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.

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 (CK7/19), 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 \(\chi^2\) 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\(^4-14,16-36\), 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\(^3\). We did not observe any significant association between HCV infection and CHC. HBV infection is more common than HCV infection in CHC patients. 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)\(^3,14,16-36\). 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...
of Hering and are thought to differentiate into either hepatocytes or cholangiocytes, can give rise to hepatic malignancies. 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. Furthermore, Suzuki et al. 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 of HPCs. In addition, tumor cells of transition zone and ICC components as well as with mature appearing hepatocytes. The morphology is related to alcoholic liver disease including cirrhosis. Many studies have examined the association between DM and HCC or ICC and yielded inconsistent findings. 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. HCV, a well-known risk factor for HCC and ICC, was also reported to be associated with DM. 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). Univariate analysis of the present study showed that DM was a significant risk factor for CHC, but multivariate analysis failed to confirm this association. It is possible that the 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 1 Univariate analysis of risk factors for combined hepatocellular-cholangiocarcinoma (n = 126)

| Risk factor                          | Cases (n = 126) | Controls (n = 504) | OR (95% CI) | P value |
|--------------------------------------|----------------|-------------------|-------------|---------|
| HBV                                  |                |                   |             |         |
| HBsAg (+)                            | 38 (30.2)      | 446 (88.5)        | 1 (Reference) | < 0.001 |
| HBsAg (-)                            | 88 (69.8)      | 58 (11.5)         | 17.808 (11.145-28.452) |         |
| HCV                                  |                |                   |             |         |
| HCV-Ab (+)                           | 125 (99.2)     | 502 (99.6)        | 1 (Reference) | 0.563   |
| HCV-Ab (-)                           | 1 (0.8)        | 2 (0.4)           | 2.008 (0.181-22.322) | 0.395   |
| Heavy smoking                        |                |                   |             |         |
| No                                   | 88 (69.8)      | 371 (73.6)        | 1 (Reference) | 0.018   |
| Yes                                  | 38 (30.2)      | 133 (26.4)        | 1.205 (0.784-1.850) |         |
| Heavy alcohol consumption            |                |                   |             |         |
| No                                   | 105 (83.3)     | 457 (90.7)        | 1 (Reference) |         |
| Yes                                  | 21 (16.7)      | 47 (9.3)          | 1.945 (1.115-3.392) |         |
| Diabetes mellitus                    |                |                   |             |         |
| No                                   | 113 (89.7)     | 479 (95.0)        | 1 (Reference) | 0.224   |
| Yes                                  | 13 (10.3)      | 25 (5.0)          | 2.046 (1.094-4.443) | 0.855   |
| Hypertension                         |                |                   |             |         |
| No                                   | 110 (87.3)     | 443 (87.9)        | 1 (Reference) | < 0.001 |
| Yes                                  | 16 (12.7)      | 61 (12.1)         | 1.056 (0.586-1.903) |         |
| Hepatolithiasis                      |                |                   |             |         |
| No                                   | 124 (98.4)     | 501 (99.4)        | 1 (Reference) | 0.636   |
| Yes                                  | 2 (1.6)        | 3 (0.6)           | 2.694 (0.445-16.294) |         |
| Family history of liver cancer       |                |                   |             |         |
| 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 |                |                   |             |         |
| 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.
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 Clonorchis sinensis and Schistosoma mansoni[30]. Hong et al[31] 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[32]. 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[33]. On the other hand, nucleoside analogue therapy use was found to be associated with reduced risk of HBV related HCC[34]. Accordingly, vaccination against and treatment of HBV might have the potential benefits in prevention of CHC. Additional studies regarding this issue are warranted.

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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 the prevention of HCC and ICC.

