World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i35.12615

World J Gastroenterol 2014 September 21; 20(35): 12615-12620
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OBSERVATIONAL STUDY

Risk factors for combined hepatocellular-cholangiocarcinoma: A hospital-based case-control study

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Received: February 14, 2014 Revised: May 22, 2014
Accepted: June 14, 2014
Published online: September 21, 2014

Abstract

AIM: To identify risk factors contributing to the development of combined hepatocellular-cholangiocarcinoma (CHC) in China.

METHODS: One hundred and twenty-six patients with CHC and 4:1 matched healthy controls were interviewed during the period from February 2000 to October 2012. Logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for each risk factor.

RESULTS: Univariate analysis showed that the significant risk factors for CHC development were hepatitis B virus (HBV) infection, heavy alcohol consumption, a family history of liver cancer, and diabetes mellitus. Multivariate stepwise logistic regression analysis showed that HBV infection (OR = 19.245, 95%CI: 13.260-27.931) and heavy alcohol consumption (OR = 2.186, 95%CI: 1.070-4.466) were independent factors contributing to the development of CHC.

CONCLUSION: HBV infection and heavy alcohol consumption may play a role in the development of CHC in China.

Key words: Risk factors; Combined hepatocellular-cholangiocarcinoma; Hepatitis B virus; Alcohol consumption; Epidemiology

Core tip: Combined hepatocellular-cholangiocarcinoma (CHC) is a rare form of primary liver malignancy that includes intimately mixed elements of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Although risk factors for the development of HCC and ICC have been studied extensively, the etiology of CHC remains unknown. We carried out a hospital-based case-control study to identify risk factors contributing to the development of CHC in China.

Zhou YM, Zhang XF, Wu LP, Sui CJ, Yang JM. Risk factors for combined hepatocellular-cholangiocarcinoma: A hospital-based case-control study. *World J Gastroenterol* 2014; 20(35): 12615-12620 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i35/12615.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i35.12615

INTRODUCTION

Histologically, primary liver cancer can be grossly classified as either hepatocellular carcinoma (HCC) arising from hepatocytes or intrahepatic cholangiocarcinoma (ICC) arising from the bile duct epithelium. Combined hepatocellular-

cholangiocarcinoma (CHC) is a rare form of primary liver malignancy that includes intimately mixed elements of both HCC and ICC[1]. Although risk factors for the development of HCC and ICC have been studied extensively, the etiology of CHC remains unknown. The aim of the present hospital-based case-control study was to identify risk factors for the development of CHC.

MATERIALS AND METHODS

Cases and controls

One hundred and twenty-six patients were treated for CHC between February 2000 and October 2012 in the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University in Shanghai, China. The pathological specimens were obtained from hepatectomy (n = 123) or needle biopsy (n = 3). The diagnosis of CHC was made based on a combination of histological findings and immunohistochemical staining. The immunoreactivity of HCC component for hepatocyte paraffin 1 (Hep Par 1) but not cytokeratin (CK)7/19, and the reactivity of ICC component for CK7/19 but not Hep Par 1 were confirmed. Patients diagnosed with other cancers within 5 years before the date of CHC diagnosis were excluded. Hospital controls without diagnoses of cancers matched 4:1 with the CHC patients by age (± 2 years) and sex were selected from individuals who underwent routine health examinations in the same hospital. This study was conducted in accordance with the Helsinki Declaration and the guidelines of the ethics committee at our institution.

Data collection

All information was obtained by review of the complete medical histories from the patient archives. The following data were recorded: (1) daily habits including alcohol consumption and smoking; (2) other medical conditions such as primary sclerosing cholangitis (PSC), inflammatory bowel disease (IBD), hepatolithiasis, liver fluke (*Clonorchis sinensis* or *Opisthorchis viverrini*) infestation, diabetes mellitus (DM), and hypertension; (3) information concerning hepatitis B virus (HBV) and hepatitis C virus (HCV) infections; and (4) information concerning cancer on the family history in first-degree relatives (parents, siblings, and children).

