CLINICAL RESEARCH STUDY

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Independent of Cirrhosis, Hepatocellular Carcinoma Risk Is Increased with Diabetes and Metabolic Syndrome

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ABSTRACT

BACKGROUND: Hepatocellular carcinoma is the most common primary liver malignancy, commonly a sequelae of hepatitis C infection, but can complicate cirrhosis of any cause. Whether metabolic syndrome and its components, type II diabetes, hypertension, and hyperlipidemia increase the risk of hepatocellular carcinoma independent of cirrhosis is unknown.

METHODS: A retrospective cohort study was conducted using the *MarketScan* insurance claims database from 2008-2012. Individuals with hepatocellular carcinoma aged 19-64 years and age and sex-matched controls were included. Multivariate analysis of hepatocellular carcinoma risk factors was performed.

RESULTS: Hepatitis C (odds ratio [OR] 2.102) was the largest risk factor for hepatocellular carcinoma. Other independent risk factors were type II diabetes (OR 1.353) and hypertension (OR 1.229). Hyperlipidemia was protective against hepatocellular carcinoma (OR 0.885). The largest risk increase occurred with hypertension with type II diabetes and hepatitis C (OR 4.580), although hypertension and type II diabetes without hepatitis C still incurred additional risk (OR 3.399). Type II diabetes and hyperlipidemia had a similar risk if hepatitis C was present (OR 2.319) or not (OR 2.395). Metformin (OR 0.706) and cholesterol medications (OR 0.645) were protective in diabetics. Insulin (OR 1.640) increased the risk of hepatocellular carcinoma compared with the general type II diabetes population.

CONCLUSION: In the absence of cirrhosis, type II diabetes and hypertension were independent risk factors for hepatocellular carcinoma. Hyperlipidemia and medical management of type II diabetes with metformin and cholesterol medication appeared to reduce the incidence of hepatocellular carcinoma. In contrast, insulin was associated with a higher risk of hepatocellular carcinoma.

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KEYWORDS: Diabetes; Hepatocellular carcinoma; Metabolic syndrome

Hepatocellular carcinoma is the most common primary liver malignancy. Although relatively uncommon, the incidence is increasing and prognosis is poor. It has nearly tripled in the US since the 1980s[1] and is projected to surpass breast and colorectal cancer by 2030.[2] Surgical resection and liver transplantation are the only curative therapies.[3] However, these modalities often cannot be used, as hepatocellular carcinoma is often diagnosed when lesions are large in size, bilobar, or multifocal.[2,3] To improve survival and opportunities for curative therapy, early detection is required.[3]

To improve early detection, risk factors for hepatocellular carcinoma must be understood. Currently, one-third of

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hepatocellular carcinoma cases in the US are attributed to hepatitis C.[4] The Centers for Disease Control and Prevention estimates that 3.5 million people in the US are infected with hepatitis C.[5] The increase in hepatocellular carcinoma has been paralleled by increasing incidence of type II diabetes obesity, and metabolic syndrome.[6,7] Some recent studies indicated that type II diabetes may increase the risk of developing hepatocellular carcinoma.[4] A Taiwanese population study indicated that patients with cirrhosis and diabetes were twice as likely to develop hepatocellular carcinoma as cirrhotics without diabetes.[8] Another study from the Department of Veterans Affairs (VA) showed that diabetes served as a risk factor only in the setting of other well-established risk factors for hepatocellular carcinoma (ie, alcoholic cirrhosis or hepatitis B or C).[9]

CLINICAL SIGNIFICANCE

- Independent of cirrhosis, type II diabetes and metabolic syndrome increase the risk of hepatocellular carcinoma.
- Metformin and statin therapy decrease the risk of hepatocellular carcinoma.
- Hepatocellular carcinoma screening in type II diabetes and metabolic syndrome without cirrhosis may be indicated after further research.

