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CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Risk Factors of Intrahepatic Cholangiocarcinoma in the United States: A Case-Control Study

YASSER H. SHAIB,*,† HASHEM B. EL–SERAG,*,† JESSICA A. DAVILA,* ROBERT MORGAN,* and KATHERINE A. MCGLYNN§

Sections of *Health Services Research and †Gastroenterology, Michael E. Debakey Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas; and §National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

Background & Aims: **The incidence of intrahepatic cholangiocarcinoma has been recently increasing in the United States. In this case-control study, we used the Surveillance, Epidemiology, and End Results–Medicare database to evaluate the prevalence of known risk factors for intrahepatic cholangiocarcinoma and explore other potential risk factors.** ***Methods:*** **We identified all patients with intrahepatic cholangiocarcinoma aged 65 years and older diagnosed between 1993 and 1999 in the population-based Surveillance, Epidemiology, and End Results registries (14% of the US population). Controls were randomly chosen from individuals without any cancer diagnosis in the underlying population of the Surveillance, Epidemiology, and End Results regions. We obtained information on risk factors from Medicare claims (parts A and B) for all cases and controls with at least 2 years of continuous Medicare enrollment. Unadjusted and adjusted odds ratios were calculated in logistic regression analysis.** ***Results:*** **A total of 625 cases and 90,834 controls satisfied the inclusion and exclusion criteria. Cases were older than controls (78.7 vs. 76.5 years; $P = .02$) and were more likely to be male (48.3% vs. 36.8%; $P < .0001$). The racial composition was similar between cases and controls. Several risk factors were significantly more prevalent among cases. These included nonspecific cirrhosis (adjusted odds ratio, 27.2; $P < .0001$), alcoholic liver disease (adjusted odds ratio, 7.4; $P < .0001$), hepatitis C virus infection (adjusted odds ratio, 6.1; $P < .0001$), human immunodeficiency virus infection (adjusted odds ratio, 5.9; $P = .003$), diabetes (adjusted odds ratio, 2.0; $P < .0001$), and inflammatory bowel diseases (adjusted odds ratio, 2.3; $P = .002$).** ***Conclusions:*** **This population-based study shows that in addition to previously well described risk factors, several others could be associated with intrahepatic cholangiocarcinoma. These include hepatitis C virus, human immunodeficiency virus, liver cirrhosis, and diabetes.**

In the United States, an estimated 17,550 primary liver cancers will be diagnosed in 2005.[1] Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) indicate that approximately 15% of these will be intrahepatic cholangiocarcinomas (ICC), the second most common primary liver tumor (after hepatocellular carcinoma). Studies using the SEER data have shown a marked increase in the incidence of ICC in the United States.[2,3] Most of this increase occurred after 1985, and it seems to be a true increase rather than an artifact of better detection or reclassification.[3] The reasons behind this increasing incidence are not clear, however, because the epidemiology of ICC is poorly understood in low-risk areas such as the United States. In these areas, ICC is known to be associated with disorders of the biliary tract, especially primary sclerosing cholangitis, and with inflammatory bowel diseases.[4] Whether the incidence of these conditions has changed is unclear. ICC among primary sclerosing cholangitis patients is most commonly diagnosed at a relatively young age (47 years in one study[5]), but the recent increase was noted to affect mostly older people.[3]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, as well as liver cirrhosis, regardless of etiology, have been examined as potential risk factors for ICC in countries other than the United States.[6–9] Given the high prevalence of HCV infection acquired during the 1960s and 1970s, it is conceivable that the increase in ICC incidence might be related to HCV infection.[10] In addition, several studies have suggested that diabetes

Abbreviations used in this paper: HIV, human immunodeficiency virus; HMO, health maintenance organization; ICC, intrahepatic cholangiocarcinoma; ICD, International Classification of Diseases; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

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mellitus also increases the risk of primary liver cancer: both hepatocellular carcinoma and ICC.[11,12] No studies conducted in the United States, however, have evaluated the role of HCV, HBV, diabetes, or chronic liver diseases with ICC. We therefore conducted this study to examine these potential associations and to explore other possible risk factors.