Total alcohol intake was assessed in grams of ethanol consumed per day (g/d) according to the mean ethanol content of wine (12% by volume), beer (5%) and white spirit (40%), based on which 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[2]. A smoker was defined as someone who had smoked one cigarette or more per day for more than 1 year. Heavy smokers were defined as those who had > 20 pack-years of smoking[3].

Blood samples were taken from all patients on the first morning of hospital admission, and tested for HBV surface antigen (HBsAg) and anti-HCV antibody using a commercial ELISA kit (Abbott Laboratories, North Chicago, IL, United States).

Statistical analysis

Univariate analyses were performed using the χ^2 or Fisher's exact test for categorical variables and t test for continuous variables. Multivariate logistic regression was performed to identify independent factors for CHC development. Odds ratios (OR) and 95%CI were calculated for each risk factor. A P-value < 0.05 was considered statistically significant. These analyses were performed using SPSS 11.0 software (SPSS Inc., Chicago, IL, United States).

RESULTS

The CHC patients and healthy controls had a similar mean age (57.7 years *vs* 58.4 years) and consisted of a similar proportion of men (82.5% *vs* 82.5%). Univariate analysis showed that HBV infection, heavy alcohol consumption, a family history of liver cancer and DM were possible risk factors contributing to the development of CHC. The prevalence of HCV infection, hypertension, hepatolithiasis and cigarette smoking were not significantly associated with the risk of CHC development (Table 1).

None of the 126 CHC patients had PSC, IBD, or liver fluke infestation. Histopathologic examination showed that 81 (64.3%) patients had liver cirrhosis, 69 of whom were serologically positive for HBV. As no information about liver cirrhosis of the controls was available, we were unable to estimate the magnitude of CHC risk associated with the factor.

Multivariate stepwise logistic regression analysis showed that HBV infection (OR = 19.245, 95%CI: 13.260-27.931) and heavy alcohol consumption (OR = 2.186, 95%CI: 1.070-4.466) were independent.

DISCUSSION

CHC is a rare entity that represents 1.0%-4.7% of primary liver malignancies[1]. Although the clinicopathologic features and radiological presentations of CHC have been studied extensively[4-14], little is known about risk factors for its development.

To the best of our knowledge, this is the first hospital-based case-control study in China to examine risk factors for CHC. Our results suggest that HBV infection is a strong risk factor for the development of CHC, which is similar to what is noted in HCC and ICC[15]. We did not observe any significant association between HCV infection and CHC. HBV infection is more common than HCV infection in China. Previous studies indicated that prevalence of HCV infection in CHC patients ranged from 0% to 70% and that of HBV infection from 7.6% to 92.8% (Table 2)[4-14,16-36]. The disparities between these series may be mainly attributed to the geographic and ethnic differences in the prevalence of viral hepatitis.

The mechanism underlying the more likelihood of CHC development in patients infected with HBV remains unclear. Hepatic progenitor cells (HPCs), also known as oval cells, which are located in the ductules and/or canal

Table 1 Univariate analysis of risk factors for combined hepatocellular-cholangiocarcinoma *n* (%)

