Epidemiology and risk factors: intrahepatic cholangiocarcinoma

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Abstract: Intrahepatic cholangiocarcinoma (ICC) is a rare entity with a distinct clinical course and epidemiology from hilar and extrahepatic cholangiocarcinoma. ICC makes up 8–10% of cholangiocarcinomas and 10–20% of all primary liver tumors. There remains a considerable amount of geographic variation in the incidence of ICC worldwide; however, the overall incidence of this malignancy appears to be rising. Several risk factors have been identified, such as infectious causes (liver flukes, viral hepatitis), biliary tract disease [primary sclerosing cholangitis (PSC), hepatolithiasis, biliary cystic diseases], metabolic syndrome, lifestyle choices (alcohol abuse, tobacco use), and cirrhosis. Despite this, a substantial number of ICC patients do not have any identifiable risk factors, underlining the need for further work into the pathogenesis of this malignancy.

Keywords: Intrahepatic cholangiocarcinoma (ICC); epidemiology; risk factors

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Epidemiology of ICC

Intrahepatic cholangiocarcinoma (ICC) is a rare entity, accounting for only 3% of worldwide gastrointestinal malignancies (1). ICC makes up 8–10% of all cholangiocarcinoma and has a distinct clinical course and epidemiology from hilar and extrahepatic cholangiocarcinoma (2-4). Furthermore, although ICC has had a historic tendency to be misdiagnosed as hepatocellular carcinoma (HCC) (5), it is now accepted that ICC accounts for 10–20% of primary hepatic cancers (4,6,7). ICC is infrequent in patients younger than 40 years old, with the peak incidence seen between the fifth and seventh decade of life (6). In the United States, there is a slight male predominance over women (1.5 fold) (6).

Increasing incidence of ICC

Despite the relative rarity of ICC, the incidence of ICC has been reported to be increasing worldwide (3,4,8). This higher incidence is independent of tumor size or tumor stage, and thus it is unlikely secondary to earlier detection, but in fact a true increase in ICC incidence (8). In a 30-year period the incidence of ICC increased 165% in the United States to 0.95 cases per 100,000 (6,8). A similar rise in ICC incidence has been reported in the United Kingdom, Japan, and Crete (7,9). Although the exact cause of this increase is uncertain, it may be secondary to the increasing incidence of ICC risk factors as discussed below.

Geographic variation

There is a tremendous discrepancy in the worldwide incidence of ICC, with significantly higher rates of ICC seen in Eastern Asia when compared to Western countries (1). This geographic disparity is explained largely by the prevalence of risk factors for ICC in these Eastern countries (3,4). This fact is further demonstrated by higher rates of ICC within the same country where certain risk factors are more prevalent (10).
**Ethnic variation**

McLean *et al.* demonstrated a significantly higher incidence of ICC of Hispanic-Americans (1.22 per 100,000) compared to other ethnic groups, with African-Americans having the lowest incidence (0.3 per 100,000). The authors concluded that this variation may reflect potential genetic, cultural, or socioeconomic differences in ICC susceptibility (11).

**Risk factors**

There are several risk factors that predispose to ICC, many of which have geographical prevalence. It should also be mentioned that almost 40% of patients diagnosed with ICC will have no currently identifiable risk factor, highlighting the need for further research in this area (12).

**Chemical exposure**

Many environmental exposure risk factors, such as thorium dioxide contrast, asbestos, and radon have been very well described previously (6), however, are primarily of historical significance and will not be discussed further here. Two separate studies identified links to the occupational exposure to 1,2-dichloropropane (1,2-DCP) and dichloromethane (DCM) in a Japanese printing plant to the development cholangiocarcinoma (13,14). As a result, the International Agency for Research on Cancer classified 1,2-DCP as a World Health Organization group 1 carcinogen, indicating that there is sufficient evidence to suggest carcinogenicity in humans. Moreover in the same monograph, DCM was classified as a group 2A carcinogen, indicating that it was probably carcinogenic to humans (15).

**Liver flukes**

Parasitic infection with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini*, is a well-established ICC risk factor. These organisms cause bile duct inflammation predisposing to ICC, and have been designated as group 1 carcinogens by the World Health Organization (12). An estimated 8–10% of people chronically infected with these liver flukes will develop ICC (6). These parasites are endemic to East Asia, including Thailand where the incidence of ICC is as high as 100 per 100,000 (6).

