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ARTICLE

Diabetes and Racial/Ethnic Differences in Hepatocellular Carcinoma Risk: The Multiethnic Cohort

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Background Diabetes is an emerging risk factor for hepatocellular carcinoma (HCC), but prospective data from different ethnic populations are scarce. We examined the association between diabetes and HCC in 168 679 African Americans, Native Hawaiians, Japanese Americans, Latinos and whites in the Multiethnic Cohort.

Methods During a 15.7-year follow up period, 470 incident HCC cases were identified. Risk factor data were obtained from the baseline questionnaire. Cox regressions were used to calculate hazard rate ratios (RRs) and 95% confidence intervals (CIs) for HCC associated with self-reported diabetes. The population attributable risk percent associated with diabetes was also calculated. All statistical tests were two-sided.

Results The RRs for developing HCC (vs whites) were 2.73 (95% CI = 2.00 to 3.72) for Latinos, 2.48 (95% CI = 1.59 to 3.87) for Hawaiians, 2.16 (95% CI = 1.52 to 3.07) for African Americans, and 2.05 (95% CI = 1.50 to 2.81) for Japanese. Diabetes was associated with HCC across ethnic groups ($RR_{Latinos}$ = 3.36 [95% CI = 2.41 to 4.70], $RR_{Hawaiians}$ = 2.50 [95% CI = 1.11 to 5.64], $RR_{Japanese}$ = 2.34 [95% CI = 1.60 to 3.41], RR_{whites} = 2.15 [95% CI = 0.95 to 4.90], and $RR_{African\ Americans}$ = 2.02 [95% CI = 1.17 to 3.48]). We estimated that 27% of HCC cases in Latinos, 18% in Hawaiians, 13% in African Americans, 12% in Japanese, and 6% in whites were attributed to diabetes.

Conclusions Latinos were at the highest risk of developing HCC, followed by Native Hawaiians, African Americans, Japanese and whites. Diabetes is a risk factor for HCC in all ethnic groups, and eliminating diabetes could potentially reduce HCC incidence in all ethnic groups, with the largest potential for reduction in Latinos.

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Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults and one of the most deadly cancers with a dismal five-year survival rate of approximately 16%. HCC is the fifth most common cancer in men worldwide and the second leading cause of cancer deaths (1). The HCC incidence in the United States has tripled over the past three decades (2). Among all major cancers, HCC has shown the single greatest annual percent increase in mortality (3). In 2013, HCC accounted for more than 21 000 deaths in the United States (3).

Racial/ethnic differences in HCC incidence have been consistently observed with excess rates seen among Asians/Pacific Islanders, Hispanics and African Americans (2,4–6). While all racial/ethnic groups in the US have been experiencing an increase in HCC incidence, Hispanics and African Americans have experienced the greatest increase over the past four decades (7,8), creating an emerging and important health disparity.

Diabetes mellitus (diabetes for short) is a suspected emerging risk factor for HCC (9), and the rapidly increasing prevalence of diabetes may contribute to the rising incidence of HCC. The prevalence of diabetes is particularly high in Hispanics and African Americans (10), but diabetes' contribution to HCC incidence in these high-risk populations and other minority populations is unknown. In this study, we examined whether the association between diabetes and HCC risk differ in African Americans, Japanese Americans, Native Hawaiians, Latinos, and whites.

Methods

Study Population

The Multiethnic Cohort (MEC) is an ongoing population-based prospective cohort study with over 215 000 men and women from Hawaii and California (mainly Los Angeles County), assembled between 1993 and 1996. The MEC was established to study dietary, environmental and genetic risk factors for cancer and other

chronic diseases. The details of the study design and baseline characteristics have been published (11). Briefly, the cohort is comprised predominantly of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Caucasians (aged 45 to 75 years at recruitment). All participants returned a self-administered baseline questionnaire that obtained information on demographic and lifestyle factors, physical activity, tobacco smoking history, diet, anthropometric measures, personal history of medical conditions, medication use, family history of cancer, as well as reproductive history and hormone use (women only). Diabetes status is defined based on self-report to a question on the baseline questionnaire asking whether a doctor had ever told the respondent that he/she had diabetes (high blood sugar). This question did not differentiate between type 1 and type 2 diabetes, but based on a previous assessment in the MEC (12), a small fraction (<3%) of the identified diabetes case patients have type 1 diabetes. The Institutional Review Boards at the University of Hawaii and at the University of Southern California approved the study protocol.

