Metabolic Syndrome Increases the Risk of Primary Liver Cancer in the United States: A Study in the SEER-Medicare Database

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Incidence rates of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) have increased in the United States. Metabolic syndrome is recognized as a risk factor for HCC and a postulated one for ICC. The magnitude of risk, however, has not been investigated on a population level in the United States. We therefore examined the association between metabolic syndrome and the development of these cancers. All persons diagnosed with HCC and ICC between 1993 and 2005 were identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. For comparison, a 5% sample of individuals residing in the same regions as the SEER registries of the cases was selected. The prevalence of metabolic syndrome as defined by the U.S. National Cholesterol Education Program Adult Treatment Panel III criteria, and other risk factors for HCC (hepatitis B virus, hepatitis C virus, alcoholic liver disease, liver cirrhosis, biliary cirrhosis, hemochromatosis, Wilson's disease) and ICC (biliary cirrhosis, cholangitis, cholelithiasis, choledochal cysts, hepatitis B virus, hepatitis C virus, alcoholic liver disease, cirrhosis, inflammatory bowel disease) were compared among persons who developed cancer and those who did not. Logistic regression was used to calculate odds ratios and 95% confidence intervals. The inclusion criteria were met by 3649 HCC cases, 743 ICC cases, and 195,953 comparison persons. Metabolic syndrome was significantly more common among persons who developed HCC (37.1%) and ICC (29.7%) than the comparison group (17.1%, $P < 0.0001$). In adjusted multiple logistic regression analyses, metabolic syndrome remained significantly associated with increased risk of HCC (odds ratio = 2.13; 95% confidence interval = 1.96-2.31, $P < 0.0001$) and ICC (odds ratio = 1.56; 95% confidence interval = 1.32-1.83, $P < 0.0001$). *Conclusion:* Metabolic syndrome is a significant risk factor for development of HCC and ICC in the general U.S. population. (HEPATOLOGY 2011;54:463-471)

The incidences of both types of primary liver cancer, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), have increased in the United States.[1,2] Major risk factors for HCC in industrialized countries are chronic infection with hepatitis C virus (HCV), chronic infection with hepatitis B virus (HBV), and excessive alcohol consumption.[3] The documented increase in HCV- and HBV-related HCC, however, does not fully explain the recent increase in HCC incidence, because 20%-

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NCEP-ATP III, U.S. National Cholesterol Education Program Adult Treatment Panel III; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

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50% of HCC cases remain idiopathic.[3] ICC has been associated with several diseases of the biliary tract or liver, such as primary sclerosing cholangitis, Caroli's disease, cholelithiasis, HCV infection, liver fluke infestation, and inflammatory bowel disease.[4] These factors account for only a small proportion of the attributable risk of ICC in the United States, because many ICC cases do not appear to be associated with any of the abovementioned risk factors.[5]

In recent years, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) have received increasing attention for their relationship with end-stage liver disease and HCC.[6-11] NAFLD and NASH are clearly associated with the metabolic syndrome, comprising a cluster of interrelated metabolic risk factors such as raised fasting glucose, central obesity, dyslipoproteinemia, and hypertension.[12-15] In concert with the recent worldwide epidemic of obesity and metabolic syndrome,[16-18] the incidence and prevalence of NAFLD has also increased. It is estimated that up to 37% of the population in industrialized countries exhibit NAFLD, turning it into the most frequent liver disease in these countries.[13,19,20]

The association between metabolic syndrome or NAFLD/NASH and HCC has been documented in case reports, case series, and longitudinal studies[7,8,11,21-24]; however, larger population-based studies investigating the magnitude of this association in the United States are lacking. Clinical studies investigating the possible impact of metabolic syndrome on ICC risk are very limited,[23,25] because the examination of this association is made difficult by the low incidence of ICC in Western countries. The goal of the current study was to investigate the association between metabolic syndrome and risk of HCC and ICC in the general population of the United States.

Patients and Methods

Data Source. The data for the study were obtained from the Surveillance, Epidemiology, and End Results (SEER)-Medicare databases, which link cancer registry data and Medicare enrollment and claims files. Details of the SEER-Medicare linkage, first linked in 1991, have been described previously.[26] Briefly, SEER registries provide individual identifiers for all persons in their files. The identifiers are matched to the identifiers contained in the Medicare master enrollment file. For each of the linkages, 93% of persons aged 65 and older in the SEER files have been matched to the Medicare enrollment file.

