

# Increasing Incidence of Intrahepatic Cholangiocarcinoma and its Relationship to Chronic Viral Hepatitis

Kwang-Yu Chang, MD;<sup>a</sup> Jang-Yang Chang, MD;<sup>a</sup> and Yun Yen, MD,<sup>b</sup> *Taiwan and Duarte, California*

## Key Words

Intrahepatic cholangiocarcinoma, hepatitis C virus, hepatitis B virus, incidence, risk factor

## Abstract

Primary liver cancer is the sixth most common cancer and third most common cause of cancer death worldwide. Cholangiocarcinoma is the second most common primary liver tumor after hepatocellular carcinoma. Because the incidence of intrahepatic cholangiocarcinoma is rising in most areas worldwide, identification of the main causes of this problem is urgently needed. Despite well-known risk factors in the development of intrahepatic cholangiocarcinoma, recent reports focus on chronic hepatitis B and C viral infections because an increasing number of studies have observed an association. The relationship, however, is still not conclusive because of the diversity in clinical reports and the lack of in vitro evidences. This issue should be emphasized and further investigation is required for clarification. (*JNCCN* 2009;7:423–427)

**P**Primary liver cancer is the sixth most common cancer and, because of a generally poor response to modern medical treatment, the third most common cause of cancer death worldwide.<sup>1</sup> Cholangiocarcinoma, which arises from bile duct epithelium, is the second

most common disease after hepatocellular carcinoma (HCC). In men, the disease contributes from 10% to 25% of liver cancer in Europe and North America, but much less in areas with high HCC incidence.<sup>2</sup> Although the prevalence of the disease is not as high as HCC, the cholangiocarcinoma to HCC ratio reaches 1:5 to 1:6 in some endemic areas, such as Hong-Kong and southern China, compared with 1:38 in southern Africa and 1:56 in Java.<sup>2</sup>

Because current management is often disappointing, cholangiocarcinoma is often a highly lethal cancer, with 1- and 2-year survival rates of 25% and 13%, respectively.<sup>3</sup> Unlike recent advancements in the treatment of HCC, treatment of cholangiocarcinoma remains challenging because no consensus exists as to the best drug treatment, with surgical resection the current treatment. Another issue is the clinical observation of cholangiocarcinoma, which highlights the global rising of incidence and mortality rates, especially the intrahepatic form of cholangiocarcinoma (IHCC).<sup>3</sup> This article focuses on this matter and discusses possible causes.

## Anatomy and Risk Factors

Cholangiocarcinomas are tumors that originate from the intrahepatic and extrahepatic biliary tracts. IHCC derives from small intrahepatic ductules and large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts, presenting as liver masses. Extrahepatic cholangiocarcinomas (EHCCs) derive from the distal part of the biliary tract, with the bifurcation as the boundary. Primary liver cancer, which is a general term for cancer disease originating from the liver, often falls into 2 distinct disease categories: IHCC or HCC. Despite the similar location, these diseases dif-

From <sup>a</sup>National Institute of Cancer Research, National Health Research Institute, Taiwan, and Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Taiwan; and <sup>b</sup>Division of Clinical and Molecular Pharmacology, City of Hope National Medical Center, Duarte, California.

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Correspondence: Yun Yen, MD, Division of Clinical and Molecular Pharmacology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010. E-mail: YYen@coh.org

fer in all aspects, including the origin and histology. For extrahepatic biliary tract cancer, the term EHCC should not be confused with cancer of the gallbladder and ampulla of Vater, because both have features unique from cholangiocarcinoma.<sup>4</sup>

Most of the cholangiocarcinoma occurs sporadically without known risk factors. Nevertheless, some predisposing factors have been identified. In general, the disease occurs mostly in individuals between 50 and 70 years of age, with the incidence slightly higher in men. Inflammation of biliary tract, such as primary sclerosing cholangitis (PSC), is an important factor leading to the formation of cancer.<sup>5</sup> In some eastern and southern Asia regions, parasitic infection of liver fluke (e.g., *Clonorchis sinensis* and *Opisthorchis viverrini*) causes the high incidence of IHCC to become an endemic disease.<sup>6–8</sup> Reports have shown that hepatolithiasis and cholelithiasis are associated with IHCC, but this linkage is less established than with gallbladder cancer.<sup>9,10</sup> Other risk factors include fibropolycystic liver disease, genetic disorders, and toxic exposure to certain chemical agents.