Case Ascertainment

Incident HCC case patients (International Classification of Diseases for Oncology version 3 topographic [C22.0] and morphology codes [8170–8175]) were identified through annual linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry; these cancer registries are part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Deaths within the cohort were determined through annual linkage to state death certificate files in California and Hawaii, and periodic linkage to the National Death Index. Case ascertainment and death information were complete through December 31, 2009 (Hawaii) and December 31, 2010 (Los Angeles). A total of 470 incident cases of HCC were identified during the follow-up period among the at-risk cohort.

Hepatitis B and C Serology

Between 2001 and 2006, the MEC collected blood samples from the cohort participants (n > 60 000). We conducted a nested case-control study of HCC within the biospecimen subcohort for serological markers of hepatitis B and C infection. All incident cases of HCC with a prediagnostic blood sample and the diagnosis of HCC before December 31, 2010 were eligible for this nested case-control study. For each case, two to three control patients matched to the index case by sex, race/ethnicity, study area (Hawaii or California), and age at blood draw, who were free of HCC on the date of cancer diagnosis of the index case, were selected from the biospecimen subcohort. We assayed serological markers of hepatitis B and C virus in blood samples of 152 case patients and 460 control patients. The presence of HBsAg, anti-HBc, and anti-HCV (Architect Assays, Abbott Laboratories, North Chicago, IL) was tested blindly without regard to case-control status.

Statistical Analysis

Participants reporting implausible diet based on macronutrient intakes (13) (n = 3585) or those with a cancer diagnosis (except for nonmelanoma skin cancer) before baseline (n = 19 190) were excluded from this analysis. We also excluded participants with missing baseline information on diabetes, education, body mass index (BMI), smoking status, and alcohol intake (n = 10 381). As a result, data on 168 679 participants (24.3% whites, 16.5% African Americans, 7.3% Native Hawaiians, 29.1% Japanese Americans, and 22.8% Latinos) were available for this analysis. Excluded subjects were similar to those who remained in the analyses with respect to age and distribution of HCC risk factors. Data on diabetes, education level, BMI, smoking status, and alcohol intake were obtained from the baseline questionnaire. Hazard rate ratios (RRs) and 95% confidence intervals (CIs) for HCC incidence associated with race/ethnicity and diabetes were calculated using Cox proportional hazard models. Age (in days) was used as the underlying time variable in the Cox regression starting with a participant's age at entry (baseline questionnaire completion) and ending with the earliest of these endpoints: date of HCC diagnosis, date of death, or end of follow-up (December 31, 2009 in Hawaii or December 31, 2010 in Los Angeles). Cox models for the diabetes-HCC association were adjusted for sex (as a strata variable) and education (≤ high school, some college, college and above), BMI (<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), smoking status (never, former, current), and alcohol intake (nondrinkers, <2 drinks/day, ≥2 drinks/day). The proportional hazards assumption was tested by assessing the Schoenfeld residuals, and no major violation was observed. Incidence rates of HCC were calculated per 100 000 and age-standardized to the US 2000 standard population. The likelihood ratio test was used to test for statistical interaction between diabetes with smoking status, alcohol drinking, BMI, and hepatitis viral infection status with respect to HCC. The test compares models with the main effect only with models that also include interaction terms for variables of interest. The population attributable risk percentage was estimated by [P(RR-1)/P(RR-1)+1] where P is the prevalence of diabetes and RR is the multivariable RR associated with diabetes. All *P* values were

Table 1. Age-adjusted incidence rates of hepatocellular carcinoma and prevalence of diabetes by racial/ethnic groups