The National Cancer Institute's SEER Program assembles information on cancer incidence and survival from population-based cancer registries in the United States.[27] During the study period 1993-2005, SEER included 13 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, Utah, Los Angeles, San Jose–Monterey, Rural Georgia, Alaska Natives) covering approximately 25% of the U.S. population. In comparison to the general U.S. population, the population covered by SEER registries is similar in educational levels and measures of poverty, but is more urban and has a higher proportion of foreign-born persons. Information on patient demographics, tumor site, morphology, stage, treatment, and follow-up are obtained by SEER registries from hospital and outpatient records. The quality and completeness of the data are ascertained in even-numbered calendar years.[27]

Medicare is the primary health insurer for 97% of the U.S. population aged 65 years and older.[26] Approximately 99% of Medicare beneficiaries receive part A benefits (hospital insurance) and approximately 95% subscribe to part B benefits (medical insurance), covering outpatient hospital care and physician visits. Data on Medicare claims are available for Medicare parts A and B. These files contain dates of service, International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology, Version 4, codes for all billed claims.

Study Population. All persons aged $\geq$65 years diagnosed with histologically confirmed HCC or ICC between 1994 and 2005 were identified. The histologic definition of HCC and ICC was based on the World Health Organization's classification.[28] During the study period, the classification and documentation of malignancies in SEER was based on the International Classification of Diseases for Oncology, Version 2 (ICD-O2).[29] HCCs were defined by topography code C22.0 (primary liver cancer) and morphology codes 8170-1875. ICCs were identified by topography code C22.0 (primary liver cancer) and morphology codes 8160 and 8161, or by topography code C22.1 (intrahepatic bile duct cancer) and morphology codes 8010, 8020, 8140, 8160, and 8161. Only persons enrolled in Medicare parts A and B for at least 3 years before diagnosis of HCC or ICC were eligible for inclusion to insure adequate time for prior diagnoses to be recorded. This criterion resulted in a minimum age of 68 years for the study participants. The following groups were excluded: persons younger

than age 65 years at diagnosis, persons enrolled in Medicare because of disabilities or end-stage renal disease, persons with unspecified diagnostic confirmation of HCC or ICC, persons with HCC or ICC identified solely by autopsy or death certificate, and persons enrolled in a health maintenance organization during the study period, because Medicare health maintenance organization plans are not required to submit individual claims to Medicare. To minimize the possibility of erroneously including cancer metastatic to the liver, persons with prior diagnoses of stomach, colon, lung, pancreatic, breast, prostate, or rectal cancers were excluded.

Individuals with no prior cancer diagnoses were selected as controls from a 5% random sample of Medicare beneficiaries residing in the geographic regions of the SEER-13 registries. Controls had to have at least 3 years of enrollment in Medicare parts A and B. Control selection was based on the same inclusion and/or exclusion criteria as used for case selection. Controls were assigned a pseudo-diagnosis date using a random number generator. Cases and controls were matched on the year of search for risk factors to minimize possible diagnostic trends.

Definition of Metabolic Syndrome. Metabolic syndrome was defined, as suggested by the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), as the presence of at least three of the following conditions: elevated waist circumference/central obesity, dyslipidemia (elevated triglycerides, lowered high-density lipoprotein), hypertension, and impaired fasting glucose.[30] The corresponding medical conditions were selected using the following ICD-9-CM codes: Overweight, obesity: 278.0, 278.1, 278.01, 278.00, V77. Dyslipoproteinemia: 272.0, 272.1, 272.2, 272.4, 272.5, 272.9; Hypertension: 401, 401.0, 401.1, 401.9, 402.0, 402.1, 402.9, 403.0, 403.1, 403.9, 404, 404.0, 404.1, 404.9, 278.0, 278.00, 278.01, 278.02, 278.1, V77.8, 783.1, 278.02; Impaired fasting glucose/diabetes mellitus: 250, 790.2, 790.21, 790.22, 790.29.[31]

Because there is no specific ICD-9-CM code for elevated waist circumference, obesity served as the proxy variable. Because of the absence of a specific ICD-9-CM code for reduced high-density lipoprotein, this condition could not be assessed.

