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Abstract

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 accurately determine body mass index (BMI), 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 ≥30 kg/m^2 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 (OR) and 95% confidence intervals (CI) were 2.6 (1.4–4.4), 2.3 (1.2–4.4), and 3.6 (1.5–8.9) for the entire population, men, and 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 is a synergistic interaction between obesity and hepatitis virus infection. However, we found no effect of obesity on the overall survival of patients with HCC.

CONCLUSION—Early adulthood obesity is associated with 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

INTRODUCTION

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 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 significantly increased over the past 3 decades,[3, 4] with a positive correlation observed between prevalence of obesity and 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 epidemiological data with obesity data to assess 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.

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 U.S. 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, e.g., alcohol consumption, smoking, family history of cancer, and hepatitis virus infection. Cases and controls were frequency-matched by age (±5 years) and sex. Between January 2004 and December 2013, 622 HCC case patients and 660 control subjects 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 use of a structured and validated questionnaire. We defined *cigarette smokers* as subjects who had smoked ≥100 cigarettes during their lifetime. *Heavy smokers* were defined as those who had >20 pack-years of smoking. We defined *ever-alcohol drinkers* as subjects who had consumed at least 4 alcoholic drinks each month for 6 months in their lifetime. We further classified ever-drinkers according to the total lifetime volume of ethanol consumed in milliliters, which was computed according to the frequency of drinking, type of serving (glass, bottle, or can), number and size of each serving, and duration of consumption, summed over the whole period of alcohol use. *Heavy alcohol consumption* was defined as

consumption of more than 60 mL of ethanol/day during the subject's period of alcohol drinking.[10]

Participants were interviewed for history of diabetes mellitus, type of diabetes, age at diagnosis, and duration of diabetes. Subjects with a history of diabetes were questioned about medications used for diabetes control and the duration of treatment, and reported results of HbA1. Information about prior history of chronic liver diseases (CLDs) was obtained including cirrhosis, hemochromatosis, primary biliary cirrhosis, Wilson disease, autoimmune hepatitis, and alpha 1 antitrypsin deficiency. A detailed questionnaire about obesity was included during the interview to obtain information about self-reported height (inches) and weight (pounds) across the life cycle before cancer diagnosis (HCC patients) or before recruitment (controls), including current weight as well as weight when patients and controls were in their mid-20s, mid-30s, mid-40s, mid-50s, and mid-60s. In addition, self-reported body size across the same ages using the validated Stunkard pictograms was obtained from each participant. BMI was calculated [(weight (kg)/height (m)^2] and classified as a four-level categorical variable: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). **Only 4** HCC patients were classified as underweight and were included among the normal weight category.

All participants were questioned to classify their past engagement in physical activity (at work or free time), as well as the type, frequency, and duration of activities during the past 5 years. Vigorous physical activity was described as enough to get sweaty, experience fast heart beats, or get out of breath. All cases and controls recalled their family history of all cancers among first- and second-degree relatives.

Detailed clinical variables were retrieved from HCC patients' medical records; these variables included information about different HCC staging scores, HCC treatment exposure, pathological differentiation, underlying cirrhosis, vascular invasion, metastasis, lymph node involvement, tumor nodularity and size, and alpha fetoprotein level.[11–13] *Overall survival* (OS) was defined as the time between HCC diagnosis and death (as a result of all causes) or end of follow-up (censored observations). Underlying cirrhosis was determined by pathological findings (diagnostic biopsies) and by computed tomography scans. In addition, all HCC patients were examined for the signs of cirrhosis including manifestations related to portal hypertension, e.g. ascites, bleeding from esophageal varices, and hepatic encephalopathy. Minor signs were also noted clinically, such as palmar erythema, spider angioma, and clubbing of the fingers.

Blood samples from cases and controls were tested for HBV and HCV. HCV antibodies, hepatitis B surface antigen, and antibodies to hepatitis B core antigen were detected by use of a third-generation enzyme-linked immunosorbent assay (ELISA) (Abbott Laboratories, North Chicago, IL). Positive results prompted repeated confirmatory ELISA testing.

Stata software (Stata Corp, College Station, TX) was used for statistical analysis. We performed multivariate unconditional logistic regression analyses. For each risk factor, we calculated the adjusted odds ratio (OR) and 95% confidence interval (CI) values, using

maximum likelihood estimation. All ORs for the association between BMI and HCC were adjusted for age, sex, race, educational level, smoking, alcohol, diabetes, family history of cancer, physical activity, and HBV or HCV infection. Hazard ratios (HRs) and 95% CIs were calculated by using Cox proportional hazard models. The population-attributable risk percentage (PAR%) of HCC was calculated, as follows: $PAR\%=\frac{P_e(OR-1)}{P_e(OR-1)+1}\times 100$, in which OR is the adjusted OR for the relationship between being obese and having HCC, and *Pe* is the prevalence of being obese in the control population in the early adulthood period before enrollment.

