Cholangiocarcinoma: Challenges and future needs

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Cholangiocarcinoma (CCA) is a malignant neoplasm that arises from the biliary tract epithelia. CCA is the second most common primary liver tumour after hepatocellular carcinoma, representing 10-25% of primary hepatic malignancies (1). CCA is rare in many parts of the world, such as Europe and the United States (US), accounting for <3% of all malignant tumours. However, there is a dramatic geographic variation in its incidence, which reflects regional differences in risk factors and epidemiology (2,3).

Treatment outcomes and survival for patients with these cancers have improved little over the past three decades, a period in which successful new treatments have increased patient survival for many other cancers (4). Patients with CCA usually present at a late stage of the disease, and symptoms might be non-specific, such as painless jaundice, weight loss or cholangitis. Therefore, these cancers remain difficult to diagnose and treat and their prognosis continues to be generally poor. CCA has an average 5-year survival rate of ~5%. Median Survival of patients with un-resectable disease is 6-12 months (5). Tumour resection is the only potential curative option for CCA, however only few patients are candidates for curative surgical resection at the time of presentation. Moreover, the outcomes after resection are poor, with 5 year survival of ~20-40% for intrahepatic (IH) cancers and up to ~40% for extrahepatic (EH) cancers (6,7).

CCA is considered a tumour with a worldwide low incidence, with the exception of Eastern countries in which endemic liver fluke is present. Nevertheless, during last decade the incidence of this cancer is increasing in many countries. If the worldwide trend is confirmed in the near future, this could possibly have an impact on public-health programs. An increased incidence of IH-CCA versus EH-CCA has been reported across many countries (8), suggesting the possible role of some new risk factor. Although it seems that the age-adjusted incidence of IH-CCA has increased in several parts of the world, the true picture is unclear and might be obscured by diagnostic misclassification (9).

As seen in the review published by Bragazzi *et al.* in the current issue, there are several well established risk factors for CCA, including parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatitis C virus (HCV), hepatitis B virus (HBV), hepatolithiasis, and toxins. However only a minority of patients presenting with CCA have known risk factors (10). Other less related predisposing factors to highlight are alcohol use, diabetes and obesity. The latter may soon have a relevant impact on the occurrence of CCA given its high incidence in more developed countries.

Multiple case - control analyses have reported an association between CCA and alcohol use (3,11,12). Both alcoholic liver disease and cirrhosis are well established risk factors for HCC (13). Conceivably, alcohol may be related to IH-CCA in a similar way, particularly as there is evidence that both types of primary liver cancers arise from common progenitor cells that may give rise to tumours with hepatocellular or cholangiocellular phenotypes (14).

Obesity is also reported as a significant, but weak, risk factor for CCA. In a study obesity and non-alcoholic liver disease were significantly associated with IH-CCA but not EH-CCA (2). In recent years, obesity and Non-Alcoholic Fatty Liver Disease (NAFLD) have received increasing attention as NAFLD may act as a co-factor in HCV- and alcohol-related liver disease (15). In addition, Non-Alcoholic Steato-Hepatitis (NASH) represents an independent risk factor for the development of liver fibrosis, cirrhosis, and ultimately HCC. The same constellation of conditions has been proven to be

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associated with IH-CCA.

A previous, already mentioned, study (2) also found that diabetes was significantly associated with EH-CCA and IH-CCA. Although elevated insulin and glucose levels may directly stimulate fibrogenesis and release of connective tissue growth factors and favour inflammatory changes (16), the interplay of the components of the metabolic syndrome (obesity, hyperlipidemia, NAFLD, diabetes) is complex, and requires further investigation to evaluate the independent contributions of each factor.

Finally as HCV infection, obesity, and chronic non-alcoholic liver disease are increasing in the US (17), these conditions may be contributing to the divergent trends in EH-CCA and IH-CCA and may also explain similar trends in IH-CCA and HCC (18).

There are indeed several challenges and needs for the future in the CCA field. An urgent necessity is to adopt a consistent and useful nomenclature and classification for this tumour. This change is essential to improve the evaluation of risk factors, to understand pathogenesis, define appropriate therapies and evaluate outcomes. In addition, several aspects may be involved but both clinical and basic research will require further development. For instance, strategies to reduce the incidence of known CCA risk factors are needed. These preventive strategies include public health measures to reduce the incidence of liver fluke infestation in regions of high endemicity, and the surgical removal of choledochal cysts, which might be associated with a high risk of malignant change. In the near future viral hepatitis prevention could also affect worldwide CCA incidence, but nowadays only industrialised countries are able to undertake public health manoeuvres aimed to contrast HCV and HBV related morbidity given the costs of prevention, follow-up and treatment. Surveillance for CCA can be also offered to individuals with high risk factors, such as patients with PSC or hepatolithiasis, but these efforts are limited at present by the relative ineffectiveness of the currently available diagnostic tests that need to be improved.

Concerted efforts to improve diagnostic techniques are needed to identify individuals who could benefit from surgical resection and improve preoperative staging. In addition to CT, MRI and cholangiography, more information might be obtained by endoscopic ultrasound, which is a useful tool for the evaluation of biliary tract obstruction and for the detection and sampling of regional nodes. Early detection is needed as a key point to improve survival rates from these devastating tumours. Multimodality approaches need to be evaluated sys¬tematically. Addressing these issues will probably require well-coordinated and collaborative efforts if any progress is to be made.

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