Risk Factor Selection. Risk factors for HCC or ICC were selected using ICD-9-CM codes.[31] Liver flukes: 121.3, 121.0; Biliary cirrhosis: 571.6; Cholangitis: 576.1; Cholelithiasis: 574; Choledochal cyst: 751.69; HBV infection: 070.2, 070.3, 070.42, 070.52, V02.61; HCV infection: 070.41, 070.44, 070.51, 070.54, 070.7, V02.62; Unspecified viral hepatitis: 070.9, 070.59, 070.49; Hemochromatosis: 275.0; Wilson's disease: 275.1. Smoking: V15.82, 305.1, 989.84; Crohn's disease: 555, 555.0, 555.1, 555.2, 555.9; Ulcerative colitis: 556, 556.0, 556.1, 556.2, 556.3, 556.5, 556.6, 556.9. Alcoholic liver disease was defined as alcoholic fatty liver disease (571.0), alcoholic hepatitis (571.1), alcoholic cirrhosis of the liver (571.2), alcoholic liver damage (571.3), or cirrhosis (571.5, 571.6) in the presence of alcoholism or other alcohol-related disorders (303, 305.0, V11.3, V79.1, 291). Nonspecific cirrhosis was defined as cirrhosis (571.5, 571.6) without HCV, HBV, or alcoholic liver disease.

Statistical Analyses. Age, race/ethnicity (white, black, Hispanic, Asian, other), geographic region (SEER-13 registry region), and state buy-in status were included as covariates. The state buy-in variable indicates whether a third-party pays a beneficiary's Medicare premiums, and was thus used as an indicator of lower socioeconomic status. Demographic features and preexisting medical conditions were compared between cases and controls using *t* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI).

Wald chi-square tests determined the significance of variables in the logistic regressions. Tests of statistical significance and CIs were two-sided. A P value < 0.05 was considered statistically significant. In addition to the main analyses, several sensitivity analyses were performed. The first sensitivity analysis excluded medical conditions diagnosed in the year preceding the cancer diagnosis, whereas the second excluded undifferentiated tumors. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

Study Population. During the study period, 16448 HCC cases and 3005 ICC cases were identified and 3649 HCC cases and 743 ICC cases met the inclusion criteria. Excluded were 6118 HCC and 1317 ICC cases without histopathological confirmation; 75 HCC and 11 ICC cases without known month of diagnosis; 286 HCC and 52 ICC cases with prior cancer diagnoses within the previous 5 years; 6286 HCC and 871 ICC cases who did not meet the age, enrollment interval, or enrollment type criteria; and 34 HCC and 11 ICC cases reported solely by autopsy or death certificate. Population controls included 195,953 persons

Table 1. Demographic Characteristics of HCC Cases, ICC Cases, and Controls

Characteristic	HCC Cases (n = 3649)		P Value*	ICC Cases (n = 743)		P Value†	Controls (n = 195,953)	
	n	%		n	%		n	%
Mean age in years (SD)	76.1 (5.9)		<0.0001	76.4 (6.0)		<0.0001	77.9 (7.2)	
Sex			<0.0001			<0.0001		
Female	1,205	33.0		390	52.5		124,795	63.7
Male	2,444	67.0		353	47.5		71,158	36.3
Ethnicity			<0.0001			<0.0001		
White	2,662	73.0		619	83.3		169,154	86.3
Black	300	8.2		41	5.5		13,284	6.8
Hispanic	151	4.1		≤35‡	–		3,879	2.0
Asian	337	9.2		38	5.1		5,142	2.6
Other	199	5.5		≤35‡	–		4,494	2.3
Geographic location			<0.0001			<0.0001		
San Francisco	171	4.7		31	4.2		7,651	3.9
Connecticut	328	9.0		88	11.8		14,437	7.4
Detroit	435	11.9		70	9.4		17,125	8.7
Hawaii	113	3.1		29	3.9		2,697	1.4
Iowa	229	6.3		82	11.0		15,991	8.2
New Mexico	135	3.7		15	2.0		5,836	3.0
Seattle	223	6.1		63	8.5		10,875	5.5
Utah	76	2.1		13	1.7		5,483	2.8
Atlanta	106	2.9		32	4.3		6,786	3.5
San Jose	87	2.4		18	2.4		4,848	2.5
Arizona Native Americans	<11‡	–		<11‡	–		1,385	0.7
Los Angeles	522	14.3		94	12.7		16,243	8.3
Rural Georgia	<11‡	–		<11‡	–		665	0.3
Greater California	407	11.2		65	8.7		26,690	13.6
Kentucky	182	5.0		40	5.4		14,752	7.5
Louisiana	184	5.0		21	2.8		11,782	6.0
New Jersey	442	12.1		80	10.8		26,690	13.6
Medicare/Medicaid dual enrollment			<0.0001			0.16		
Yes	918	25.2		120	16.2		35,549	18.1

SEER-Medicare–linked databases, 1993-2005.

