

# Epidemiology and Risk Factors of Cholangiocarcinoma

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## Keywords

Epidemiology · Risk factors · Cholangiocarcinoma · Screening · Surveillance

## Summary

**Background:** Cholangiocarcinoma (CCA) is the second most common primary liver cancer, being characterized by its late diagnosis and fatal outcome. Recent epidemiological reports indicate an increasing worldwide incidence of intrahepatic CCA but a decreasing incidence of extrahepatic CCA. **Methods:** In this review, we present an overview of the incidence and epidemiology of CCA and possible strategies for screening and surveillance. **Results:** Efficient strategies for the screening and surveillance of CCA have not been established so far. The vast majority of CCA occur sporadically without any apparent cause; however, several risk factors such as liver flukes, chronic biliary and liver diseases, and lifestyle-related aspects causing chronic inflammation and cholestasis in the liver have been linked to the development of CCA. These risk factors likely contribute to the increased incidence observed in some countries and also explain the wide geographical differences in the incidence of CCA. **Conclusion:** Several risk factors for CCA have been identified. Given the dismal prognosis of advanced CCA, regular surveillance examinations with a combination of ultrasonography and laboratory tests appear to be useful in patients at risk and need to be explored in prospective trials.

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## Introduction

Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies that can emerge from the canals of Hering to the main bile duct. CCA are rare tumours comprising approximately 3% of gastrointestinal tumours and have an overall incidence of less than

2/100,000 [1]. They are the second most common primary hepatic malignancies following hepatocellular carcinoma (HCC). CCA accounts for about 20% of the deaths from hepatobiliary cancers, which cause 13% of the total cancer mortality worldwide. Epidemiologic studies suggest that its incidence has been increasing in Western countries during the last decades [1, 2]. CCA is one of the most fatal cancers: although 1-year mortality has improved over time, the 5-year survival is still as low as 10% [3]. The only curative option for patients with CCA is surgical resection. Despite the rate of resectability having been reported to be as high as 65%, curative resection rates are less than 50% [4]. Unfortunately, two-thirds of CCA remain clinically silent and are only diagnosed in more advanced stages [5]. At advanced stage, CCA has a devastating prognosis with a median overall survival of only 12–15 months [6, 7].

## Incidence

The most common classification of CCA is based on its anatomical location. CCA are commonly staged into intrahepatic (IH-CCA) and extrahepatic (EH-CCA) tumours. EH-CCA can further be subdivided into perihilar CCA, which are also called Klatskin, and distal tumours [8]. The epidemiological profiles of the different subtypes of CCA display significant geographical variation, reflecting the exposure to different risk factors and most likely different genetic backgrounds. Epidemiological studies looking at trends in different countries and regions have mostly but not uniformly reported a rise in CCA. There are consistent reports of an increasing incidence of IH-CCA and a decreasing or stable incidence of EH-CCA from the World Health Organization (WHO) database [9], from US cancer registries [10–12], and also from Japanese and different European cohorts (fig. 1) [13–15]. A very recent analysis from the Surveillance, Epidemiology, and End Results (SEER) database confirmed that the incidence of IH-CCA has risen by 128% in the USA between 1973 and 2012, whereas the incidence of EH-CCA remained stable [16]. Interestingly, the incidence of cancer of unknown primary (CUP) has fallen dramatically during the same time period, suggesting that improved evaluation of CUP through ad-