Recent evidence has also recognized an increasing number of other diseases that may be associated with IHCC, including cirrhosis of liver, hepatitis C virus (HCV), hepatitis B virus (HBV), and diabetes.<sup>11,12</sup> Among these, chronic hepatitis viral infections particularly draw physicians' attention, not only as an important public health issue but also in terms of the available management over disease prevention and viral treatment.

### Increasing Incidence of Intrahepatic Cholangiocarcinoma

Although the incidence of cholangiocarcinoma varies worldwide, an increasing global trend has been observed in the past few years as reported in the United States, Crete (Greece), and Japan.<sup>2,13,14</sup> Because most cholangiocarcinoma leads to death, mortality rates increase simultaneously. In the United States, Patel<sup>15</sup> reported that incidence and mortality rates from IHCC had markedly increased during 1973 to 1997, with an estimated annual percent change of 9.11% (95% CI, 7.46–10.78) and 9.44% (95% CI, 8.46–10.41), respectively. The analysis of WHO databases indicated similar results of increasing mortality worldwide.<sup>3,16</sup> On the contrary, the databank analysis from 1978 through 2002 in Denmark had

an opposite finding, showing decreasing incidence of cholangiocarcinoma.<sup>17</sup> The reason for this discrepancy has not been identified.

Subgroup analysis of the anatomic site of biliary tract malignancies has shown distinct results of the incidence trend. The rising mortality rate worldwide has been observed in IHCC but not in extrahepatic biliary tract malignancies.<sup>3</sup> In the United States, the age-adjusted incidence rates of IHCC increased by 165%, from 0.32 per 100,000 in 1975 to 1979, to 0.85 per 100,000 in 1995 to 1999, whereas EHCC declined by 14%.<sup>18</sup> Similar observation in England and Wales showed a marked rise in age-standardized mortality rates in IHCC compared with other primary liver tumors and EHCC, especially for patients older than 45 years.<sup>19</sup> Whether the increased incidence is merely the reflection of recoding in the registration has been questioned.

Welzel et al.<sup>20</sup> analyzed the impact of misclassification between the first and second versions of the International Classification of Diseases for Oncology (ICD-O). Results showed that the rising incidence could not be explained by the different version. Because the classification factor should have equal impact on sex differences, the study conducted by Patel<sup>3</sup> highlighted the uneven increase in incidence among men. These findings showed that the classification factor is a minor contributor to the increased incidence. Although incidence of IHCC increases and EHCC decreases in most the areas, exceptions still exist in some countries. In Denmark, incidences of IHCC and EHCC decreased for unexplained reasons.<sup>17</sup> In Shanghai, incidences for malignancies deriving from the biliary tract, such as gallbladder, extrahepatic bile ducts, and ampulla of Vater, increased from 1972 to 1994.<sup>21</sup>

Although the cause of this global rise in incidence has not been confirmed, efforts have been made to recognize the factors involved. As a major risk, the increasing rate of PSC is certainly a candidate.<sup>22</sup> Because PSC-induced cholangiocarcinoma has a mean age occurrence of 47 years,<sup>23</sup> Shaib et al.<sup>14</sup> proposed a trend toward younger age at IHCC diagnosis in the United States. The final result, however, did not reflect the change and queried the hypothesis.