*P value of *t* test or chi-square test comparing persons who developed HCC to controls.

†P value of *t* test or chi-square test comparing persons who developed ICC to controls.

‡Cell sizes less than 35 for ethnicity and less than 11 for geographic location are suppressed according to the SEER-Medicare data use agreement.

without any prior cancer diagnosis who met the inclusion criteria as specified above.

Baseline Characteristics and Demographic Data. Table 1 shows the features and demographic characteristics of the study population. The HCC and ICC cases were younger ($P < 0.0001$) and more likely to be male ($P < 0.0001$) than were the controls. Although the majority of the cases and controls were white, the racial/ethnic distribution of the groups significantly varied ($P < 0.0001$). The distributions of the participants by geographic area also varied significantly ($P < 0.0001$). HCC ($P < 0.0001$), but not ICC ($P = 0.16$) cases, were more likely to have dual Medicare/Medicaid enrollment than were controls. Because of the differences in demographic features (SEER registry, dual enrollment status), these factors were included as covariates in the analysis.

Risk Factors for HCC and ICC. Table 2 displays the associations of HCC with the medical conditions categorized into four main categories: infectious diseases, chronic noninfectious liver diseases, smoking, and metabolic conditions.

Infectious etiologies, as expected, were significantly more common among persons who developed HCC than among controls ($P < 0.0001$). A diagnosis of "unspecified viral hepatitis" was also significantly associated with HCC ($P < 0.0001$). Among chronic liver diseases, alcoholic liver disease, nonspecified cirrhosis, biliary cirrhosis, and inherited metabolic disorders (hemochromatosis, Wilson's disease) were all significantly associated with the development of HCC ($P < 0.0001$). None of the HCC cases or controls had previously been diagnosed with autoimmune hepatitis (data not shown). Smoking, however, was significantly associated with the development of HCC ($P < 0.0001$).

Among the individual conditions of the metabolic syndrome, impaired fasting glucose/diabetes, dyslipoproteinemia, hypertension, and obesity were each

Table 2. Comparison of Preexisting Medical Conditions and Smoking Between Persons Who Developed HCC, and Control Persons

Preexisting Medical Conditions and Smoking	HCC Cases (N = 3649)		Controls (N = 195,953)		
	N	%	N	%	*P* Value
Infectious diseases					
HBV infection	268	7.3	442	0.2	<0.0001
HCV infection	668	18.3	616	0.3	<0.0001
Unspecified viral hepatitis	119	3.3	317	0.2	<0.0001
Chronic noninfectious liver diseases					
Alcoholic liver disease	617	16.9	832	0.4	<0.0001
Nonspecified cirrhosis	536	14.7	634	0.3	<0.0001
Biliary cirrhosis	104	2.9	140	0.1	<0.0001
Hemochromatosis	106	2.9	722	0.4	<0.0001
Wilson's disease	<11*	–	22	0.0	<0.0001
Smoking	533	14.6	9,647	4.9	<0.0001
Metabolic conditions					
Impaired fasting glucose/ diabetes mellitus	1,995	54.7	52,691	26.9	<0.0001
Dyslipoproteinemia	2,013	55.2	91,798	46.8	<0.0001
Hypertension	2,982	81.7	134,069	68.4	<0.0001
Obesity	308	8.4	9,983	5.1	<0.0001
Metabolic syndrome (overall)†	1,352	37.1	33,434	17.1	<0.0001

*Cell sizes less than 11 are suppressed according to the SEER-Medicare data use agreement.

†Following the 2001 U.S. NCEP-ATP III definition.

significantly associated with the development of HCC ($P < 0.0001$). A combination of these conditions revealed that metabolic syndrome was significantly associated with HCC (37.1% versus 17.1%, $P < 0.0001$).

Table 3 shows the associations of ICC with medical conditions as categorized in six groups. Of the bile duct diseases, biliary cirrhosis, cholangitis, cholelithiasis, and choledochal cysts were significantly more common among persons who developed ICC ($P < 0.0001$). Liver flukes were not present in any person who developed ICC. Chronic viral hepatitis infections of all types were significantly predisposed to the development of ICC ($P < 0.0001$). Chronic noninfectious liver diseases also were significantly more common among persons who developed ICC ($P < 0.0001$). Among inflammatory bowel diseases, ulcerative colitis ($P < 0.0001$) predisposed to the development of ICC, but Crohn's disease did not ($P = 0.21$). Smoking was also significantly more common among persons who developed ICC ($P < 0.0001$).

