0

doi:10.1053/jhep.2002.33713

Table 1. Pretransplantation Characteristics Between the BMI Groups

	Obese				
	<25 kg/m ² (22.4 ± 1.9 kg/m ²) n = 7,089	25-30 kg/m ² (27.3 ± 1.4 kg/m ²) n = 6,824	30-35 kg/m ² (32.1 ± 1.4 kg/m ²) n = 3,378	35-40 kg/m ² (37.1 ± 1.4 kg/m ²) n = 1,380	>40 kg/m ² (43.2 ± 2.6 kg/m ²) n = 600
Age (yr)	48.6 ± 11.9	50.3 ± 10.1	50.7 ± 9.1	50.2 ± 8.6	49.3 ± 8.6
Female (%)	45	34	37	43	52
Race (%)					
White	77	79	81	82	84
Black	8	6	7	7	6
Hispanic	10	12	11	10	9
Asian	5	3	1	1	1
Diabetes (%)	12	15	20*	22*	23*
Creatinine (mg/dL)†	1.2 ± 1.2	1.3 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	1.2 ± 1.0
Bilirubin (mg/dL)†	7.1 ± 10	6.5 ± 9.4	6.2 ± 9.1	6.2 ± 8.5	6.1 ± 8.6
Albumin (g/dL)†	2.9 ± 0.7	2.8 ± 0.8	2.8 ± 0.6	2.8 ± 0.8	2.8 ± 0.6
Waiting time (days)†	217 ± 268	220 ± 257	235 ± 259	237 ± 261	260 ± 312
Etiology (%)					
Hepatitis C	29	36	37	35	35
Alcoholic cirrhosis	21	19	18	15	8*
Primary biliary cirrhosis	14	7	5	4	4
Cryptogenic cirrhosis	10	12	18	21*	26*

NOTE. All percentages are rounded off to the nearest whole number.

* $P < .05$ when compared with the lean (BMI, <25 kg/m²) group.

†Kruskal-Wallis test (non-normally distributed data).

were further categorized as mildly obese (BMI, 30.1–35 kg/m²), severely obese (BMI, 35.1–40 kg/m²), and morbidly obese (BMI, >40 kg/m²). The incidence of HCC in each group was based on the UNOS listing of HCC in the explants. In addition, information was also collected on the demographic features, diabetes status, waiting time, etiology of liver disease, and UNOS status. We excluded cases with absent information regarding the finding of HCC in the explants, pediatric recipients (younger than 18 years), patients whose height or weight were not listed, and, due to sample size considerations, all individuals with extremely high BMI (>50 kg/m²).

Analysis. Continuous variables were compared between the nonobese, overweight, and 3 different obese groups using ANOVA with Tukey's post-hoc analysis. Continuous data that were not normally distributed were analyzed by Kruskal-Wallis test. Categorical data were compared using χ^2 tests. Univariate analysis was performed to identify whether factors such as age, sex, race, diabetes status, etiology of liver disease, obesity (BMI <25 kg/m² vs. BMI >30 kg/m²), and waiting time for liver transplantation predicted the risk of HCC. A multivariate analysis was then used to determine whether any of the identified factors in the univariate analysis were independently associated with HCC. Similarly, a separate multivariate analysis was performed for each disease to determine the risk of HCC in obesity (BMI <25 kg/m² vs. BMI >30 kg/m²). For all analyses, a 2-tailed P value less than .05 was considered significant. Statistical software used was SPSS 10.0 for Windows (Chicago, IL).

Results

A total of 30,201 adult liver transplantations (patients 18 years and older) were performed between 1991 and 2000 in the United States. Patients were excluded from the study for the following reasons: extremely high BMI (>50 kg/m²; $n = 51$), lack of information about height and/or weight ($n = 1,095$), or lack of information regarding HCC in the explants ($n = 9,784$). Among the remaining 19,271 cases, 7,089 were nonobese (BMI, <25 kg/m²), 6,824 were overweight (BMI, 25.1–30 kg/m²), and 5,358 were obese (BMI, >30 kg/m²) as follows: 3,378 were mildly obese (BMI, 30.1–35 kg/m²), 1,380 were severely obese (BMI, 35.1–40 kg/m²), and 600 were morbidly obese (BMI, >40 kg/m²).

