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ORIGINAL RESEARCH

Risk and Prognosis of Hepatocellular Carcinoma in Mexican Americans with Type 2 Diabetes Mellitus

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Introduction: Hepatocellular carcinoma (HCC) disproportionately affects Hispanic persons with higher age-specific incidence and increased mortality rates compared to non-Hispanic Whites. These high rates of incidence and mortality may be explained by the variation in risk factors. Given the high prevalence of type 2 diabetes mellitus (DM) among the Hispanic population, we aimed to assess the risk and prognosis of HCC in Mexican Americans with type 2 DM with consideration of treatment for DM.

Methods: A case-control study of 241 Mexican American HCC patients and 500 healthy controls in Texas was conducted. Multivariable logistic regression analysis was performed to determine the association between type 2 DM and HCC risk while adjusting for other risk factors. Also, a restricted analysis of patients with type 2 DM was conducted to determine the effects of age at onset and duration of DM on HCC risk. Interactions among DM, heavy alcohol consumption, and viral hepatitis infection were examined. Overall survival was examined, and multivariable Cox proportional hazards regression analysis was performed for HCC patients with type 2 DM.

Results: The adjusted odds ratio (AOR) for DM was 2.74 ($P < 0.01$). Compared with patients who had DM for 2–10 years, those who had it for at least 20 years had an AOR of 4.60 ($P = 0.04$). Metformin use was associated with a reduced risk of death in HCC cases with type 2 DM, with a hazard ratio of 0.72 ($P = 0.01$) as compared with non-users.

Conclusion: Our results demonstrate that type 2 DM was independently associated with increased risk of HCC among Mexican Americans. Metformin use was associated with improved survival among HCC patients with type 2 DM. Type 2 DM significantly increased the risk of HCC alone and in conjunction with other parameters of metabolic syndrome in the Mexican American population after adjusting for other risk factors.

Keywords: diabetes mellitus, Mexican Americans, hepatocellular carcinoma, metformin, interactions

Introduction

Hepatocellular carcinoma (HCC) is rarely diagnosed early and is one of the leading causes of cancer mortality worldwide.[1] The incidence of HCC has substantially increased globally and in the United States over the past several decades.[2,3] Several authors have reported variation in HCC incidence and mortality according to race and ethnicity,[4–6] with the Hispanic population having the second highest HCC incidence rate in the US. Similarly, high HCC incidence and mortality rates are observed in Latin America, including Mexico, Central America, and Peru.[7] Despite a recent decline in HCC incidence according to Surveillance, Epidemiology, and End Results data, studies continue to

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demonstrate racial disparities in HCC incidence annually, with Hispanics having among the highest annual incidence at 9.74 per 100,000 persons.[8]

Racial and ethnic disparities in cancer diagnosis and treatment result from differences in social determinants, access to health care, and support mechanisms.[9] Barriers to care for HCC patients include health literacy and concerns about time commitment and transportation for treatment.[9,10] Authors postulated that the racial variation in risk of and prognosis for HCC is a result of changing risks associated with chronic viral hepatitis, type 2 diabetes mellitus (DM), alcohol consumption, obesity, and other metabolic factors.[7,11–13] Owing to the increased prevalence of obesity and metabolic syndrome (MS), studies predicted that MS-related HCC cases will increase given the consequences of metabolic dysfunction-associated steatotic liver disease (MASLD).[14,15] The global prevalence of MASLD has increased significantly with a rate that was 50.4% higher in 2016–2019 than in 1990–2006 ($P < 0.001$).[16] The highest prevalence rate from 1990 to 2019 of MASLD was in Latin America at 44.37%.[16] Moreover, DM is a major public health problem among Hispanics who experience the highest prevalence of DM in the United States.[17] The rise in MASLD-related HCC cases in the United States may be explained by these racial disparities. Compared to non-Hispanic Whites, Hispanic patients are diagnosed with HCC at an older age, with higher body mass index, and are more likely to have type 2 DM and hypertension.[18]

Despite slow population growth among Hispanics over the past decade, they still make up about 18% of the US population, with Latinos accounting for 52% of all US population growth from 2010 to 2020.[19] The Hispanic population in the United States has varying subpopulations, and although their ethnic origins are not always distinguished,[20] the largest subpopulation is Mexican Americans. However, there is limited information examining the natural history of HCC among the subpopulation of Mexican Americans. In this subpopulation, chronic diseases related to metabolic disorders, such as type 2 DM, obesity, and hyperlipidemia, are pronounced.[20]

Although evidence in the literature supports racial and ethnic disparities in HCC incidence,[21–23] the magnitude of these disparities has not been completely elucidated owing to limitations in current epidemiological studies. The main challenges in these studies are 1) lack of detailed information on DM (eg, duration of disease and treatment), 2) limited numbers of incident HCC cases among Hispanics, and 3) a lack of adjustment for confounding effects of strong risk factors, including viral hepatitis infection and alcohol consumption. The present study focused on the Mexican American population in Texas to highlight the urgent need to better understand the risk factors and prognosis for HCC in this group.

Methods

Study Design and Participant Recruitment

This study included patients with HCC involved in an active epidemiological study approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. All Mexican American patients diagnosed with HCC, who were enrolled in that study from January 2000 through December 2020, were included in the present analysis. Written informed consent was obtained from each participant enrolled in the study. Control participants were selected from a pool of Mexican American participants in a large population-based prospective study of Mexican American households, the Mano a Mano Mexican American Cohort Study, which was initiated by the Department of Epidemiology at MD Anderson.

Study patients were prospectively recruited from among patients evaluated for and given treatment of HCC at the MD Anderson Gastrointestinal Medical Oncology outpatient clinic. Inclusion criteria for the patients were a pathologically or radiologically confirmed diagnosis of HCC, Hispanic ethnicity of Mexican origin, Texas residence, and the ability to communicate in English. Exclusion criteria were the presence of other types of primary liver cancer (ie, fibrolamellar HCC, cholangiocarcinoma), concurrent or past diagnosis of cancer at another site, diagnosis of a primary tumor of unknown origin, and ethnicity other than Hispanic of Mexican origin.

In total, 272 Hispanic patients with a confirmed HCC diagnosis from January 2000 through December 2020 were identified, 265 of whom were eligible for our study based on residence status. An additional 24 patients were excluded for having an ethnicity other than Hispanic of Mexican origin. Thus, 241 Mexican American HCC patients were included in the present analysis.

Control participants were defined as eligible participants in the Mano a Mano Mexican American Cohort Study. These participants were recruited from community centers, local health clinics, or house by house in predominantly Mexican American neighborhoods in Texas, as well as through networking with already enrolled participants.[24,25] Inclusion criteria for control participants were US residence, Hispanic ethnicity of Mexican origin, and no cancer diagnosis. A random sample of 500 cancer-free participants was selected as the controls. An unmatched case-control design was performed to allow for adjustment for the confounding impact of the demographic variables.

