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Sex and Ethnic Differences in the Association of Obesity with Risk of Hepatocellular Carcinoma

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Abstract

Background & Aims—Obesity is associated with increased risk for hepatocellular carcinoma (HCC), but the risk associated with obesity may vary by sex or ethnicity. We examined whether the association of body mass index (BMI) with HCC incidence, as well as correlations of BMI with total, visceral, and hepatic adiposity, differs among ethnic groups.

Methods—We collected data from the Multiethnic Cohort Study, a population-based prospective cohort study of more than 215,000 men and women from Hawaii and California, assembled from 1993 through 1996. After a median follow up of 16.6 years, 482 incident HCC cases were identified among 168,476 participants. BMI and risk factor data were obtained from a baseline questionnaire. Cox regression analyses were used to calculate hazard ratios (HRs) and confidence intervals (CIs) for HCC associated with BMI. The African Americans in the Southern Community Cohort Study (SCCS) were included as a replication cohort.

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Results—BMI was associated with HCC in men (HR per 5 kg/m² increase=1.26; 95% CI, 1.12–1.42) but not in women (HR=1.06; 95% CI, 0.90–1.25) ($P_{\text{interaction}}=.009$). Although BMI was strongly associated with HCC in Japanese, white, and Latino men, there was no association in African-American men ($P_{\text{interaction}}=.002$). Similarly, no association was found in the African-American who participated in the SCCS. BMI correlated with total fat mass, measured by dual-energy X-ray absorptiometry, in men and women and in all ethnic groups ($R=0.9$). However, there was a lower correlation value for BMI and visceral or liver fat measured by abdominal MRI in African-American men ($R<0.5$) and in women ($R<0.8$).

Conclusions—Based on an analysis of data from the Multiethnic Cohort Study, the association between BMI and HCC differs between sexes and among ethnicities. The lack of association in African-American men warrants further investigation. Rather than studying markers of total adiposity, studies of obesity and HCC should move beyond BMI and use a better measure for fat-specific depots.

Keywords

Liver Cancer; MEC study; epidemiology; visceral adiposity

The incidence of hepatocellular carcinoma (HCC) in the United States (US) has tripled during the past three decades¹. The health impact of the increasing incidence of HCC is compounded by its poor prognosis, since its overall 5-year survival is <12%². Among all major cancers in the US, HCC has shown the greatest annual percent increase in mortality rate between 1975 and 2010³. In 2013, HCC was the 7th most common cause of cancer mortality in the US, accounting for more than 21,000 deaths³.

While all ethnic groups have shown an increase in HCC incidence, marked differences in rates have been reported by race/ethnicity⁴. Asians/Pacific Islanders and Hispanics have the highest incidence rates, at 3-fold and 2-fold higher than the rates among non-Hispanic whites, respectively⁵. The rates for Hispanics are rising the fastest among all racial/ethnic groups^{5, 6}.

The obesity epidemic, in part through development of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), is thought to have contributed to these increasing HCC trends^{7, 8}. Obesity as measured by BMI has been associated with HCC risk⁴. However, a previous study suggested that obesity was positively associated with HCC in whites, but not in African Americans⁹.

Previous studies suggest that there are substantial ethnic differences in body fat distribution^{10–12}. Compared to whites with similar total adiposity, Latinos and Asians are more likely, and African Americans less likely, to accumulate fat in the abdominal visceral compartment and in the liver^{13–15}. We hypothesized that if such ethnic differences in the obesity-HCC association are confirmed, they may be explained by variation in body fat distribution. Indeed, visceral adiposity has been suggested to be more important for predicting HCC risk than total adiposity^{16–18}.

The purpose of this study was to examine the association of BMI with HCC incidence as well as the correlations of BMI with total, visceral and hepatic adiposity in five ethnic groups from the Multiethnic Cohort (MEC) Study.