	White	African American	Native Hawaiian	Japanese	Latino	All groups
No. subjects	41 018	27 808	12 290	49 123	38 440	168 679
No. case patients	53	78	31	150	158	470
Mean age at diagnosis (SD), y	69.2 (7.8)	71.5 (9.1)	71.2 (8.7)	74.9 (7.9)	72.3 (6.9)	72.6 (8.0)
Incidence rate*	7.5	16.6	21.3	16.8	22.5	
RR† (95% CI)	1.00 (referent)	2.16 (1.52 to 3.07)	2.48 (1.59 to 3.87)	2.05 (1.50 to 2.81)	2.73 (2.00 to 3.72)	
Mean body mass index) (SD), kg/m^2	26.1 (4.7)	28.4 (5.4)	28.8 (5.7)	24.4 (3.7)	27.6 (4.6)	
Prevalence of diabetes§	5.6%	15.2%	14.3%	10.3%	15.4%	*P* < .001

* Rate per 100 000 and age-standardized to the United States 2000 standard population. CI = confidence interval; RR = hazard rate ratio.

† Adjusted by sex (as a strata variable) and age by Cox regression.

§ At baseline, standardized to the age and sex distribution of the at- risk cohort. *P* value was from two-sided χ^2 test.

two-sided; statistical significance was set at P less than .05. Statistical analyses were performed with SAS 9.2 software (SAS Institute, Inc., Cary, NC).

Results

After a median 15.7 years of follow-up, 470 incident cases of HCC (53 whites, 78 African Americans, 31 Native Hawaiians, 150 Japanese Americans, and 158 Latinos) were identified among the 168 679 at-risk cohort participants (Table 1). The mean age of diagnosis was 72.6 years (ranging from 69.2 in whites to 74.9 in Japanese Americans). The highest incidence rate of HCC was observed in Latinos (22.5 per 100 000), followed by Native Hawaiians (21.3), Japanese Americans (16.8), African Americans (16.6), and whites (7.5). Compared with whites, the age-adjusted RRs for HCC were 2.73 (95% CI = 2.00 to 3.72) for Latinos, 2.48 (95% CI = 1.59 to 3.87) for Native Hawaiians, 2.16 (95% CI = 1.52 to 3.07) for African Americans, and 2.05 (95% CI = 1.50 to 2.81) for Japanese. The mean BMI was highest in Native Hawaiians (28.8 kg/m^2), followed by African Americans (28.4 kg/m^2), Latinos (27.6 kg/m^2), whites (26.1 kg/m^2), and Japanese (24.4 kg/m^2). The prevalence of diabetes in the cohort varied across ethnic groups (P < .001), with the highest prevalence in Latinos (15.4%) and African Americans (15.2%), followed by Native Hawaiians (14.3%) and Japanese Americans (10.3%), with the lowest prevalence in whites (5.6%).

Table 2 shows selected baseline characteristics among participants according to diabetes status. The diabetics were older, were less educated, had higher BMIs, consumed less alcohol, and were more likely to be former smokers than the nondiabetics (P < .001).

Table 2. Distributions of selected baseline characteristics in subjects with or without a history of diabetes at baseline

Characteristics*	Nondiabetics n = 149398	Diabetics n = 19281
Age at cohort entry		
Mean (SD), y	59.7 (8.8)	62.5 (8.1)
Sex		
Men	68 472 (45.8)	9620 (49.9)
Women	80 926 (54.2)	9661 (50.1)
Education		
High school	62 878 (42.1)	10 740 (55.7)
Some college	44 672 (29.9)	5166 (26.8)
College and above	41 848 (28.0)	3375 (17.5)
Body mass index, kg/m^2		
Normal/underweight (<25)	64 877 (43.4)	4947 (25.7)
Overweight (25 to <30)	57 674 (38.6)	7711 (40.0)
Obese (≥30)	26 847 (18.0)	6623 (34.4)
Smoking history		
Never	66 700 (44.6)	7722 (40.1)
Former	58 036 (38.8)	8796 (45.6)
Current	24 662 (16.5)	2763 (14.3)
Alcohol intake		
Non drinkers	72 094 (48.3)	13 360 (69.3)
<2 drinks/day	59 084 (39.6)	4760 (24.7)
≥ 2 drinks/day	18 220 (12.2)	1161 (6.0)

* All characteristics were significantly different at P < .001 between nondiabetics and diabetics, as tested by two-sided t test for continuous and two-sided χ^2 test for categorical measures.