Pretransplantation Characteristics Versus Obesity. Irrespective of BMI, hepatitis C was the most common indication for liver transplantation (Table 1). Cryptogenic cirrhosis was the second most common indication for transplantation in obese patients, with a progressive increase in the proportion of patients with cryptogenic cirrhosis becoming evident as BMI increased. This is consistent with recent reports indicating that nonalcoholic steatohepatitis might be the likely cause in many patients with cryptogenic cirrhosis.^{9,10}

Univariate Analysis. Table 2 shows the incidence of HCC for nonobese, overweight, and obese (mild, severe, and morbid) individuals according to age and sex. Among overweight and obese men, a progressive increase in the incidence of HCC was observed as age increased, with a

Table 2. Incidence of HCC in Each BMI Group Categorized According to Age and Sex

Age	18-30 yr		31-40 yr		41-50 yr		51-60 yr		Older Than 60 yr	
	M	F	M	F	M	F	M	F	M	F
Nonobese n = 16 (3.0%)	0.7	0.0	2.0	2.4	3.4*	1.3	5.5*	2.9	5.1*	2.5
Overweight n = 235 (3.4%)	0.9	1.4	2.2	1.3	4.1*	0.5	4.9*	1.8	5.75	3.5
Mildly obese n = 131 (3.9%)	0.1	0	1.9	0.1	3.5	2.7	6.4*	2.5	7.0	3.3
Severely obese n = 56 (4.1%)	0	0	1.2	1.6	3.8*	1.5	7.3*	4.2	7.6*	3.0
Morbidly obese n = 21 (3.5%)	0	0	4.7	0	2.3*	0	10.3*	0.0	20.8	4.8

NOTE. All values are given as percentages rounded off to the nearest whole number.

Abbreviations: M, male; F, female.

* $P < .05$ (χ^2 test, comparison between sex within each age and BMI group).

significantly higher incidence beyond 40 years of age (Table 2). The mean age of patients with HCC was significantly higher than the mean age of patients without HCC (53 vs. 49 years; $P = .001$; Mann-Whitney test). HCC was more common among men (4.4% vs. 2.2% in women; $P = .0001$). Interestingly, the overall incidence of HCC was higher in obese patients when compared with nonobese patients (4.0% vs. 3.0%; $P = .013$). In addition, univariate analysis also confirmed a higher incidence of HCC in patients with diabetes (5% vs. 3.1%; $P = .0001$). The overall incidence of HCC was higher among Asian patients (6% vs. 3% in white patients; $P = .001$). The incidence of HCC was similar in white patients (3%), black patients (3%), and Hispanic patients (3.1%). As expected, patients with viral hepatitis (both hepatitis B virus and hepatitis C virus)

had a higher incidence of HCC compared with other diseases (Table 3). The incidence of HCC was lowest among patients with autoimmune liver disease and primary biliary cirrhosis.

Multivariate Analysis for All Liver Diseases. Results of the multivariate analysis for all liver diseases are shown in Table 4. Obesity (obese [BMI, >30 kg/m²] vs. nonobese [BMI, <25 kg/m²]) was an independent predictor with an odds ratio (OR) of 1.65 (95% CI, 1.22-2.22; $P = .001$). Other variables that were predictive of HCC were age (OR, 1.04; 95% CI, 1.02-1.06; $P = .0001$), male sex (OR, 2.57; 95% CI, 1.86-3.55; $P = .0001$), Asian race (OR, 3.55; 95% CI, 2.14-5.19; $P = .0001$), diabetes status (OR, 1.48; 95% CI, 1.07-2.03; $P = .02$), and waiting time (OR, 1.02; 95% CI, 1.01-1.03; $P = .0001$).