Materials and Methods

Data Source

Data used for this study were obtained from the SEER–Medicare database, which is the linkage of SEER registry information with Medicare claims data. The SEER program is an ongoing contract-supported program of the National Cancer Institute to collect population-based cancer incidence and survival data. The SEER program has included, since 1992, population-based cancer registries in 5 states and 6 metropolitan areas that represent approximately 14% of the US population.[13] These registries include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and 6 metropolitan areas: Los Angeles, San Francisco/Oakland, San Jose, Detroit, Seattle, and Atlanta. For each case identified, the SEER program collects demographic features, as well as information on the date of cancer diagnosis, cancer site, and histology. The International Classification of Diseases (ICD) for Oncology version 2 is used by SEER to classify the primary tumor site and histological type for all cancers ascertained by the program.[14]

Medicare claims data are collected for both Medicare part A and part B benefits. Medicare is the primary health insurer for approximately 97% of individuals aged 65 years and older in the United States. Persons younger than 65 years of age can be eligible for Medicare benefits because of disability or end-stage renal disease. However, these patients are significantly different from patients aged 65 years and older with regard to demographic features and clinical characteristics. Approximately 95% of Medicare beneficiaries are covered by both part A and part B benefits.[13] Medicare claims data for all part B–covered benefits include outpatient hospital services and physician office visits. These files contain dates of services, as well as both ICD 9th revision, clinical modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology version 4 codes for all billed claims.[13]

The linkage of SEER–Medicare data is a collaborative effort by the National Cancer Institute, the SEER registries, and Centers for Medicare and Medicaid Services.[13] This database contains Medicare part A and part B claims data for all patients identified by SEER registries between 1973 and 1999, although Medicare claims are available only beginning in 1991. To link patients identified by the SEER registries to information contained in the Medicare claims files, the SEER and Medicare Enrollment Databases are merged by using an algorithm that matches on social security number, name, sex, and date of birth. Using this method to perform the linkage captures approximately 93% of patients in the SEER database aged 65 years and older. Additional details regarding this linkage have been described previously.[13]

Study Population

Cases. All patients aged 65 years and older diagnosed with ICC in SEER registries who were also enrolled in Medicare between 1993 and 1999 were eligible for inclusion. Eligibility was limited to persons diagnosed no earlier than 1993 and who had 2 years of Medicare data before the date of diagnosis. Only patients with diagnostic confirmation of ICC (ICD for Oncology histology codes 8160, 8162, 8260, 8481, 8500, and 8560) were included in our analysis. Diagnostic confirmation was defined as having positive histology, cytology, laboratory test/marker study, direct visualization, or positive radiology tests. Patients with clinical diagnoses only or an unknown method of confirmation were excluded. In addition, we excluded patients diagnosed with stomach, colon, lung, pancreatic, breast, or rectal cancers within the 5 years before the date of ICC diagnosis to further ensure the inclusion of only ICC, rather than metastatic liver cancers.

Controls. The controls included in the study were derived from the 5% random sample of Medicare-enrolled beneficiaries with no cancer of any type residing in the geographic regions of SEER registries. These are noncancer controls that are linked to the SEER–Medicare data. The same inclusion/exclusion criteria used in case selection were applied to controls.

To include cases and controls with equal exposure to risk factor information, we selected only patients with continuous enrollment in Medicare parts A and B for at least the 2 years before and up to 1 year after ICC diagnosis or until death. Cases and controls were matched on the years of search for risk factors to minimize the possibility of differing testing and diagnosis trends. We excluded patients enrolled in a health maintenance organization (HMO) during this time frame because Medicare HMO plans have historically not been required to submit individual claims to Centers for Medicare and Medicaid Services for specific services received by patients enrolled in Medicare.[13] Patients whose ICC diagnoses were reported exclusively by death certificates or at autopsy were also excluded.

We studied several potential risk factors for ICC belonging to 4 broad categories: bile duct diseases, infectious etiologies, chronic noninfectious liver diseases, and 1 group of miscellaneous potential risk factors. Bile duct diseases included liver flukes (ICD-9 codes 121.1, 121.0, 121.3), nonsuppurative cholangitis (ICD-9 code 571.6), cholangitis (ICD-9 codes 575.8 and 576.1), choledocholithiasis (ICD-9 code 574.5), choledochal cysts (ICD-9 code 751.69), cholestasis (ICD-9 code 576.8), biliary cirrhosis (ICD-9 code 571.6), and anomalous bile duct (ICD-9 code 751.60). Primary sclerosing cholangitis does not have an ICD code separate from that of cholangitis (ICD-9 codes 575.8 and 576.1), so it could not be examined outside that grouping. The infectious diseases group included human immunodeficiency virus (HIV) infection