All of the individual components of the metabolic syndrome were each significantly more common among persons who developed ICC than among controls ($P < 0.0005$). Metabolic syndrome was also significantly associated with the development of ICC (29.7% versus 17.1%, $P < 0.0001$).

Logistic Regression Analyses. Tables 4 and 5 display the adjusted results of the multiple logistic regression analyses. All risk factors that were statistically significantly associated with the development of HCC or ICC in the univariate analyses remained significant in the adjusted analyses.

In the metabolic conditions group, impaired fasting glucose and/or diabetes mellitus was associated with 2.90- and 1.82-fold increased risks of HCC and ICC ($P < 0.0001$). Similarly, dyslipoproteinemia, hypertension, and obesity were each significantly ($P < 0.0001$) associated with increased risks, ranging from 1.35-1.93, of developing HCC and ICC. Combining the metabolic variables, metabolic syndrome was associated with a statistically significant 2.58- and 2.04-fold increased risk of HCC and ICC, respectively (95% CI = 2.4-2.76 [HCC] and 1.74-2.40 [ICC], $P < 0.0001$).

To investigate whether the significant associations between metabolic syndrome and risk of HCC and ICC were independent of other major liver cancer risk factors, we used a logistic regression model that adjusted for all demographic variables, as well as all risk factors that were significantly associated with HCC and ICC in the univariate analyses. As shown in

Table 3. Comparison of Preexisting Medical Conditions and Smoking Between Persons Who Developed ICC, and Control Persons

Preexisting Medical Conditions and Smoking	ICC Cases (N = 743)		Controls (N = 195,953)		
	N	%	N	%	*P* Value
Bile duct diseases					
Liver flukes	0	0.0	19	0.0097	1.0
Biliary cirrhosis	<11*	–	140	0.1	<0.0001
Cholangitis	101	13.6	420	0.2	<0.0001
Cholelithiasis	240	32.3	9.039	4.6	<0.0001
Choledochal cysts	32	4.3	213	0.1	<0.0001
Infectious diseases					
HBV infection	<11*	–	442	0.2	<0.0001
HCV infection	20	2.7	616	0.3	<0.0001
Unspecified viral hepatitis	11	1.5	317	0.2	<0.0001
Chronic noninfectious liver diseases					
Alcoholic liver disease	21	2.8	832	0.4	<0.0001
Nonspecified cirrhosis	53	7.1	634	0.3	<0.0001
Inflammatory bowel diseases	22	3.0	2,251	1.1	<0.0001
Crohn's disease	<11*	–	955	0.5	0.21
Ulcerative colitis	18	2.4	1,509	0.8	<0.0001
Smoking	78	10.5	9,647	4.9	<0.0001
Metabolic conditions					
Impaired fasting glucose/ diabetes mellitus	299	40.2	52,691	26.9	<0.0001
Dyslipoproteinemia	444	59.8	91,798	46.8	<0.0001
Hypertension	570	76.7	134,069	68.4	<0.0001
Obesity	59	7.9	9,983	5.1	0.0004
Metabolic syndrome (overall)†	221	29.7	33,434	17.1	<0.0001

*Cell sizes less than 11 are suppressed according to the SEER-Medicare data use agreement.

†Following the 2001 U.S. NCEP-ATP III definition.

Table 4. Multiple Logistic Regression Analysis Examining the Association Between HCC and Each Preexisting Medical Condition and Smoking, Adjusting for Age, Sex, Race, Geographic Location, and Medicare/Medicaid Dual Enrollment

Preexisting Medical Conditions and Smoking	Adjusted OR	95% CI	*P* Value
Infectious diseases			
HBV infection	19.87	(16.76-23.57)	<0.0001
HCV infection	62.92	(55.39-71.46)	<0.0001
Unspecified viral hepatitis	13.46	(10.68-16.97)	<0.0001
Chronic noninfectious liver diseases			
Alcoholic liver disease	35.29	(31.37-39.69)	<0.0001
Nonspecified cirrhosis	50.15	(44.03-57.12)	<0.0001
Biliary cirrhosis	46.08	(34.89-60.86)	<0.0001
Hemochromatosis	6.73	(5.43-8.35)	<0.0001
Wilson's disease	8.86	(3.21-24.49)	<0.0001
Smoking	2.97	(2.70-3.28)	<0.0001
Metabolic conditions			
Impaired fasting glucose/ diabetes mellitus	2.90	(2.71-3.10)	<0.0001
Dyslipoproteinemia	1.35	(1.26-1.45)	<0.0001
Hypertension	2.22	(2.04-2.42)	<0.0001
Obesity	1.93	(1.71-2.18)	<0.0001
Metabolic syndrome (overall)*	2.58	(2.40-2.76)	<0.0001

