Letters

RESEARCH LETTER

Association of High Body Mass Index and Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection: A Korean Population-Based Cohort Study

It is well established that obesity is associated with higher risk of hepatocellular carcinoma (HCC) in the general population.[1] However, it is unclear whether body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) is associated with the risk of HCC in patients with chronic hepatitis B virus (HBV) infection because previous studies have reported inconsistent results.[2,3] In this study, using data from a large nationwide, population-based cohort database, we provide clinical evidence on the association between BMI and development of HCC among men and women with chronic HBV infection.

Methods | We used the National Health Insurance Service (NHIS) data, which provides compulsory health insurance coverage and national health screening for all citizens in the Republic of Korea. The institutional review board (IRB) at the Seoul National University Hospital approved our study. We identified adult men and women (age ≥18 years) with chronic HBV infection who underwent health examinations between January 1, 2002, and December 31, 2006, in the NHIS database. We excluded patients with a history of cancer and those who died before the follow-up period. The patients were grouped into the BMI categories based on the World Health Organization classification for Asian populations. Patients were followed up from January 1, 2007, to December 31, 2015, and censored at the event of HCC, death, or end of follow-up, whichever occurred first. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% CIs across the BMI categories using 18.5 to 22.9 as the reference group, and we graphically assessed the strength of the relationship between BMI and HCC with restricted cubic spline models in men and women for BMI categories and covariates (**Table**). Partial likelihood ratio tests in the Cox regression model were used to compare the magnitude of the association of BMI with HCC between men and women. Sensitivity analyses were conducted by excluding events of HCC up to 4 years, as well as patients with liver comorbidities.

Table. Risk of Hepatocellular Carcinoma According to BMI Among Patients With Chronic HBV Infection

Characteristic	BMI					P_{trend}[a]
	<18.5	18.5-22.9	23.0-24.9	25.0-29.9	≥30.0	
Men						
Patients, No.	3965	68 247	58 323	76 392	7240	
HCC, No.	202	3762	3118	3816	343	
Person-years	28 987	516 814	446 087	587 629	55 747	
Multivariable-adjusted HR (95% CI), Model 1[b]	0.76 (0.66-0.88)[c]	1 [Reference]	1.05 (1.00-1.10)	1.04 (1.00-1.09)	1.19 (1.07-1.34)[d]	<.01
Multivariable-adjusted HR (95% CI), Model 2[e]	0.81 (0.71-0.94)[d]	1 [Reference]	1.03 (0.99-1.08)	1.04 (0.99-1.09)	1.22 (1.09-1.36)[d]	<.01
Women						
Patients, No.	7152	67 109	35 951	40 610	5333	
HCC, No.	73	1140	847	1133	175	
Person-years	56 094	526 467	280 546	315 249	41 088	
Multivariable-adjusted HR (95% CI), Model 1[b]	0.73 (0.57-0.92)[d]	1 [Reference]	1.14 (1.04-1.25)[d]	1.26 (1.16-1.37)[c]	1.56 (1.33-1.83)[c]	<.001
Multivariable-adjusted HR (95% CI), Model 2[e]	0.81 (0.64-1.03)	1 [Reference]	1.14 (1.04-1.24)[d]	1.25 (1.15-1.36)[c]	1.46 (1.24-1.71)[c]	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; NAFLD, nonalcoholic fatty liver disease.

[a] *P* values were 2-sided, and $P < .05$ was considered statistically significant.