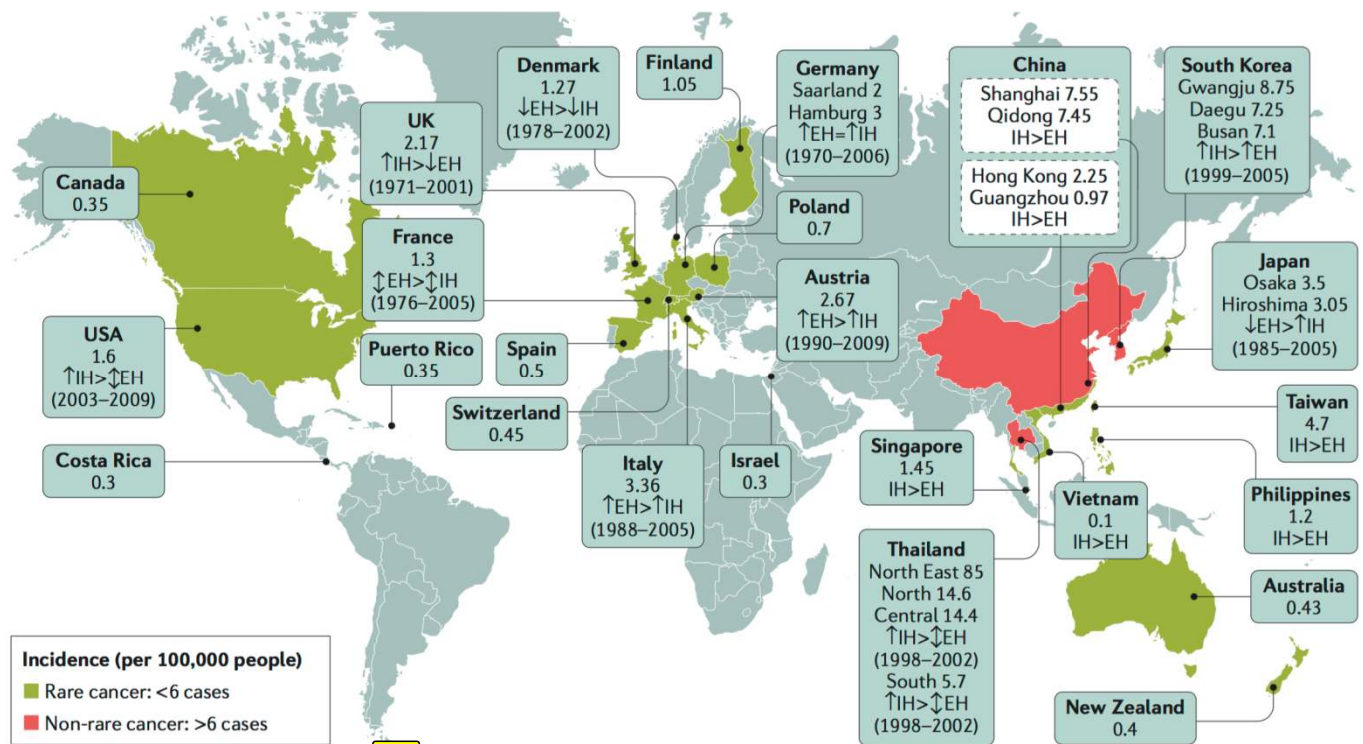


Fig. 1. Global incidence rates of CCA [71]

vanced imaging, molecular diagnostics, and histopathologic techniques contributes to the increasingly recognized incidence of IH-CCA. As the use of molecular diagnostics for the identification of druggable lesions, such as IDH1/2 mutations and FGFR2 fusions, is likely to increase in the near future, the accurate diagnosis of these tumours may further improve along with a better understanding of the true incidence of ICC. In Germany, mortality attributed to hepatobiliary cancers has largely been constant over the past 30 years, while overall liver disease mortality has slightly declined. Among hepatobiliary malignancies, IH-CCA stands out because mortality has more than tripled both in men and women between 1998 and 2008. Over the same time period, HCC and EH-CCA have remained constant while gallbladder cancers have declined twofold [17]. In line with the increased mortality data the number of reported cases of IH-CCA also increased between 1970 and 2006. In contrast, there are also two recent studies from Denmark and France reporting stable and even falling incidence rates of IH-CCA and EH-CCA, respectively [18, 19]. These epidemiological discrepancies between neighbouring countries that are environmentally and culturally similar are largely unclear and may also result from the challenging classification and discrimination of CCA, in particular for hilar CCA or CCA at advanced stages [20, 21].

CCA mainly occur not earlier than in the fourth decade of life and rather in men than in women [22, 23]. This sex-specific disparity has recently been confirmed and reported to become even more pronounced with increasing age in an updated analysis of the 2000–2011 SEER population-based cancer registry including 11,296 patients with IH-CCA and 8,672 patients with EH-CCA from the USA [23]. This analysis also revealed the highest inci-

dence in Asians among all ethnic groups and CCA types (IH-CCA as well as EH-CCA). These results confirm that the incidence rates of CCA most likely vary in different geographic regions due to environmental and genetic differences. The highest incidence rates of IH-CCA have been reported in the north of Thailand (up to 113 per 100,000 person-years in men and 50 per 100,000 person-years in women), where the liver fluke *Opisthorchis viverrini* is endemic [24]. In this area, CCA comprise 89% of primary liver cancers [25], which is 100 times higher than in the Western World [26].

