J Gastrointest Canc (2012) 43:137–147
DOI 10.1007/s12029-011-9284-y

REVIEW ARTICLE

Risk Factors for Gallbladder Cancer and Cholangiocarcinoma: Similarities, Differences and Updates

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Published online: 20 May 2011

Abstract
Introduction Far-ranging variation in the incidence of gallbladder cancer (GBC) and cholangiocarcinoma (CCA) in different geographic regions on the globe may reflect the risk factor distribution for these tumors
Methods The authors give a comprehensive review on the known risk factors for GBC and CCA, and analyze both similarities and differences between the risk factors for the two main types of biliary cancer
Discussion and Conclusion Leading risk factors for GBC include gallstones, female gender, and advancing age. Primary sclerosing cholangitis, nitrosamine exposure, choledochal cysts, *Clonorchis sinensis* and *Opisthorchis viverrini* represent important risk factors for CCA, although a specific risk factor cannot be identified for many patients. While both cancers affect mostly individuals in their sixth decade or older, CCA has a male predominance and GBC—a predilection for females. Although the current level of understanding of the molecular pathogenesis of GBC and CCA at the interface with specific risk factors is significantly lower than for other gastrointestinal malignancies, it continues to evolve and may soon open new avenues for the therapy of biliary cancers.

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Keywords Risk factors · Gallbladder · Cancer · Cholangiocarcinoma · Gallstones · Liver fluke · Cholelithiasis

Introduction

Both gallbladder cancer (GBC) and cholangiocarcinoma (CCA) are highly lethal cancers with limited survival as most cases are diagnosed in late stages. This is because of the absence of specific symptoms, physical examination findings, or laboratory abnormalities in the early or premalignant stages in most cases.

Fewer than 5,000 new cases of GBC are diagnosed each year (incidence of 2–3 cases per 100,000 population) in the US [1]. The majority is found incidentally in patients undergoing exploration for cholelithiasis; a cancer will be found in less than 1% of such cases [1–4]. In the United States, GBC is the fifth most common gastrointestinal cancer and the most common cancer involving the biliary tract [1, 5]. In contrast to the situation in general population, GBC is the most common gastrointestinal malignancy in both Southwestern Native Americans and in Mexican Americans [6].

CCA is a rare hepatobiliary malignancy originating from bile duct epithelium, which accounts for approximately 3% of all gastrointestinal cancers worldwide [7]. The reported incidence in the United States is approximately 1 case per 100,000 population and its prevalence in autopsy studies is 0.01% to 0.46% [7]. On the basis of its anatomic distribution, CCA has been classified as either intrahepatic or extrahepatic. Although, the annual incidence of intrahepatic and extrahepatic CCA had been shown in earlier studies to be almost equal (2,600 cases of intrahepatic and 2,000–3,000 cases of extrahepatic CCA) [8–10], more

recent data suggests that intrahepatic CCA accounts for approximately one quarter of all CCA. However, the true incidence data are difficult to interpret because intrahepatic CCA are often included in the analysis together with primary liver cancers, while extrahepatic CCA are in a separate category that sometimes includes GBC [8–10]. The incidence of intrahepatic CCA has been reported to rise internationally over the past two decades [9–16], likely related to a concomitant increase in certain risk factors such as cirrhosis, alcoholic liver disease, and hepatitis C viral (HCV) infection [17]. Part of this increase may be explained by the ascertainment bias owing to the growing availability of endoscopic retrograde cholangiopancreatography. Increasing use of better diagnostic imaging modalities such as CT and MRI scans, more patients undergoing surgery, and advances in pathology examination techniques could probably explain the better differentiation from hepatocellular carcinoma, and thus might account for the increasing incidence of CCA.

The wide variation in the incidence of GBC and CCA in different areas on the globe may reflect the variability in the distribution of risk factors for these tumors. The main objective of this article is to comprehensively review the risk factors for GBC and CCA. Furthermore, it analyzes the similarities and differences between the risk factors and etiopathogenesis for the two biliary cancers.