Analysis of covariance was used to analyze patients' mean age at HCC onset by BMI status. Linear regression models were used to estimate the mean differences in age at HCC onset associated with BMI after adjusting for other factors associated with age at onset in this study population.

We used multiple logistic regression models to investigate possible interactions on an additive scale of prior adulthood history of obesity with hepatitis virus infection (HCV and HCV), alcohol consumption, and diabetes mellitus. To assess deviation from the additive model (which assumes no interaction between variables), we calculated the synergism index $S=\frac{(OR_{11}-1)}{(OR_{01}+OR_{10})-2}$, in which OR_{11} = OR of the joint effect of two risk factors, and OR_{10} and OR_{01} = OR of each risk factor in the absence of the other. A value of *S* equal to unity was indicative of additivity, whereas a value greater than unity was indicative of superadditivity and synergism.[14, 15]

RESULTS

The baseline demographic characteristics of patients and controls are summarized in table 1. Most study subjects were non-Hispanic white men; the men-to-women ratio was 3.2 to 1 for HCC patients. Case patients were slightly older than control subjects, with a mean difference of 3 years (95% CI, 2 to 5); the mean [± standard error (SE)] ages were 63 ± .4 years for HCC patients and 60 ± .4 years for controls. Higher education (≥ college degree) was more frequent among control subjects than among HCC patients. Cases and controls had a similar distribution of geographical region (US state of residency) where 369 (59.3%) cases and 401 (60.8%) controls were from state of Texas, *P* =.1.

This study continued to support the association between HCC and several risk factors reported previously by us[16–19] and by other investigators, including alcohol drinking, cigarette smoking, diabetes mellitus, HCV, HBV, and family history of cancer.[20–24]

Figure 1A shows the distribution of overweight and obesity among HCC cases and controls at ages ranging from their mid-20s to mid-60s.

The prevalence of ever experience of obesity during lifetime was recalled by 38.4% (95% CI, 33.7%–43.4%) of HCC case patients and by 30.6% (95% CI, 27.1%–34.3%) of healthy controls (*P* = .03).

We calculated the average BMI during early adulthood (mid-20s to mid-40s) and then classified BMI into normal, overweight, and obese. The prevalence of obesity (BMI ≥30) in early adulthood (mid-20s to mid-40s) was significantly higher in HCC cases than in controls (Figure 1B; $P = .002$). Table 2 shows that among all study subjects, more cases (21.8%) than controls (18.7%) reported overweight in their mid-20s ($P = .02$). A prior history of obesity in the mid-20s, mid-30s, and mid-40s was significantly associated with increased HCC risk in the whole study population and in absence of major HCC risk factors (Table 2).

Table 3 shows that the mean age at HCC onset among case patients who recalled a prior history of early adulthood obesity in their mid-20s to mid-40s was significantly lower than the mean age at onset of those with normal BMIs at the same life cycle ($P = .01$, <.001, <.001, respectively). For example, in those with obesity history in their mid-20s, HCC was diagnosed more than 3 years sooner than in those at normal weight. The mean ages (years ± SD) at diagnosis were 63.4 (±11.19), 63.0 (±10.6), and 60.1 (±11.6) years for those in their mid-20s who were normal weight, overweight, and obese, respectively. We observed similar results when we examined the mean age at HCC onset in patients in their mid-30s and mid-40s, comparing those who were obese/overweight with those with normal weight. The mean difference in age at HCC onset between obese individuals and those with normal body weight was determined to be statistically significant after adjusting for other factors associated with age at HCC onset (Table 3). We estimated that each 1-unit increase in BMI at early adulthood (mid-20s to mid-40s) before HCC diagnosis was associated with a 3.89-month decrease in the age at HCC diagnosis ($P = <.001$). The estimated coefficient = −3.89 and 95% CI (−5.60 to −2.18) after controlling for the confounding effect of HCC risk factors ($P < .0001$).

Only 12% of obese cases and 4% of obese controls recalled weight reduction over time; among whom 6% of the case patients and 2% of the controls experienced ≥ 10% weight reduction. These reductions had no significant effect on the risk of HCC development.

Restricted analyses among white subjects, men, women, nondrinkers, non-HCV/-HBV–infected subjects, nondiabetics, and nonsmokers indicated no significant association between early adulthood overweight (mid-20s to mid-40s) with HCC development (Figure 2A). However, the odds for developing HCC are approximately 2- to 4-fold greater for subjects with early adulthood obesity than for subjects with normal BMI (Figure 2B). A total of 21 HCC cases and 0 controls recalled a prior history of CLD; excluding these cases from analysis did not meaningfully change the significant association between early adulthood obesity and HCC.