**Biliary tract disease**

Primary sclerosing cholangitis (PSC) is a well-known risk factor for the development of ICC. The underlying biliary inflammation with resulting progenitor cell proliferation is thought to predispose to ICC formation (3,6). Patients with PSC have been reported to have a 5–10% lifetime incidence of cholangiocarcinoma, with half of those being diagnosed within 2 years of the diagnosis of PSC (3). Furthermore, Shaib *et al.* demonstrated an increased risk of ICC (OR, 2.2; 95% CI, 1.2–3.9) in patients with ulcerative colitis but not Crohn's disease (12). PSC patients tend to present with ICC earlier, with most cases diagnosed between the 3rd and 5th decade of life.

Primary biliary stones have been associated with chronic biliary tract inflammation and increased cancer risk. ICC incidence has been reported to be as high as 7% in patients with hepaticolithiasis (3). This increase in ICC rate was supported by significantly higher risk in a Western patient population (OR, 4.0; 95% CI, 1.9–8.5) (12). Furthermore, Asian studies have demonstrated hepaticolithiasis in patients with resected cholangiocarcinoma as high as 70% in Taiwan (6).

Lastly, congenital disorders of the biliary system, such as Caroli’s disease and fibrocystic liver disease, impart up to 15% lifetime risk of ICC after the second decade of life (6). Caroli’s disease is defined by cystic dilation of the intrahepatic ducts, usually in a bilobar pattern. The associated bile stasis, cholangitis, and chronic inflammation have been suggested as drivers of the increased ICC risk seen in these patients (16-18).

**Viral hepatitis**

Viral hepatitis has recently been shown to be associated with ICC (6). Multiple studies in Europe and Asia have demonstrated a relationship between hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and ICC. In a prospective Japanese study, ICC developed in 2.3% of patients with HCV cirrhosis; substantially higher than healthy controls (19). A Korean group reported HCV and HBV rates of 13.8% and 12.5% in ICC patients, which were significantly higher than rates seen in healthy patients (3.5% and 2.8%, respectively) (20). An Italian study also demonstrated a relationship between viral hepatitis and ICC. ICC patients had rates of HCV and HBV of 23.1% and 11.5%, respectively, as compared with 6.1% and 5.5% in controls (21). Furthermore, an American group found HCV or HBV nucleic acid in 27% of ICC tumor samples, suggesting a possible role of these viruses in tumor development (22). Interestingly, American studies have...
failed to show a relationship between HBV infection and ICC development. A large population-based study by Welzel et al. demonstrated an increased risk of ICC in patients with HCV infection but not with HBV infection (23). Furthermore, Shaib et al. found a strong association between HCV and ICC (OR, 5.2; 95% CI, 2.1–12.8) while HBV did not impart an increased risk of ICC (CI, 0.8; 95% CI, 0.1–5.9) (12).

**Metabolic syndrome**

The development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are clearly associated with development of chronic liver disease and cirrhosis. NAFLD has been strongly associated to the constellation of conditions making up the metabolic syndrome, defined as 3 or more of the following: central obesity, dyslipidemia, hypertension, and impaired fasting glucose. A review of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database revealed that the presence of the metabolic syndrome was a significant risk factor for development of ICC (OR, 1.56; 95% CI, 1.32–1.83) (23). A recent meta-analysis corroborated these data by identifying higher risk of ICC development in patients with diabetes (OR, 1.9; 95% CI, 1.74–2.07) and obesity (OR, 1.56; 95% CI, 1.26–1.94) (5). Based on these results, it is not surprising that NASH itself has been shown to be an independent risk factor for ICC development, especially in patients with hepatic fibrosis (24). Welzel et al. suggested that the increasing prevalence of these risk factors may, in part, account for the increasing incidence of ICC seen in Western countries (23).

**Other risk factors**

Tobacco smoking has been shown to be associated with increased risk of several different malignancies, and the same is true for ICC (OR, 1.8; 95% CI, 1.2–2.7) (12). Alcoholic liver disease has also been implicated in ICC development (OR, 2.81; 95% CI, 1.52–5.21), further demonstrating the association between liver injury and ICC susceptibility (12).

**Cirrhosis**

Cirrhosis has long been identified as a significant risk factor in HCC development, and a similar pathogenesis has been suggested for ICC in cirrhotics. Non-specific cirrhosis was identified to be a very strong predictor of ICC development (OR, 27.2; 95% CI, 19.9–37.1) (12). This high level of association is not surprising when it is considered that many of the above-mentioned risk factors converge at the process of liver fibrosis and cirrhosis. It is interesting to note that cirrhosis is a common risk factor in both ICC and HCC development. In fact, some groups have suggested a common pathogenesis for these primary hepatic cancers (5), a hypothesis supported by the overlapping patterns of gene expression found in some ICC and HCC specimens (25–27). Moreover, the identification of a combined hepatocellular-cholangiocellular carcinoma, representing less than 1% of liver cancers, may represent an intermediate phenotype of a spectrum of disease (3,5).

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**Footnote**

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**References**


