Increased Risk of Hepatobiliary Cancers After Hospitalization for Autoimmune Disease

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BACKGROUND & AIMS: **Some autoimmune diseases are associated with increased risk of liver cancer. However, there has been no comprehensive evaluation of autoimmune diseases among patients who develop different subtypes of hepatobiliary cancer. We examined the association between autoimmune diseases and cancers of the liver and biliary tract in the Swedish population.**

METHODS: **We analyzed data from national datasets at the Center for Primary Health Care Research (Lund University, Sweden). Data on patients with autoimmune disorders were retrieved from the Swedish Hospital Discharge Register, from 1964 through 2008; 33 diseases were evaluated. Hepatobiliary cancer cases were retrieved from the Swedish Cancer Registry. We calculated standardized incidence ratios (SIRs) and hazard ratios for incident cancers and deaths from hepatobiliary cancers.**

RESULTS: **Among 402,462 patients with autoimmune disorders, 582 were diagnosed with primary liver cancer, 330 with gallbladder cancer, 115 with extrahepatic bile duct cancer, and 43 with ampulla of Vater cancers. We identified 14 autoimmune conditions that were significantly associated with increased risk of primary liver cancer (overall SIR [any autoimmune disease], 2.1; 95% confidence interval [CI], 2.0–2.3), 5 conditions associated with gallbladder cancer (overall SIR, 1.3; 95% CI, 1.1–1.4), and 3 associated with extrahepatic bile duct cancer (overall SIR, 1.6; 95% CI, 1.3–1.9). The autoimmune disorders with the strongest association with primary liver cancer were primary biliary cirrhosis (SIR, 39.5; 95% CI, 28.2–53.8) and autoimmune hepatitis (SIR, 29.0; 95% CI, 9.1–68.2); ulcerative colitis was strongly associated with extrahepatic bile duct cancer (SIR, 5.6; 95% CI, 3.6–8.4). Celiac disease, Crohn's disease, systemic sclerosis, and ulcerative colitis were associated with at least 2 types of cancer. Increased hazard ratios were observed only for patients with biliary tract cancer who had been hospitalized for autoimmune conditions.**

CONCLUSIONS: **In a study of the Swedish population, we identified an increased risk of hepatobiliary cancers among individuals diagnosed with autoimmune disease. Associations among different cancer types indicate that shared immunomodulatory mechanisms determine susceptibility to hepatobiliary cancer.**

Keywords: Risk Factor; Cohort; Survival; Hepatocellular Carcinoma.

Cancers of the hepatobiliary tract are a highly fatal group of tumors that include primary liver cancer (hepatocellular carcinoma and intrahepatic bile duct cancer), extrahepatic bile duct, gallbladder, and ampulla of Vater cancers. Although biliary tract cancers are relatively rare, hepatocellular carcinoma is the third leading cause of cancer deaths worldwide.[1] Incidence of liver and extrahepatic bile duct cancers are increasing in most developed countries.[2,3] These tumors have distinct clinical and biologic features but share several risk factors including obesity, chronic inflammation, and viral infections, which supports a common etiologic mechanism with a strong immune component.[4,5]

Immune perturbations, including autoimmune diseases, have been associated with increased risk of cancer.[6–10] However, only a few studies have specifically

Abbreviations used in this paper: CI, confidence interval; ICD, *International Classification of Diseases*; SIR, standardized incidence ratio.

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examined patients diagnosed with tumors located in the hepatobiliary tract or have evaluated the effects of a single autoimmune condition on the risk of liver and biliary tract cancers.[5,11,12] Understanding the role of autoimmune diseases across each hepatobiliary site may provide insight into their etiology and impact screening practices for patients with autoimmune diseases.

Autoimmune diseases have been also associated with poor cancer survival.[13] In a previous study, patients with digestive tract cancer hospitalized for autoimmune conditions, including pernicious anemia, systemic lupus erythematosus, and psoriasis, had poorer cancer prognosis than those who did not suffer from an autoimmune disease,[14] but individual types of hepatobiliary cancer were not evaluated. Similarly, patients with hepatocellular carcinoma with autoimmune hepatitis[15] had poorer survival than those without autoimmune hepatitis, but biliary tract cancers were not assessed.