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

REFERENCES

1. Yeh MM. Pathology of combined hepatocellular-cholangiocarcinoma. J Gastroenterol Hepatol 2010; 25: 1485-1492 [PMID: 20765614 DOI: 10.1111/j.1440-1741.2010.06430.x]
2. Lee TY, Lee SS, Jung SW, Jeon SH, Yun SC, Oh HC, Kwon S, Lee SK, Seo DW, Kim MH, Suh D. Hepatitis B virus infection and intrahepatic cholangiocarcinoma in Korea: a case-control study. Am J Gastroenterol 2008; 103: 1716-1720 [PMID: 18555716 DOI: 10.1111/j.1572-0241.2008.01796.x]
3. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthney JN, Fisters PW, Evans DB, Khan R, Chou TH, Lenzi R, Jiao L, Li D. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007; 102: 2696-2707 [PMID: 17764494 DOI: 10.1111/j.1572-0241.2007.01510.x]
4. Aoki K, Takayasu K, Kawano T, Muramatsu Y, Moriyama N, Wakao F, Yamaguchi R, Yano H. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma: clinical features and computed tomographic findings. Hepatology 1993; 18: 1090-1095 [PMID: 7693572]
5. Haratake J, Hashimoto H. An immunohistochemical analysis of 13 cases with combined hepatocellular and cholangiocellular carcinoma. Liver 1995; 15: 9-13 [PMID: 7539881]
6. Maeda T, Adachi E, Kajiyama K, Sugimachi K, Tsuchinoey M. Combined hepatocellular and cholangiocarcinoma: proposed criteria according to cytokeratin expression and analysis of clinicopathologic features. Hum Pathol 1995; 26: 956-964 [PMID: 7545644]
7. Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojio M. A clinicopathological study on combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol 1996; 11: 758-764 [PMID: 8827274]
8. Sasaki M, Yamato T, Nakamura Y. Expression of sialyl-Tn, Tn and T antigens in primary liver cancer. Pathol Int 1999; 49: 325-331 [PMID: 10565852]
9. Yano Y, Yamamoto J, Kosuge T, Sakamoto Y, Yamazaki S, Shimada K, Ojima H, Sakamoto M, Takayama T, Mackuchi M. Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. Jpn J Clin Oncol 2003; 33: 283-287 [PMID: 12919302 DOI: 10.1093/jjco/hyg056]
10. Sanada Y, Shiozaki S, Aoki H, Takakura N, Yoshida K, Yamaguchi Y. A clinical study of 11 cases of combined hepatocellular-cholangiocarcinoma Assessment of enhancement patterns on dynamics computed tomography before resection. Hepatol Res 2005; 32: 185-195 [PMID: 15978872]
11. Aishima S, Kuroda Y, Asayama Y, Taguchi K, Nishihara Y, Taketomi A, Tsuchinoey M. Prognostic impact of cholangio-cellular and sarcomatous components in combined hepatocellular and cholangiocarcinoma. Hepatol Pathol 2006; 37: 283-291 [PMID: 16613323 DOI: 10.1016/j.humpath.2005.08.019]
12. Wakasa T, Kakasa K, Shutuo T, Hais S, Kabo S, Hirohashi K, Umesita K, Monden M. A histopathological study on combined hepatocellular and cholangiocarcinoma: cholangiocarcinoma component is originated from hepatocellular carcinoma. Hepatogastroenterology 2007; 54: 508-513 [PMID: 1752309]
13. Ariizumi S, Koteria Y, Katagiri S, Nakano M, Yamamoto M. Combined hepatocellular-cholangiocarcinoma had poor outcomes after hepatectomy regardless of Allen and Lisa class or the predominance of intrahepatic cholangiocarcinoma cells within the tumor. Ann Surg Oncol 2012; 19: 1628-1636 [PMID: 22113592 DOI: 10.1245/s10434-011-1215-0]