Participant Assessment

HCC patients and control participants were personally interviewed by trained research coordinators upon recruitment using a structured and validated questionnaire[26,27] to collect demographic characteristics and risk factors for all cancers, including HCC. Potential risk factors included type 2 DM, cigarette smoking, obesity, viral hepatitis infection (hepatitis B virus [HBV] or hepatitis C virus [HCV]), family history of cancer, and alcohol consumption.

For our assessment of risk factors, participants were asked about their history of type 2 DM, including age at diagnosis and duration of the disease. HCC patients with a history of type 2 DM were further questioned about medications used to control type 2 DM and the duration of treatment.

Cigarette smokers were defined as individuals who smoked at least 100 cigarettes during their lifetime. *Heavy smokers* were defined as those with more than 20 pack-years of smoking. Alcohol consumption status and amount were also examined. Subjects were defined as *ever-alcohol consumers* if they had consumed at least 4 alcoholic drinks per month for 6 months in their lifetime. The total lifetime volume of alcohol consumption in milliliters was calculated by examining the frequency, type of serving (glass, bottle, or can), and number and size of servings during the entire duration of alcohol consumption. Participants defined as *heavy alcohol consumers* had consumed at least 60 mL of ethanol per day.

Obesity in participants was assessed during the interviews to obtain information about self-reported height (inches) and weight (pounds) at the time of enrollment (control participants) or time of cancer diagnosis (HCC case patients). Body mass index (BMI) was calculated using the formula: $\mathrm{BMI} = (\mathrm{Weight(kilograms)})/(\mathrm{Height\,in\,meters})^2$. The calculated BMI was then classified into 4 levels: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2).

Baseline clinical features at the time of HCC diagnosis were retrieved from the patients' electronic medical records. Pathological, radiological, and clinical evidence of performance status (Eastern Cooperative Oncology Group score of 0–5), vascular invasion, tumor involvement, portal thrombosis, metastasis, tumor nodularity, and evidence of cirrhosis were documented. The patients' baseline laboratory test results were also collected from MD Anderson electronic database at the time of HCC diagnosis. Moreover, each patient's TNM stage was assigned and confirmed using the collected clinical, radiological, and laboratory data. Patients were categorized into baseline treatment groups of surgical therapy (resection or transplantation), radiofrequency ablation, local therapy, systemic therapy, or best supportive care as the first treatment provided after HCC diagnosis.

Statistical Analysis

Stata software (version 13; StataCorp, College Station, TX) was used for all statistical analyses. Multivariable unconditional logistic regression analyses were conducted to identify significant independent risk factors. For each risk factor, the adjusted odds ratio (AOR) and its corresponding 95% confidence interval (CI) were calculated using maximum likelihood estimation. All AORs and 95% CIs were adjusted for age, sex, education level, chronic viral hepatitis infection, cigarette smoking, alcohol consumption, type 2 DM, presence of 2 or more metabolic factors (ie, hypertension, hyperlipidemia, obesity), and family history of cancer. The population attributable risk (PAR) percentage for type 2 DM was calculated using the equation $PAR\% = \frac{P_e(OR-1)}{P_e(OR-1)+1}\,x\,100$, in which OR is the adjusted OR for the association between type 2 DM and having HCC, and P_e is the prevalence of pre-existing type 2 DM in the controls.[28] Interactions were tested among major HCC risk factors (type 2 DM, chronic viral hepatitis infection, heavy alcohol consumption) using the additive model. The synergy index for the interactions was calculated as described by Rothman.[29] A restricted analysis of participants diagnosed with type 2 DM more than 1 year prior to HCC diagnosis or prior to recruitment for control participants was conducted to examine the onset and duration of DM.

Overall survival (OS) was defined as the time from HCC diagnosis and to death or the end of the follow-up period. The median OS was estimated using the Kaplan-Meier method, and differences in OS between groups were examined using a Log rank test. To identify independent prognostic factors for OS, a multivariable Cox proportional hazards regression analysis was performed to calculate hazard ratios (HR) and 95% CIs. OS and HRs with their 95% CIs were examined for the whole population and for HCC patients with type 2 DM. The multivariable Cox proportional hazard model included metformin use, evidence of cirrhosis, vascular invasion, portal thrombosis, tumor involvement, extrahepatic metastasis, tumor nodularity, TNM staging, ECOG, and baseline therapy. Furthermore, the model was adjusted for the confounding effects of age, sex, educational level, cigarette smoking, alcohol consumption, viral hepatitis infection, family history of cancer, and presence of 2 or more metabolic factors. For all analyses, *P* values less than 0.05 were considered statistically significant.

Results

Participant characteristics, including demographics and risk factors for HCC at recruitment to the Mano a Mano study or diagnosis of HCC, are summarized in Table 1. Our analysis included a total of 241 HCC patients and 500 control

Table 1 Characteristics of Patients with Hepatocellular Carcinoma (HCC Cases; n=241) and Control Participants (n=500) in Our Analysis

Variable	Overall		Cases		Controls		*P* value
	N=741	%	N=241	%	N=500	%	
DEMOGRAPHICS							
Age							
≤60 years	366	49.4	93	38.6	273	54.6	<0.01
>60 years	375	50.6	148	61.4	227	45.4	
Mean ± SE age, years	61.37 ± 0.27		63.95 ± 0.64		60.12 ± 0.26		<0.01
Sex							
Male	515	69.5	182	75.5	333	66.6	0.01
Female	226	30.5	59	24.5	167	33.4	
Marital status							
Not married	170	22.9	63	26.1	107	21.4	0.15
Married	571	77.1	178	73.9	393	78.6	
Educational level							
Less than high school	456	61.5	82	34.0	374	74.8	<0.01
High school graduate or GED	130	17.5	71	29.5	59	11.8	
Greater than high school	155	20.9	88	36.5	67	13.4	
Birth Country[a]							
Born outside United States	412	55.6	41	17.0	371	74.2	<0.01
Born in United States	328	44.3	200	83.0	128	25.6	
RISK FACTORS							
Chronic viral hepatitis infection[b]							
No	641	86.5	151	62.7	490	98.0	<0.01
Yes	100	13.5	90	37.3	10	2.0	
Family history of cancer							
No	457	61.7	81	33.6	376	75.2	<0.01
Yes	284	38.3	160	66.4	124	24.8	
Cigarette smoking[c]							
No	361	48.7	101	41.9	260	52.0	0.03
Yes	379	51.1	140	58.1	239	47.8	
Mean ± SE starting age of smoking, years	18.02 ± 0.34		18.49 ± 0.56		17.75 ± 0.42		0.29

(*Continued*)

Table 1 (Continued).