The present study examined the association between autoimmune diseases and liver and biliary tract cancer incidence and cancer-specific survival in the Swedish population.

Patients and Methods

Data from national datasets at the Center for Primary Health Care Research, Lund University, Malmö, Sweden[9,10] were used in this study, which was approved by the regional ethical review board at Lund University. National coverage was obtained by linkage of all regional Swedish registers. Data on autoimmune patients were retrieved from the Swedish Hospital Discharge Register, which includes all hospital discharges, dates of hospitalization, and diagnoses in some regions since 1964 and nationwide since 1986. We used the 7th, 8th, 9th, and 10th revisions of the *International Classification of Diseases* (ICD) to identify codes specific for autoimmune diseases, as described previously.[9] A total of 33 diseases were evaluated. No hepatobiliary cancer cases were found among patients diagnosed with chorea minor, diabetes mellitus type I, and Reiter syndrome. The individual national identification number was replaced by a serial number during the linkage to guarantee anonymity.

Cancers were identified from the nationwide Swedish Cancer Registry using ICD seventh revision (ICD-7) codes for cancers of primary liver (155.0), gallbladder (155.1), extrahepatic bile ducts (155.2), ampulla of Vater (155.3), and unspecified bile passages (155.9). Person-years of follow-up were calculated from date of the first hospital discharge diagnosis for an autoimmune disease until diagnosis of cancer, death, emigration, or end of study (December 31, 2008). In sensitivity analyses, last hospitalization was used to reduce the possibility for biased surveillance in patients who underwent treatment for autoimmune diseases. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases for autoimmune diseases that presented at least 5 cancer cases. Expected numbers were calculated based on the part of the Swedish population that was not hospitalized for autoimmune disease (Supplementary Figure 1). The expected numbers of cases were calculated as the sum of the age- (5-year groups), gender-, period- (5-year groups), region-, and socioeconomic status–specific person-years at risk in the cohort multiplied by correspondingly stratified national cancer incidence rates. Additional adjustments were made for smoking using hospitalization for chronic obstructive pulmonary disease as a surrogate (ICD-7 = 500–502; ICD-8 = 490–493; ICD-9 = 490–496; ICD-10 = J40–J49), for obesity (ICD-7 = 287.00, 287.09; ICD-8 = 277.99; ICD-9 = 278A; ICD-10 = E65-E68), and for alcoholism (ICD-9 = 303; ICD-10 = F10.1–F10.9). Ninety-five percent confidence intervals (95% CI) were calculated assuming a Poisson distribution. The impact of reverse causality was assessed by estimating the risk for all site cancers in 3 follow-up periods after last hospitalization: <1 year, 1–10 years, and >10 years. We evaluated the distribution of multiple conditions to consider the potential effect of multiple diagnoses. Given the low number of overlapping conditions (<15%), it is unlikely that the results would be affected by multiple conditions and diagnoses (data not shown).

We also examined survival associated with autoimmune conditions among hepatobiliary cancer cases (at least 5 observed cancer cases). The Cox regression analyses were used to estimate hazard ratios. The proportional hazard assumption, tested by Schoenfeld residuals and by plotting the log of the negative log of the survival function versus the log of time, was met for each of the survival models. All analyses were carried out using SAS statistical package (version 9.1; SAS Institute, Cary, NC).

Results

Among 402,462 autoimmune patients, 582 (51.3%) were diagnosed with primary liver cancer, 330 (29.1%) with gallbladder cancer, 115 (10.1%) with extrahepatic bile duct cancer, 43 (3.8%) with ampulla of Vater cancer, and 64 (5.7%) with unspecified biliary tract cancers (Table 1). The median follow-up time was <1 year (range, 0–25 years) and most of the cancer cases with an autoimmune disease were hospitalized only once for that condition.

A total of 14 autoimmune conditions were significantly associated with an increased risk of all hepatobiliary tumors combined (Table 2) (overall SIR, 1.6; 95% CI, 1.5–1.7). The risk of primary liver cancer was increased after hospitalization for 14 autoimmune diseases (overall SIR, 2.1; 95% CI, 2.0–2.3). Five autoimmune diseases were associated with an increased risk for gallbladder cancer (overall SIR, 1.3; 95% CI, 1.1–1.4), and three with extrahepatic bile duct cancer (overall SIR, 1.6;