14. Akiba J, Nakashima O, Hattori S, Tanikawa K, Takenaka M, Nakayama Y, Kondo R, Nomura Y, Koura K, Ueda K, Sanada S, Naito Y, Yamaguchi R, Yano H. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. Ann Surg Pathol 2013; 37: 496-505 [PMID: 23388123 DOI: 10.1097/PAS.0b013e3182733280]
15. Lee CH, Chang CJ, Lin YJ, Yeh CN, Chen MF, Hsieh SY. Viral hepatitis-associated intrahepatic cholangiocarcinoma shares common disease processes with hepatocellular carcinoma. Br J Cancer 2009; 100: 1765-1770 [PMID: 19436294 DOI: 10.1038/sj.bjc.6605865]
16. Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, Rhee JC, Cho JW, Park CK, Kim HJ. Clinicopathologic features and prognosis of combined hepatocellular carcinoma. Ann Surg 2005; 189: 120-125 [PMID: 15701504 DOI: 10.1016/j.amjsurg.2004.03.018]
17. Lee WS, Lee KW, Heo JS, Kim SJ, Choi SH, Kim YI, Joh JW. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Surg Today 2006; 36: 892-897 [PMID: 16998683 DOI: 10.1007/s00595-006-3276-8]
18. Shin CI, Lee JM, Kim SH, Choi YJ, Lee JY, Han JK, Jo SY, Choi BI. Recurrence patterns of combined hepatocellular-cholangiocarcinoma on enhanced computed tomography. J Comput Assist Tomogr 2007; 31: 109-115 [PMID: 17259842 DOI: 10.1097/01.rct.0000253572.34088.9b]
19. Kim KH, Lee SG, Park EH, Hwang S, Ahn CS, Moen DB, Ha TY, Song GW, Jung DH, Kim KM, Kim YS, Lee HC, Chung YH, Lee YS, Suh D. Surgical treatments and prognoses of patients with combined hepatocellular carcinoma and cholangiocarcinoma. Ann Surg Oncol 2009; 16: 623-629 [PMID: 19130133 DOI: 10.1245/s10434-008-0278-3]
20. Kim JH, Yoon HK, Ko GY, Gwon DI, Jang CS, Song HY, Shin JH, Sung KB. Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: analysis of the response and prognostic factors after transcatheter arterial chemoembolization. Radiology 2010; 255: 270-277 [PMID: 20308463 DOI: 10.1148/radiol.09091076]
21. Lee JH, Chung GE, Yu SJ, Hwang SY, Kim JS, Kim HY, Yoon JH, Lee HS, Yi NJ, Suh KS, Lee KU, Jang JI, Kim YJ. Long-term prognosis of combined hepatocellular and cholangiocarcinoma after curative resection comparison with hepatocellular carcinoma and cholangiocarcinoma. J Clin Gastroenterol 2011; 45: 69-75 [PMID: 20422575 DOI: 10.1097/MCG.0b013e3181e5bd4a]
22. Park H, Choi KH, Choi SB, Choi JW, Kim do Y, Ahn SH, Kim KS, Choi JS, Han KH, Choi YJ, Park YJ. Clinicopathological characteristics in combined hepatocellular-cholangiocarcinoma: a single center study in Korea. Yonsei Med J 2011; 52: 793-798 [PMID: 21786439 DOI: 10.3349/ymj.2011.52.5.753]
23. Zuo HQ, Yan LN, Zeng Y, Yang YJ, Luo HZ, Liu JW, Zhou LX. Clinicopathological characteristics of 15 patients with combined hepatocellular carcinoma and cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 2007; 6: 161-165 [PMID: 17354757]
24. Zhang F, Chen XP, Zhang W, Dong HH, Xiang S, Zhang...
Risk factors for combined hepatocellular-cholangiocarcinoma