Materials and Methods

Study Population

The details of the MEC and baseline characteristics have been published¹⁹. Briefly, the MEC is a population-based prospective cohort study of over 215,000 men and women from Hawaii and California (mainly Los Angeles County), assembled between 1993 and 1996. Potential participants, aged 45 to 75 years at recruitment, were identified primarily through Department of Motor Vehicles drivers' list, voter registration lists, and Health Care Financing Administration data files. All participants returned a self-administered 26-page questionnaire that obtained information on demographic, anthropometric measures, and lifestyle factors including diet.

For the current study, we excluded participants not from the five major ethnic groups (N=13,988), participants with cancer diagnosis except non-melanoma skin cancer prior to cohort entry as reported on the baseline questionnaire or as identified by linkage to the tumor registries (N=19,385), participants with implausible dietary energy and macronutrient intakes (N=8,257), and participants with missing data on baseline weight, height, diabetes, smoking status, alcohol intake, and education (N=5,461). A total of 168,476 participants were available for analysis.

Case Ascertainment

Incident HCC cases [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, which are part of the NCI's Surveillance, Epidemiology and End Results (SEER) program. Case ascertainment was complete through December 31, 2010. After a median duration of follow up of 16.6 years, a total of 482 incident HCC cases were identified. Linkages to the National Death Index and death certificate files in Hawaii and California provided information on vital status.

Assessment of BMI and other risk factors

On the baseline questionnaire, participants were asked to self-report their current weight and height. BMI was calculated as weight in kg divided by height in m². Data on demographic factors and other risk factors including alcohol intake, smoking status, and physician-diagnosed type 2 diabetes were also obtained from the baseline questionnaire²⁰. Waist and hip measurements were not collected at baseline.

MEC adiposity data

For the BMI-fat depot correlation analysis, specifically for visceral and hepatic adiposity, we utilized data from a subset of 256 MEC participants who were re-contacted to undergo detailed adiposity measurements (whole-body DXA, abdominal MRI, and anthropometry)

for a separate project. Subjects who were 60–72 years of age in January 2013 and living in Oahu or Los Angeles county were recruited using stratified sampling to obtain a balanced representation of each sex and ethnic group in each of six BMI categories (18.5–22, 22>–25, 25>–27.5, 27.5>–30, 30>–35, >35 kg/m²), following a previously tested protocol^{21, 22}. After accounting for the sampling scheme which allowed a comparison of regional fat depots across ethnicities at various levels of total adiposity, the samples were generally representative of the entire cohort. The Institutional Review Boards at the University of Hawaii (UH) and the University of Southern California (USC) approved the study, and all participants signed an informed consent. Total and regional body fat mass in the trunk, arms and legs was measured using Hologic Discovery/A DXA systems (Hologic, Inc., Bedford, MA) at UH and USC. Visceral and subcutaneous fat and hepatic fat were estimated from abdominal MRI scans performed with a 3-Tesla system [Siemens TIM Trio scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) at UH, GE HDx (GE Healthcare, Madison, WI) at USC]. Visceral and subcutaneous fat area (cm²) was measured in a series of water-suppressed lipid scans at each of the L1–L5 intervertebral positions, and liver fat (% volume) was estimated in axial triple gradient-echo scans of the lateral portion of the right lobe²¹.

Southern Community Cohort Study (SCCS)

The SCCS is a prospective cohort study, focused on cancer disparities related to race, of black and white adults enrolled primarily from community health centers in the southeastern US between 2002 and 2009^{23, 24}. Given the small number of HCC cases among African Americans in the MEC, we additionally included African-American participants from the SCCS in order to enhance our ability to examine the BMI-HCC association specifically in this population group for which a previous study did not show an association⁹. For this study, we utilized a nested case-control study of incident HCC and four controls matched to each case by age ($\pm$ 2 years), race, menopausal status (women) and enrollment location. We included 83 African-American cases and 332 controls in our analysis. The number of HCC cases was small in whites (N=18) and they were excluded from our analysis. Similar to the MEC, BMI was calculated based on self-reported weight and height at baseline questionnaire; smoking status, diabetes, and alcohol intake were also assessed at baseline.