Risk factor	Cases (*n* = 126)	Controls (*n* = 504)	OR (95%CI)	*P* value
HBV				< 0.001
HBsAg (-)	38 (30.2)	446 (88.5)	1 (Reference)	
HBsAg (+)	88 (69.8)	58 (11.5)	17.808 (11.145-28.452)	
HCV				0.563
HCV-Ab (-)	125 (99.2)	502 (99.6)	1 (Reference)	
HCV-Ab (+)	1 (0.8)	2 (0.4)	2.008 (0.181-22.322)	
Heavy smoking				0.395
No	88 (69.8)	371 (73.6)	1 (Reference)	
Yes	38 (30.2)	133 (26.4)	1.205 (0.784-1.850)	
Heavy alcohol consumption				0.018
No	105 (83.3)	457 (90.7)	1 (Reference)	
Yes	21 (16.7)	47 (9.3)	1.945 (1.115-3.392)	
Diabetes mellitus				0.024
No	113 (89.7)	479 (95.0)	1 (Reference)	
Yes	13 (10.3)	25 (5.0)	2.204 (1.094-4.443)	
Hypertension				0.855
No	110 (87.3)	443 (87.9)	1 (Reference)	
Yes	16 (12.7)	61 (12.1)	1.056 (0.586-1.903)	
Hepatolithiasis				0.262
No	124 (98.4)	501 (99.4)	1 (Reference)	
Yes	2 (1.6)	3 (0.6)	2.694 (0.445-16.294)	
Family history of liver cancer				< 0.001
No	108 (85.7)	489 (97.0)	1 (Reference)	
Yes	18 (14.3)	15 (3.0)	5.433 (2.655-11.120)	
Family history of other malignancies				0.636
No	99 (78.6)	386 (76.6)	1 (Reference)	
Yes	27 (21.4)	118 (23.4)	0.892 (0.556-1.431)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HbsAg: Hepatitis B surface antigen; HCV-Ab: Anti-HCV antibody.

of Hering and are thought to differentiate into either hepatocytes or cholangiocytes, can give rise to hepatic malignancies. Theise *et al*[37] found that the tumors contained undifferentiated cells that merged with both HCC and ICC components as well as with mature appearing hepatocytes. The morphological and immunohistochemical features of these cells are strikingly similar to those of HPCs. In addition, tumor cells of transition zone in CHC have been shown to frequently express HPC markers such as CK7, CK19 and c-kit[24]. Furthermore, Suzuki *et al*[38] demonstrated that HPCs isolated from the 3,5-diethoxycarbonyl-1,4-dihydrocollidine-treated p53-null mouse liver could form tumors with some characteristics of both HCC and ICC in NOD/SCID mice. Therefore, it could be postulated that CHC may derive from HPCs undergoing a malignant transformation. Hepatitis B virus X (HBX) protein, a small 17-kDa soluble protein, functions as a transcriptional activator that is implicated in HBV-associated hepatocarcinogenesis. There is evidence that HBX treatment resulted in an increase in the S phase cell cycle fraction and a decrease in apoptosis of HPCs[39].

Cirrhosis was identified in 64.3% CHC cases in our series. Indeed, most CHC patients have underlying cirrhosis in a world context (Table 2). It is possible that cirrhosis is a premalignant condition that predisposes to CHC, as is the case with HCC and ICC.

In addition to the association with HBV infection, our study also revealed an association between CHC and heavy alcohol consumption. It is possible that this association is related to alcoholic liver disease including cirrhosis.

Many studies have examined the association between DM and HCC or ICC and yielded inconsistent findings[40,41]. DM is suggested as a risk factor for nonalcoholic fatty liver disease and more severe nonalcoholic steatohepatitis, which can lead to liver fibrosis, cirrhosis, and subsequently to liver cancer[40]. HCV, a well-known risk factor for HCC and ICC, was also reported to be associated with DM[42]. A case-control study from the United States reported that DM increased the risk of HCC (OR = 1.57) only in the presence of HCV, HBV, or alcoholic cirrhosis but not in cases without these risk factors (OR = 1.08)[43]. Similarly, another case-control study from the United States reported that DM was not a significant risk factor for ICC after controlling for race, age, gender, HCV, HBV, and heavy drinking[44]. Univariate analysis of the present study showed that DM was a significant risk for CHC, but multivariate analysis failed to confirm this association. It is possible that that DM might be a confounding factor associated with other risk factors rather than a true risk factor *per se*.