Table 4 shows the relative excess risk for patients having prior history of early adulthood obesity (mid-20s to mid-40s) and HCV/HBV, alcohol consumption, or diabetes mellitus. By crossing each risk factor with early adulthood obesity (mid-20s to mid-40s), a dummy variable of 4 categories was obtained: two for the presence of each factor in the absence of the other, one indicating the presence of joint factors, and one for unexposed to either factor. The “unexposed to either factor” category was used as the reference category in the regression model. For example, the ORs (95% CI) for hepatitis virus infection in the absence of obesity, obesity in the absence of virus infection, and combined virus infection and

obesity were 31.7 (19.3–52.3), 2.5 (1.5–4.3), and 72.5 (9.2–574.2), respectively. Using the OR as an estimate for the relative risk of disease development, the relative excess risk for patients having early adulthood obesity plus hepatitis virus infection exceeded the sum of the relative excess risks for the virus infection and obesity alone, that is, 72.5−1.0 > (31.7−1.0) + (2.5−1.0), indicating a departure from additivity in the joint effect of early adulthood obesity with HCV/HBV (***S*** = 2.2; 95% CI, 1.2–3.9). This may suggest that obesity, in addition to its own direct effects, may exacerbate the effect of chronic hepatitis virus infection on HCC. A similar approach was performed for the joint effect of diabetes and alcohol consumption with early adulthood obesity. Unlike with hepatitis virus infection (HCV/HBV), we found no risk modification for the joint effect between alcohol consumption or diabetes mellitus with early adulthood obesity (mid-20s to mid-40s) (Table 4).

In our control group, the prevalence of diabetes, early adulthood obesity, and combined diabetes with early adulthood obesity were 9.85%, 5%, and 2.12%, respectively. Therefore, according to the ORs values in Table 4, the estimated PARs% were 21% for diabetes, 10% for early adulthood obesity, and 11% for the combination of diabetes and early adulthood obesity.

The clinical features of HCC did not significantly vary by the status of early adulthood BMI (normal, overweight, obese) (Table 5). The estimated median OS (95% CI) values were 21.9 (18.7–25.2), 18.9 (13.2–24.8), and 19.9 (16.7–23.2) for normal BMI, overweight, and obesity, respectively (P = .6). In addition, multivariate Cox regression analysis indicated that early adulthood obesity (mid-20s to mid-40s) was not associated with a significantly increased total mortality (HR = .9; 95% CI, .6–1.4) (P = .6).

DISCUSSION

The current study is, to our knowledge, the first to show that obesity in early adulthood (mid-20s to mid-40s) in both men and women is associated with increased risk of HCC development and with early onset of HCC, regardless of the confounding effects of the established risk factors of HCC such as HCV, HBV, alcohol consumption, cigarette smoking, and diabetes mellitus.

Approximately 42% of our HCC cases could be explained by obesity and diabetes, which was comparable to the 38.9% reported by the McGlynn group.[25] However, the uniqueness of our study is its ability to analyze diabetes and obesity separately, specifically, in determining that 10% of the HCC cases in our study could be attributed to early adulthood obesity independent from diabetes mellitus or other HCC risk factors.

The association between increased body weight and liver cancer has been determined through meta-analyses and systematic reviews.[8, 9, 25–28] One potential limitation of these review studies, which is highlighted by their authors, is that many of the individual studies did not adjust for the major risk factors of HCC, including HCV, HBV, diabetes, and alcohol consumption.[29] In addition, population selection in the individual studies in these reviews was not exclusive to a diagnosis of HCC. Also, relying on BMI at the time of case

ascertainment (HCC diagnosis) from case-control studies is subject to miscalculation (overestimation) because of the presence of ascites among many HCC patients with underlying cirrhosis. Moreover, in the included cohort studies, BMI had been estimated at initial enrollment and weight change monitored for only a small number of patients with HCC.

The potential biological mechanism for the association between obesity and HCC can be related to a number of physiological changes.[30–32] Obese individuals often experience hepatic steatosis with potential progression to steatohepatitis and cirrhosis.[33, 34] Key transcription factors in fatty acid oxidation, such as peroxisome proliferator-activated receptors, may play a dual role in hepatocellular proliferation and in cyclooxygenase-2 expression, which may explain terminal disease progression from steatohepatitis to HCC.[35] Yet, cirrhosis is not the only explanation for the association between obesity and HCC. In this study, we found that ~62% of HCC patients had underlying cirrhosis and that among these patients, there were no significant differences in the proportions with normal weight, overweight, or obesity. Many obese individuals develop some degree of insulin resistance with elevated insulin-like growth factors,[36] which may have tumorigenic activity and have a role in cell growth/proliferation and fatty degeneration.[37]