Statistical Analysis

BMI was categorized as <25, 25–<30, and ≥ 30 kg/m². The association between BMI and HCC in the MEC was assessed by hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards regression while adjusting for known risk factors and potential confounders. 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, 2010). Adjustment variables in the Cox model included ethnicity (as a stratum variable), sex (as a stratum variable), age at cohort entry (continuous), education (high school or less, some college, college graduate or higher), history of diabetes (yes, no), cigarette smoking status (never, past, current), and alcohol intake (never, <24 g/day, ≥ 24 g/day ethanol). The proportional hazards assumption was tested by assessing the Schoenfeld residuals and no major violation was observed. The BMI-HCC association in the

SCCS was assessed by odds ratios (ORs) and 95% CI from conditional logistic regression stratified by matching set and adjusted for smoking status, diabetes, and alcohol intake. Tests for trend were performed by entering the ordinal values (i.e., 1,2,3) representing categories of BMI as continuous variables in the models. Test of heterogeneity for risks between sex or ethnic groups was assessed using the Wald test for the cross-product terms between BMI trend variable and sex or ethnicity. For the BMI-fat depot correlation analysis, the age-adjusted partial correlation of BMI with total, visceral and liver fat was computed. All analyses were done using SAS 9.2 (SAS Institute, Cary, NC). All P values were two-sided.

Results

Baseline characteristics of the study population by sex and race/ethnicity are shown in Table 1. Japanese and African Americans represented the oldest groups and Native Hawaiians the youngest group. Whites and Japanese had the highest level of education (college graduate or more), while the majority of Latinos had completed high school or less. There was a five-fold difference in the prevalence of obesity (BMI ≥ 30 kg/m²) across the five ethnic groups. With the exception of Japanese (8% in men and 6% in women), obesity was more frequent in all of the non-white groups (~25% in Latinos and African American men, 29% in Latinas, ~35% in Native Hawaiians, and 38% in African-American women) than in whites (17% in men, 18% in women). The prevalence of diabetes was highest in Latinos, followed by African Americans, Native Hawaiians, Japanese, and whites. Current smoking was most common among African-American men (27%), while heavy alcohol drinking was most common among white men (27%).

Table 2 shows the associations between BMI and HCC incidence by sex. Increasing BMI conferred a greater risk of HCC in men than in women (P interaction =0.036). Men who were overweight (BMI 25-<30 kg/m²) and obese (BMI ≥ 30 kg/m²) had a 1.5- and 1.8-fold increased HCC risk compared with those of normal weight, respectively (P for trend=0.0002). For a change of 5 kg/m² in BMI levels, men had a 26% increase in risk of HCC, which was significantly greater than the 6% non-significant increase in risk in women (P interaction=0.009).

Because of the limited number of female cases and non-significant BMI-HCC association in women, the ethnic-specific results are presented only in men (Table 3). The association of BMI with HCC differed significantly across ethnic groups (P interaction=0.003). Having a BMI ≥ 30 kg/m² was associated with HCC risk in Japanese (HR=3.43; 95% CI: 1.76, 6.69), Latinos (HR=2.18; 95% CI: 1.21, 3.93), whites (HR=1.82; 95% CI: 0.82, 4.03), and Native Hawaiians (HR=1.41; 95% CI: 0.47, 4.19), but not in African Americans (HR =0.61; 95% CI: 0.27, 1.36). Japanese, Latinos, whites, and Native Hawaiians had an increased risk of 77%, 34%, 20% and 17% per change of 5 kg/m² in BMI, respectively. No corresponding significant association was seen in African Americans (HR=0.78; 95% CI: 0.55, 1.11). We also found that BMI was not associated with HCC in African-American men (54 cases; OR =0.86; 95% CI: 0.63, 1.19) in the SCCS. Using a fixed-effect meta-analysis model, the combined association for African Americans across the two cohorts was 0.82 (95% CI: 0.65, 1.04; P heterogeneity=0.69).

