Published in final edited form as:

Hepatology. 2011 August ; 54(2): 463–471. doi:10.1002/hep.24397.

Metabolic syndrome increases the risk of primary liver cancer in the United States: a population-based case-control study

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Abstract

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 U.S. 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% CI=1.96–2.31, $p < 0.0001$) and ICC (odds ratio=1.56; 95% CI= 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.

Keywords

Hepatocellular Carcinoma; Intrahepatic Cholangiocarcinoma; Metabolic Syndrome; SEER-Medicare-linked database

Introduction

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 as 20–50% of HCC 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 only for a small proportion of the attributable risk of ICC in the United States as many ICC cases do not appear to be associated with any of the above mentioned risk factors.⁵

In recent years, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have received increasing attention for their relationship with end-stage liver disease and hepatocellular carcinoma.^{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} as 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 percent of persons age 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 US 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 physicians' visits. Data on Medicare claims are available for Medicare parts A and B. These files contain dates of service, International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology (CPT, Version 4) codes for all billed claims.

Study Population

All persons aged 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 (HMO) during the study period as Medicare HMO 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/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 US 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 HDL), hypertension, and impaired fasting glucose.³⁰ The corresponding medical conditions were selected using the following ICD-9 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

As there is no specific ICD-9 code for elevated waist circumference, obesity served as the proxy variable. Due to the absence of a specific ICD-9 code for low HDL, this condition could not be assessed.

Risk Factor Selection

Risk factors for HCC or ICC were selected using ICD-9 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 (ICD-9 codes 571.5, 571.6) in the presence of alcoholism or other alcohol-related disorders (ICD-9 codes 303, 305.0, V11.3, V79.1, 291). Nonspecific cirrhosis was defined as cirrhosis (ICD-9 code 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 pre-existing 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 χ^2 tests determined the significance of variables in the logistic regressions. Tests of statistical significance and confidence intervals 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, while 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 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 2a displays the associations of HCC with the medical conditions categorized into four main categories: infectious diseases, chronic non-infectious liver diseases, smoking and metabolic conditions.

Infectious etiologies, as expected, were significantly more common among persons who developed HCC than 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, non-specified 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 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% vs. 17.1%, $p<0.0001$).

Table 2b 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 metabolic syndrome were each significantly more common among persons who developed ICC than among controls ($p<0.0001$). Metabolic syndrome was also significantly associated with the development of ICC (29.7% vs. 17.1%, $p<0.0001$).

Logistic regression analyses

Tables 3a and 3b 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/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 to 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 4, 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/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 investigating the association between metabolic syndrome and risk for both primary liver cancers, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). The results indicate that pre-existing metabolic syndrome, as defined by the 2001 US 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 HCC and 43.3% of the ICC patients 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 and 11.6% of the ICC cases. Among the remaining patients who did not have at least 3 conditions of 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, 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 (CVD), coronary heart disease and all-cause mortality in patients with metabolic syndrome. The combined relative risks for these outcomes, as reported in three meta-analyses, range from 1.27 to 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 they are an important HCC risk factor.^{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 by 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 a 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 As most of these studies were single-center studies of referral patients, the generalizability of the reported HCC prevalence rates to the general US population may be limited. In addition, some of these studies were based on a 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, as well as 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 factors' 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 central 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} Additionally, factors which 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 < 65 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, as the median age at diagnosis in SEER registries is 70–74 years.

As Medicare claims are collected for billing rather than research purposes, the prevalences of smoking, overweight and obesity were almost certainly underestimated. Due to the absence of a specific ICD-9 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, as HCC and ICC cases 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, ACE-inhibitors, angiotensin receptor blockers, sulfonylureas, insulin, biguanides, thiazolidinediones) suggested to 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 non-differential. Finally, detailed information on alcohol consumption was not available.

Finally, due to the limited time frame for the risk factor information, the duration-response relationship between metabolic syndrome, liver histologies 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, as SEER registries are selected to be highly representative of the US population, the study findings should be highly generalizable to the US population aged 65 years and older; yet, the more urban population and higher proportion of foreign-borne persons of the SEER registries deserve consideration when generalizing the data to the general US population. To avoid diagnostic misclassification, only patients with histologically confirmed HCC and ICC were included in the study. Although a conservative approach, such restriction was necessary to maximize the study's accuracy. As 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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Table 1

Demographic characteristics of hepatocellular carcinoma (HCC) cases, intrahepatic cholangiocarcinoma (ICC) cases and controls. SEER-Medicare linked-databases, 1993 and 2005

Characteristic	HCC Cases (n=3649)		p-value ¹		ICC Cases (n=743)		p-value ²		Controls (n=195,953)	
Mean age in years (SD)	76.1	(5.9)	<.0001		76.4	(6.0)	<.0001		77.9	(7.2)
Sex	n	%			n	%			n	%
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			<.0001				<.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			<.0001				<.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 Indians	<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

Characteristic	HCC Cases (n=3649)		p-value ¹	ICC Cases (n=743)		p-value ²	Controls (n=195,953)	
	407	11.2		65	8.7		26,690	13.6
Greater California								
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			<.0001			0.16		
Yes	918	25.2		120	16.2		35,549	18.1

¹ p-value of t-test or chi-square test comparing persons who developed HCC to controls

² p-value of t-test or chi-square test comparing persons who developed ICC to controls

