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

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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 that was 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 black subjects in the Southern Community Cohort Study were included as a replication cohort.**

RESULTS: **BMI was associated with HCC in men (HR per 5 kg/m^2 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 black men ($P_{\text{interaction}} = .002$). Similarly, no association was found in the blacks who participated in the Southern Community Cohort Study. BMI correlated with total fat mass, measured by dual-energy x-ray absorptiometry, in men and women and in all ethnic groups ($R \geq 0.9$). However, there was a lower correlation value for BMI and visceral or liver fat measured by abdominal magnetic resonance imaging in black men ($R < 0.5$) and in women ($R < 0.8$).**

CONCLUSIONS: **On the basis of 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 black 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 has tripled during the past 3 decades.[1] The health impact of the increasing incidence of HCC is compounded by its poor prognosis, because its overall 5-year survival is <12%.[2] Among all major cancers in the United States, HCC has shown the greatest annual percent increase in mortality rate between 1975 and 2010.[3] In 2013, HCC was the 7th most common cause of cancer mortality in the United States, accounting for more than 21,000 deaths.[3]

Although all ethnic groups have shown an increase in HCC incidence, marked differences in rates have been reported by race/ethnicity.[4] Asians/Pacific Islanders and Hispanics have the highest incidence rates at 3-fold and 2-fold higher than the rates among non-Hispanic whites,

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; HCC, hepatocellular carcinoma; HR, hazard ratio; MEC, Multiethnic Cohort Study; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; SCCS, Southern Community Cohort Study.**

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respectively.[5] The rates for Hispanics are rising the fastest among all racial/ethnic groups.[5,6]

The obesity epidemic is thought to have contributed to these increasing HCC trends in part through development of metabolic syndrome and nonalcoholic fatty liver disease (NAFLD).[7,8] Obesity as measured by body mass index (BMI) has been associated with HCC risk.[4] However, a previous study suggested that obesity was positively associated with HCC in whites but not in blacks.[9]

Previous studies suggest that there are substantial ethnic differences in body fat distribution.[10–12] Compared with whites with similar total adiposity, Latinos and Asians are more likely and blacks 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 5 ethnic groups from the Multiethnic Cohort (MEC) Study.

Materials and Methods

Study Population

The details of the MEC and baseline characteristics have been published.[19] Briefly, the MEC is a population-based prospective cohort study of more than 215,000 men and women from Hawaii and California (mainly Los Angeles County) that was assembled between 1993 and 1996. Potential participants, aged 45–75 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 5 major ethnic groups (N = 13,988), participants with cancer diagnosis except non-melanoma skin cancer before 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 = 8257), and participants with missing data on baseline weight, height, diabetes, smoking status, alcohol intake, and education (N = 5461). 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 National Cancer Institute's Surveillance, Epidemiology and End Results 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 Body Mass Index 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 m^2. 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 questionnaire.[20] Waist and hip measurements were not collected at baseline.

Multiethnic Cohort Adiposity Data

For the BMI–fat depot correlation analysis, specifically for visceral and hepatic adiposity, we used data from a subset of 256 MEC participants who were recontacted to undergo detailed adiposity measurements (whole-body dual-energy x-ray absorptiometry [DXA], abdominal magnetic resonance imaging [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 by using stratified sampling to obtain a balanced representation of each sex and ethnic group in each of 6 BMI categories (18.5–22, >22–25, >25–27.5, >27.5–30, >30–35, >35 kg/m^2), following a previously tested protocol.[21,22] After accounting for the sampling scheme that 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 and the University of Southern California approved the study, and all participants signed an informed consent. Total and regional body fat mass in the trunk, arms, and legs was measured by using Hologic Discovery/A DXA systems (Hologic, Inc, Bedford, MA) at University of Hawaii and University of Southern California. 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 University of Hawaii; GE HDx, GE Healthcare, Madison, WI at University of Southern California). Visceral and subcutaneous fat area (cm^2) was measured in a series of water-suppressed lipid scans at