Table 4 shows the correlations between BMI and fat distribution by sex and by ethnicity in the subset of 256 participants. In general, in men, BMI was equally and quite strongly correlated with total and visceral fat but more weakly with liver fat. In contrast to the other groups, in African-American men, the correlation with BMI was weaker for both visceral and liver fat. In women, BMI was highly correlated with total fat but less so with visceral fat and even less so with liver fat, this in a more similar manner across ethnic groups than for men.

Discussion

In this large prospective study, we observed significant sex- and ethnic-differences in the association between BMI and HCC risk. We found BMI to be significantly associated with HCC risk only in men. Furthermore, whereas BMI was strongly associated with HCC risk in Japanese-American, white and Latino men, it was not associated with HCC risk in African-American men. We also showed that BMI correlated well with total fat mass measured by total body DXA in men and women and in all ethnic groups. However, the correlations of BMI with visceral or liver fat measured by abdominal MRI were weaker in African-American men and in women.

Previous meta-analyses showed that risk of HCC associated with increasing BMI levels was either stronger in men than in women^{25, 26} or only seen in men²⁷. Our results are consistent with these previous data. It is known that men have more visceral fat compared to women^{28–30}. It has also been suggested that visceral adiposity maybe more important for predicting HCC risk than total adiposity^{16–18}. Visceral adipose tissue is thought to modulate a range of systemic and end-organ effects through the release of adipocytokines, growth factors and inflammatory markers, and it has been associated with hyperinsulinemia, NAFLD, and severity of liver inflammation and fibrosis in non-alcoholic steatohepatitis (NASH)^{18, 31}. Two studies to date have investigated the association between body fat distribution and HCC^{32, 33}. The first study from the EPIC cohort showed that across all anthropometric indices (BMI, height, waist circumference, waist-to-hip ratio, *etc.*), waist-to-height ratio, a surrogate for abdominal obesity, had the strongest association with HCC risk³². In a multivariable analysis, adjusting for other anthropometric measures, BMI was no longer associated with HCC, while the association with waist-to-height ratio remained³². The second study found that computed tomography-determined visceral fat was an independent risk factor for HCC recurrence in Japanese patients with suspected NASH³³. The stronger BMI-HCC association observed in men could be explained by the sexual dimorphism in visceral fat accumulation and/or with the weaker correlations between BMI and visceral and liver fat in women.

To our knowledge, only one study has examined whether the association of obesity and HCC differs by race⁹, and this study included mainly white and African-American men, with no Asian Americans and limited Hispanic Americans. This US veteran study found that the ICD-9-identified obesity (ICD-9=278.0) was associated with HCC in opposite directions for African-American men (RR=0.68; 95% CI: 0.49, 0.94) and white men (RR=1.44; 95% CI: 1.28, 1.61; P<0.001). In both the MEC and SCCS, we observed no association between BMI and HCC risk among African-American men which could be explained by a lower

amount of visceral fat^{30, 34}, lower correlations between BMI and visceral and liver fat, and/or other factors that may attenuate the risk of HCC among obese persons in this population.

As discussed by El-Serag and Kanwal³⁵, BMI is a rather gross and likely distal operator in explaining the link between obesity and HCC. BMI does not distinguish more metabolically active visceral fat or liver fat from other body fat³⁰ and it does not distinguish fat from lean mass³⁶. To add to the complexity, our results show that the correlations of BMI with the size of specific fat depots differ by sex and ethnic group.