Variable	Overall		Cases		Controls		*P* value
	N=741	%	N=241	%	N=500	%	
Pack-Years of cigarette smoking[d]							
Nonsmoker	361	48.7	101	41.9	260	52.0	0.08
≤20 cigarettes per year	256	34.5	94	39.0	162	32.4	
>20 cigarettes per year	122	16.5	45	18.7	77	15.4	
Mean ± SE pack-years	23.58 ± 3.66		19.10 ± 1.86		26.19 ± 5.68		0.35
Smoker status[e]							
Nonsmoker	361	48.7	101	41.9	260	52.0	<0.01
≤5 years since quit smoking	57	7.7	28	11.6	29	5.8	
>5 years since quit smoking	236	31.8	93	38.6	143	28.6	
Current smoker	85	11.5	19	7.9	66	13.2	
Heavy drinking status[f]							
Nondrinker	284	38.3	56	23.3	228	45.7	<0.01
<60 mL of ethanol per day	348	47.0	129	53.5	219	43.9	
≥60 mL of ethanol per day	108	14.6	56	23.6	52	10.2	
BMI[g]							
Underweight (<18.5 kg/m^2)	5	0.7	3	1.2	2	0.4	0.21
Normal (18.5–24.9 kg/m^2)	96	13.0	37	15.4	59	11.8	
Overweight (25–29.9 kg/m^2)	302	40.8	86	35.7	216	43.2	
Obese (≥30 kg/m^2)	321	43.3	109	45.2	212	42.4	
CHRONIC MEDICAL CONDITIONS							
Type 2 DM							
No	459	61.9	120	49.8	339	67.8	<0.01
Yes	282	38.1	121	50.2	161	32.2	
Mean ± SE age of onset, years	50.72 ± 0.57		51.48 ± 0.90		50.16 ± 0.73		0.25
Mean ± SE duration of disease, years	12.34 ± 0.56		15.09 ± 0.70		10.27 ± 0.69		<0.01
Hypertension							
No	401	54.1	126	52.3	275	55.0	0.48
Yes	340	45.9	115	47.7	225	45.0	
Mean ± SE age of onset, years	45.07 ± 1.05		45.26 ± 1.76		44.97 ± 1.31		0.90
Mean ± SE duration of disease, years	17.23 ± 1.03		19.27 ± 1.78		16.18 ± 1.25		0.15
Hyperlipidemia							
No	540	72.9	164	68.0	376	75.2	0.04
Yes	201	27.1	77	32.0	124	24.8	
≥2 metabolic factors[h]							
No	382	51.6	104	43.2	278	55.6	<0.01
Yes	359	48.4	137	56.8	222	44.4	
History of cirrhosis of the liver							
No	559	75.4	66	27.4	493	98.6	<0.01
Yes	182	24.6	175	72.6	7	1.4	

Notes: [a]Missing birth country information for 1 control participant. [b]Chronic viral hepatitis infection with hepatitis B virus or hepatitis C virus. [c]Missing cigarette smoking status for 1 control participant. [d]Missing pack-year cigarette smoking amount for 1 HCC case patient and 1 control participant. [e]Missing smoker status for 1 control participant. [f]Missing heavy drinking status amount for 1 control. [g]Missing BMI information for 6 HCC case patients and 11 control participants. [h]Metabolic factors included hypertension, hyperlipidemia, and obesity.

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participants. Most study subjects were men; the male-to-female ratios were 3.1:1.0 for HCC patients and 2.1:1.0 for control participants. The HCC patients were slightly older than the control participants, with a mean difference of 3.8 years (95% CI, 2.2–5.3 years); the mean (± standard error [SE]) ages were 63.95 ± 0.64 years for HCC patients and 60.12 ± 0.26 years for control participants. Approximately 75% of the control participants had less than a high school education, whereas most of the HCC patients (66%) had a high school education or greater. Most of the control participants were born outside of the United States, whereas most of the HCC patients were born in the United States.

The prevalence of chronic viral hepatitis infection, family history of cancer, cigarette smoking (current or former), and heavy alcohol consumption was significantly higher for the HCC patients than for the control participants. Our previous reports demonstrated that all these factors are independent risk factors for HCC development.[30–32]

We highlighted the proportions of major risk factors for HCC among the patients with it based on the presence of pathologically or radiologically confirmed cirrhosis (Figure 1). Most of the HCC patients (72.6%) had confirmed cirrhosis at the time of clinical presentation. The most common risk factor for HCC was heavy alcohol consumption (41.0% of patients with cirrhosis and 53.9% of patients without cirrhosis). However, 33.8% of the patients with cirrhosis had HCV infection, whereas 18.6% of patients who did not have cirrhosis had HCV infection. The prevalence of type 2 DM was similar in those with and without cirrhosis.

A total of 121 HCC patients (50.2%) and 161 control participants (32.2%) had a history of type 2 DM. DM was significantly more prevalent in the HCC patients than in the control participants. The mean (± SE) ages at diagnosis of DM were similar for the two groups (51.48 ± 0.90 years for HCC patients and 50.16 ± 0.73 years for control participants). HCC patients had longer durations of DM than did control participants, with a mean difference of 4.8 years (95% CI, 3.1–6.5 years). We also observed that the prevalence of hyperlipidemia, cirrhosis, and presence of 2 or more metabolic factors (ie, hypertension, hyperlipidemia, obesity) was significantly higher in HCC patients than in control participants (Table 1).

Multivariable logistic regression analysis demonstrated that type 2 DM, age of at least 60 years, education level, family history of cancer, viral hepatitis infection, heavy alcohol consumption, and presence of 2 or more metabolic factors were associated with increased odds of developing HCC (Table 2). Individuals with a history of type 2 DM had a 2.74-fold increase (95% CI, 1.68–4.48) in the odds of developing HCC than individuals without type 2 DM. Having an education level greater than high school was associated with lower odds of HCC development than was having a high school education or GED. Chronic viral hepatitis was associated with increased odds of HCC; this factor had the highest AOR among all the risk factors described above (AOR=25.03; 95% CI, 11.45–54.73). In contrast, persons with heavy alcohol consumption ≥60mL of ethanol daily had 6.03-fold increase (95% CI, 2.89–12.59) in the odds of developing HCC compared to nondrinkers. We estimated that the population attributable risk explained by type 2 DM in Mexican Americans residing in Texas was 35.9% (95% CI, 29.6–42.2).