Table 3. Etiology of Liver Disease and BMI-Adjusted Incidence of HCC in the Explanted Livers

Etiology of Cirrhosis	Nonobese	Overweight	Obese		
			Mild	Severe	Morbid
Hepatitis C n = 207/5,235 (4.1%)	4.5	3.7	4.8	3.7	1.7
Hepatitis B n = 28/792 (3.8%)	3.5	2.8	3.6	7.1	7.7†
Alcoholic cirrhosis n = 65/2,985 (2.3%)	1.2	2.6	3.8†	1.7	7.7†
Autoimmune liver disease n = 11/923 (1.3%)	0.8	1.8	1	1.4	0
Primary biliary cirrhosis n = 10/1,387 (0.8%)	1.0	0.3	0.8	2.2	0
Cryptogenic cirrhosis n = 35/2,121 (1.7%)	0.2	1.4	2.2†	4.1†	2.9†
Hemochromatosis n = 5/182 (2.9%)	1.9	4.2	0	9.1	0
α 1-antitrypsin deficiency n = 7/108 (2.9%)	4.7	0	0	7.9	3.1

NOTE. All values are given as percentages. Only a single diagnosis is shown (*i.e.*, patients with combined diagnoses, for example, alcoholic cirrhosis and hepatitis C, are not shown), % of HCC based on a definitive report on HCC in the explants (*i.e.*, when data on HCC is not reported, those patients were excluded).

† $P < .05$.

Table 4. Multivariate Analysis of HCC Incidence

	OR	95% CI	P Value
Age	1.04	1.02-1.06	.0001
Sex (indicator female)			
Male	2.57	1.86-3.55	.0001
Race (indicator white)			
Black	0.59	0.25-1.32	NS
Hispanic	0.95	0.58-1.55	NS
Asian	3.55	2.14-5.19	.0001
Obesity*			
BMI >30 kg/m ²	1.65	1.22-2.22	.002
Diabetes status	1.48	1.07-2.03	.007
Waiting time	1.02	1.01-1.03	.0001

NOTE. Data are not adjusted for disease.

*BMI of <25 kg/m² was used as indicator variable, and the OR reflects risk of obese patients (BMI >30 kg/m²) against lean patients (BMI <25 kg/m²).

Multivariate Analysis for Each Liver Disease. Figure 1 shows the ORs for obesity (obese [BMI, >30 kg/m²] vs. nonobese [BMI, <25 kg/m²]) in each liver disease after controlling for age, sex, diabetes status, and race. As can be seen, obesity was independently predictive of HCC only in patients with alcoholic cirrhosis (OR, 3.2; 95% CI, 1.5-6.6; *P* = .002) and cryptogenic cirrhosis (OR, 11.1; 95% CI, 1.5-87.4; *P* = .02). In alcoholic liver disease, age (OR, 1.06; 95% CI, 1.02-1.11; *P* = .009) and Asian race (OR, 10.2; 95% CI, 2.0-52.1; *P* = .005) were other independent predictors. In cryptogenic cirrhosis, age (OR, 1.08; 95% CI, 1.01-1.14; *P* = .015) and male sex (OR, 3.33; 95% CI, 1.20-8.57; *P* = .13) were additional risk factors.

Obesity was not an independent predictor of HCC in chronic hepatitis C, chronic hepatitis B, primary biliary cirrhosis, or inherited liver diseases. Male sex (OR, 2.15; 95% CI, 1.36-3.38; *P* = .001) and age (OR, 1.04; 95% CI, 1.01-1.06; *P* = .003) were the most important independent predictors of HCC in hepatitis C.