*Following the 2001 U.S. NCEP-ATP III definition.

Table 6, metabolic syndrome was associated with a significant 2.13-fold increased risk of HCC (95% CI = 1.96-2.31) and a significant 1.56-fold increased risk of ICC (95% CI = 1.32-1.83). Both associations were independent of all other major HCC or ICC risk factors.

Sensitivity Analyses. Several sensitivity analyses were conducted. To minimize the possibility of diagnostic detection bias, the first analysis excluded conditions that were diagnosed in the year prior to cancer diagnosis. This limited the power to detect significant associations for some rare conditions (e.g., Wilson's disease for HCC and choledochal cysts, infectious liver diseases and alcoholic liver disease for ICC). However, as in the main analysis, metabolic syndrome remained significantly associated with an increased and independent risk of both HCC and ICC (data not shown). To minimize the possibility of diagnostic misclassification, the analyses were also repeated, but restricted to histologically confirmed and well-differentiated or moderately differentiated tumors. In this analysis, ORs remained similar to the main analysis; however, the power to detect statistically significant associations between HBV infection, alcoholic liver disease, biliary cirrhosis, and ICC risk were limited. In the adjusted analyses that excluded undifferentiated tumors, metabolic syndrome remained associated with a 2.07-fold increased risk of HCC and 1.80-fold increased risk of ICC (95% CI = 1.83-2.34, $P < 0.0001$ for HCC and 1.33-2.43, $P < 0.0002$ for ICC, respectively).

Discussion

This is the first large population-based study in the United States that investigated the association between metabolic syndrome and risk for both primary liver cancers: HCC and ICC. The results indicate that preexisting metabolic syndrome, as defined by the 2001 U.S. NCEP-ATP III criteria, confers a statistically significant 2.13- and 1.56-fold increased risk for HCC and ICC that is independent of other risk factors. An indicator of the validity of the findings is that other major and previously defined HCC and ICC risk factors were confirmed in this study population.[5]

Of the patients included in this study, 42.9% of the patients with HCC and 43.3% of the patients with ICC did not have a history of any previously established risk factor (excluding metabolic conditions). Of the patients with idiopathic disease, metabolic syndrome was present in 15.7% of the HCC cases and 11.6% of the ICC cases. Among the remaining patients who did not have at least three conditions of

Table 5. Multiple Logistic Regression Analysis Examining the Association Between ICC and Each Preexisting Medical Condition and Smoking, Adjusting for Age, Sex, Race, Geographic Location, and Medicare/Medicaid Dual Enrollment

Preexisting Medical Conditions and Smoking	Adjusted OR	95% CI	*P* Value
Bile duct diseases			
Liver flukes	-	-	-
Biliary cirrhosis	17.08	(8.89-32.83)	<0.0001
Cholangitis	75.23	(59.18-95.64)	<0.0001
Cholelithiasis	10.23	(8.74-11.96)	<0.0001
Choledochal cysts	43.03	(29.16-63.49)	<0.0001
Infectious diseases			
HBV infection	3.07	(1.43-6.58)	0.004
HCV infection	8.05	(5.08-12.75)	<0.0001
Unspecified viral hepatitis	7.66	(4.14-14.18)	<0.0001
Chronic noninfectious liver diseases			
Alcoholic liver disease	5.69	(3.65-8.86)	<0.0001
Nonspecified cirrhosis	22.11	(16.47-29.68)	<0.0001
Inflammatory bowel diseases			
Crohn's disease	1.68	(0.75-3.77)	0.21
Ulcerative colitis	3.30	(2.06-5.28)	<0.0001
Smoking	2.21	(1.74-2.81)	<0.0001
Metabolic conditions			
Impaired fasting glucose/ diabetes mellitus	1.82	(1.56-2.11)	<0.0001
Dyslipoproteinemia	1.65	(1.42-1.92)	<0.0001
Hypertension	1.63	(1.37-1.93)	<0.0001
Obesity	1.71	(1.30-2.23)	0.0001
Metabolic syndrome (overall)*	2.04	(1.74-2.40)	<0.0001

*Following the 2001 U.S. NCEP-ATP III definition.