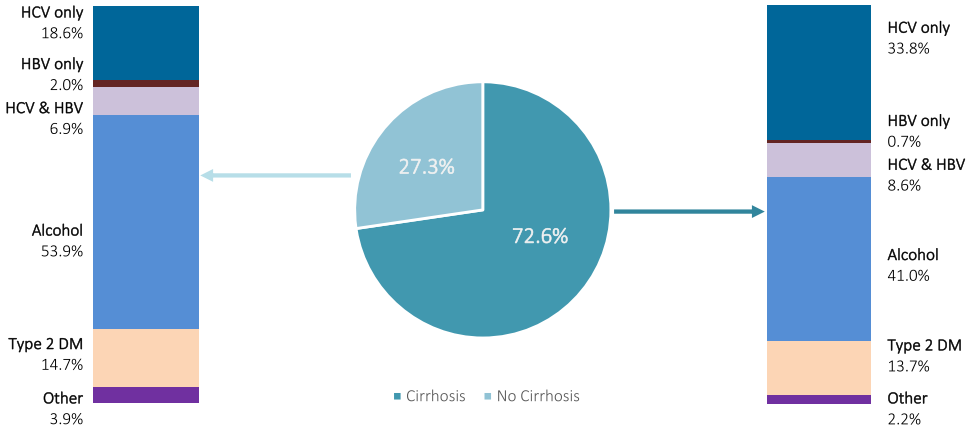

Figure 1 Proportion of major risk factors for hepatocellular carcinoma (HCC) among case patients (HCC cases; n=241) according to presence of pathologically or radiologically confirmed cirrhosis.
Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; alcohol, consumption of ≥60 mL of ethanol per day; and Type 2 DM, Type 2 diabetes mellitus.

Table 2 Risk Factors Associated with the Development of Hepatocellular Carcinoma in Our Cohort (HCC Cases; n=241 and Controls; n=500)

Variable	Adjusted odds ratio	95% CI	*P* value
Type 2 DM			
No	1.0 (reference)		
Yes	2.74	1.68–4.48	<0.01
Age			
≤60 years	1.0 (reference)		
>60 years	1.97	1.29–3.01	<0.01
Sex			
Females	1.0 (reference)		
Males	1.11	0.63–1.72	0.66
Education			
Less than high school	1.0 (reference)		
High school graduate or GED	5.80	3.39–9.93	<0.01
Greater than high school	4.79	2.90–7.95	<0.01
Family history of cancer			
No	1.0 (reference)		
Yes	5.17	3.40–7.87	<0.01
Chronic viral hepatitis[a]			
No	1.0 (reference)		
Yes	25.03	11.45–54.73	<0.01
Pack-years of cigarette smoking			
Nonsmoker	1.0 (reference)		
≤20 pack-years	1.35	0.84–2.17	0.17
>20 pack-years	1.01	0.55–1.83	0.99
Heavy drinking status			
Nondrinker	1.0 (reference)		
<60 mL of ethanol per day	3.57	2.03–6.31	<0.01
≥60 mL of ethanol per day	6.03	2.89–12.59	<0.01
≥2 metabolic factors[b]			
No	1.0 (reference)		
Yes	1.39	1.24–1.65	<0.01

Notes: [a]Chronic viral hepatitis infection with hepatitis B virus or hepatitis C virus. [b]Metabolic factors included hypertension, hyperlipidemia, and obesity.

Table 3 shows the independent and joint effects of heavy alcohol consumption (≥60 mL of ethanol per day), viral hepatitis infection, and type 2 DM. In the whole study population, the combined effects of viral hepatitis and type 2 DM, viral hepatitis infection and heavy alcohol consumption, and type 2 DM and heavy alcohol consumption were greater than the sum of the individual effects. Specifically, we observed synergism for all 3 pairwise interactions. These interactions fit the assumption of additive scales. The estimated synergism index indicated a departure from additivity for all 3 interactions. For example, viral hepatitis, in addition to its own direct effects, may exacerbate the effects of type 2 DM on HCC risk. When we estimated the independent and joint effects of heavy alcohol consumption and type 2 DM in the absence of viral hepatitis infection on HCC risk, we continued to observe a departure from additivity as indicated by a synergism index of 1.15 (95% CI, 1.05–3.53).

The association of age at onset and duration of type 2 DM with the odds of HCC development are presented in Table 4. In the whole study population, individuals who had type 2 DM had higher odds of HCC development than did those without DM (duration, 11–20 years: AOR 2.56 [95% CI, 1.56–11.85; $P = 0.03$]; duration, >20 years: AOR 4.18 [95% CI, 1.74–23.66; $P = 0.01$]). This indicates a dose response, in which an increased duration of type 2 DM is associated with increased odds of HCC development. Age at type 2 DM onset was not associated with HCC development.

Table 3 Interaction of Type 2 Diabetes Mellitus (DM), Heavy Alcohol Consumption (≥60 mL of Ethanol per Day), and Chronic Viral Hepatitis Infection (Hepatitis B Virus or Hepatitis C Virus) in the Whole Study Population (HCC Cases; n=241 and Controls; n=500) and Nonviral Population (HCC Cases; n=151 and Controls; n=490)

Interaction variables		Case/control	Adjusted odds ratio[a]	95% CI	*P*	Synergy index (95% CI)[b]
Whole study population						
Viral hepatitis	**Type 2 DM**					
Negative	Negative	79/332	1.0 (reference)			3.52 (2.21–6.94)
Positive	Negative	7/41	16.56	6.38–43.00	<0.01	
Negative	Positive	72/158	2.18	1.29–3.70	<0.01	
Positive	Positive	49/3	59.92	15.71–228.47	<0.01	
Viral hepatitis	**Alcohol**					
Negative	Negative	116/444	1.0 (reference)			2.61 (1.33–5.86)
Positive	Negative	69/5	16.84	5.84–52.67	<0.01	
Negative	Positive	35/46	2.86	1.58–5.15	<0.01	
Positive	Positive	21/5	47.27	16.64–134.32	<0.01	
Alcohol	**Type 2 DM**					
Negative	Negative	19/148	1.0 (reference)			2.26 (1.11–4.90)
Positive	Negative	101/190	2.96	1.65–5.18	<0.01	
Negative	Positive	37/80	2.96	1.12–7.30	<0.01	
Positive	Positive	84/81	9.88	4.67–25.56	<0.01	
Nonviral population (no chronic viral hepatitis infection)						
Alcohol	**Type 2 DM**					
Negative	Negative	8/147	1.0 (reference)			1.15 (1.05–3.53)
Positive	Negative	71/184	7.74	1.98–14.71	<0.01	
Negative	Positive	19/78	5.40	3.22–18.57	<0.01	
Positive	Positive	53/80	13.82	5.24–36.40	0.04	

Notes: [a]Odds ratio adjusted for the confounding effect of age, sex, education level, pack-year cigarette smoking, heavy alcohol consumption, viral hepatitis status, family history of cancer, and metabolic factors. [b] S = Synergy index = $(OR_{11} - 1)/(OR_{01} + OR_{10} - 2)$, where OR_{11} = odds ratio of the joint effect of two risk factors; and OR_{01} and OR_{10} = OR of each risk factor in the absence of the other.