Type II diabetes is often associated with metabolic syndrome. Current data suggest that nearly 25% of the US population meets criteria for metabolic syndrome.[6] Metabolic syndrome includes a combination of type II diabetes, obesity, hypertension, and hyperlipidemia. The suggestion of type II diabetes as a potential risk factor for hepatocellular carcinoma raises the question of whether other metabolic syndrome components, for example, hypertension, hyperlipidemia, and obesity, may also increase hepatocellular carcinoma risk.

Recently, hepatocellular carcinoma has been associated with components of metabolic syndrome in the setting of cirrhosis. However, with the magnitude of hepatocellular carcinoma and its projected increase in the US, meaningful prevention and screening may need to begin prior to the detection of cirrhosis. For this reason, we set out to determine if type II diabetes, metabolic syndrome, or its components are risk factors for hepatocellular carcinoma independent of cirrhosis.

MATERIALS AND METHODS

Population

The *MarketScan Commercial Claims and Encounters Database* (Truven Health Analytics, Bethesda, Md) captures clinical utilization, expenditures, and prescription drug claims data from a selection of large employers and health plans, including commercial insurance companies, Blue Cross and Blue Shield plans, and third-party administrators. The database includes data from approximately 100 payers, and represents insured employees and their dependents, early retirees, *Consolidated Omnibus Budget Reconciliation Act* (COBRA) individuals, and Medicare-eligible retirees with employer-provided Medicare Supplemental plans. Data from 2008 to 2012 were used, which include information on over 56 million covered lives annually.

The study population included adults >18 years of age represented in the *MarketScan Database* between 2008 and 2012 who had an outpatient visit with a primary or secondary diagnosis code of hepatocellular carcinoma (International Classification of Diseases, Ninth Revision [ICD-9] code: 155.0). In order to minimize the error that can occur with insurance coding, the diagnosis had to be present on 2 separate occasions to be included. The total number of patients with hepatocellular carcinoma was 17,446. Patients with concomitant diagnoses of hepatitis B (ICD-9: 070.2, 070.22, 070.3, 070.32), alcoholic liver damage (ICD-9: 571.0, 571.1, 571.3), hereditary hemochromatosis (ICD-9: 275.0), nonalcoholic fatty liver disease (ICD-9: 571.8), nonalcoholic steatohepatitis (ICD-9: 571.8), cirrhosis (ICD-9: 571.2, 571.5, 571.6), alpha-1 antitrypsin deficiency (ICD-9: 273.4), autoimmune hepatitis (ICD-9: 571.42), and Wilson disease (ICD-9: 275.1) were excluded. Because hepatitis C is the largest known risk factor for hepatocellular carcinoma in the US, these patients were included in the analysis to evaluate the contribution of hepatitis C with and without type II diabetes or metabolic syndrome. There were 7473 patients remaining after exclusions were applied. Controls were age and sex matched in a 1:3 fashion, creating a control group of 22,110 individuals that complied with the same exclusion criteria. The **Figure** describes how the study sample was constructed. The mean age was 57.7 years (SD ± 9.08 years), with a range of 19-64 years (**Table 1**). There was an equal distribution of males and females between cases and controls; confirming age and sex match at a rate of 1:3 (99%) was effective. Cases were categorized based on geographic region of health care consumption. Most cases were from the South at 39.72%, with the Northeast, North-central, and West regions being nearly equal in distribution (19.4%, 20.62%, and 19.19%). The geographic region was unknown in 1.06% of cases.

Methods

A univariate analysis was performed with type II diabetes (ICD-9: 250.xx), hypertension (ICD-9: 401.0, 401.1, 401.9), and hyperlipidemia (ICD-9: 272.4), as well as with hepatitis C (ICD-9: 070.54, 070.70, 070.71). The first 3 variables were chosen as they represent significant components of the metabolic syndrome. Hepatitis C was analyzed as a variable, as it currently represents the largest known risk factor for hepatocellular carcinoma. A conditional multivariable logistic regression analysis was then