Discussion

There are several reasons why obesity might be an additional risk factor for HCC. Obesity is associated with insulin resistance and elevated insulin-like growth factor, which is a mitogen that stimulates cell growth.¹¹⁻¹³ Interestingly, alterations in the expression of insulin-like growth factor and insulin-like growth factor receptors have been implicated in the pathogenesis of HCC associated with chronic hepatitis B and aflatoxin.¹⁴⁻¹⁶ In addition, hepatic steatosis, frequently seen in obesity, predisposes to lipid peroxidation and excess free radical activity with the potential risk of genomic mutations.¹⁷⁻²¹ Hyperplasia of hepatocytes has recently been described in *ob/ob* mice with fatty liver disease and insulin resistance, which raises the possibility of malignant change second-

ary to hepatic steatosis.²² Obesity is also associated with an increase in circulating estrogens,^{23,24} a well-recognized risk factor for hepatic adenomas. The current study was prompted by these considerations.

Based on an analysis of HCC in explanted liver specimens in patients with advanced cirrhosis, we found that obesity is an independent risk factor for HCC in alcoholic liver disease and cryptogenic cirrhosis. Obesity was not an independent risk factor for HCC in viral hepatitis, primary biliary cirrhosis, or metabolic liver diseases such as hemochromatosis and α_1 -antitrypsin deficiency. A potential limitation of the current study is the lack of information regarding the presence of ascites, because this could affect the BMI calculations and hence the definitions of obesity. In a large database such as the UNOS database, where there is likely to be substantial differences in the means of grading ascites, it is difficult to accurately adjust the BMI for ascites. However, there are several aspects of the current study that help overcome this potential difficulty in interpreting the data. First, we chose a BMI less than 25 kg/m² as the indicator variable in the multivariate analysis rather than a BMI less than 30 kg/m², which might have biased the analysis by including borderline cases. Second, an extremely high BMI (>35 kg/m²) is unlikely to be the result of ascites *per se*. Finally, the potential confounding effect of ascites in the calculation of BMI should be true for all types of cirrhosis. The fact that our study found that obesity is independently associated with HCC only in 2 diseases further supports the analysis.

The reasons for the disease-specific association of obesity and HCC are not clear, and this could be difficult to explore without further studies. However, steatosis is a prominent histologic finding in patients with alcoholic liver diseases, and clinical and laboratory features consistent with nonalcoholic steatohepatitis have recently been described in cryptogenic cirrhosis.^{9,10} It could be specu-

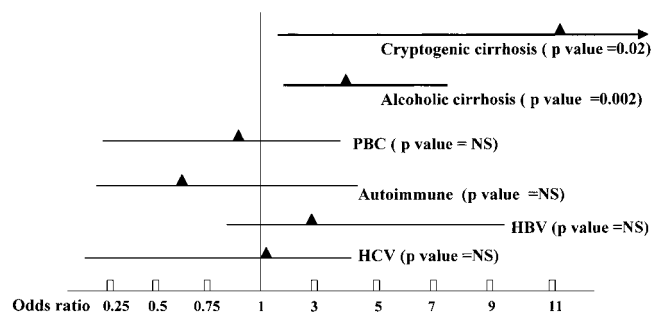


Fig. 1. Multiple regression analysis showing the ORs for obese (BMI, >30 kg/m²) versus lean (BMI, <25 kg/m²) patients with different liver diseases after controlling for age, sex, diabetes status, and waiting time. Obesity is an independent predictor only in alcoholic and cryptogenic cirrhosis. PBC, primary biliary cirrhosis; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus.

lated that obesity accentuates hepatic steatosis in alcoholic liver disease and through this mechanism increases the risk of tumorigenesis. In support of this hypothesis, it should be noted that hepatocyte hyperplasia has recently been reported in *ob/ob* mice, a model wherein there is substantial hepatic steatosis.²² In addition, obesity can also accentuate hyperestrogenism in alcoholic patients. Several lines of evidence link HCC with sex hormones. Endogenous hormones, androgens, and estrogen are likely to be involved in hepatic carcinogens through a receptor-mediated process.^{25,26}