Table 4 Association Between Type 2 Diabetes Mellitus Age (DM) of Onset and Duration with Development of Hepatocellular Carcinoma (HCC) in the Whole Study Population and in a Restricted Analysis of Persons Who Had Been Diagnosed with Type 2 Diabetes Mellitus for at Least 1 Year Before Diagnosis of HCC (HCC Cases; n=126) or Recruitment (Controls; n=147)

Variable	HCC Cases No. (%)	Controls No. (%)	Adjusted Odds Ratio[a]	95% CI	*P*
Whole study population					
Type 2 DM age of onset					
Nondiabetics	120 (50.6)	339 (69.8)	1.0 (reference)		
≤50 years	57 (24.1)	82 (16.9)	1.74	0.16–3.42	0.70
>50 years	60 (25.3)	65 (13.4)	2.08	0.55–7.89	0.28
Duration of type 2 DM					
Nondiabetics	120 (50.6)	339 (69.8)	1.0 (reference)		
2–10 years	45 (19.0)	88 (18.1)	1.12	0.29–4.45	0.88
11–20 years	44 (18.6)	42 (8.6)	2.56	1.56–11.85	0.03
>20 years	28 (11.8)	17 (3.5)	4.18	1.74–23.66	0.01

(*Continued*)

Table 4 (Continued).

Variable	HCC Cases No. (%)	Controls No. (%)	Adjusted Odds Ratio[a]	95% CI	*P*
Restricted analysis among persons with type 2 DM					
Type 2 DM age of onset					
>50 years	60 (51.3)	65 (44.2)	1.0 (reference)		
≤50 years	57 (48.7)	82 (55.8)	0.44	0.15–1.28	0.13
Duration of type 2 DM					
2–10 years	45 (38.5)	88 (59.9)	1.0 (reference)		
11–20 years	44 (37.6)	42 (28.6)	2.76	0.96–7.88	0.06
>20 years	28 (23.9)	17 (11.6)	4.60	1.01–20.87	0.04

Notes: [a]Odds ratio adjusted for the confounding effects of age, sex, education level, pack-years of cigarette smoking, heavy alcohol consumption, viral hepatitis status, family history of cancer, and metabolic factors.

To ensure that DM was not induced by HCC, we analyzed of the association between type 2 DM and HCC only for those diagnosed with type 2 DM for more than 1 year before HCC diagnosis or before recruitment as a control participant (126 HCC patients and 147 control participants) (Table 4). Compared with those who had had type 2 DM for 2–10 years, the estimated AOR for those who had had type 2 DM for more than 20 years was 4.60 (95% CI, 1.01–20.87; $P = 0.04$). As in the whole study population, age at type 2 DM onset was not associated with odds of HCC development in the restricted analysis.

Using Kaplan-Meier, median survival was 12.0 months (95% CI, 8.8–15.2) for all HCC patients and 15.0 months (95% CI, 12.6–19.5) for HCC patients with type 2 DM (Supplementary Figures 1A and 1B). HCC patients with type 2 DM taking metformin had a better median overall survival than patients not taking metformin (16.0 months [95% CI, 12.6–19.3] vs 8.0 months [95% CI, 4.5–11.5], $P = 0.04$) (Supplementary Figure 1C). Results of the multivariable Cox proportional hazards regression analysis of OS for participants with type 2 DM and HCC are shown in Table 5. Metformin use, TNM stage, Eastern Cooperative Oncology Group performance status, and type of baseline treatment of HCC were significant predictors of OS in this subpopulation. Metformin use was associated with a 28% decrease in the risk of death in HCC patients with type 2 DM (adjusted HR, 0.72 [95% CI, 0.58–0.92]; $P = 0.01$). However, when compared with the whole study population, metformin use was not significantly associated with survival (adjusted HR,

Table 5 Cox Proportional Hazards Regression Results for Overall Survival in Mexican Americans with Type 2 Diabetes Mellitus and Hepatocellular Carcinoma (HCC Cases; N=126)

Variable	No.	Death	AHR (95% CI)[a]	*P*
Metformin use				
No	16	16	1.0 (reference)	
Yes	105	92	0.72 (0.58–0.92)	0.01
Vascular invasion				
No	95	87	1.0 (reference)	
Yes	24	20	2.09 (0.95–4.61)	0.07
Cirrhosis				
No	39	34	1.0 (reference)	
Yes	82	74	1.18 (0.53–1.62)	0.12
Portal thrombosis				
No	104	94	1.0 (reference)	
Yes	15	13	1.59 (0.33–2.63)	0.10
Tumor involvement				
≤50%	84	75	1.0 (reference)	
>50%	29	27	1.24 (0.79–1.97)	0.46

(*Continued*)

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Table 5 (Continued).

Variable	No.	Death	AHR (95% CI)[a]	*P*
Extrahepatic metastasis				
No	27	24	1.0 (reference)	
Yes	94	84	0.99 (0.55–1.80)	0.99
Nodularity				
Single	47	41	1.0 (reference)	
Multiple	71	65	1.36 (0.92–2.00)	0.12
TNM Staging				
I–II	42	37	1.0 (reference)	
III	33	31	1.29 (0.78–2.12)	0.32
IV	39	34	1.85 (1.06–3.22)	0.03
ECOG[b]				
0	65	54	1.0 (reference)	
1–2	155	139	1.66 (1.09–2.51)	0.02
3–4	18	16	2.72 (1.27–5.80)	0.01
Baseline Treatment				
Supportive	31	30	1.0 (reference)	
Surgery	7	6	0.38 (0.15–0.94)	0.04
Ablation	6	2	0.24 (0.08–0.70)	0.01
Local	33	30	0.42 (0.25–0.70)	<0.01
Systemic	42	39	0.53 (0.33–0.83)	0.01

Notes: [a]AHR=adjusted hazard ratio. Adjusted for the confounding effects of age, sex, education level, pack-years of cigarette smoking, heavy alcohol consumption, viral hepatitis status, family history of cancer, and metabolic factors. [b]Eastern Cooperative Oncology Group performance status.