Table 1 Risk factors for GBC

Established risk factors
Advanced age
Female gender
Cholelithiasis
Geographic distribution: South American countries (Chile, Bolivia, and Ecuador), India, Pakistan, Japan and Korea
Ethnicity: Caucasians, Southwestern Native Americans, Mexican Americans
Porcelain gallbladder
Gallbladder polyps
Congenital biliary cysts
Abnormal pancreaticobiliary duct junction
Carcinogen exposure (such as Thorotrast)
Possible risk factors
Medications: methyldopa, OCPs, isoniazid, estrogen
Infections: *Salmonella*, *Helicobacter*
Smoking
Obesity

Major Risk Factors

While a majority of patients who develop biliary cancers have no well-defined risk factors, several factors have been identified to increase the risk of these malignancies. Main risk factors for GBC include cholelithiasis, female gender, and advanced age. Primary sclerosing cholangitis (PSC), liver fluke infestation, nitrosamine exposure and choledochal cysts have been defined as major risk factors for CCA, although a specific risk factor cannot be identified for many patients [18]. Studies have shown that approximately 90% of patients diagnosed with CCA in Western countries do not have a recognized risk factor [19, 20]. In the United States and Europe, the main risk factors are PSC and choledochal cysts, whereas infection with liver fluke is the most common risk factor for CCA in Asian countries.

Tables 1 and 2 enumerate the risk factors for GBC and CCA, respectively. Table 3 shows the common risk factors for the two malignancies.

Cholelithiasis

Carcinogenesis in biliary cancers is thought to be secondary to chronic inflammation leading to dysplasia, induced by various agents. Both gallstones and biliary duct stones have been implicated as risk factors for GBC and CCA. While cholelithiasis is a well-described and strongest risk factor for GBC, the association between gallstones and CCA is

Table 2 Risk factors for CCA

Advancing age
Male gender
Primary sclerosing cholangitis
Inflammatory bowel disease
Fibropolycystic liver disease
Choledochal cysts
Caroli's disease
Lynch syndrome
Bile duct adenomas
Biliary papillomatosis
Liver flukes: *Clonorchis* and *Opisthorchis*
Cholelithiasis
Hepatolithiasis
Viral hepatitis- HBV, HCV
HIV infection
NAFLD
Diabetes
Obesity
Smoking
Alcohol
Toxic exposures - asbestos, nitrosamines, radon
Thorotrast

Table 3 Common risk factors for GBC and CCA

Cholelithiasis
Advanced age
Congenital biliary cysts
Obesity
Smoking

less well established. Yet, at least three epidemiologic studies note an increased risk for CCA among patients with symptomatic gallstone disease, though of a lower magnitude than for GBC [21–23]. However, there is a clear association between chronic intrahepatic stone disease (hepatolithiasis, also called Oriental cholangiohepatitis) and CCA [24–31]. The biliary stones are thought to cause bile stasis, predisposing to recurrent bacterial infections and chronic inflammation. While stone disease affecting only the intrahepatic bile ducts is exceedingly rare in the West, it is endemic in certain parts of Southeast Asia. In Taiwan, 50% to 70% of patients undergoing resection for CCA have associated hepatolithiasis [26, 28], while in Japan the incidence is much lower (6% to 18%) [25, 30, 31].

Gallstones are present in 70% to 90% of patients with GBC [22, 32], and a history of gallstones appears to be one of the strongest risk factors for the development of GBC [22, 33–37]. As an example, in a case–control study from Shanghai, China, that included 368 patients with GBC and 959 healthy controls, individuals with symptomatic gallbladder disease (gallstones or self-reported cholecystitis) were 34-fold more likely to develop GBC [22].