Several studies have examined the association between obesity and clinical outcome in various cancers including HCC.[38–42] However, HCC studies have shown that mortality was not influenced by BMI.[40, 43] Moreover, the association between obesity and life-threatening morbidities and complications after hepatic resection has not been conclusive, with some studies suggesting that hepatic resection in overweight and obese HCC patients is safe.[39, 41, 42]

The reasons for the poor prognosis observed in obese cancer patients is unclear but can be correlated with comorbidities or cancer consequences typically seen in obese patients such as heart diseases.[41] Other pathways have been hypothesized including the observed low level of adiponectin in men and women with high BMI[44]; in fact, a more favorable prognosis was observed in HCC patients with higher expression of adiponectin.[45, 46] In addition, angiogenesis dysregulation induced by the adipose tissue through leptin expression has been suggested.[47] Siegel and colleagues showed that obesity is associated with microvascular invasion, resulting in poor HCC survival.[48] In our study, vascular invasion was observed more frequently in overweight and obese patients than in normal-weight patients, but the differences were not statistically significant.

Increased risk of HCC associated with obesity was previously reported for chronic carriers of HBV and HCV[49] and for alcohol drinkers,[50] suggesting that obesity-induced oxidative stress may increase the liver's susceptibility to chronic inflammation, DNA damage, fatty liver, and cirrhosis progression.[50,34]

The current study has some limitations, specifically, 1) the use of hospital-based case patients, many of whom were diagnosed as having advanced-stage disease, and 2) the use of weight and height data recalled from the distant past. Given the poor prognosis of this cancer, it is difficult to rely on a population-based design for recruiting patients with newly

diagnosed HCC for a large-scale clinico-epidemiological study. To minimize ascertainment or selection bias related to misdiagnosis of case patients, we chose to use a hospital-based design, in which all cases had a confirmed diagnosis of HCC. Similar to the natural history of HCC where majority of the patients are presented with advanced stage,[51–54] approximately 64% of our patients are diagnosed as having advanced-stage disease (TNM III–IV) at time of initial evaluation.

Control subjects were selected to represent the population from which the HCC patients were ascertained. Only U.S. patients and controls were included, and the geographic distribution of their residential states was similar. Therefore, it is unlikely that our findings were confounded by selection bias of cases or controls. The prevalence of ever history of obesity during lifetime in the control group was 30.6%, which is consistent with the recently reported U.S. estimate by Ng and colleagues.[1]

All participants were personally interviewed to obtain information about self-reported weight across the life cycle before cancer diagnosis (HCC patients) or before recruitment (controls). We observed consistent agreement in interview response between self-reported weight and body size (Stunkard pictograms) across different ages for HCC cases and healthy controls. Moreover, we found no discrepancy between interview information and patients' records with respect to HCC risk factors. There was strong evidence supporting the reliability and validity of self-reported diabetes mellitus, where agreement between self-reported disease diagnosis and medical conditions was observed.[55–57] In addition, several studies reported high correlations between recalled and measured weight and height in young adulthood among middle-aged and older men and women.[58–62]

The current study continues to show the multifactorial origin of HCC. Variation in the magnitude of ORs for the association between environmental exposures and HCC in various epidemiological studies, including our early study, could be partially explained by the type of controls included in the study, that is, healthy versus sick controls.[19] Another explanation was lack of quantitative assessment of environmental exposures including alcohol consumption and cigarette smoking by some studies. Consideration of diabetes duration with the exclusion of patients with a recent diagnosis may have affected the magnitude of reported ORs of HCC risk factors.

In conclusion, this study provides robust epidemiological evidence to support the association between obese adults in their mid-20s to mid-40s and risk of HCC in American men and women, with obese subjects more susceptible than non-obese subjects to early-onset HCC.

Educational interventions and public awareness may be key to reducing the incidence of obesity at a young age. Behavioral modification, including abstaining from alcohol and restricting diet, especially among patients with chronic viral infection, may reduce the incidence of end-stage CLDs.

The effect of obesity on viral activity and the treatment response of HCV and HCC among these high-risk patients has not yet been investigated. In addition, experimental studies are warranted to describe the underlying mechanisms responsible for the effect of obesity on HCC in the absence of cirrhosis. Finally, future investigation of the preventive and favorable

prognostic role of metformin and statin in patients with CLDs including HCC should be initiated.