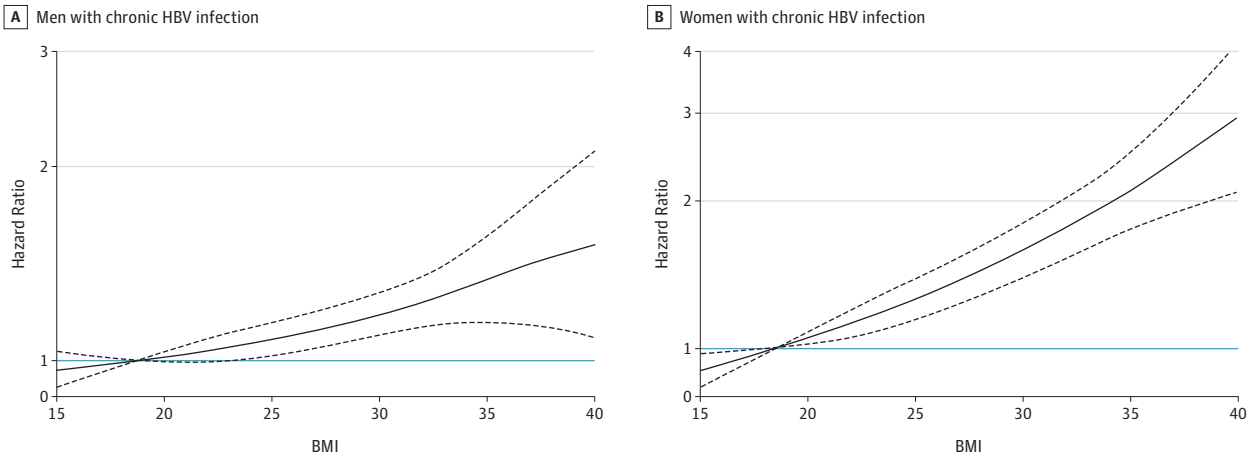
[b] Derived from the Cox proportional hazards models adjusted for sociodemographic factors (age, residential area, insurance premium), lifestyle factors (smoking status, alcohol use, physical activity), and health status (fasting serum glucose level, total cholesterol level, alanine aminotransferase level).

[c] $P < .001$.

[d] $P < .01$.

[e] Adjusted for medication use (aspirin, metformin, NSAID, statin, anti-HBV treatment) and comorbidities (liver cirrhosis, alcoholic liver disease, NAFLD, hepatitis C virus coinfection, Charlson comorbidity index) in addition to the variables included in Model 1.

Figure. Relationship Between BMI and Hepatocellular Carcinoma in Individuals With Chronic HBV Infection



The models were fitted with restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of BMI (model selection and knot placement via Bayesian information criterion). The solid line represents the hazard ratio, and the broken lines represent corresponding 95% CI. The reference BMI is the 18.5 to 22.9 category, and the curves were adjusted for variables in a multivariable model including sociodemographic factors (age, residential area, and insurance premium), lifestyle factors (smoking status, alcohol use, physical activity), health status (fasting serum glucose level, total cholesterol level, alanine aminotransferase level), medication use (aspirin, metformin, nonsteroidal anti-inflammatory drug, statin, anti-HBV treatment), and comorbidities (liver cirrhosis, alcoholic liver disease, nonalcoholic fatty liver disease, hepatitis C virus coinfection, Charlson comorbidity index). BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HBV, hepatitis B virus.

Results | Our study cohort of patients with chronic HBV infection comprised of 214 167 men and 156 155 women. During the 8 years of follow-up, there were 11 241 HCCs in men and 3368 HCCs in women. The risk of HCC was positively associated with BMI in a dose-response manner both in men (P_{trend} < .01) and women (P_{trend} < .001). In severely obese men and women (BMI≥30), the HR for HCC were 1.22 (95% CI, 1.09-1.36) and 1.46 (95% CI, 1.24-1.71) compared with those whose BMI was between 18.5 and 22.9 (Table). The magnitude of the association between BMI and HCC was stronger in women who were overweight compared with men (P < .001). The correlation between BMI and HCC was also higher in women compared with men (**Figure**). Similar results were found in the sensitivity analyses.

Discussion | Our study showed that BMI is significantly associated with higher risk of HCC among patients with chronic HBV infection, and that the risk may differ by sex. The relationship between BMI and risk of HCC was significant and independent of underlying liver diseases in patients with chronic HBV infection. The difference between male and female patients with chronic HBV infection found in our study may be partially explained by the sex difference in the relationship of BMI to total body fat.[4] A major limitation of our study should be noted: the NHIS database lacked information on serum HBV DNA levels, which is a clinically important predictor for the development of liver cirrhosis and HCC among patients with chronic HBV infection.[5] Our findings have both clinical and public health implications that support the need for intervention strategies and medical attention for obese patients with chronic HBV infection, especially in women.

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Study concept and design: Kim, Park.
Acquisition, analysis, or interpretation of data: Kim, Choi.
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