We also observed a relationship between a family history of liver cancer and the risk of CHC, but this effect was not confirmed by multivariate analysis. HBV infection is thought to be one of the main environmental factors responsible for familial aggregations of liver cancer. In the current study, the proportion of HBsAg positivity was higher in CHC patients with a family history of liver cancer than those without a family history of liver cancer (88.9% *vs* 66.7%; $P = 0.057$). It is possible that in the

Table 2 Rates of cirrhosis, hepatitis B virus and hepatitis C virus infection in studies with more than 10 cases of combined hepatocellular-cholangiocarcinoma

Author	Country	Year	No. of patients	Male/Female	Age year[1]	Cirrhosis *n* (%)	HBsAg *n* (%)	HCV-Ab *n* (%)
Aoki *et al*[4]	Japan	1993	20	18/2	55.8	12 (60)	5 (25)	NA
Haratake *et al*[5]	Japan	1995	13	10/3	64.8	11 (84.6)	1 (7.6)	3/5 (60)
Maeda *et al*[6]	Japan	1995	29	27/2	59.8	10 (34.5)	6 (22.2)	10/16 (62.5)
Taguchi *et al*[7]	Japan	1996	23	15/8	64.0	9 (39)	4 (17)	14/20 (70)
Sasaki *et al*[8]	Japan	1999	21	NA	NA	17 (80.9)	7 (33.3)	5/16 (31.3)
Yano *et al*[9]	Japan	2003	26	23/3	57.0	14 (54)	7 (27)	10 (38)
Sanada *et al*[10]	Japan	2005	11	7/4	66.4	5 (46)	5 (46)	6 (55)
Aishima *et al*[11]	Japan	2006	40	36/4	58.1	11 (27.5)	17/37 (45.9)	12/32 (37.5)
Wakasa *et al*[12]	Japan	2007	18	14/4	56.7	5 (27.7)	4 (22.2)	7/16 (43.8)
Ariizumi *et al*[13]	Japan	2011	44	31/11	65.0	23 (52)	11 (25)	24 (55)
Akiba *et al*[14]	Japan	2013	54	45/9	66.0	14 (25.9)	14 (25.9)	21 (38.8)
Koh *et al*[16]	Korea	2005	24	16/8	55.0	13 (54.2)	13 (54.2)	3 (12.5)
Lee *et al*[17]	Korea	2006	33	22/11	52.0	16 (48.5)	16 (48.5)	4 (12.1)
Shin *et al*[18]	Korea	2007	12	11/1	48.1	8 (66.6)	9 (75)	1 (8.3)
Kim *et al*[19]	Korea	2009	29	23/6	53.0	17 (58.6)	22 (75.9)	1 (3.4)
Kim *et al*[20]	Korea	2010	50	41/9	56.3	27 (54)	40 (80)	2 (4)
Lee *et al*[21]	Korea	2011	30	26/4	61.1	22 (73.3)	19 (63.3)	1 (3.3)
Park *et al*[22]	Korea	2011	21	15/6	59.0	13 (62)	17 (81)	0
Zuo *et al*[23]	China	2007	15	11/4	49.0	11 (73.3)	11 (73.3)	3 (20)
Zhang *et al*[24]	China	2008	12	8/4	48.0	7 (58.3)	7 (58.3)	0
Yu *et al*[25]	China	2011	14	12/2	53.6	10 (71.4)	13 (92.8)	0
Yin *et al*[26]	China	2012	103	83/20	50.0	69 (66.9)	76 (73.4)	1 (0.97)
Zhan *et al*[27]	China	2012	27	24/3	58.3	10 (37)	8 (29.6)	4 (14.8)
Yap *et al*[28]	Taiwan	2012	11	8/3	61.0	8 (72)	6 (54)	2 (18)
Lee *et al*[29]	Taiwan	2013	65	48/17	55.7	27/47 (57.4)	32 (49.2)	11 (16.9)
Ng *et al*[30]	Hong Kong	1998	21	18/3	49.7	10 (47.6)	12/16 (75)	NA
Chantajitr *et al*[31]	Thailand	2006	25	18/7	53.4	11 (50.0)	12 (66.7)	2 (13.3)
Phongkitkarun *et al*[32]	Thailand	2007	10	7/3	53.5	5 (50)	4 (40)	1 (10)
Jarnagin *et al*[33]	USA	2002	27	14/13	61.0	0	4 (15)[2]	NA
Panjala *et al*[34]	USA	2010	12	8/4	61.0	10 (83.3)	2 (16.6)	5 (41.6)
Cazals-hatem *et al*[35]	France	2004	15	14/1	59.8	4 (27)	NA	4 (27)
Portolani *et al*[36]	Italy	2008	18	NA	NA	14 (77.7)	3 (16.6)	11 (61.1)