Table 6. Multiple Logistic Regression Analysis Examining the Association Between Metabolic Syndrome and HCC or ICC, Adjusting for Demographic Variables and Major HCC or ICC Risk Factors

	HCC			ICC		
	Adjusted OR†	95% Confidence interval	*P* Value	Adjusted OR‡	95% CI	*P* Value
Metabolic syndrome*	2.13	(1.96-2.31)	<0.0001	1.56	(1.32-1.83)	<0.0001

*Following the 2001 U.S. NCEP-ATP III definition.

†HCC risk factors are adjusted for demographic characteristics and HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, unspecified cirrhosis, biliary cirrhosis, hemochromatosis, Wilson's disease, and smoking.

‡ICC risk factors are adjusted for biliary cirrhosis, cholangitis, cholelithiasis, choledochal cysts, HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, nonspecified cirrhosis, inflammatory bowel disease, (Crohn's disease, ulcerative colitis), and smoking.

the metabolic syndrome, 22.4% and 24.2% of the HCC and ICC cases had a diagnosis of at least one metabolic risk factor (impaired fasting glucose/diabetes mellitus, dyslipoproteinemia, hypertension, or obesity). These findings suggest that metabolic syndrome as well as its individual components could possibly explain a relevant proportion of the idiopathic HCC or ICC cases in this study population.

The magnitude of the association between metabolic syndrome and both primary liver cancers (HCC, ICC) is similar to the risk for incident cardiovascular disease, coronary heart disease, and all-cause mortality in patients with metabolic syndrome. The relative risks for these outcomes, as reported in three meta-analyses, range from 1.27-1.93.[32-34] Given the very high prevalence of metabolic syndrome, even small increases in the absolute risk of HCC may lead to a large number of HCC cases.

The recent increase in metabolic syndrome incidence has turned NAFLD, the hepatic component of metabolic syndrome, into the most frequent liver disease in the United States and in Western countries.[6,7,19,20] In particular, NASH, defined as coexistence of hepatic fat accumulation and inflammatory changes, promotes the progression to liver fibrosis, cirrhosis, end-stage liver disease, and HCC.[6,7,9,10] Recent studies have reported that 26%-37% of persons with NAFLD and up to 9% of the persons with NASH progress to liver fibrosis and cirrhosis, suggesting that these conditions are important HCC risk factors.[7-10] There is evidence that metabolic syndrome–related HCC may also occur in the absence of cirrhotic liver changes.[22,24]

Prospective studies of metabolic syndrome and development and progression of liver disease are hampered by the large number of patients and long duration of follow-up needed to observe a relevant number of cancer outcomes. For ICC, the investigation of this association is even more difficult due to its low incidence. Several longitudinal studies investigating HCC risk in patients with NAFLD or NASH with follow-up periods between 7.6 and 19.5 years reported an incidence of HCC between 0.5%-2.8%.[7,8,21] A recent prospective study that investigated liver cancer risk in patients with NASH-related cirrhosis found a yearly cumulative HCC incidence of 2.6%, compared to 4% in patients with HCV-related cirrhosis.[35] Because most of these studies were single-center studies of referral patients, the generalizability of the reported HCC prevalence rates to the general U.S. population may be limited. In addition, some of these studies were based on small patient numbers and/or limited duration of follow-up, which may have affected their power.

The pathogenesis of NAFLD and the factors promoting the progression to NASH and end-stage liver disease among patients with metabolic syndrome are complex. Recent research has generated stimulating hypotheses on the roles of oxidative stress and lipotoxicity, cytokine action, and molecular and genetic factors that may promote development and progression of NAFLD.[36-39] The frequent co-occurrence of metabolic conditions and their interplay complicates the examination of each individual metabolic factor's contribution to liver disease and hepatocarcinogenesis. For example, it has been acknowledged that the hyperinsulinemia and insulin resistance that frequently co-occur with (central) obesity plays a main role in the development of hepatic steatosis through deposition of free fatty acids and their metabolites in liver tissue.[6,37] However, chronic liver disease may also cause hepatic insulin resistance, favoring *de novo* lipogenesis and progression of hepatic steatosis, as well as the development of metabolic risk factors such as diabetes mellitus, dyslipoproteinemia, and hypertension.[6,37] In addition, factors that cause necroinflammation (e.g., cytokines, oxidative stress) may also promote hepatic steatosis, which further complicates the delineation of cause and effect.[6] Over the last couple of years, several cohort, case-control and population-based studies have reported the association of diabetes mellitus, obesity, and risk for both types of liver cancer (HCC,

ICC).[40,41] These findings support an individual contribution of metabolic conditions to the development of NAFLD. Few of these studies, however, investigated the combined effects of all metabolic risk factors as defined by the metabolic syndrome on HCC and ICC risk.