Table 3. Association between diabetes and hepatocellular carcinoma by racial/ethnic groups

	White		African American		Native Hawaiian		Japanese American		Latino	
	No. Case patients	RR* (95% CI)	No. Case patients	RR* (95% CI)	No. Case patients	RR* (95% CI)	No. Case patients	RR* (95% CI)	No. Case patients	RR* (95% CI)
Diabetes										
No	46	1.00 (referent)	60	1.00 (referent)	22	1.00 (referent)	113	1.00 (referent)	99	1.00 (referent)
Yes	7	2.15 (0.95 to 4.90)	18	2.02 (1.17 to 3.48)	9	2.50 (1.11 to 5.64)	37	2.34 (1.60 to 3.41)	59	3.36 (2.41 to 4.70)
		P = .07		P = .01		P = .03		P < .001		P < .001

* Hazard rate ratios adjusted for sex (as a strata variable) and for education (≤ high school, some college, college and above), body mass index (<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), smoking status (never, former, current), and alcohol intake (nondrinkers, <2 drinks/day, ≥2 drinks/day) by Cox regression using age as the time metric. All statistical tests were two-sided. CI = confidence intervals; RR = hazard rate ratio.

A history of diabetes was associated with a more than two- to three-fold HCC risk across the five racial/ethnic groups (Table 3). The RR was 3.36 (95% CI = 2.41 to 4.70) in Latinos, 2.50 (95% CI = 1.11 to 5.64) in Hawaiians, 2.34 (95% CI = 1.60 to 3.41) in Japanese, 2.02 (95% CI = 1.17 to 3.48) in African Americans, and 2.15 (95% CI = 0.95 to 4.90) in whites. No heterogeneity was observed across groups (P = .36). In all ethnic groups combined, diabetes was associated with 2.62-fold risk of developing HCC (95% CI = 2.13 to 3.23).

We further examined whether known HCC risk factors, ie, BMI, smoking, alcohol intake, and hepatitis viral infection status, modify the association between diabetes and HCC (Table 4). No statistically significant differences were observed across the subgroups of these risk factors ($P \geq .14$). It is worth noting that the diabetes-HCC association was strong among normal-weight individuals (RR = 3.05, 95% CI = 2.03 to 4.58), nonsmokers (RR = 3.68, 95% CI = 2.47 to 5.48), and nondrinkers (RR = 2.35, 95% CI = 1.78 to 3.13). In the nested case-control analysis, diabetes remained statistically significantly associated with HCC (odds ratio [OR] = 2.03, 95% CI = 1.04 to 3.95) in participants who tested negative for both hepatitis B virus (HBV) and hepatitis C virus (HCV).

Finally, the population-attributable risk percent was used to estimate the proportion of HCC cases that may have been avoided in the cohort by the elimination of diabetes. We estimated that 27% of HCC cases in Latinos, 18% in Hawaiians, 13% in African Americans, 12% in Japanese, and 6% in whites may have been prevented if diabetes were to be eliminated.

Discussion

In this large multiethnic cohort, we found that Latinos were at the highest risk of developing HCC, followed by Native Hawaiians, African Americans, Japanese Americans, and whites. We observed that diabetes is a strong independent risk factor for HCC in all five ethnic groups and that the interethnic differences in the prevalence of diabetes were consistent with the pattern of HCC incidence observed across ethnicities. We also showed that eliminating diabetes could potentially reduce HCC incidence in all racial/ethnic groups, with the largest potential for reduction in Latinos.

A recent meta-analysis study showed a 2.3-fold increased risk of HCC among diabetics compared with nondiabetics (9). In our study, diabetes is associated with more than two-fold increased risks of HCC in Latinos, Native Hawaiians, African Americans, Japanese Americans, and whites. Not only are our results consistent with the literature, they also fill the gap by providing data for minority populations in the United States.

