REVIEW ARTICLE

# Cholangiocarcinoma: Epidemiology and risk factors

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**ABSTRACT**

Cholangiocarcinoma (CCA) is a malignant tumour, arising from biliary epithelium at any portion of the biliary tree, characterized by a bad prognosis and poor response to current therapies. CCA is currently classified as intrahepatic (IH-CCA) or extrahepatic (EH-CCA). The distinction between IH-CCA and EH-CCA has become increasingly important, as the epidemiological features (i.e., incidence and risk factors), the biologic and pathologic characteristics and the clinical course are largely different. New insights into hepatic and biliary tree stem cell niches organization, into cancer cells of origin and cancer stem cell biology are currently under evaluation as the biological bases of the observed heterogeneity of CCA and could explain the differences in epidemiology and risk factors between IH- and EH-CCA. The purpose of this manuscript is to revise recent literature dealing with the descriptive epidemiology, risk factors and clinical-pathological heterogeneity of CCA with a special effort to compare IH- versus EH-CCA.

**KEY WORDS**

Intra-hepatic cholangiocarcinoma; extra-hepatic cholangiocarcinoma; epidemiology; risk factors; incidence

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## Introduction

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 includes a group of tumors largely heterogeneous from epidemiologic, morphologic, biologic and clinical point of view. CCA is currently classified as intrahepatic (IH-CCA) or extrahepatic (EH-CCA), the second-order bile ducts acting as the separation point (1,2). The EH-CCA is comprised of the perihilar form (Klatskin tumor) and distal form where the separation point being posed at the level of the cystic duct. The distinction between IH- and EH-CCA has become increasingly important, as the epidemiological 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 general, a number of biases and criticisms should be taken into consideration in evaluating the literature dealing with epidemiology and risk factors of CCA and especially of the two main forms, the IH- and EH-CCA: (I) in many cancer registries CCA is combined with other primitive liver cancers and the perihilar EH-CCA has been often considered as IH-CCA. Indeed, some authors described the epidemiology and the risk factors for CCA clearly considering the Klatskin TOMOR (8162) as IH-CCA; (II) until 2006, perihilar CCA was assigned by ICD-O (International Classification of Diseases Oncology)-2

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