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CLINICAL—LIVER

Obesity Early in Adulthood Increases Risk but Does Not Affect Outcomes of Hepatocellular Carcinoma

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BACKGROUND & AIMS: Despite the significant association between obesity and several cancers, it has been difficult to establish an association between obesity and hepatocellular carcinoma (HCC). Patients with HCC often have ascites, making it a challenge to determine body mass index (BMI) accurately, and many factors contribute to the development of HCC. We performed a case–control study to investigate whether obesity early in adulthood affects risk, age of onset, or outcomes of patients with HCC. **METHODS:** We interviewed 622 patients newly diagnosed with HCC from January 2004 through December 2013, along with 660 healthy controls (frequency-matched by age and sex) to determine weights, heights, and body sizes (self-reported) at various ages before HCC development or enrollment as controls. Multivariable logistic and Cox regression analyses were performed to determine the independent effects of early obesity on risk for HCC and patient outcomes, respectively. BMI was calculated, and patients with a BMI of 30 kg/m^2 or greater were considered obese. **RESULTS:** Obesity in early adulthood (age, mid-20s to mid-40s) is a significant risk factor for HCC. The estimated odds ratios were 2.6 (95% confidence interval [CI], 1.4–4.4), 2.3 (95% CI, 1.2−4.4), and 3.6 (95% CI, 1.5–8.9) for the entire population, for men, and for women, respectively. Each unit increase in BMI at early adulthood was associated with a 3.89-month decrease in age at HCC diagnosis ($P < .001$). Moreover, there was a synergistic interaction between obesity and hepatitis virus infection. However, we found no effect of obesity on the overall survival of patients with HCC. **CONCLUSIONS:** Early adulthood obesity is associated with an increased risk of developing HCC at a young age in the absence of major HCC risk factors, with no effect on outcomes of patients with HCC.

Keywords: Obesity; HCC; Case-Control; Risk Factor.

Overweight and obesity are major public health problems in both economically developed and developing countries. Between 1980 and 2013, the global prevalence of overweight and obesity combined increased by 27.5% for adults and by 47.1% for children.[1] The increase was higher in developed than in developing countries. If such trends continue, by 2030, up to 57.8% of the world's adult population could be either overweight or obese.[2]

Concurrent with the increased rate of obesity in the United States, the incidence of hepatocellular carcinoma (HCC) has increased significantly over the past 3 decades,[3,4] with a positive correlation observed between the prevalence of obesity and the incidence of HCC.[5,6]

Despite the reported significant association between obesity and several cancers in the United States,[7] the association between obesity and HCC[8,9] has been difficult to confirm for the following reasons: (1) rarity and poor prognosis of HCC, making large-scale studies difficult to conduct; (2) underlying cirrhosis associated with portal hypertension and ascites that can preclude accurate assessment of body mass index (BMI) at the time of HCC diagnosis; (3) missing BMI estimates in medical records of HCC patients; and (4) the multifactorial origin of HCC, necessitating adjustments for the confounding effects of the major HCC risk factors including hepatitis C virus (HCV), hepatitis B virus (HBV), diabetes mellitus, and alcohol consumption.

To investigate the association between HCC and obesity before HCC development, we embarked on a large case–control study in which we integrated clinical and epidemiologic data with obesity data to assess the following: (1) the independent effect of excess body weight across an individual's life cycle on HCC risk, (2) the synergistic interaction between obesity and other HCC risk factors, and (3) the effect of obesity on age at HCC onset or on overall survival rate of HCC patients.

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OR, odds ratio; S, synergetic index.**

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Materials and Methods

This investigation was part of an active hospital-based, case-control study, which was approved by the Institutional Review Board at The University Texas MD Anderson Cancer Center (protocol ID00-083). Written informed consent for participation was obtained from each participant.