Cryptogenic cirrhosis was another disorder in which obesity was found to be an independent risk factor. Cryptogenic cirrhosis likely represents a spectrum of diseases including nonalcoholic steatohepatitis as well as undiagnosed autoimmune liver disease and undiagnosed viral hepatitis. However, as shown in 2 recent studies, obese patients with cryptogenic cirrhosis are likely to have had unrecognized nonalcoholic steatohepatitis.^{9,10} Our finding of a higher incidence of HCC in obese patients with cryptogenic cirrhosis leads to the question of whether there may be a high incidence of HCC in nonalcoholic steatohepatitis compared with other diseases. Further studies on the incidence of HCC in nonalcoholic steatohepatitis are needed to properly address this issue.

Diabetes mellitus was found to be a risk factor for HCC in patients with advanced cirrhosis independent of age, sex, BMI, and etiology of liver disease. Several case-control studies in the past have also found a higher incidence of HCC in diabetes.²⁷⁻³³ Some of the studies have found a stronger association with type 2 diabetes mellitus,^{4,34} implying the role of hyperinsulinemia.³⁵⁻³⁷ A recent report also showed that there is a statistically significant loss of heterozygosity of the p53 tumor-suppressor gene in patients with HCC and diabetes.³⁷ However, most of these studies did not adequately control for the severity of liver disease, which may have been an unrecognized confounding factor because patients with severe liver disease are more likely to develop glucose intolerance. Also, these patients are at a higher risk for HCC by virtue of their long-standing disease. To control for this factor, we performed a separate analysis of patients from 1998, when a new UNOS system based on Child-Pugh score was introduced for organ allocation, including only patients with a Child-Pugh score of 10 or more (UNOS status 2A or 2B). However, analysis of this group of patients with Child's C cirrhosis did not show that diabetes was an independent predictor of HCC (data not shown).

It seems that from the present study as well as prior studies from Southeast Asia on patients with chronic hepatitis B that age and male sex are important additional risk

factors for HCC. Asian race was found to be an independent risk factor for HCC in all liver diseases when compared with white patients. Black and Hispanic patients were not at a higher risk compared with white patients. It is not clear why there is a predisposition among Asian patients, although cryptic or previous hepatitis B virus infection might have been a contributing factor.

Because the present study focused on a transplantation population, our results cannot be easily extrapolated to the general population. It is also not known whether our findings hold true for patients with less advanced cirrhosis (Child's A), older patients who were not considered for transplantation, and those without cirrhosis. On the other hand, a study based on the explanted liver specimens has a major strength in that it includes even small tumors that are not otherwise detectable. By using a nontransplantation population, there is the risk of introducing bias by including patients with radiologically undetectable or histologically undocumented tumors.

A potential limitation of the study is the lack of information regarding the presence of ascites because this could affect the BMI calculations and hence the definitions of obesity. In a large database such as the UNOS database, where there are likely to be substantial differences in the means of proper grading of ascites, it is difficult to accurately adjust the BMI for ascites. Because of this concern, we chose a BMI less than 25 kg/m² as the indicator variable in the multivariate analysis rather than a BMI less than 30 kg/m², which might have biased the analysis by including borderline cases. In addition, an extremely high BMI (>35 kg/m²) is unlikely to be the result of ascites *per se*. Approximately one third of the patients who underwent transplantation had no information on the presence of HCC. We separately analyzed the demographics of these patients and found that they are similar to the overall study population. Hence, it is unlikely that the exclusion of these patients influenced our results.

In conclusion, obesity is an independent risk factor for HCC in patients with advanced cirrhosis. However, the risk seems to be primarily associated with alcoholic liver disease and cryptogenic cirrhosis. More frequent surveillance for HCC using ultrasonography and α -fetoprotein measurements may be warranted in obese patients with alcoholic cirrhosis and cryptogenic cirrhosis.

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