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Abbreviations

BMI	Body Mass Index
OR	Odds Ratio
S	synergetic Index
HCV	hepatitis C Virus
HBV	hepatitis B Virus
HCC	hepatocellular carcinoma
IQR	interquartile range R
AOR	Adjusted Odds Ratio
TNM	Tumor–Nodes–Metastases
CLIP	Cancer of the Liver Italian Program
BCLC	Barcelona Clinic Liver Cancer
AFP	alpha-fetoprotein levels
X^2	chi-square test
PAR%	population-attributable risk percentage
S	synergism index

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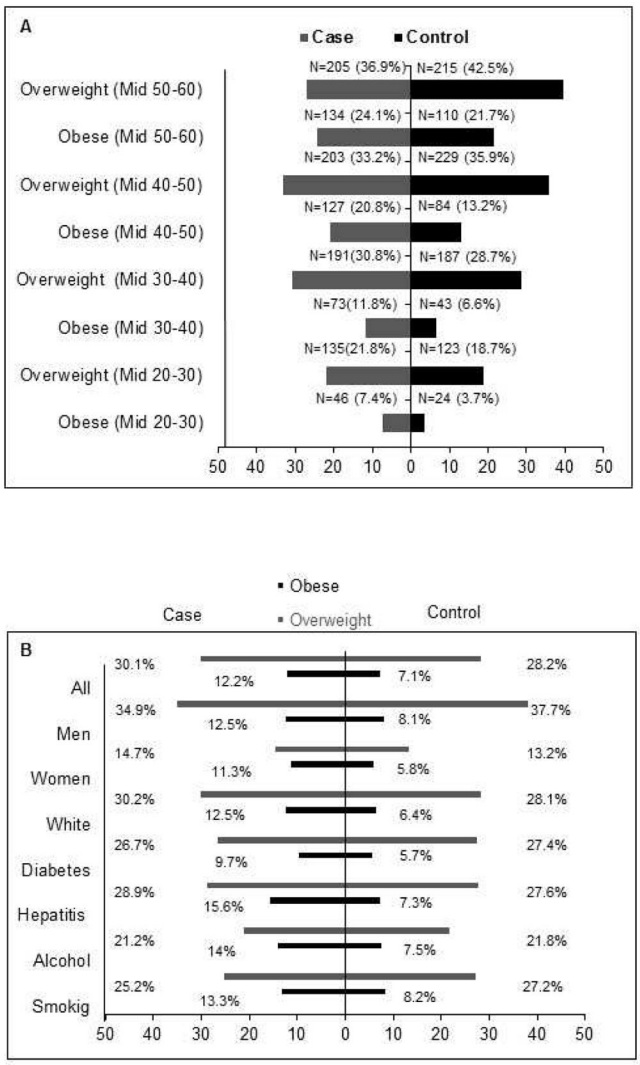

Figure 1.

(A) Frequency of overweight and obesity at various ages during the life cycle before hepatocellular carcinoma diagnosis or control recruitment.

(B) Distribution of body mass index status by percentages (overweight, obese) by HCC risk factors in cases and controls in their mid-20s to mid-40s.

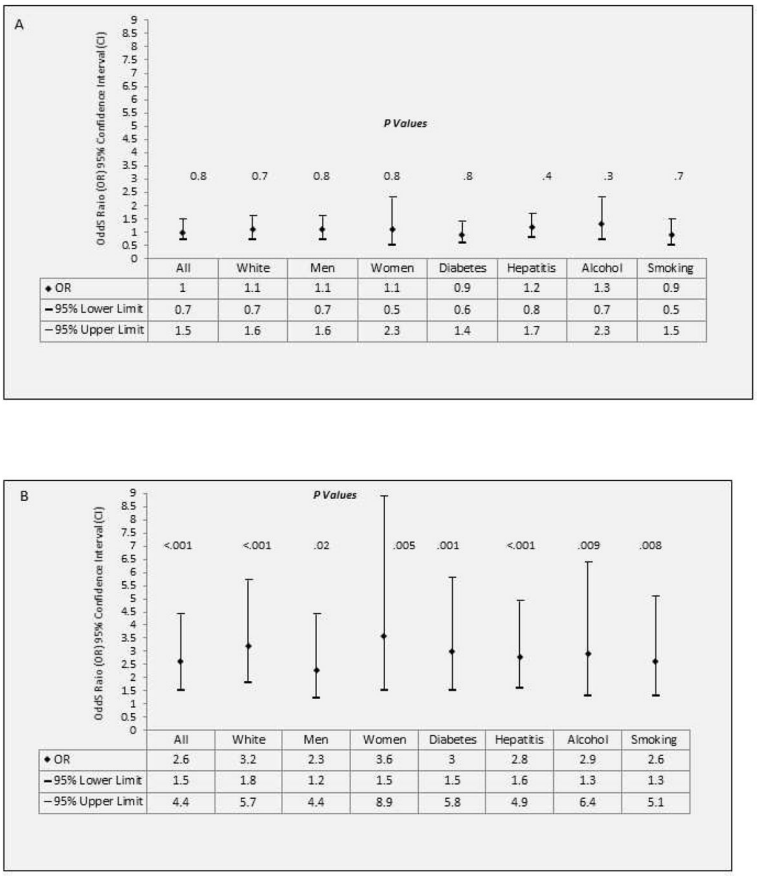

Figure 2.

