Risk factors of intrahepatic cholangiocarcinoma in patients with hepatolithiasis: a case-control study

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BACKGROUND: **Why 3.3% to 10% of all patients with hepatolithiasis develop intrahepatic cholangiocarcinoma (ICC) remains unknown. We carried out a hospital-based case-control study to identify risk factors for the development of ICC in patients with hepatolithiasis in China.**

METHODS: **Eighty-seven patients with pathologically diagnosed hepatolithiasis associated with ICC and 228 with hepatolithiasis alone matched by sex, age (±2 years), hospital admittance and place of residence were interviewed during the period of 2000-2008. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each risk factor.**

RESULTS: **Among the patients with hepatolithiasis associated with ICC, the mean age was 57.7 years and 61.0% were female. Univariate analysis showed that the significant risk factors for ICC development in hepatolithiasis were smoking, family history of cancer, appendectomy during childhood (under age 20), and duration of symptoms >10 years. In multivariate stepwise logistic regression analysis, smoking (OR=1.931, 95% CI: 1.000-3.731), family history of cancer (OR=5.175, 95% CI: 1.216-22.022), and duration of symptoms >10 years (OR=2.348, 95% CI: 1.394-3.952) were independent factors.**

CONCLUSION: **Smoking, family history of cancer and duration of symptoms >10 years may be risk factors for ICC in patients with hepatolithiasis.**

(***Hepatobiliary Pancreat Dis Int 2011; 10: 626-631***)

KEY WORDS: **risk factors; intrahepatic cholangiocarcinoma; hepatolithiasis; case-control study**

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common malignancy after hepatocellular carcinoma among the primary liver cancers, accounting for 3% of all gastrointestinal cancers worldwide.[1] There is a marked regional variation in the incidence of ICC, linked strongly to the distribution of risk factors. Hepatolithiasis is uncommon in Western countries, but is prevalent in East Asia including China, Japan, and Korea because of poor nutritional status and poor sanitation.[2, 3] A strong correlation has been reported between hepatolithiasis and ICC.[4-13] However, why 3.3% to 10% of all patients with hepatolithiasis develop ICC remains unknown. The present hospital-based case-control study was undertaken to identify risk factors for the development of ICC in patients with hepatolithiasis.

Methods

Study population

One hundred and thirty-seven patients diagnosed with hepatolithiasis associated with ICC in Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Shanghai, China) between February 2000 and May 2008 were eligible for inclusion. To ensure the inclusion of patients, only those with histologically confirmed ICC were selected and those diagnosed with other cancers within 5 years before the date of ICC diagnosis were excluded. We excluded 33 patients with a clinical diagnosis only, 8 with combined hepatocellular cholangiocarcinoma, and 9 who had been diagnosed

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doi: 10.1016/S1499-3872(11)60106-9

with other cancers within 5 years before the diagnosis of ICC. Finally, the remaining 87 patients with histopathologically confirmed ICC were enrolled in this study.

Eligible control subjects were 547 patients with hepatolithiasis alone who underwent hepatectomy in our hospital between 2000 and 2008. We excluded patients diagnosed with cancers or who were missing any data regarding risk factors and cancers. After excluding unsuitable individuals, we identified 228 patients matched with the case group by sex, age (±2 years), and date of admission. This study was conducted in accordance with the *Helsinki Declaration* and the guidelines of the Ethics Committee of our hospital.

Data collection

Data were obtained by review of the complete medical history collected from patient files. The following data were recorded in a protocol: 1) duration of symptoms; 2) family history of cancer in first-degree relatives; 3) previous biliary surgery and other surgery; 4) other present diseases such as diabetes mellitus, hypertension, primary sclerosing cholangitis, inflammatory bowel disease, and liver fluke infection (*Clonorchis sinensis* or *Opisthorchis viverrini*); and 5) smoking, alcohol consumption, and exposure to chemicals. We assessed total alcohol intake in grams of ethanol consumed per day (g/day) according to the average ethanol content of wine (12% by volume), beer (5%) and white spirit (40%). An overall measure of lifetime alcohol intake was then calculated. Heavy alcohol consumption was defined as drinking at least 80 g of alcohol per day.[12] A smoker was defined as someone who had smoked 20 cigarettes or more per day for more than 1 year.[14]

Blood samples were taken from all patients in the first morning after hospital admission, and tested for HBsAg and anti-HCV using commercial enzyme-linked immunosorbent assays (ELISA; Abbott Laboratories, North Chicago, IL., USA).

Statistical analysis

Univariate analysis was performed using the Chi-square or Fisher's exact test for categorical variables and Student's *t* test for continuous variables. Variables with a *P* value of less than 0.05 in the univariate analysis were further tested in a multiple logistic regression analysis using conditional logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each risk factor. All statistical tests were two-sided with a significance level of 0.05. These analyses were performed using SPSS 11.0 software (SPSS Inc., Chicago, IL., USA).

Results

The sex and age distributions of the two groups were similar. Among the cases of hepatolithiasis associated with ICC, the mean age was 57.7 years, and 61.0% were female. With regard to location, the tumor was present in both liver lobes in 8 patients, only in the right lobe in 18, and only in the left lobe in 61. Right upper quadrant pain was the most frequent symptom encountered in the two groups. Anorexia and weight loss occurred more

Table 1. Clinical characteristics of cancer and matched control groups

Variables	Cancer group (*n*=87, %)	Control group (*n*=228, %)	*P* value
Sex			0.8240
Female	53 (61.0)	142 (62.3)	
Male	34 (39.0)	86 (37.7)	
Age (mean±SD, yr)	57.7±9.2	58.3±6.7	0.5444
<50	7 (8.0)	14 (6.1)	
≥50	80 (92.0)	214 (93.9)	
CA19-9 >37.0 U/mL	77 (88.5)	67 (29.4)	<0.0001
Symptoms			<0.0001
Right upper quadrant pain	72 (82.8)	207 (90.8)	
Fever and chills	26 (29.9)	97 (42.5)	
Anorexia	11 (12.6)	8 (3.5)	
Weight loss	13 (14.9)	3 (1.3)	
Jaundice	3 (3.4)	29 (12.7)	
Type of biliary surgery			<0.0001
Exploratory laparotomy biopsy with or without T tube	17 (19.5)	0 (0)	
Left lateral sectionectomy	6 (6.8)	112 (49.1)	
With choledochostomy	4 (4.5)	74 (32.4)	
With choledochojejunostomy	0 (0)	6 (2.6)	
Left hepatectomy	37 (42.5)	26 (11.4)	
With choledochostomy	0 (0)	12 (5.2)	
With choledochojejunostomy only	0 (0)	6 (2.6)	
With CBD resection	21 (24.1)	0 (0)	
With caudate lobe and CBD resection	4 (4.5)	0 (0)	
Left trisegmentectomy	2 (2.2)	2 (0.8)	
Right hepatectomy	18 (20)	38 (16.7)	
With choledochostomy	0 (0)	27 (11.8)	
With CBD resection	9 (10.3)	0 (0)	
With caudate lobe and CBD resection	3 (3.4)	0 (0)	
Right segmentectomy	5 (5.7)	13 (5.7)	
With choledochostomy	0 (0)	9 (3.9)	
Bilateral hepatectomy	2 (2.2)	23 (10.1)	
Choledochostomy only	0 (0)	14 (6.1)	

CBD: common bile duct.

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