The biologic mechanisms by which diabetes affects HCC risk are incompletely understood, but hyperinsulinemia, hyperglycemia, and chronic inflammation are thought to be the major links between diabetes and cancer (14). It has been suggested that diabetes is associated with HCC through the development of nonalcoholic steatohepatitis (NASH) (7), which is characterized by steatosis, inflammation, and hepatocyte injury with and without fibrosis. The major pathogenesis of NASH involves insulin resistance and inflammation, and up to 75% of NASH patients are diabetics. NASH can progress to cirrhosis, which can then progress to HCC. The prevalence of NASH in the United States has increased steadily over the past two decades (15). Interestingly, Hispanics have been shown to have the highest rates of both cryptogenic cirrhosis and NASH (16), and they are the population that experienced the largest increase in HCC incidence in the United States (5,6).

Our study has several strengths and limitations. The strengths include its large size, prospective design, exclusion of subjects with cancer at baseline, and the availability of most HCC risk factors collected up to 19 years prior to diagnosis. The MEC has been shown to be representative of the populations represented in the cohort (11), and thus our results are broadly generalizable to US populations. One limitation is that our analysis is based on diabetes status collected at

Table 4. Association between diabetes and hepatocellular carcinoma by known risk factors

	No diabetes		Diabetes		
HCC risk factor	**Case patients**	**RR* (95% CI)**	**Case patients**	**RR* (95% CI)**	**$P_{interaction}$†**
BMI, kg/m^2					
<25	117	1.00 (referent)	31	3.05 (2.03 to 4.58)	.70
25-<30	157	1.00 (referent)	54	2.34 (1.70 to 3.21)	
≥ 30	66	1.00 (referent)	45	2.82 (1.91 to 4.16)	
Smoking					
Never	79	1.00 (referent)	39	3.68 (2.47 to 5.48)	.14
Former	161	1.00 (referent)	62	2.23 (1.65 to 3.02)	
Current	100	1.00 (referent)	29	2.52 (1.64 to 3.88)	
Alcohol intake					
Nondrinkers	152	1.00 (referent)	74	2.35 (1.78 to 3.13)	.42
<2 drinks/day	118	1.00 (referent)	38	2.91 (2.00 to 4.22)	
≥2 drinks/day	70	1.00 (referent)	18	3.25 (1.92 to 5.51)	
Hepatitis B or C§					
Negative	70	1.00 (referent)	21	2.03 (1.04 to 3.95)	.25
Positive	48	1.00 (referent)	13	0.77 (0.27 to 2.14)	

* Hazard rate ratios adjusted for race/ethnicity and sex (as strata variables) and for education (≤ high school, some college, college and above), body mass index (<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), smoking status (never, former, current), and alcohol intake (nondrinkers, <2 drinks/day, ≥2 drinks/day) by Cox regression using age as the time metric. BMI = body mass index; CI = confidence intervals; HCC = hepatocellular carcinoma; RR = hazard rate ratio.

† P value from the test of multiplicative interaction between diabetes and risk factor of interest. All statistical tests were two-sided.

§ Based on the nested case–control study.

baseline and self-reported, and thus exposure misclassification possibly has occurred; the misclassification is likely to be nondifferential and result in bias toward the null. Another limitation is the unavailability of HBV/HCV infection status in all cohort members for adjustment in the analysis, which could have positively biased our results if diabetics were more likely to have these infections than nondiabetics. However, in a subset of the study population with viral hepatitis status, we observed a clear and strong association between diabetes and HCC among those negative for viral HBV/HCV serology, which strengthens the notion that the association is direct.

In summary, our study represents the first prospective analysis from multiethnic US populations with different levels of diabetes prevalence and risk for HCC, and our results strongly support a substantial role of diabetes in the development of HCC across diverse populations. With rapidly increasing prevalence of obesity and diabetes, the incidence of HCC is expected to continue to rise. Public health efforts to prevent and control diabetes in high-risk populations could contribute to a significant reduction in the liver cancer burden.

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