Another major risk factor for IHCC is infection with liver fluke. This factor had a large impact on disease incidence in endemic areas, but is not likely to affect the general population because a global

breakout has not been noted.<sup>3,14</sup> Interestingly, reversing factors for decreasing incidence of IHCC in Denmark are also not identified, with the paradoxical result not related to other previously known risk factors, such as inflammatory bowel disease, diabetes, smoking, or thorotrast.<sup>17</sup>

Because the major risk factors are still obscure, some experts may believe the trend only reflects a better case ascertainment and diagnosis, made possible through modern diagnostic tools, such as retrograde cholangiopancreatography (ERCP). The hypothesis was unsupported in the study conducted by Taylor-Robinson et al.,<sup>19</sup> because in their observation the increasing trend was observed before ERCP became the standard diagnostic tool of cholangiocarcinoma. In addition, although ERCP provides accurate detection in EHCC, a simultaneous increasing rate of EHCC is not noted. Therefore, the existence of unconfirmed risk factors is still the likely reason for a global rising incidence of IHCC in the past few decades.

### Chronic Viral Hepatitis as a Risk Factor of IHCC

HBV and HCV are well-known risk factors leading to liver cirrhosis and HCC, and both have been global health problems for some time. The seroprevalence of HBsAg, a seromarker of HBV infection, varies from more than 8% in high endemic areas, mostly located in Asia and Africa, to less than 2% in North America and Australia.<sup>24</sup> Similarly, various prevalence is also noted in HCV, with a higher percentage in Asia and Africa (> 2.9%) versus a much lower one in North America, Australia, and western Europe.<sup>25</sup> Because the long-term sequelae of chronic HBV and HCV leads to severe liver disease, the WHO emphasizes prevention of these viral infections. As hepatitis B vaccine is integrated into national immunization programs of all highly endemic countries and others, the prevalence of HBV is expected to decrease. However, HCV remains a severe problem because of the lack of an effective vaccine and because more effort is required to avoid risk factors, such as implementing screening programs as part of blood donation procedures.

Recent investigations have emphasized the association between cirrhosis of the liver and cholangiocarcinoma. In a U.S. case-control study, Shaib

et al.<sup>11</sup> showed a higher prevalence rate of nonspecific cirrhosis in patients with cholangiocarcinoma compared with controls, with an odds ratio of 27.2. Another case-control study also recognized the risk factor in Pusan, Korea.<sup>26</sup> The association between cirrhosis and cholangiocarcinoma, however, is not as apparent as it is between cirrhosis and HCC. The cohort study conducted in Denmark showed that patients with cirrhosis had a standardized incidence ratio (SIR) of 10 for developing cholangiocarcinoma. Compared with an SIR of 59.9 in HCC, this elevation is minor but still significant.<sup>27</sup> This finding might explain why cirrhosis is disregarded as a major risk factor for cholangiocarcinoma over a long period.

Because chronic HCV is an important risk factor for development of cirrhosis of the liver, it is not surprising that it is one of the factors for IHCC. The association, however, was obscure until it was first presented as a case report in 1991.<sup>28</sup> In a later study analyzing 141 patients with primary liver cancer, Tomimatsu et al.<sup>29</sup> recognized the existence of HCV as a factor for development of not only HCC but also cholangiocarcinoma and combined HCC–cholangiocarcinoma, accounting for 30.8% in 13 cases and 71.4% in 7, respectively. Since then, increasing studies have shown evidence of viral hepatitis, particularly HCV, as a risk factor for cholangiocarcinoma.<sup>12,30,31</sup>

In a study conducted by Kobayashi et al.,<sup>31</sup> the authors prospectively observed patients positive for HCV who later developed cirrhosis during 1980 to 1997. During the observation period, the cumulative rates of newly diagnosed primary cholangiocarcinoma of the liver was 1.6% at 5 years and 3.5% at 10 years, which was approximately 1000 times higher than the estimated incidence in the general population of Japan.<sup>31</sup>

In the United States, the case-control study conducted by Shaib et al.<sup>11</sup> showed that HCV, and other factors such as nonspecific cirrhosis, alcoholic liver disease, HIV infection, diabetes, and inflammatory bowel disease, were significantly more prevalent among IHCC cases. This indicates that HCV may be directly involved in inducing IHCC through chronic inflammation.

