The Development of Cholangiocarcinoma: Epidemiology, Risk Factors, and Diagnosis

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Cholangiocarcinoma (CCA) arises from the malignant proliferation of cholangiocytes, the epithelial cells lining the biliary tree, and is characterized by a bad prognosis and poor response to current therapies. CCA may emerge at any portion of the biliary tree and comprises a group of tumors largely heterogeneous from the epidemiologic, morphologic, biologic, and clinical point of view. CCA is currently classified as intrahepatic (IH-CCA) or extrahepatic (EH-CCA) with the second-order bile ducts acting as the separation point (Fig. 1).[1,2] The EH-CCA comprises the perihilar form (Klatskin tumor) and distal form, with the separation point being posed at the level of the cystic duct (Fig. 1). The distinction between IH- and EH-CCA has become increasingly important, as the epidemiologic features (i.e., incidence and risk factors), the biologic and pathologic characteristics, and the clinical course are largely different.[1,2]

Epidemiology

The epidemiologic data on CCA and its different forms are affected by the lack of worldwide uniform classification.[1-5] In many cancer registries, for example, CCA is combined with other primitive liver cancers, and the perihilar EH-CCA often is considered to be IH-CCA. In addition, diagnosis often occurs at an advanced stage when the anatomical site of origin is difficult to establish.[1-5] Finally, the histologic heterogeneity and the lack of definitive immunohistochemical markers favor frequent misclassification.[1-5] Current efforts to characterize and define the cell of origin of CCA and other primitive liver cancers could help in the near future. With all these considerations in mind, the incidence of CCA is higher in men than in women and shows large geographic variation.[1-5] Very high incidence rates (84.6/100,000 in men) have been reported in northeast Thailand, where CCA represents approximately 90% of total primitive liver cancers, and other Asian countries such as China, Korea, Vietnam, and Laos.[4] In contrast, lower incidence rates occur in Western countries including Australia (0.2/100,000 men, less than 3% of total primitive liver cancers).[4] In many Western countries, the incidence of IH-CCA is progressively growing, while that of EH-CCA is stable or slightly decreasing.[3,4,5] Specifically, in the last 2 decades, epidemiologic studies reported an increased incidence of III-CCA in Italy, Germany, England-Wales, and Korea while in the United States, the incidence of IH-CCA progressively increased during the period from 1973 to 1995-1999 and decreased thereafter (2000-2005).

Risk Factors

The definite and probable CCA risk factors are reported in Table 1. Hepatic infections by liver flukes (Clonorchis sinensis, Opisthorchis viverrini) and hepatolithiasis are associated with the high incidence of CCA in Asian countries.[3,6,7] In Western countries, accumulating evidence sustains hepatitis C virus infection (HCV) as a risk factor and the burden of HCV could explain the increased incidence of CCA in these countries.[3,6,7] In general, there are some risk factors that are exclusive for IH-CCA (hepatolithiasis, HCV, hepatic schistosomiasis, cirrhosis) or EH-CCA (abnormal pancreatico-biliary junction) and risk factors shared by the two forms of CCA.[6] All risk factors