Case patients were recruited from the population of patients with newly diagnosed HCC who were evaluated and treated at MD Anderson Cancer Center's gastrointestinal medical oncology and surgical oncology outpatient clinics. The inclusion criteria were a pathologically or radiologically confirmed diagnosis of HCC and US residency. The exclusion criteria were the presence of other types of primary liver cancer (such as cholangiocarcinoma or fibrolamellar hepatocarcinoma), unknown primary tumors, and concurrent or past history of cancer at another organ site.

Control subjects were healthy (cancer-free) and genetically unrelated family members (such as spouses) of cancer patients at MD Anderson. However, we excluded family members and spouses of patients with liver, gastrointestinal, lung, or head and neck cancer. The reason for such exclusion was to prevent the introduction of selection bias connected with shared environmental and genetic factors that are highly associated with HCC (eg, alcohol consumption, smoking, family history of cancer, and hepatitis virus infection). Cases and controls were frequency-matched by age (±5 y) and sex. Between January 2004 and December 2013, there were 622 HCC case patients and 660 control subjects who participated in this investigation. HCC patients and controls were recruited simultaneously and were interviewed in person for demographic features and HCC risk factors (Table 1) with the use of a structured and validated questionnaire. We defined cigarette smokers as subjects who

Table 1. Multivariate Adjusted ORs and 95% CIs of Hepatocellular Carcinoma for Demographic and Other Factors

	HCC patients ($N = 622$)		Controls ($N = 660$)			
Demographic variables	n	%	n	%	Adjusted OR[a] (95% CI)	*P* value
Sex						
Female	149	24	257	38.9	1 (reference)	
Male	473	76	403	61.1	0.9 (0.6–1.2)	.5
Age, *y*						
<60	229	36.8	314	47.6	1 (reference)	
≥60	393	63.2	346	52.4	2.7 (1.8–4)	.001
Ethnicity						
Non-Hispanic white	421	67.7	596	90.3	1 (reference)	
Hispanic	88	14.1	41	6.2	2.5 (1.5–4.4)	.001
African American	67	10.8	19	2.9	3.9 (1.8–8.8)	.001
Asian	46	7.4	4	0.6	12.7 (3.7–43.4)	<.001
Educational level						
<College education	268	43.1	178	27.0	1 (reference)	
≥College education	354	56.9	482	73.0	1.3 (0.9–1.9)	.06
Hepatitis virus infection						
No virus infection	311	50	635	96.2	1 (reference)	
HCV alone	141	22.7	2	0.3	169.9 (40.4–715.6)	<.001
HBV alone	83	13.3	21	3.2	8.3 (4.4–15.4)	<.001
HCV and HBV	87	14	2	0.3	94.5 (22.1–403.5)	<.001
Cigarette smoking						
No smoking	225	36.2	353	53.5	1 (reference)	
≤20 pack-years	171	27.5	142	21.5	0.9 (0.6–1.3)	.5
>20 pack-years	226	36.2	165	25.0	1.5 (1.1–1.9)	.006
Alcohol drinking						
No drinking	178	28.6	295	44.7	1 (reference)	
<60 mL ethanol/day	310	49.8	329	49.8	1.7 (1.2–2.4)	.002
≥60 mL ethanol/day	134	21.5	36	5.5	4.5 (2.5–8.1)	<.001
Prior history of diabetes						
No diabetes mellitus	411	66.1	581	88	1 (reference)	
Diabetes ≤1 year	14	2.3	18	2.7	1.9 (0.9–4.4)	.2
Diabetes >1 year	197	31.7	61	9.2	4.7 (3.2–7.1)	<.001
Family history of cancer						
No	117	18.8	228	34.5	1 (reference)	
Yes	505	81.2	432	65.5	3.7 (2.6–5.1)	<.001
State of residency						
Texas, Louisiana, Arkansas, New Mexico, and Oklahoma	448	72	497	75.3	1 (reference)	
Other states	174	28	163	24.7	0.8 (0.7–1.1)	.2

[a]The adjusted ORs were estimated from a multiple logistic regression model that included sex, age, ethnicity, education level, hepatitis virus infection, alcohol drinking, cigarette smoking, history of diabetes, and family history of cancer.