In contrast to the relatively sufficient evidence for HCV's association with cholangiocarcinoma, for HBV it does not prove that the virus leads to chol-

angiocarcinoma. Nevertheless, because HBV is also an important cause leading to chronic inflammation of the liver, this remains an attractive topic. Because the pathogen is more obscure, laboratory data might clarify whether it is responsible for the development of IHCC. In an *in vitro* study by Zou et al.<sup>32</sup> and Qu et al.,<sup>33</sup> the transcriptional regulation of human telomerase reverse transcriptase (hTERT), which is a crucial step in tumorigenesis and cellular senescence, had a dramatic increase in its mRNA expression in normal human cholangiocytes and cholangiocarcinoma cell lines (QBC939) after HBV X gene transfection compared with empty vector.

Despite preclinical data, supportive evidence from clinical observation is scarce. Wang et al.<sup>34</sup> studied more than 40 patients with IHCC in China for HBV expression. Results showed that HBV, especially HbxAg protein, was a common finding in the immunohistochemistry of tumor tissue. In a case-control study conducted in Italy, the odds ratio for demographic factors by logistic regression was 3.7 (95% CI, 0.4–18.4) for HBsAg to be associated with IHCC.<sup>35</sup> The clinical association between HBV and IHCC, however, is not as consistent as that for HCV. The largest United States population-based case-control study did not show HBV to be a risk factor like HCV.<sup>11</sup> Moreover, the case-control study conducted in Pusan, Korea, which is also a high HBV-endemic area, failed to prove the association.<sup>26</sup>

Immunization programs of hepatitis B vaccine are expected to decrease the prevalence of the viral infection in the future, followed by the decrease of related tumors. However, because this issue remains equivocal, it will require more investigation for confirmation.

Even for *in vitro* studies, little is known about the mechanism for chronic hepatitis virus to cause cholangiocarcinoma in addition to long-term inflammation. The aforementioned change of hTERT to be regulated by HBV X gene transfection might provide an evidence of intracellular signal change.<sup>32,33</sup> In the study conducted by Liu et al.,<sup>36</sup> the transfection of HCV core protein into QBC939, a cholangiocarcinoma cell line, was associated with the detection of NF- $\kappa$ B expression. In a retrospective study, Chen et al.<sup>37</sup> associated HCV core protein in hilar cholangiocarcinoma to higher apoptosis index and proliferating cell nuclear antigen index in surgical specimens. They concluded that the protein promotes cellular

proliferation but inhibits apoptosis in the cell. These results, however, do not explain the full mechanism of tumorigenesis. Further studies are necessary to study the detail mechanism of viral hepatitis to cause IHCC.

## Summary

As one of the cancers with rising incidence in most areas of the globe, identifying the major risk factors leading to cholangiocarcinoma is urgently needed to prevent the disease. Because most of the identified risk factors do not result in the problem, chronic viral hepatitis might be a candidate for further investigation. Nevertheless, the theory that viral hepatitis leads to the disease has its disadvantages. Why IHCC is not as prevalent as HCC if chronic inflammation of the liver is such an important factor in both diseases is not clear. One explanation is the existence of unidentified concordant factors that might play pivotal roles, which results in the carcinogenesis of different histologic tissue, ultimately leading to HCC if hepatocytes are affected or to IHCC if the bile duct is impacted. Another possibility is the overwhelmed relationship between chronic viral hepatitis and HCC in the past few decades, which masked the fact that cholangiocarcinoma, although lower in incidence, was a serious consequence of the disease. Regardless of whether the rising incidence is associated with chronic viral hepatitis, future efforts to clarify this relationship *in vitro* and *in vivo* are essential to its understanding.

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