(A) Odds Ratio, 95% Confidence Interval for the association between adulthood overweight (mid-20s to mid-40s) with hepatocellular carcinoma risk in the absence of major risk factors and with adjustment of confounding factors.

(B) Odds Ratio, 95% Confidence Interval for the association between adulthood obesity (mid-20s to mid-40s) with hepatocellular carcinoma risk in the absence of major risk factors and with adjustment of confounding factors.

Example: The estimated odds ratios, 95% confidence intervals for the association between adulthood overweight/obesity and HCC among non-diabetics were .9 (.6–1.4), *P*=.8 and 3.0 (1.5–5.8), *P*=.001 respectively, after adjustment for confounding factors including age, ethnicity, HCV, HBV, education level, alcohol drinking, cigarette smoking, physical activity, and family history of cancer.

Table 1

Multivariate-adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of hepatocellular carcinoma for demographic and other factors

Demographic variables	No.	(%)	No.	(%)	AOR* (95% CI)	*P* value
	HCC patients (*N* = 622)		Controls (*N* = 660)			
Sex						
Female	149	24	257	38.9	1 (reference)	
Male	473	76	403	61.1	.9 (.6–1.2)	.5
Age (years)						
<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 (.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

Demographic variables	No.	(%)	No.	(%)	AOR* (95% CI)	*P* value
	HCC patients (*N* = 622)		Controls (*N* = 660)			
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	.9 (.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 ≤I year	14	2.3	18	2.7	1.9 (.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						
TX, LA, AK, NM, OK †	448	72	497	75.3	1 (reference)	
Other states	174	28	163	24.7	.8 (.7–1.1)	.2

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

[*] The AORs 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.

[†] States of Texas (TX), Louisiana (LA), Arkansas (AK), New Mexico (NM), and Oklahoma (OK)

Table 2

AOR (95% CI)* for the associations between prior history of overweight/obesity and risk of hepatocellular carcinoma in all population, men, women, and in absence of risk factors (HCV, HBV, Alcohol Drinking, Diabetes)

Previous BMI	Overweight (BMI 24–29.9)											
	All				Men				Women			
	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*
Mid-20s	135	123	**1.6 (1.1–2.3)**	**.02**	124	109	1.5 (.9–2.3)	.078	11	14	2.4 (.9–3.0)	.089
Mid-30s	191	187	1.2 (.9–1.8)	.27	172	158	1.3 (.9–2.1)	.174	19	29	1.2 (.5–2.6)	.734
Mid-40s	203	229	.9 (.6–1.2)	.41	174	178	.9 (.6–1.4)	.709	29	51	.8 (.4–1.6)	.589
Mid-50s	205	215	.6 (.4–1.1)	.10	170	156	.5 (.3–.9)	.014	35	59	.9 (.5–1.7)	.788

	Overweight (BMI 24–29.9)											
	No Diabetes				No-HCV/HBV infection				No Alcohol Drinking			
	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*
Mid-20s	82	107	1.5 (.9–2.3)	.093	74	118	**1.6 (1.1–2.4)**	**.024**	22	36	1.7 (.8–3.6)	.139
Mid-30s	113	160	1.3 (.8–1.9)	.279	94	178	1.4 (.9–1.9)	.118	35	61	1.4 (.8–2.7)	.277
Mid-40s	132	200	.9 (.6–1.3)	.512	99	214	1.2 (.8–1.7)	.430	39	91	.7 (.4–1.3)	.268
Mid-50s	127	194	.6 (.4–.9)	.012	108	204	.8 (.5–1.2)	.237	50	89	.7 (.4–1.3)	.265

	Obesity (BMI ≥30)											
	All				Men				Women			
	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*
Mid-20s	46	24	**2.5 (1.3–4.8)**	**.009**	33	18	1.8 (.8–4.1)	.174	13	6	**5.2 (1.6–7.2)**	**.007**
Mid-30s	73	43	**2.9 (1.7–5.1)**	**<.001**	58	31	**3.1(1.6–6)**	**.001**	15	12	**3.3 (1.3–8.6)**	**.013**
Mid-40s	127	84	**2.1 (1.3–3.3)**	**.002**	101	56	**2.2 (1.2–4)**	**.001**	26	28	**2.1 (1.1–4.5)**	**.0489**
Mid-50s	134	110	.9 (.6–1.5)	.7	104	70	.8 (.4–1.4)	.381	30	40	1.2 (.5–2.5)	.715