Despite the increased risk of GBC in patients with gallstones, the overall incidence of GBC in patients with cholelithiasis is only 0.5% to 3% [1]. The risk appears to be higher with larger gallstones (in one study, patients with stones larger than 3 cm had a tenfold higher risk of GBC compared to those with stones less than 1 cm in size) [38] and with longer duration of cholelithiasis (particularly over 40 years) [39].

Chemical and Pharmaceutical Agents

Exposure to chemical agents and toxins has been implicated as risk factor for both GBC and CCA. A clear association exists between exposure to the radiologic contrast agent Thorotrast and subsequent development of CCA; this malignancy usually develops 30–35 years after exposure [40], and the carcinogenesis is related to alpha-radiation effect [41]. A *beagle model* of cholangiocarcinomas also exists after exposure to americium supporting the role of radiation as a risk factor for CCA. In this experimental model, CCA was the second most frequently occurring neoplasm following bile duct adenoma in both plutonium (Pu-239)- and americium (Am-241)-treated dogs [42]. An increased incidence of CCA has been less strongly associated with several occupations, including the auto, rubber, chemical, and wood-finishing industries. Similarly, an increased risk of GBC has been described in workers in oil, paper, chemical, shoe, textile and cellulose acetate fiber manufacturing industries, and in miners exposed to radon [43–45].

Some drugs such as methyldopa, oral contraceptive agents, and isoniazid have also been implicated in GBC tumorigenesis [46–48]. However, the association between oral contraceptive use and GBC remains controversial [49, 50]. No similar association exists between these agents and CCA.

Studies on the association between smoking and alcohol intake and the risk of CCA are conflicting [51–54]. Excess alcohol usage was higher in patients with intrahepatic CCA (22%) compared to controls (4%) in a recent US case–control study [54]. Another study found smoking to be associated with intrahepatic CCA. An increased risk for GBC has also been noted in cigarette smokers. The habit of chewing betel nut with tobacco has emerged as a risk factor for CCA [55].

For CCA, epidemiological associations have also been made with industrial toxins such as dioxins and nitrosamines [56]. Consumption of nitrosamine-contaminated food, beverages, raw fish, tobacco-specific nitrosoamines and volatile nitrosoamines [55] from smoking has been described as a major risk factor for CCA, particularly in North-Eastern Taiwan [57]. Of note, the liver fluke *Opisthorchis viverrini* infection has been shown to increase the potential for endogenous formation of carcinogenic nitrosamines and also increase the carcinogenic action of nitrosodimethylamine from exogenous sources such as food items and tobacco consumption.

Age and Gender

Incidence of GBC was shown to increase steadily with age, with most GBC occurring in the sixth and seventh decades of life [58, 59]. Women are affected two to six times more often than men [58, 59]. GBC is more common in Caucasians than in blacks [60].

The typical patient with CCA is between 50 and 70 years of age. In contrast to GBC, where female gender predominates, the incidence of CCA is slightly higher in men, possibly secondary to the higher incidence of PSC in men [61].

Geographic Prevalence

Worldwide, there is a distinct geographic variability of GBC prevalence that correlates with the prevalence of

cholelithiasis. High rates of GBC are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan, and Korea [33, 62]. In Chile, mortality rates from GBC are the highest in the world. These populations all share a high prevalence of gallstones and/or salmonella infection, both recognized risk factors for GBC [43, 63, 64]. Taiwan has the highest prevalence of CCA and mortality from CCA in the world [57].

Infections and Parasitic Illnesses

Multiple infections have been postulated as risk factors for both GBC and CCA. In Asia, particularly in Thailand and China, parasitic infestation with liver flukes of the genera *Clonorchis sinensis* and *O. viverrini* is strongly associated with intrahepatic CCA [7] [65–67] [68–71]. These organisms are foodborne trematodes that chronically infect the bile ducts and induce a chronic inflammatory state in the proximal biliary tree, leading to oxidative DNA-damage and malignant transformation of the infected biliary epithelium [72]. *O. viverrini* [69, 73–75] appears to have a stronger association with CCA than *C. sinensis* [67, 76, 77] [19]. Shin et al. calculated the overall relative risk of infection with liver fluke (both *C. sinensis* and *O. viverrini*) to be 4.8 (95% CI: 2.8–8.4) [78].