WG, Zhang BX. Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: immunohistochemical and double-fluorescence immunostaining evidence. *Histopathology* 2008; 52: 224-232 [PMID: 18184271 DOI: 10.1111/j.1365-2559.2007.09299.x]

Yu XH, Xu LB, Zeng H, Zhang R, Wang J, Liu C. Clinicopathological analysis of 14 patients with combined hepatocellular carcinoma and cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int* 2011; 10: 620-625 [PMID: 22146626]

Yin X, Zhang BH, Qiu SJ, Ren ZG, Zhou J, Chen XH, Zhou Y, Fan J. Combined hepatocellular carcinoma and cholangiocarcinoma: clinical features, treatment modalities, and prognosis. *Ann Surg Oncol* 2012; 19: 2869-2876 [PMID: 22451237 DOI: 10.1245/s10434-012-2238-0]

Zhan Q, Shen BY, Deng XX, Zhu ZC, Chen H, Peng CH, Li HW. Clinical and pathological analysis of 27 patients with combined hepatocellular-cholangiocarcinoma in an Asian center. *J Hepatobiliary Pancreat Sci* 2012; 19: 361-369 [PMID: 21744084 DOI: 10.1007/s00554-011-0417-2]

Yap AQ, Chen CL, Yong CC, Ku Fy, Wang SHL, Lin CC, Liu YW, Lin TL, Li WF, Millan CA, Wang CC. Clinicopathological factors impact the survival outcome following the resection of combined hepatocellular carcinoma and cholangiocarcinoma. *Surg Oncol* 2013; 22: 55-60 [PMID: 23102615 DOI: 10.1016/j.suronc.2012.09.003]

Lee CH, Hsieh SY, Chang CJ, Lin YJ. Comparison of clinical characteristics of combined hepatocellular-cholangiocarcinoma and other primary liver cancers. *J Gastroenterol Hepatol* 2013; 28: 122-127 [PMID: 23034166 DOI: 10.1111/1440-1746.12709.x]

Ng IO, Shek TW, Nicholls J, Ma LT. Combined hepatocellular-cholangiocarcinoma: a clinicopathological study. *J Gastroenterol Hepatol* 1998; 13: 34-40 [PMID: 9737569]

Chantajitr S, Wilasrusmee C, Lertsitichai P, Phromsopha N. Combined hepatocellular and cholangiocarcinoma: clinical features and prognostic study in a Thai population. *J Gastroenterol Hepatol* 2006; 13: 537-542 [PMID: 17139428 DOI: 10.1007/s00534-006-1117-1]

Phongkitkarun S, Sirisuwann T, Sornmaypura P, Chatvacha J. Combined hepatocellular and cholangiocarcinoma: CT findings with emphasis on multiphasic helical CT. *J Med Assoc Thai* 2007; 90: 113-120 [PMID: 17621741]

Jarnagn WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, DeMatteo RP, Blumgart LH, Klimstra D. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. *Cancer* 2002; 94: 2040-2046 [PMID: 11932907 DOI: 10.1002/cncr.10392]

Panjala C, Senecal DL, Bridges MD, Kim GP, Nakhele RE, Nguyen JH, Harnois DM. The diagnostic conundrum and liver transplantation outcome for combined hepatocellular-cholangiocarcinoma. *Ann J Transplant* 2010; 10: 1263-1267 [PMID: 20420633 DOI: 10.1111/j.1600-6143.2010.03062.x]

Cazals-Hatem D, Rebouissou S, Bioulac-Sage P, Bluteau O, Rebours V, Blanché H, Franko D, Monges G, Belghiti J, Su Cunha A, Laurent-Puig P, Degott C, Zucman-Rossi J. Clinical and molecular analysis of combined hepatocellular-cholangiocarcinomas. *J Hepatol* 2004; 41: 292-298 [PMID: 15288479 DOI: 10.1016/j.jhep.2004.04.030]

Portolani N, Baoiocchi GL, Congilio A, Piardi T, Grazioi L, Benetti A, Ferrari Bravo A, Giulini SM. Intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma: a Western experience. *Ann Surg Oncol* 2008; 15: 1880-1890 [PMID: 18443881 DOI: 10.1245/s10434-008-9933-y]

Theise ND, Yao JL, Harada K, Hytiroglou P, Portmann B, Huang SN, Tsui W, Ohta H, Nakamura Y. Hepatic 'stem cell' malignancies in adults: four cases. *Histopathology* 2003; 43: 263-271 [PMID: 12904779 DOI: 10.1046/j.1365-2559.2003.01707.x]

Suzuki A, Sekiya S, Onishi M, Oshima N, Kiyonari H, Takehara T. Long-term effect of lamivudine treatment on the risk factors for intrahepatic cholangiocarcinoma. *Hepatology* 2012; 56: 69-76 [PMID: 22420979 DOI: 10.1002/hep.24590]

Zhou YM, Zhou J, Yao JL, Harada K, Hytiroglou P, Portmann B, Huang SN, Tsui W, Ohta H, Nakamura Y. Hepatic 'stem cell' malignancies in adults: four cases. *Histopathology* 2003; 43: 263-271 [PMID: 12904779 DOI: 10.1046/j.1365-2559.2003.01707.x]

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