0.97 [95% CI, 0.76–1.23]; $P = 0.79$) (Supplementary Table 1). Vascular invasion, cirrhosis, portal thrombosis, tumor involvement, and extrahepatic metastasis were not significantly associated with OS for patients with type 2 DM, but they were in the whole population (Supplementary Table 1).

Discussion

The present case-control study is the first of its kind to be conducted in Mexican Americans. Specifically, it highlights the association between HCC and a detailed history of type 2 DM including disease duration, co-occurrence of type 2 DM with other metabolic factors, interactions of type 2 DM with viral hepatitis infection and alcohol consumption, correlation of HCC risk factors with cirrhosis, and treatment of DM. In this large case-control study, we highlighted the impact of type 2 DM and obesity on HCC development among Mexican Americans. We observed that the presence of 2 or more metabolic factors (ie, hypertension, hyperlipidemia, obesity) is significantly associated with HCC. Notable findings in our study were the increased odds of HCC development in individuals who have had type 2 DM at least 11 years and up to 4-fold increase in the odds of it in those who had type 2 DM for more than 20 years. These results are consistent with the literature[33–35] and they fill a gap in knowledge by providing information about HCC risk and prognosis for the Hispanic population, who have higher HCC incidence and mortality than do the Asian and non-Hispanic White populations in the United States.[5]

It is estimated that HCC is explained by MS in 32% of Mexican American patients.[36] Moreover, we previously highlighted the significance of the duration of DM regarding the risk of HCC development.[30] This suggests that type 2 DM is not an epiphenomenon of HCC diagnosis but rather is an etiological factor. The role of a DM duration greater than 10 years on HCC risk was further highlighted in a meta-analysis performed by Wang et al.[37]

In addition to the independent impact of type 2 DM as a main factor in MS, our finding that the presence of 2 or more metabolic factors, including obesity or hypertension, was associated with increased odds of HCC development, regardless of the presence of other major HCC risk factors was not surprising. MS may play a role in cell growth, proliferation, fatty degeneration,

and tumorigenesis of the hepatocytes.[38] Due to the frequent co-occurrence of metabolic conditions, their interplay complicates investigation of each metabolic factor's individual contribution to chronic liver disease and hepatocarcinogenesis.[11]

The impact of type 2 DM on HCC among American Hispanics extends to modification of its risk by alcohol consumption or past exposure to chronic viral infection. A population-based case-control study conducted in California among Hispanic and African American populations demonstrated independent synergistic effects of these pair-wise interactions on the risk of HCC in Los Angeles County that were similar to our results.[39]

Although the biological mechanisms involving type 2 DM or MS and HCC are not fully understood and difficult to elucidate, it has been reported that hyperinsulinemia, hyperglycemia, chronic inflammation, cell growth, proliferation, fatty degeneration, and tumorigenesis of the hepatocytes are involved in HCC development.[34] Several explanations have been proposed to confirm the risk modification of type 2 DM risk by other HCC risk factors. For example, epidemiological and clinical studies revealed that patients with chronic HCV infections have a higher prevalence of glucose intolerance than does the general population.[40] Also, insulin resistance in an HCV-infected patient is associated with excess liver fat and iron deposition.[41] A fatty liver with high iron deposits may lead to a synergistic effect of viral and metabolic factors causing hepatocarcinogenesis.[40] A growing body of evidence demonstrates that metabolic risk factors, including type 2 DM and obesity, are associated with progression of chronic liver disease, especially in the presence of HCV infection owing to associations with insulin resistance and steatosis.[42] A study in Japan demonstrated a 1.7-fold increase in the development of HCC in HCV-infected patients with type 2 DM.[43]

Unlike the relationship between type 2 DM and HCV infection, the relationship between type 2 DM and hepatitis B virus related HCC remains unclear, with very few studies investigating the potential mechanisms underlying this association. Instead, more studies have focused on HCV-related HCC because of its strong association with insulin resistance.[40,44] The literature reported that prevalence of type 2 DM was lower in hepatitis B virus-infected than in HCV-infected individuals or was similar in the 2 groups.[44] With regards to heavy alcohol consumption and type 2 DM, oxidative stress has been implicated to have a role in the pathogenesis and complications of DM owing to hyperglycemia.[35,39] Alcohol-induced oxidative stress may increase the susceptibility of patients with type 2 DM to cirrhosis, DNA damage, and HCC.[35]

We confirmed pathological and radiological evidence of cirrhosis in 72.6% of the HCC cases in the present study, which was consistent with the prevalence in our previous study among non-Hispanic populations.[45] Despite the potential complications of type 2 DM induced fatty liver disease and progression to cirrhosis, only 13.7% of the cirrhosis-induced HCC patients in our study had a history of type 2 DM, a proportion similar to that in non-cirrhosis related-HCC patients (14.7%). This may suggest that the underlying chronic liver disease progression and cirrhosis development is not the only pathway for HCC development, and that other biological mechanisms are involved.

Although evidence that type 2 DM is significantly related to poor survival of HCC patients is lacking,[46] treatment of type 2 DM with biguanides was associated with reduced mortality of HCC.[30] The observed protective role of metformin regarding HCC survival in the present study was consistent with our previous report[30] and those by other investigators.[47–50] In fact, the association between use of metformin and reduced mortality was documented for other cancers, including pancreatic and colorectal cancers.[51,52] Such a risk reduction was associated with the duration and dosage of metformin treatment.[47] The improved survival of HCC in patients who received metformin in our study may be related to reduced circulating levels of insulin. Bowker et al reported that patients with type 2 DM exposed to metformin had a lower risk of cancer-related mortality than did patients who received exogenous insulin and sulfonylureas.[53] Furthermore, pre-clinical evidence has revealed metformin to have an immunomodulatory effect on cancer cells through observed inhibition of proliferation and induction of cell cycle arrest and apoptosis in HCC cells.[54,55] Future research with prospective trials on understanding the potential benefits of metformin as a therapeutic agent is needed.

The median overall survival in the Mexican American HCC patient population was consistent with other reports in Hispanic patients with HCC.[18,56] Evidence suggests that Hispanic ethnicity remains a significantly independent predictor of HCC-related mortality.[56] One possible explanation for this finding may be the disparity in access to proper screening and treatment availability for Hispanic patients diagnosed with HCC.[56,57] Our study confirmed that baseline treatment plays a significant role in reducing HCC mortality; therefore, future research on the impact of cancer therapy, with detailed information about treatment type, on the clinical outcome of HCC, is highly warranted among minority patients.