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b. Comparison of pre-existing medical conditions and smoking between persons who developed intrahepatic cholangiocarcinoma (ICC) and control persons				
Pre-existing Medical Conditions and Smoking	ICC Cases (N=743)	Controls (N=195,953)	P-value	
Cholelithiasis	240	9,039	4.6	<.0001
Choledochal cysts	32	213	0.1	<.0001
Infectious diseases				
HBV infection	<11	442	0.2	<.0001
HCV infection	20	616	0.3	<.0001
Unspecified viral hepatitis	11	317	0.2	<.0001
Chronic noninfectious liver diseases				
Alcoholic liver disease	21	832	0.4	<.0001
Nonspecified cirrhosis	53	634	0.3	<.0001
Inflammatory bowel diseases				
Crohn's Disease	<11	2,251	1.1	<.0001
Ulcerative Colitis	18	1,509	0.8	<.0001
Smoking				
Metabolic conditions				
Impaired fasting glucose/Diabetes mellitus	299	52,691	26.9	<.0001
Dyslipoproteinemia	444	91,798	46.8	<.0001
Hypertension	570	134,069	68.4	<.0001
Obesity	59	9,983	5.1	0.0004
Metabolic Syndrome (overall)*	221	33,434	17.1	<.0001

* Following the 2001 US NCEP-ATP III definition.

* Following the 2001 US NCEP ATP II definition

Table 3

a. Multiple logistic regression analysis examining the association between hepatocellular carcinoma (HCC) and each pre-existing medical condition and smoking, adjusting for age, gender, race, geographic location, and Medicare/Medicaid dual enrollment			
Pre-existing Medical Conditions and Smoking	Adjusted odds ratio	95% Confidence Interval	P-value
Infectious diseases			
HBV infection	19.87	(16.76–23.57)	<.0001
HCV infection	62.92	(55.39–71.46)	<.0001
Unspecified viral hepatitis	13.46	(10.68–16.97)	<.0001
Chronic noninfectious liver diseases			
Alcoholic liver disease	35.29	(31.37–39.69)	<.0001
Nonspecified cirrhosis	50.15	(44.03–57.12)	<.0001
Biliary cirrhosis	46.08	(34.89–60.86)	<.0001
Hemochromatosis	6.73	(5.43–8.35)	<.0001
Wilsos disease	8.86	(3.21–24.49)	<.0001
Smoking	2.97	(2.70–3.28)	<.0001
Metabolic conditions			
Impaired fasting glucose/Diabetes mellitus	2.90	(2.71–3.10)	<.0001
Dyslipoproteinemia	1.35	(1.26–1.45)	<.0001
Hypertension	2.22	(2.04–2.42)	<.0001
Obesity	1.93	(1.71–2.18)	<.0001
Metabolic Syndrome (overall) *	2.58	(2.40–2.76)	<.0001

b. Multiple logistic regression analysis examining the association between intrahepatic cholangiocarcinoma (ICC) and each pre-existing medical condition and smoking, adjusting for age, gender, race, geographic location, and Medicare/Medicaid dual enrollment			
Pre-existing Medical Conditions and Smoking	Adjusted odds ratio	95% Confidence interval	P-value
Bile duct diseases			
Liver flukes	-	-	-
Biliary cirrhosis	17.08	(8.89–32.83)	<.0001
Cholangitis	75.23	(59.18–95.64)	<.0001
Cholelithiasis	10.23	(8.74–11.96)	<.0001
Cholecochal cysts	43.03	(29.16–63.49)	<.0001
Infectious diseases			
HBV infection	3.07	(1.43–6.58)	0.004
HCV infection	8.05	(5.08–12.75)	<.0001
Unspecified viral hepatitis	7.66	(4.14–14.18)	<.0001
Chronic noninfectious liver diseases			
Alcoholic liver disease	5.69	(3.65–8.86)	<.0001
Nonspecified cirrhosis	22.11	(16.47–29.68)	<.0001
Inflammatory bowel diseases			

b. Multiple logistic regression analysis examining the association between intrahepatic cholangiocarcinoma (ICC) and each pre-existing medical condition and smoking, adjusting for age, gender, race, geographic location, and Medicare/Medicaid dual enrollment			
Pre-existing Medical Conditions and Smoking	Adjusted odds ratio	95% Confidence interval	P-value
Crohn's Disease	1.68	(0.75–3.77)	0.21
Ulcerative Colitis	3.30	(2.06–5.28)	<.0001
Smoking	2.21	(1.74–2.81)	<.0001
Metabolic conditions			
Impaired fasting glucose/Diabetes mellitus	1.82	(1.56–2.11)	<.0001
Dyslipoproteinemia	1.65	(1.42–1.92)	<.0001
Hypertension	1.63	(1.37–1.93)	<.0001
Obesity	1.71	(1.30–2.23)	0.0001
Metabolic Syndrome (overall) *	2.04	(1.74–2.40)	<.0001

* Following the 2001 US NCEP ATP III definition

* Following the 2001 US NCEP ATP III definition

Table 4

Multiple logistic regression analysis examining the association between metabolic syndrome and HCC or ICC, adjusting for demographic variables and major HCC¹ or ICC² risk factors

	Hepatocellular Carcinoma		Intrahepatic Cholangiocarcinoma	
	Adjusted Odds ratio ¹	95% Confidence interval	Adjusted Odds ratio ²	95% Confidence interval
Metabolic Syndrome *	2.13	(1.96 – 2.31)	1.56	(1.32 – 1.83)
				<.0001

* Following the 2001 US NCEP III definition

¹ Adjusted for demographic characteristics and HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, unspecified cirrhosis, biliary cirrhosis, hemochromatosis, Wilson’s disease, smoking

² Adjusted for biliary cirrhosis, Cholangitis, cholelithiasis, choledochal cysts, HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, non-specified cirrhosis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, smoking