The vast majority of CCA (70%) occur sporadically without any apparent cause. However, several risk factors have been identified, which not least vary depending on the geographic region [5, 22].

### Parasitic Infections

In East Asia, parasite infestation with the liver flukes *O. viverrini* and *Clonorchis sinensis* by ingestion of raw, undercooked, or pickled fish is the most important risk factor for cholangiocarcinogenesis [27]. *O. viverrini* is endemic in northeast Thailand, Laos, and Cambodia [28], whereas China, Taiwan, Korea, and Vietnam are endemic areas for *C. sinensis*. The parasites inhabit the bile ducts for years causing cholangitis, obstructive jaundice, hepatomegaly, fibrosis of the periportal system, cholecystitis, and cholelithiasis [28]. Importantly, periductal fibrosis remains even after treatment with anthelmintics, which may subsequently contribute to CCA development, particularly when associated with such co-factors as nitrite-rich diets via fish consumption, smoking, and alcohol consumption [29]. Other potential risk factors for *O. viverrini*

rini-associated infections are coinfection with *Helicobacter* and diabetes mellitus. A case-control study from 1991 demonstrated that infection with *O. viverrini* led to a fivefold increase of the risk of CCA development [30]. A meta-analysis of case-control studies confirmed the strong association between infection with *O. viverrini* or *C. sinensis* and CCA [31].

### Primary Sclerosing Cholangitis

The strongest association of CCA in Western populations has been established for primary sclerosing cholangitis (PSC), with or without inflammatory bowel diseases, mainly ulcerative colitis (UC) [32]. A very recent case-control study including 2,395 CCA confirmed PSC as the most significant risk factor for CCA. Within this large study, biliary tract diseases were identified as a risk factor, followed by hepatitis B virus (HBV) infection, diabetes, and tobacco smoking after exclusion of PSC patients [32]. PSC is a chronic, autoimmune disease which involves both the intra- and extrahepatic bile duct system [33]. PSC may cause bile duct strictures, dilations, cholestasis as well as biliary cirrhosis and may promote cholangiocarcinogenesis [33]. In population-based series, the lifetime incidence to develop CCA ranges from 6 to 36%, and the cumulative incidence is between 7 and 14% [34–36]. Approximately 50% of CCA are diagnosed within the first year of diagnosis of PSC, while the CCA incidence decreases over time [36, 37]. The mean age of CCA development in patients with PSC is the fourth decade of life compared with the seventh decade in the general population. The prognostic impact of a coexisting inflammatory bowel disease still remains unclear. However, CCA occurred nearly twice as frequently in patients with UC than in those with Crohn's disease, suggesting a stronger association of cholangiocarcinogenesis in patients with PSC and UC rather than PSC and Crohn's disease [37]. Altogether, there is still an unmet need for identification of refined risk factors for cholangiocarcinogenesis in patients with PSC.

### Cholelithiasis

Cholangiocarcinogenesis has been associated with different forms of cholelithiasis [11, 38]. Cholelithiasis can be subdivided into hepatolithiasis, choledocholithiasis, and cholecystolithiasis. Hepatolithiasis are gallstones located in the intrahepatic bile ducts, which is an established risk factor for CCA. The incidence of IH-CCA in patients with hepatolithiasis is reported to be 4–11% [39]. CCA development in patients with hepatolithiasis is very likely caused by recurrent cholangitis and chronic inflammation of the biliary epithelium [40]. Smoking, family history of cancer, appendectomy in childhood, and duration of symptoms longer than 10 years have been proposed as contributing risk factors for cholangiocarcinogenesis in patients with hepatolithiasis [41].