The strengths of this study include its ethnic diversity, prospective design, long follow up, large sample size and detailed information on most HCC risk factors. Another strength is that in the BMI-adiposity correlation analysis, we used the gold standard measurements of body fat to allow for a more precise and valid comparison of body fat distribution across ethnic/groups. There are also several study limitations. Our analysis is based on exposure collected at baseline based on self-report, and thus exposure misclassification, as well as changes in exposures during follow up, cannot be ruled out. Even in our relatively large cohort, the number of cases within categories of BMI by sex and ethnic group were small. The limited number of female cases might reduce our ability to observe substantial excess risk in any or many of the specific subgroups in contrast to what was observed in males. Hepatitis B (HBV) and C viral infection (HCV) status were not available for the entire study population; thus, they could not be adjusted for in the analyses. In the nested case-control study of HCC within the MEC with HBV and HCV serologic data^{20, 37} infection status was not associated with BMI and the interaction between BMI and viral hepatitis on HCC risk was not statistically significant. However, a recent study showed an interaction between BMI and viral hepatitis on HCC risk³⁸; thus, we cannot exclude potential confounding or effect modification by viral hepatitis in our study.

In conclusion, the association of BMI with risk of HCC varies by sex and ethnic groups. The lack of association in African-American men is particularly interesting and warrants further investigation. Rather than studying total adiposity, studies of obesity and HCC should move beyond BMI and use better and more specific markers for fat-specific depots.

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Abbreviations

BMI	body mass index
CI	confidence interval
DXA	dual-energy X-ray absorptiometry
HCC	hepatocellular carcinoma

HR	hazard ratios
MEC	Multiethnic Cohort Study
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
SCCS	Southern Community Cohort Study

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Table 1

Characteristics of the study population by sex and race/ethnicity

Characteristics	Male					Female				
	White	African American	Nat. Hawaiian	Japanese American	Latino	White	African American	Nat. Hawaiian	Japanese American	Latino
No. of at risk	19,341	10,178	5,588	23,830	19,137	21,620	17,620	6,771	25,154	19,237
No. of HCC cases	47	52	28	100	112	9	26	6	57	45
Age at cohort entry (years) mean (SD)	58.3 (8.9)	61.0 (8.9)	56.4 (8.4)	60.7 (9.2)	59.9 (7.7)	58.4 (8.9)	60.3 (9.0)	55.8 (8.6)	60.5 (9.0)	59.1 (7.7)
Education, %										
High school or less	22.0	40.8	50.0	36.4	64.3	29.5	39.7	54.8	41.3	72.1
Some college	29.2	36.7	30.8	30.3	23.6	33.4	37.6	28.8	29.4	19.6
College graduate or more	48.8	22.5	19.2	33.3	12.1	37.1	22.7	16.4	29.3	8.4
BMI (kg/m ²), %										
<25	37.4	29.5	19.6	49.8	24.9	53.3	25.1	31.7	69.4	31.6
25-<30	45.6	47.8	43.7	42.4	53.6	28.4	37.1	33.1	24.2	39.8
30	16.9	22.7	36.7	7.9	21.5	18.3	37.8	35.2	6.4	28.6
Diabetes, %	6.0	15.8	15.8	11.9	16.4	5.2	14.9	13.3	8.8	14.6
Smoking status, %										
Never	32.3	24.5	31.8	29.3	31.7	45.3	45.7	45.1	68.9	65.0
Past	51.1	48.1	46.3	55.4	50.0	38.1	34.3	31.4	21.9	24.4
Current	16.6	27.4	21.9	15.3	18.3	16.6	19.9	23.5	9.2	10.5
Alcohol intake, %										
None	28.0	43.4	41.5	44.7	35.5	40.3	62.6	62.7	77.2	64.3
<24 ethanol g/day	45.0	40.5	39.6	39.3	48.4	47.7	32.6	32.7	21.2	33.4
24 ethanol g/day	27.0	16.1	18.9	16.0	16.0	12.0	4.8	4.6	1.6	2.3

Table 2

Association of BMI with hepatocellular carcinoma incidence by sex

	Male		Female		P interaction ²
	No. Cases	HR ¹ (95% CI)	No. Cases	HR ¹ (95% CI)	
BMI (kg/m ²)					
<25	90	1.00	62	1.00	
25-<30	173	1.50 (1.16, 1.95)	43	0.98 (0.65, 1.48)	0.036
30	76	1.82 (1.31, 2.52)	38	1.32 (0.83, 2.11)	
P trend		0.0002		0.29	
Per 5 kg/m ² increase	339	1.26 (1.12, 1.42)	143	1.06 (0.90, 1.25)	0.009

¹ Adjusted for age at cohort entry, race/ethnicity, education, alcohol intake, smoking status, and diabetes.² Interaction between sex and BMI was tested by the Wald test with 1 degree of freedom.