Despite the strong association of type 2 DM and MS with HCC risk in individuals all races and ethnicities, the American Association for the Study of Liver Diseases guidelines for HCC surveillance do not recommend screening patients with MS for early detection of HCC.[58] Instead, surveillance is restricted to those with underlying cirrhosis. Only

13.7% of the HCC patients with type 2 DM in our study had cirrhosis, which is comparable with previous reports.[59,60] Risk stratification of type 2 DM patients without cirrhosis in the Hispanic population may be warranted. Genetic predisposition for HCC may redefine the population of HCC patients with type 2 DM at risk for HCC who should be screened for it. We recently highlighted the role of genetic susceptibility of HCC in the absence of viral infection among non-Hispanic White individuals with significant interaction with type 2 DM.[61] Future genetic studies of Hispanics in the absence of viral infections may assist in defining the high-risk populations among Hispanics with type 2 DM and modification of the American Association for the Study of Liver Diseases guidelines for HCC screening.

In conclusion, our study provides important data on the risk and prognosis of HCC in Mexican Americans. Hispanic patients present with higher rates of comorbidities and more advanced liver disease compared to White HCC patients, thus leading to increased mortality in this group. This may be explained by a combination of metabolic risk factors, evidence of cirrhosis, and other environmental factors like viral hepatitis infection and alcohol consumption.

Abbreviations

AOR, adjusted odds ratio; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver; MS, metabolic syndrome; OS, overall survival; HR, hazard ratio; PAR, population attributable risk.

Data Sharing Statement

Raw data that support the findings of this study are available from the corresponding author, upon request.

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Author Contributions

All authors made significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects to the work.

Statement of Ethics

This study included patients with HCC involved in an active epidemiological study and healthy controls from the Mano a Mano Mexican American Cohort Study approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Written informed consent was obtained from each participant enrolled in the study. This study complies with the Declaration of Helsinki.

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Disclosure

The authors have no conflicts of interest to declare.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379:1245–1255. doi:10.1016/S0140-6736(11)61347-0
2. Ramirez AG, Munoz E, Holden AE, Adeigbe RT, Suarez L. Incidence of hepatocellular carcinoma in Texas Latinos, 1995-2010: an update. *PLoS One*. 2014;9:e99365. doi:10.1371/journal.pone.0099365

3. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med*. 2003;139:817–823. doi:10.7326/0003-4819-139-10-200311180-00009
4. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19:223–238. doi:10.1016/j.cld.2015.01.001
5. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol*. 2014;109:542–553. doi:10.1038/ajg.2014.11
6. Ha J, Yan M, Aguilar M, et al. Race/ethnicity-specific disparities in cancer incidence, burden of disease, and overall survival among patients with hepatocellular carcinoma in the United States. *Cancer*. 2016;122:2512–2523. doi:10.1002/cncr.30103
7. Carrilho FJ, Paranaguá-Vezozzo DC, Chagas AL, Alencar R, da Fonseca LG. Epidemiology of Liver Cancer in Latin America: current and Future Trends. *Semin Liver Dis*. 2020;40:101–110. doi:10.1055/s-0039-3399561
8. Shiels MS, O'Brien TR. Recent Decline in Hepatocellular Carcinoma Rates in the United States. *Gastroenterology*. 2020;158:1503–1505.e2. doi:10.1053/j.gastro.2019.12.030
9. Ellis L, Canchola AJ, Spiegel D, et al. Racial and Ethnic Disparities in Cancer Survival: the Contribution of Tumor, Sociodemographic, Institutional, and Neighborhood Characteristics. *J Clin Oncol*. 2018;36:25–33. doi:10.1200/JCO.2017.74.2049
10. Farvardin S, Patel J, Khambaty M, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. *Hepatology*. 2017;65:875–884. doi:10.1002/hep.28770
11. Welzel TM, Graubard BI, Zeuzem S, et al. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology*. 2011;54:463–471. doi:10.1002/hep.24397
12. Saunders D, Seidel D, Allison M, Lyratzopoulos G. Systematic review: the association between obesity and hepatocellular carcinoma - epidemiological evidence. *Aliment Pharmacol Ther*. 2010;31:1051–1063. doi:10.1111/j.1365-2036.2010.04271.x
13. Campbell PT, Newton CC, Freedman ND, et al. Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults. *Cancer Res*. 2016;76:6076–6083. doi:10.1158/0008-5472.CAN-16-0787
14. Chen Y, Wang W, Morgan MP, Robson T, Annett S. Obesity, non-alcoholic fatty liver disease and hepatocellular carcinoma: current status and therapeutic targets. *Front Endocrinol*. 2023;14:1148934. doi:10.3389/fendo.2023.1148934
15. Phoolchund AGS, Khakoo SI. MASLD and the Development of HCC: pathogenesis and Therapeutic Challenges. *Cancers*. 2024;16(2):259. doi:10.3390/cancers16020259
16. Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77:1335–1347. doi:10.1097/HEP.0000000000000004
17. Kirk JK, Passmore LV, Bell RA, et al. Disparities in A1C levels between Hispanic and non-Hispanic white adults with diabetes: a meta-analysis. *Diabetes Care*. 2008;31:240–246. doi:10.2337/dc07-0382
18. Pomenti S, Gandle C, Abu Sbeih H, et al. Hepatocellular Carcinoma in Hispanic Patients: trends and Outcomes in a Large United States Cohort. *Hepatol Commun*. 2020;4:1708–1716. doi:10.1002/hep4.1575
19. Suro R, Passel JS. *The Rise of the Second Generation: Changing Patterns in Hispanic Population Growth*. ERIC; 2003.
20. Garza AL, Vatcheva KP, Pan -J-J, et al. Liver and Other Gastrointestinal Cancers Are Frequent in Mexican Americans. *J Racial Ethn Health Disparities*. 2016;3:1–10. doi:10.1007/s40615-015-0104-0
21. Alvarez CS, Petrick JL, Parisi D, et al. Racial/ethnic disparities in hepatocellular carcinoma incidence and mortality rates in the United States, 1992-2018. *Hepatology*. 2022;76:589–598. doi:10.1002/hep.32394
22. Ajayi F, Jan J, Singal AG, Rich NE. Racial and Sex Disparities in Hepatocellular Carcinoma in the USA. *Curr Hepatol Rep*. 2020;19:462–469. doi:10.1007/s11901-020-00554-6
23. Vidal AC, Moylan CA, Wilder J, et al. Racial disparities in liver cancer: evidence for a role of environmental contaminants and the epigenome. *Front Oncol*. 2022;12:959852. doi:10.3389/fonc.2022.959852
24. Shen J, Hernandez D, Ye Y, et al. Metabolic hormones and breast cancer risk among Mexican American Women in the Mano a Mano Cohort Study. *Sci Rep*. 2019;9:9989. doi:10.1038/s41598-019-46429-9
25. Chow W-H. Cohort Profile: the Mexican American Mano a Mano Cohort. *Int J Epidemiol*. 2017;46(2):e3. doi:10.1093/ije/dyv016
26. Spitz MR, Fueger JJ, Borrud LG, Newell GR. The development of a comprehensive, institution-based patient risk evaluation program: i. Development, content, and data management. *Am J Prev Med*. 1988;4:183–187. doi:10.1016/S0749-3797(18)31171-1
27. Spitz MR, Fueger JJ, Newell GR, Newell GR. The development of a comprehensive, institution-based patient risk evaluation program: II. Validity and reliability of questionnaire data. *Am J Prev Med*. 1988;4:188–193. doi:10.1016/S0749-3797(18)31172-3
28. Antwi SO, Craver EC, Nartey YA, Sartorius K, Patel T. Metabolic Risk Factors for Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease: a Prospective Study. *Cancers*. 2022;14(24):6234. doi:10.3390/cancers14246234
29. Rothman KJ. The estimation of synergy or antagonism. *Am J Epidemiol*. 1976;103:506–511. doi:10.1093/oxfordjournals.aje.a112252
30. Hassan MM, Curley SA, Li D, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. *Cancer*. 2010;116:1938–1946. doi:10.1002/cncr.24982
31. Hassan MM, Spitz MR, Thomas MB, et al. Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer*. 2008;123:1883–1891. doi:10.1002/ijc.23730
32. Hassan MM, Spitz MR, Thomas MB, et al. The association of family history of liver cancer with hepatocellular carcinoma: a case-control study in the United States. *J Hepatol*. 2009;50:334–341. doi:10.1016/j.jhep.2008.08.016
33. Li X, Wang X, Gao P. Diabetes Mellitus and Risk of Hepatocellular Carcinoma. *Biomed Res Int*. 2017;2017:5202684. doi:10.1155/2017/5202684
34. Setiawan VW, Hernandez BY, Lu SC, et al. Diabetes and racial/ethnic differences in hepatocellular carcinoma risk: the multiethnic cohort. *J Natl Cancer Inst*. 2014;106:dju326–dju326. doi:10.1093/jnci/dju326
35. Hassan MM, Hwang L-Y, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*. 2002;36:1206–1213. doi:10.1053/jhep.2002.36780
36. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–359. doi:10.1001/jama.287.3.356
37. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Int J Cancer*. 2012;130:1639–1648. doi:10.1002/ijc.26165