	Obesity (BMI ≥30)											
	No diabetes				No-HCV/HBV infection				No alcohol drinking			
	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*
Mid-20s	22	15	**2.7 (1.1–6.6)**	**.038**	28	23	**2.7 (1.3–5.5)**	**.006**	17	12	**3.9 (1.6–9.7)**	**.004**

	Obesity (BMI ≥30)											
	No diabetes				No-HCV/HBV infection				No alcohol drinking			
	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*	Cases	Controls	AOR (95% CI)	*P*
Mid-30s	39	31	**2.9 (1.5–5.7)**	**.002**	49	41	**3.4 (1.9–5.9)**	**<.001**	27	19	**2.5 (1.2–4.9)**	**.01**
Mid-40s	66	63	**2.2 (1.3–3.9)**	**.006**	72	82	**2.5 (1.5–4.1)**	**<.001**	41	40	1.6 (.8–2.9)	.166
Mid-50s	65	80	.9 (.5–1.6)	.817	80	106	1.1 (.7–1.8)	.763	41	58	.7 (.4–1.5)	.381

Abbreviations: AOR, multivariate-adjusted odds ratio; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus.

*AOR for sex, age, ethnicity, education level, HCV, HBV, alcohol drinking, cigarette smoking, history of diabetes, physical activity, and family history of cancer

Table 3

Association between BMI status before HCC diagnosis and age at onset of HCC (Multiple Linear Regression)

Age (Range)	Patients (N)	Age at HCC onset (years)		Mean difference (95% CI)	*P* Value
		Median (IQR)	Mean (±SD)		
Mid-20s					
Normal weight	438	70 (62–79)	63.4 (±11.19)		
Overweight	135	62 (56–70)	63.0 (±10.6)	−2.0 (−4.1 to .06)	**.057**
Obese	46	61 (55–70)	60.1 (±11.6)	−4.1 (−7.2 to .85)	**.013**
Mid-30s					
Normal weight	356	63 (56–72)	63.7 (±11.3)		
Overweight	191	64 (56–70)	63.2 (±10.5)	−1.6 (−3.5 to 21)	.084
Obese	73	60 (55–69)	61.3 (±10.2)	−5.1 (−7.7 to 2.4)	**<.001**
Mid-40s					
Normal weight	281	65 (56–73)	64.3 (±11.9)		
Overweight	203	64 (57–71)	64.3 (±9.1)	−.5 (−2.3 to 1.3)	.589
Obese	127	60 (56–68)	61.7 (±9.1)	−4.14 (−6.2 to 2.1)	**<.001**
Mid-50s					
Normal weight	217	64 (56–74)	64.7 (±12.3)	.9 (−.8 to 2.7)	.3
Overweight	205	66 (60–72)	66.5 (± 8.5)	−1.7 (−3.8 to .3)	.09
Obese	134	63 (59–69)	64.3 (±6.9)		

Abbreviations: BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; IQR, interquartile range

Table 4

Risk modification of early adulthood obesity (mid-20s to mid-40s) by hepatitis virus infection, alcohol consumption, and diabetes mellitus on HCC development: AOR* (95% CI) using multivariate logistic regression analyses

	Variables	Cases N=622	Controls N=660	Model	AOR (95% CI)	*P*
HCV/HBV*	Early Adulthood Obesity			(1)†		
No	No	266	589		1 (reference)	
Yes	No	281	24		31.7 (19.3–52.3)	<.0001
No	Yes	48	46		2.5 (1.5–4.3)	<.0001
Yes	Yes	27	1		72.5 (9.2–574.2)	<.0001
Diabetes	Early Adulthood Obesity			(2)‡		
No	No	375	548		1 (reference)	
Yes	No	172	65		3.9 (2.6–5.7)	<.0001
No	Yes	39	33		3.3 (1.7–6.4)	<.0001
Yes	Yes	36	14		6.5 (3.2–13.5)	<.0001
Alcohol	Early Adulthood Obesity			(3)§		
No	No	155	273		1 (reference)	
Yes	No	392	340		2.1 (1.5–3.0)	<.0001
No	Yes	25	22		2.7 (1.2–5.9)	<.0001
Yes	Yes	50	25		5.0 (2.4–10.1)	<.0001

*AOR= Adjusted Odds Ratio; HBV, hepatitis B virus; HCV, hepatitis C virus

†Model (1) adjustment for age, ethnicity, education level, alcohol drinking, cigarette smoking, history of diabetes, physical activity, and family history of cancer