Table 3
Association of BMI with hepatocellular carcinoma incidence in men by race/ethnicity

	White			African American			Native Hawaiian			Japanese American			Latino		
	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	P interaction ²
Multiethnic Cohort Study															
BMI (kg/m ²)															
<25	13	1.00	21	1.00	6	1.00	32	1.00	18	1.00					
25-<30	21	1.22 (0.61, 2.46)	22	0.67 (0.37, 1.23)	13	1.25 (0.47, 3.32)	55	2.23 (1.44, 3.47)	62	1.66 (0.98, 2.82)					0.003
30	13	1.82 (0.82, 4.03)	9	0.61 (0.27, 1.36)	9	1.41 (0.47, 4.19)	13	3.43 (1.76, 6.69)	32	2.18 (1.21, 3.93)					
P trend		0.15		0.17		0.54		<0.0001		0.009					
Per 5 kg/m ² increase	47	1.20 (0.87, 1.66)	52	0.78 (0.55, 1.11)	28	1.17 (0.83, 1.65)	100	1.77 (1.42, 2.19)	112	1.34 (1.09, 1.63)					0.002
Southern Community Cohort Study															
BMI (kg/m ²)			No. Cases	OR** (95% CI)											
<25			20	1.00											
25-<30			25	1.46 (0.70, 3.06)											
30			9	0.88 (0.35, 2.21)											
P trend				0.95											
Per 5 kg/m ² increase			54	0.86 (0.63, 1.19)											

* HR adjusted for age at cohort entry, education, smoking status, diabetes, and alcohol intake.

** OR stratified by matching set and adjusted for smoking status, diabetes and alcohol intake.

² Interaction between race/ethnicity and BMI was tested by the Wald test with 4 degrees of freedom.

Table 4

Correlation of BMI with total, visceral and liver adiposity by sex and race/ethnicity

	All	White	African American	Native Hawaiian	Japanese American	Latino
Men	N=127	N=27	N=21	N=27	N=29	N=23
Age (Mean, SD)	68.4 (2.5)	68.5 (2.3)	68.1 (2.1)	68.3 (3.1)	68.2 (2.2)	68.8 (2.6)
BMI (Mean, SD)	27.9 (4.8)	27.6 (5.1)	28.2 (4.1)	28.7 (5.0)	27.8 (4.6)	27.2 (4.9)
	Correlation Coefficient ^a					
Total fat (kg)	0.89*	0.94*	0.89*	0.87*	0.89*	0.90*
Visceral fat at L3L4 (cm ²)	0.81*	0.91*	0.50	0.73*	0.87*	0.91*
Liver fat (% volume)	0.55*	0.69*	0.35	0.71*	0.65	0.61
Women	N=129	N=24	N=27	N=26	N=27	N=25
Age (Mean, SD)	68.4 (2.9)	68.4 (2.4)	69.4 (2.5)	67.0 (3.6)	68.7 (2.4)	68.5 (2.8)
BMI (Mean, SD)	27.7 (5.3)	27.3 (5.7)	28.7 (6.0)	28.0 (5.2)	27.2 (4.3)	27.3 (5.4)
	Correlation Coefficient ^a					
Total fat (kg)	0.88*	0.91*	0.89*	0.92*	0.87*	0.95*
Visceral fat at L3L4 (cm ²)	0.69*	0.83*	0.74*	0.79*	0.64	0.52
Liver fat (% volume)	0.41*	0.58	0.45	0.50	0.43	0.37

^a adjusted for age at examination;

* P<0.0001