Patients with cholecystolithiasis or choledocholithiasis are at an increased risk of developing EH-CCA, and this risk increases with the size of gallstones, calcification of epithelium, and duration of

disease [42]. To date, there is no consensus on whether choledocholithiasis or cholecystolithiasis also contribute to IH-CCA development. However, a recent meta-analysis of seven case-control studies including altogether 123,771 participants suggests that the presence of choledocholithiasis alone in the absence of hepatolithiasis is associated with a high risk of IH-CCA, whereas the evidence for cholecystolithiasis was less clear and pronounced [43]. Subgroup analysis indicates that the cancer risk was lower for choledocholithiasis alone than for choledocholithiasis accompanied by hepatolithiasis. The mechanism by which choledocholithiasis contributes to IH-CCA development is not completely understood and may be related to cholestasis, changes in bile composition, or accompanying metabolic syndromes such as diabetes and hyperlipidaemia.

### Biliary Disorders

Bile duct cysts are rare congenital anomalies characterized by cystic dilatation of the bile ducts. The association with CCA is well established, and these patients develop CCA at a mean age of 32 years, with a lifetime incidence ranging from 6 to 30%. The tumour can arise from cysts as well as from undilated parts of the biliary tree [44]. Usually, the risk of malignancy decreases after cyst excision but for some types the cancer risk remains increased even after cyst excision [44, 45].

As a particular cystic disease, Caroli's disease is a congenital disorder characterized by segmental saccular communicating dilation of the large intrahepatic bile ducts resulting in recurrent episodes of bacterial cholangitis [44]. Caroli's disease must be distinguished from Caroli's syndrome. The latter is a combination of cystic bile duct disease with congenital hepatic fibrosis [46]. Several studies with up to 33 patients with Caroli's disease suggest that there is an increased incidence of CCA in patients with Caroli's disease [47–49].

### Hepatitis B and C

Recently, liver cirrhosis and viral hepatitis B and C have been recognized as risk factors for cholangiocarcinoma, especially intrahepatic disease [50–52]. Viral hepatitis-associated cholangiocarcinogenesis is most probably linked to chronic inflammation and increased cell proliferation [53]. However, the contribution of hepatitis infection in CCA cases varies geographically between Western countries and Asia, where HBV is endemic. In studies from Western countries, hepatitis C virus (HCV) was shown to be a risk factor for CCA [54], whereas studies from Asia have shown more consistently HBV as a risk factor for IH-CCA [55]; a Japanese study confirmed findings from Western countries where IH-CCA association was stronger with HCV exposure than with HBV. The association of HBV and HCV with IH-CCA has also been recently confirmed in two meta-analyses of case-control and cohort studies with an odds ratio (OR) of 4.84 (2.41–9.71) for HCV and of 5.10 (2.91–8.95) for HBV [56, 57]. The risk estimates for IH-CCA were increased for

both HBV and HCV, whereas the association of HBV and IH-CCA was greater in Asian patients but lower for HCV and CCA as compared to Western patients [56, 57]. For HBV infection alone, the risk of CCA was confirmed to be greater in Asia than in the West [58].

Liver cirrhosis was evaluated as a potential risk factor for IH-CCA in a meta-analysis including seven studies from the USA, Japan, Denmark, Italy, and China [56]. Cirrhosis was found to be significantly associated with IH-CCA regardless of the underlying aetiology with an OR of 22.92 (95% CI: 18.24–28.79).

Altogether, there is strong evidence of an association between endemic HBV and IH-CCA. HCV might also be associated with IH-CCA rather in Western than in Asian patients. Liver cirrhosis is an independent risk factor for IH-CCA.

### Lifestyle-Related and Other Risk Factors

Diabetes, obesity, alcohol consumption, and tobacco smoking are increasingly recognised as risk factors for CCA, however, with inconsistent reports [19, 36, 59, 60]. Diabetes and tobacco smoking represented risk factors in the large case-control study by Choi et al. [32] after the exclusion of patients with PSC. Moreover, a significant association between elevated body mass index and cholangiocarcinogenesis has been observed [61]. A meta-analysis of US and Danish studies identified an association of IH-CCA with diabetes with an OR of 1.89 (95% CI: 1.74–2.07) and obesity with an OR of 1.56 (1.26–1.94) [56]. Alcohol abuse/alcoholic cirrhosis has been associated with an increased risk for IH-CCA and EH-CCA in a Danish study [62]. These potential risk factors need to be evaluated more profoundly in the future.