38. Berzigotti A, Abraldes JG. Impact of obesity and insulin-resistance on cirrhosis and portal hypertension. *Gastroenterol Hepatol*. 2013;36:527–533. doi:10.1016/j.gastrohep.2013.03.005
39. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. *Cancer*. 2004;101:1009–1017. doi:10.1002/cncr.20427
40. Kawaguchi Y, Mizuta T. Interaction between hepatitis C virus and metabolic factors. *World J Gastroenterol*. 2014;20:2888–2901. doi:10.3748/wjg.v20.i11.2888
41. Petit JM, Bour J-B, Galland-Jos C, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol*. 2001;35:279–283. doi:10.1016/S0168-8278(01)00143-X
42. Fujii H, Kawada N, Japan Study Group Of Nafld J-N. The Role of Insulin Resistance and Diabetes in Nonalcoholic Fatty Liver Disease. *Int J Mol Sci*. 2020;21:3863. doi:10.3390/ijms21113863
43. Arase Y, Kobayashi M, Suzuki F, et al. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology*. 2013;57:964–973. doi:10.1002/hep.26087
44. Papatheodoridis GV, Chrysanthos N, Savvas S, et al. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepat*. 2006;13:303–310. doi:10.1111/j.1365-2893.2005.00677.x
45. Hassan MM, Abdel-Wahab R, Kaseb A, et al. Obesity Early in Adulthood Increases Risk but Does Not Affect Outcomes of Hepatocellular Carcinoma. *Gastroenterology*. 2015;149:119–129. doi:10.1053/j.gastro.2015.03.044
46. Howell J, Yiu M, Gibson R, et al. Type 2 diabetes does not worsen prognosis in hepatocellular carcinoma. *Clin Res Hepatol Gastroenterol*. 2011;35:214–220. doi:10.1016/j.clinre.2010.11.002
47. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005;330 (7503):1304–1305. doi:10.1136/bmj.38415.708634.F7
48. Libby G, Donnelly LA, Donnan PT, et al. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care*. 2009;32:1620–1625. doi:10.2337/dc08-2175
49. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;52:1766–1777. doi:10.1007/s00125-009-1440-6
50. Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. *Ann Transl Med*. 2017;5:270. doi:10.21037/atm.2017.04.41
51. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clin Cancer Res*. 2012;18:2905–2912. doi:10.1158/1078-0432.CCR-11-2994
52. Tarhini Z, Manceur K, Magne J, et al. The effect of metformin on the survival of colorectal cancer patients with type 2 diabetes mellitus. *Sci Rep*. 2022;12:12374. doi:10.1038/s41598-022-16677-3
53. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care*. 2006;29:254–258. doi:10.2337/diacare.29.02.06.dc05-1558
54. Chae YK, Arya A, Malecek M-K, et al. Repurposing metformin for cancer treatment: current clinical studies. *Oncotarget*. 2016;7:40767–40780. doi:10.18632/oncotarget.8194
55. Cunha Júnior AD, Bragagnoli AC, Costa FO, Carvalheira JBC. Repurposing metformin for the treatment of gastrointestinal cancer. *World J Gastroenterol*. 2021;27:1883–1904. doi:10.3748/wjg.v27.i17.1883
56. Younossi ZM, Stepanova M. Hepatitis C virus infection, age, and Hispanic ethnicity increase mortality from liver cancer in the United States. *Clin Gastroenterol Hepatol*. 2010;8:718–723. doi:10.1016/j.cgh.2010.04.017
57. Rich NE, Carr C, Yopp AC, Marrero JA, Singal AG. Racial and Ethnic Disparities in Survival Among Patients With Hepatocellular Carcinoma in the United States: a Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol*. 2022;20:e267–e288. doi:10.1016/j.cgh.2020.12.029
58. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78:1922–1965. doi:10.1097/HEP.0000000000000466
59. García-Compeán D, Jáquez-Quintana JO, Lavalle-González FJ, et al. The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis. A prospective study. *Ann Hepatol*. 2012;11:240–248. doi:10.1016/S1665-2681(19)31030-0
60. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol*. 2000;32:209–217. doi:10.1016/S0168-8278(00)80065-3
61. Hassan MM, Li D, Han Y, et al. Genome-wide association study identifies high-impact susceptibility loci for hepatocellular carcinoma in North America. *Hepatology*. 2024. doi:10.1097/HEP.0000000000000800