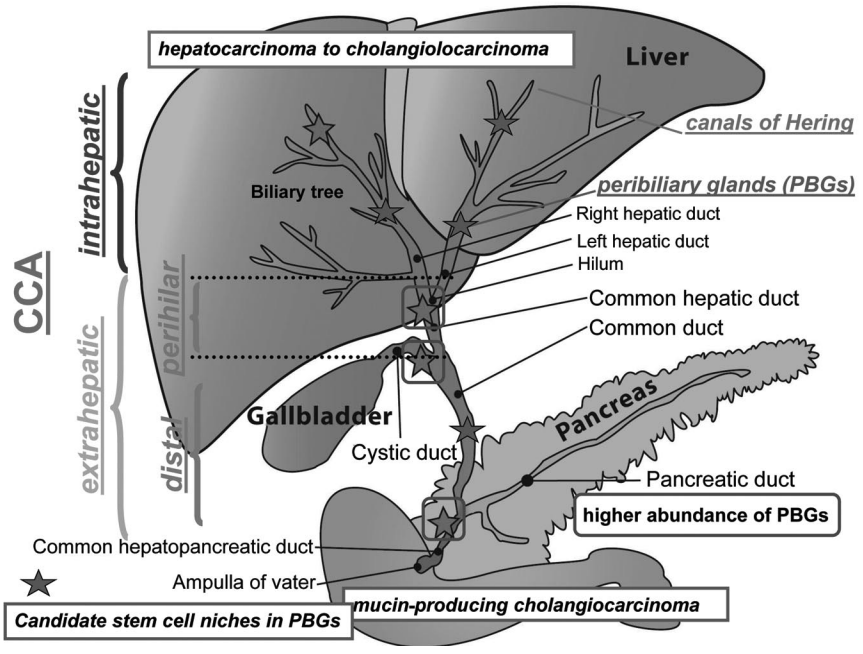

Fig. 1. CCA is currently classified as IH-CCA or extrahepatic EH-CCA, with the second-order bile ducts acting as the separation point. The EH-CCA comprises the perihilar form (Klatskin tumor) and distal form with the separation point being posed at the level of the cystic duct. Stem cell niches have been identified within the liver in the Canals of Hering where stem cells can differentiate into hepatocytes and cholangiocytes. Malignant transformation of these stem cells can result in hepatocarcinoma, combined hepatocholangiocarcinoma or cholangiolocarcinoma. Peribiliary glands (PBGs) are candidate stem cell niches within the biliary tree (stars). PBGs are distributed along the biliary tree starting with the hepatopancreatic common duct near the duodenum and ending intrahepatically with the septal ducts. PBGs exist in particularly high numbers in the cystic duct, hilum, and periampular region, sites at which EH-CCA typically emerge. Transformation of a hepatic or biliary stem cell can give rise to tumors comprised of heterogenous cellular phenotypes. This allows us to hypothesize that IH-CCA could arise from two distinct cellular lineages: the lineage originating from the hepatic stem cells residing in the Canals of Hering, giving rise to a range of phenotypes including hepatocarcinoma, CCA, and combined hepatocholangiocarcinoma; and one originating from stem cells within the PBGs, giving rise to mucin-producing CCA. Abbreviations: CCA, cholangiocarcinoma; PBGs, peribiliary glands.

Table 1. Risk Factors for Cholangiocarcinoma

Definitively established risk factors for CCA	**IH-CCA**	**EH-CCA**
Liver flukes (Clonorchis sinensis, Opisthorchis viverrini)		
Hepatolithiasis	X	
Primary sclerosing cholangitis		
Choledochal cysts		
Toxins (Thorotrast, dioxins)		
HCV	X	
Probable risk factors for CCA		
IBD		
HBV	X	
Abnormal pancreatico-biliary junction		X
Surgical biliary-enteric drainage		
Liver cirrhosis	X	
Caroli's disease		
Cholangitis and choledocholithiasis		
Diabetes, obesity, alcohol, tobacco smoking		
Cholelithiasis		X
Cholecystectomy		X
Hepatic schistosomiasis	X	
Genetic polymorphisms		

Some risk factors are exclusive for IH-CCA or EH-CCA as indicated (X) while other risk factors are common for both CCA types.
Abbreviations: CCA, cholangiocarcinoma; IH-CCA, intrahepatic cholangiocarcinoma; EH-CCA, extrahepatic cholangiocarcinoma; HCV, hepatitis C virus infection; IBD, inflammatory bowel disease; HBV, hepatitis B virus infection.

share bile duct chronic inflammation, cholestasis, and cholangiocyte damage/proliferation as common features sustaining CCA emergence and, in this regard, CCA could be considered as a prototype of inflammation-associated cancer. However, in more than 60% of the cases of CCA no putative risk factor is detectable, indicating that there is still very little known about this topic. Very recently, greater attention has been given to the role of cancer stem cells in cholangiocarcinogenesis, and in this regard an important advance could be indicated by the identification of stem cell niches in peribiliary glands (PBGs) of the biliary tree (Fig. 1).[8] Indeed, PBGs are particularly high in density at the level of cystic duct, hilum, and periampular region, sites where EH-CCAs typically emerge.[8] Intrahepatic stem cell niches, residing in the Canals of Hering, and the other stem cell niches residing in the PBGs (Fig. 1) are differently activated in the course of hepatic and biliary pathologies, and this could have important pathologic implications in the link between risk factors and CCA emergence.[6,8]

Diagnosis

The diagnosis of CCA is often made when no effective therapeutic intervention is possible.[1,2,9,10] Clinical presentation does not help. In a recent survey promoted in Italy by scientific societies, curative surgery was possible in only 45% and 29% of newly diagnosed IH- and EH-CCA cases respectively.[9] In this analysis, the most frequent clinical presentation was jaundice for EH-CCA and abdominal pain for IH-CCA where diagnosis was incidental in about one-third of the cases. In addition, in approximately 40% of the cases, IH-CCA was associated with cirrhosis or positivity for hepatitis virus markers, mimicking hepatocarcinoma. In general, the diagnostic work-up is time- and cost-consuming and requires multiple approaches (imaging, endoscopy, biopsy). As is the case for other cancers, early diagnosis is imperative—unfortunately, however, no effective serum or biliary biomarker for screening and surveillance leads to clinical benefit at this time.[10]

Conclusions

CCA is a heterogeneous, devastating cancer with an increasing worldwide incidence and mortality. The main risk factors are liver flukes in Asian countries and primary sclerosing cholangitis and HCV in Western countries. The intrahepatic CCA frequently emerges in the setting of chronic liver disease, requiring differential diagnosis with respect to hepatocarcinoma. It is difficult to diagnose and frequently presents at a late stage when no effective therapeutic intervention is possible.

Author's Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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