Among other HCC and ICC risk factors, HCV infection can cause hepatic steatosis and insulin resistance that is mediated by a genotype-dependent interference of the viral core protein with intracellular insulin signaling.[42] Some studies also suggest a synergistic effect of HCV infection, metabolic risk factors, and liver cancer risk.[43,44] In this study, however, no statistically significant interaction was observed between HCV infection and metabolic syndrome (data not shown).

Although the size of the current study (3649 HCC cases, 743 ICC cases) is quite large, the study had several limitations, including the reliance on medical claims data. It should be noted, however, that Medicare files capture 100% of the coverage claims for tests, outpatients visits, and hospitalizations for patients age 65 years and older with continuous enrollment in Medicare part A and part B. To minimize the possibility of missing medical diagnosis information, we restricted all analyses to patients with a minimum of 3 years continuous Medicare enrollment. This led to the exclusion of persons $\leq$68 years of age, which may limit the generalizability of the study findings. However, the study population is representative of most persons at risk of HCC and ICC, because the median age at diagnosis in SEER registries is 70-74 years. Because Medicare claims are collected for billing rather than research purposes, the prevalences of smoking, overweight, and obesity were almost certainly underestimated. Because of the absence of a specific ICD-9-CM code for central obesity, this study likely missed persons with central adiposity who were not otherwise obese. In addition, the possibility of some misclassification of HCC as ICC at the initial hospital histopathological review can not be excluded. However, a sensitivity analysis that restricted the analyses to well and moderately differentiated tumors confirmed the significant association between metabolic syndrome and risk for both cancers. Furthermore, there is a possibility of diagnostic detection bias, because persons with HCC and ICC are more likely to undergo diagnostic workup and testing than are other persons. Analyses excluding all diagnoses in the year preceding the cancer diagnosis limited the statistical power for some conditions, but did confirm the association between metabolic syndrome and HCC and ICC, respectively.

Detailed information on the use of medications (e.g., statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sulfonylureas, insulin, biguanides, and thiazolidinediones) that might modify liver cancer risk in patients with diabetes and other metabolic risk factors were not available.[39] However, it is likely that the prescription of these drugs was equally distributed among cases and controls with a diagnosis of metabolic conditions preceding the cancer diagnosis, so that this possible bias would be nondifferential. In addition, detailed information on alcohol consumption was not available.

Finally, due to the limited time frame for the risk factor information, the duration–response relationship among metabolic syndrome, liver histologic analysis results, and risk over time could not be estimated in the present study.

Important strengths of the study are related to the data source, as well as the case and control definitions. The SEER registries maintain a 99% completeness rate for case ascertainment, and yearly data quality control checks are conducted. In addition, because SEER registries are selected to be highly representative of the U.S. population, the study findings should be highly generalizable to the U.S. population aged 68 years and older; yet, the predominantly urban population and higher proportion of foreign-born persons included in the SEER registries deserve consideration when generalizing the data to the general U.S. population. To avoid diagnostic misclassification, only patients with histologically confirmed HCC and ICC were included in the study. Although this is a conservative approach, such restriction was necessary to maximize the study's accuracy. Because the liver is a frequent site for metastatic disease, all patients with prior cancer diagnoses in the 5 years preceding the tumor diagnosis were excluded. Finally, the identification of preceding medical conditions using Medicare claims records rather than personal interview data likely avoided recall bias.

In summary, the results of this population-based study indicate that metabolic syndrome is a significant risk factor for development of both types of primary liver cancer, regardless of the presence of all other major HCC and ICC risk factors. As a result, metabolic syndrome may explain a relevant proportion of idiopathic HCC or ICC in the United States. Consequently, approaches to control the recent worldwide epidemic of metabolic syndrome could contribute to a reduction in the liver cancer burden.

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