CLINICAL RESEARCH STUDY

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Risk of Cancer in Patients with Cholecystitis: A Nationwide Population-based Study

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ABSTRACT

OBJECTIVE: The objective of this study was to evaluate the risk of cancer in patients diagnosed with cholecystitis and possible interactions between cholecystitis and cholecystectomy.

METHODS: A retrospective population-based cohort study was conducted among patients diagnosed with cholecystitis that were registered in the National Health Insurance Research Database in Taiwan between January 1, 2000 and December 31, 2010. Standardized incidence ratios (SIRs) were calculated to compare the incidence of cancer in these patients to that of the general population. Adjusted hazard ratios (HRs) were also calculated to investigate whether cholecystitis increased the risk for specific cancers.

RESULTS: During a median observation period of 5.4 years, 1541 cancers occurred in 20,431 patients with cholecystitis, yielding a SIR of 1.97 (95% confidence interval [CI], 1.88-2.07). A significantly greater risk of biliary tract cancer (adjusted HR 1.72; 95% CI, 1.08-2.75) was observed after adjusting for potential risk factors. In contrast, cholecystectomy was found to attenuate the cancer risk, with the reduction of adjusted HR from 2.34 (95% CI, 1.62-3.37) to 1.28 (95% CI, 0.76-2.14).

CONCLUSION: Cholecystitis is an independent risk factor to extrahepatic biliary tract cancers, whereas cholecystectomy can attenuate the cancer risk of cholecystitis.

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KEYWORDS: Cancer risk; Cholecystectomy; Cholecystitis

Acute cholecystitis is an inflammatory disease of the gallbladder that often results from a complication of cholelithiasis. It is frequently observed clinically and accounts for approximately 3%-10% of hospitalizations for abdominal pain.[1] Cholecystectomy is generally used to treat patients with cholecystitis or symptomatic gallstones.

Many studies have shown that the risk of gastrointestinal cancers increases with cholelithiasis or after cholecystectomy.[2-8] In addition to the well-established association between inflammation and carcinogenesis,[9] increased or consistent exposure to bile or secondary bile acids were found to be carcinogenic in epithelial tissues outside of the gallbladder.[10-12] Furthermore, elevated serum

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cholecystokinin is also thought to increase the risk of pancreatic and colon cancers.[13-15] A recent Norwegian study also revealed twofold increase in the overall cancer risk for patients with acute cholecystitis compared with patients with symptomatic gallstones.[16] This suggested that more pronounced inflammation is associated with a greater cancer risk. However, most of these studies had limited adjustment for the potential risk factors for each specific cancer. In addition, no study to date has focused on the general and specific cancer risks in patients with cholecystitis in a nationwide population. By using the National Health Insurance Research Database (NHIRD) of Taiwan, we examined the relative risk of malignancies, including specific cancer types, of patients with cholecystitis compared with the general population, with adjustment of a large number of documented risk factors for the cancers, and detailed analysis of interaction between cholecystitis and cholecystectomy.

CLINICAL SIGNIFICANCE

- Cholecystitis is an independent risk factor for extrahepatic biliary tract cancers even after adjusting for several demographic characteristics and comorbidities.
- Cholecystectomy might attenuate the cancer risk of cholecystitis.

METHODS

Data Sources

Beginning in 1995, the National Health Insurance (NHI) program was established as a mandatory, universal health insurance program in Taiwan that covers more than 99% of the Taiwanese population.[17] The NHIRD is managed by the National Health Research Institute of Taiwan and consists of detailed health care data from more than 25 million enrollees that cover outpatient, inpatient, emergency, dental, traditional Chinese medicine services, and prescription drugs. The Longitudinal Health Insurance Database (LHID) is a subset of the NHIRD and is a representative database containing 1,000,000 patients that are randomly sampled from the registry of all enrollees. The Registry for Catastrophic Illness was used to identify subjects who were diagnosed with cancer (International Classification of Diseases, 9th Revision, Clinical Modification code [ICD-9-CM]: 140-208) and contains comprehensive enrollment information for all patients with severe diseases who have received copayment exemption under the NHI program. Applications for a Catastrophic Illness Certificate require histological confirmation. The accuracy of diagnosis of major diseases in the NHIRD has been validated in several studies.[17-19]

All information that could potentially identify an individual patient was encrypted. Confidentiality of data was maintained in accordance with the data regulations of the Bureau of National Health Insurance and the National Health Research Institute. This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (IRB number 2013−01−006AC).

Study Population

Cholecystitis Cohort. A retrospective cohort study was conducted between January 1, 2000 and December 31, 2010 using the LHID. Inpatients who had cholecystitis (ICD-9-CM: 574.00, 574.01, 574.10, 574.11, 574.30, 574.31, 574.40, 574.41, 574.60, 574.61, 574.70, 574.71, 574.80, 574.81, 575.0, 575.10) in the first 5 discharge diagnoses, and outpatients who had cholecystitis in the first 3 diagnostic codes between January 2000 and December 2009, were 20 years of age or older, and had no prior malignancies (ICD-9-CM: 140-208 from 1995 to 1999 in NHIRD) were enrolled in the *cholecystitis cohort*. Different definitions of enrollment (coding of cholecystitis twice or thrice in the medical records) were also used to test whether the results remained robust.

LHID Cohort. All enrollees in LHID who were 20 years of age or older and had no prior malignancies were enrolled in the LHID cohort, which was a representative sample of the general population. The observation period of this cohort was also from January 1, 2000 to December 31, 2010.

Statistical Analyses

Standardized Incidence Ratio of Malignancies in the Cholecystitis Cohort. The main dependent variable was the occurrence of cancer. The cohorts were followed until cancer developed, death occurred, the patient dropped out of the NHI program, or until the end of the year 2010. The risk of cancer among the cohorts was determined by calculating the standardized incidence ratio (SIR) defined as the observed number of cancer occurrences divided by the expected number of occurrences. The number of expected occurrences was calculated by multiplying the national incidence rate of cancers stratified by sex, calendar year, and age in 5-year intervals by the corresponding stratum-specific person-time accrued in the cohort. The incidence rates of cancers among the general population were obtained from the Taiwan National Cancer Registry. The 95% confidence interval (CI) for each SIR was estimated based on the assumption that the observed number of cancers followed a Poisson probability distribution. SIRs for subgroups according to sex, age, and duration of follow-up were also calculated.

Hazard Ratios of Cholecystitis for Specific Types of Cancer in the LHID Cohort. In the LHID cohort, crude and adjusted hazard ratios (HRs) of cholecystitis were estimated by a Cox proportional hazard model for each type of cancer that yielded a significantly increased SIR in our data. The adjusted risk factors, listed by ICD-9-CM code, included hepatitis B (070.2, 070.3, V02.61), hepatitis C (070.41, 070.44, 070.51, 070.54, V02.62), liver cirrhosis