[1]Mean or median; [2]Hepatitis B or C. NA: Not available; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HCV-Ab: Anti-HCV antibody.

absence of environmental factors, a familial tendency for CHC is not expressed.

A study from a United States reported that two of their 27 CHC patients had documented intrahepatic infection with *Clonorchiasis sinensis* and *Schistosoma mansoni*[33]. Hong *et al*[45] reported a case of CHC from the Philippines with underlying *Schistosoma mansoni*, maintaining that the HCC and ICC each developed coincidentally or subsequently from fibrosis after recurrent inflammation at the site of *Schistosoma mansoni* infection. However, no patient in our series showed evidence of liver fluke infestation. Further research on the etiological relationship between liver fluke infestation and CHC is needed.

The present study has some limitations. (1) it is a hospital-based rather population-based study in a single medical institution, which may lead to selection bias; (2) the number of CHC cases in our study was small because of the relatively low incidence of this disease, resulting in a wide confidence interval in the estimated OR; and (3) virological factors, including positive HBeAg, genotype C compared to B, pre-S deletion, precore mutations and basal core promoter mutations, have been identified to be associated with an increased risk of HCC[46]. Given the absence of adequate information concerned in this study, further studies are needed to investigate the role of these virological factors in the development of CHC.

In conclusion, our results suggest that HBV infection and heavy alcohol consumption may be risk factors for CHC in China. Vaccination plays a central role in HBV prevention strategies worldwide, and a decline in the incidence of HCC following the introduction of neonatal HBV vaccination has been observed in China. Compared with 1980-1983, liver cancer incidence during 1990-1993 significantly decreased 3.4-fold at ages 20-24, and 1.9-fold at ages 25-29 when the first vaccinees were < 11 years old[47]. On the other hand, nucleoside analogue therapy use was found to be associated with reduced risk of HBV related HCC[48]. Accordingly, vaccination against and treatment of HBV might have the potential benefits in prevention of CHC. Additional studies regarding this issue are warranted.

ACKNOWLEDGMENTS

We thank Doctor Yan-Fang Zhao (Department of Health Statistics, Second Military Medical University, Shanghai 200438, China) for her critical revision of the statistical analysis section.

COMMENTS

Background

Histologically, primary liver cancer can be grossly classified as either hepatocellular carcinoma (HCC) arising from hepatocytes or intrahepatic cholangiocarcinoma (ICC) arising from the bile duct epithelium. Combined hepatocellular-cholangiocarcinoma (CHC) is a rare form of primary liver malignancy that includes intimately mixed elements of both HCC and ICC. Although risk factors for the development of HCC and ICC have been studied extensively, the etiology of CHC remains unknown.

Research frontiers

The present hospital-based case-control study was to identify risk factors for the development of CHC.

Innovations and breakthroughs

This is the first hospital-based case-control study in China to examine risk factors for CHC. The authors found that hepatitis B virus (HBV) infection is a strong risk factor for the development of CHC, which is similar to what is noted in HCC and ICC.

Applications

Vaccination against and treatment of HBV might have the potential benefits in prevention of CHC.

Peer review

The paper deals with an important clinical problem, *i.e.*, the risk factors for hepatocellular-cholangiocarcinoma.

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P- Reviewer: Festi D, Nakano H **S- Editor**: Nan J
L- Editor: Wang TQ **E- Editor**: Du P

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ISSN 1007-9327
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