‡Model (2) adjustment for age, ethnicity, HCV, HBV, education level, alcohol drinking, cigarette smoking, physical activity, and family history of cancer

§Model (3) adjustment for age, ethnicity, HCV, HBV, education level, history of diabetes, cigarette smoking, physical activity, and family history of cancer

Table 5

Distribution of hepatocellular carcinoma clinical features by BMI status at early adulthood (mid-20s to mid-40s)

Clinical Feature*	Normal N=360 (%)	Overweight N=187 (%)	Obese N= 75(%)	*P value*†
Presence of Cirrhosis				.1
Yes	214 (59.6)	128 (68.4)	43 (57.3)	
No	145 (40.4)	59 (31.6)	32 (42.7)	
Evidence of Vascular Invasion				0.2
Yes	107 (29.8)	70 (37.4)	25 (33.3)	
No	252 (70.2)	117 (62.6)	50 (66.7)	
Evidence of Portal Thrombosis				0.7
Yes	82 (22.8)	49 (26.2)	19 (25.3)	
No	277 (77.2)	138 (73.8)	56 (74.7)	
Extra-hepatic Metastasis				0.9
Yes	95 (26.5)	47 (25.1)	21 (28)	
No	264 (73.5)	140 (74.9)	54 (72)	
Lymph Node Involvement				
Yes	60 (16.8)	45 (24.1)	17 (22.7)	0.1
No	298 (83.2)	142 (75.9)	58 (77.3)	
Tumor Involvement				
>50%	71 (20.4)	41 (22.2)	23 (31.1)	0.2
≤50%	272 (78.2)	143 (77.3)	51 (68.9)	
Tumor Nodularity				0.4
Multi-nodular	222 (62)	109 (58.3)	50 (66.7)	
Solitary-nodule	119 (33.2)	75 (40.1)	24 (32)	
Performance Status				0.1
(≥ 2)	44 (12.2)	24 (12.8)	9 (12)	
(< 2)	316 (87.8)	163 (87.2)	66 (88)	
Tumor Differentiation				0.1
Well-Differentiated	83 (23.1)	49 (26.4)	19 (25.3)	
Moderate-Differentiated	114 (31.7)	54 (29)	24 (32)	
Poor-Differentiated	44 (12.2)	35 (18.8)	8 (10.7)	
Not Reported	113 (31.4)	48 (25.8)	24 (32)	
CLIP				0.2
CLIP Score (0–2)	276 (79.5)	138 (74.6)	50 (67.6)	
CLIP Score (3)	40 (11.5)	29 (15.7)	14 (18.9)	
CLIP Score (4–6)	27 (7.8)	17 (9.2)	10 (13.5)	
Okuda				0.1
Stage-I	211 (58.9)	93 (49.7)	34 (45.3)	

Clinical Feature*	Normal N=360 (%)	Overweight N=187 (%)	Obese N= 75(%)	*P value*†
Stage-II	132 (36.9)	88 (47.1)	37 (49.3)	
Stage-III	11 (3.1)	5 (2.7)	4 (5.3)	
BCLC				0.3
Early Stage (0-A)	27 (7.5)	10 (5.3)	3 (4)	
Intermediate Stage (B)	66 (18.3)	35 (18.7)	13 (17.3)	
Advances Stage (C)	241 (66.9)	136 (72.7)	52 (69.3)	
End Stage (D)	17 (4.7)	4 (2.1)	7 (9.3)	
TNM				0.8
I–II	119 (33)	60 (32.1)	21 (28)	
IIIA-IIIB-IIIC	93 (25.9)	55 (29.4)	24 (31.9)	
IVA–IVB	131(36.4)	67 (35.8)	27 (36)	
Treatment				0.4
Surgery and Transplant	58 (16.1)	21 (11.2)	8 (10.7)	
Ablation Therapy	11 (3.1)	7 (3.7)	3 (4)	
Local Therapy	118 (32.8)	69 (36.9)	19 (25.3)	
Systemic Therapy	153 (42.5)	78 (41.7)	37 (49.3)	
No therapy	20 (5.6)	12 (6.4)	8 (10.7)	
AFP (> 400 ng/ml)	125 (34.7)	56 (29.9)	34 (45.3)	0.1

Abbreviations: Tumor–Nodes–Metastases (TNM), Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer (BCLC), alpha-fetoprotein levels (AFP)

*Some baseline (at time of diagnosis) clinical information were missing from patients' medical records including (cirrhosis, 1; vascular invasion, 1; portal thrombosis, 1; extra-hepatic metastasis, 1; lymph node metastasis, 2; tumor involvement, 21; tumor nodularity, 23; tumor differentiation, 7; CLIP score, 21; OKUDA stage, 7; BCLC stage, 11; TNM stage, 25)

†*P* value using chi-square test