Long-term exposure of workers in printing factories to chemicals that include high concentrations of dichloromethane and/or 1,2-dichloropropane is strongly suspected to be associated with cholangiocarcinogenesis, and this type of CCA has been defined as 'occupational CCA' in Japan [63].

Moreover, the formerly used radiographic contrast agent Thorotrast, which is not used anymore, has been reported to contribute to cholangiocarcinogenesis [64].

### Aspirin

Very recently, a case-control study including 2,395 CCA cases seen at the Mayo Clinic from 2000 to 2014 investigated the impact of aspirin. Aspirin was used by 591 (24.7%) CCA cases and 2,129 (44.6%) controls. Aspirin use was significantly associated with a 2.7- to 3.6-fold decreased risk for all CCA subtypes [65]. Preclinical studies have already revealed that COX-2 is implicated in cholangiocarcinogenesis in vitro and in tumour growth in rats [66, 67]. Accordingly, aspirin has been proposed to reduce the incidence and mortality of various cancer types within observational studies [68]. However, prospective randomized controlled trials investigating the role of aspirin in patients with CCA will most probably be difficult to conduct due to the broad availability of aspirin and

the low incidence rates of CCA, but might be feasible in selected risk groups such as PSC patients or men exposed to flukes.

### Prevention, Surveillance, and Perspectives

Prevention is relevant for endemic regions for parasites and HBV, including health education, vaccination, and antiviral therapies as well as avoiding exposure to toxins. Surveillance including imaging, laboratory tests, and biliary cytology has been suggested for early cancer detection in patients with PSC as the major risk factor for CCA. However, there is a lack of consistent recommendations concerning the methods and frequency of investigations, pointing out an urgent need for the development of surveillance standards for patients with PSC and also for patients with other biliary disorders and cholelithiasis [1, 2].

A recent study evaluated the changes in ultrasound and laboratory values before and after the diagnosis of CCA in 9 patients who were occupationally exposed to organic solvents, as described before [63]. Interestingly, levels of aminotransferases were elevated, and ultrasound revealed regional bile duct dilatation already several years prior to the first diagnosis, suggesting that regular ultrasound and liver-relevant laboratory examinations should be performed in patients at high risk.

Concerning diagnostic tumour markers, carbohydrate antigen (CA) 19-9 is characterized by a high specificity of more than 90% as well as a moderate sensitivity of 50–80% and is most widely used in clinical practice. There are inconsistent reports about the sensitivity and specificity of carcinoembryonic antigen (CEA). So far, several novel, promising diagnostic biomarkers from serum or bile, such as metalloproteinases or serotonin, have been suggested [69]. However, their validation and applicability for clinical routine are outstanding.

The Khon Kaen University in northeast Thailand, a region with very high incidences of liver flukes, has started the 'Cholangiocarcinoma Screening and Care Program' (CASCAP) in collaboration with the National Health Security Office (NHSO) and the Ministry of Public Health. The aim of this study is to systematically improve the diagnosis and treatment of CCA patients throughout the northeast of Thailand [70]. For the screening cohort, annual ultrasound examination and – as appropriate – biopsy will be provided in order to establish diagnosis as early as possible. This cohort is expected to include at least 150,000 individuals coming from high-risk areas for CCA. 25,000 CCA patients are estimated for the patient cohort. These patients will be followed up similar to a conventional cancer registry. This study is very promising to prospectively provide a large database of CCA cases and of patients at risk for CCA. The results could provide valuable updates on epidemiology and profound information on potential risk factors, such as lifestyle-related influences, which are not yet completely understood.

### Disclosure Statement

The authors have no conflict of interest to declare.

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In the article by Kirstein MM, Vogel A:

**Epidemiology and Risk Factors of Cholangiocarcinoma.**

Visc Med 2016;32:395–400 the legend of figure 1 was incorrectly given.

The correct legend is as follows:

**Fig. 1.** Global incidence rates of CCA (originally published by Banales et al. [71] ([www.nature.com/nrgastro/journal/v13/n5/full/nrgastro.2016.51.html](http://www.nature.com/nrgastro/journal/v13/n5/full/nrgastro.2016.51.html)); Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)).