An association between HCV and CCA was initially suggested in 1991 [79]. Since then, several reports have noted a higher than expected rate of HCV-associated cirrhosis in patients with CCA, although the risk is much lower than for hepatocellular cancer [10, 17, 53, 80–85]. A prospective case–control study from Japan reported the risk of developing CCA in patients with cirrhosis related to HCV to be 3.5% at 10 years [80]. A large cohort study in the United States found a significant association between intrahepatic CCA and hepatitis C after adjustment for potential confounders including cirrhosis (adjusted RR 2.55, 95% CI 1.31–4.95) [86].

An association between hepatitis B virus (HBV) and CCA has also been suggested, although the data are less compelling than for HCV [24, 67, 87]. The association between either HBV or HCV and subsequent development of CCA in a meta-analysis by Shin et al. was statistically significant [78]. They reported relative risks of infection with HBV and HCV for CCA to be 2.6 (1.5–4.6), and 1.8 (1.4–2.4), respectively [78].

HIV infection has been shown to be an independent risk factor for intrahepatic CCA (adjusted OR=6.4) [17]. Of note, HBV, HCV, and HIV infections have not been associated with increased incidence of GBC in the existing literature.

Several reports suggest an association between chronic *Salmonella typhi* carrier status and elevated risk of GBC [88–90]. A prospective case–control study performed on patients with GBC and gallstones (cases) or gallstones alone (controls) identified the *S. typhi* carrier state as an independent risk factor for GBC (OR=14) [90]. Because chronic carrier state occurs more often in individuals with cholelithiasis, gallstones are thought to represent a potential nidus for maintaining an ongoing infection.

Helicobacter infection, particularly *Helicobacter bilis* colonization of the biliary epithelium, has been implicated in the pathogenesis of gallbladder disease including GBC [91–95].

Gallbladder bile infection with *E. coli* is very common, and accounts for more than 50% of positive bile cultures. Although less strongly, it has also been shown to be associated with the risk of GBC [96].

Congenital Anomalies and Genetic Traits

A rare inherited disorder, multiple biliary papillomatosis is characterized by multiple adenomatous polyps in the bile ducts, and repeated episodes of abdominal pain, jaundice, and acute cholangitis [97]. This disorder is considered a premalignant condition for biliary cancers, with a high proportion of these lesions (83% in one study [97]) undergoing malignant transformation [98]. It is unclear whether adenomatous polyps represent premalignant lesions and, if so, what is the frequency with which they progress to carcinoma [99]. Unlike with GBC, gallbladder polyps tend not to occur in patients with cholelithiasis, chronic inflammation is generally absent, and cancer-defining molecular changes that are seen in GBC have not been identified in adenomas [99]. Nevertheless, larger polyps are more likely to contain foci of invasive cancer, and some studies suggest a correlation between the presence of gallbladder polyps and the risk of GBC [100].

Biliary cysts are associated with an increased risk of CCA, and the incidence of CCA varies with age in this setting. In a review of all published series on biliary cysts, the incidence of cancer was 0.7% in patients under 10 years of age, 6.8% in patients 11 to 20 years of age, and 14.3% in patients over 20 years of age [101]. An incidence as high as 50% has been reported in older patients. One study suggests that the increased incidence of carcinoma in biliary cysts is confined to patients with an anomalous pancreaticobiliary duct junction [102].

Congenital abnormalities of the biliary tree (Caroli's syndrome, congenital hepatic fibrosis, and choledochal cysts) carry an approximately 15% risk of malignant transformation into CCA in the adult years (average age at diagnosis 34) [103–105]. The overall incidence of CCA in patients with untreated cysts is as high as 28% [103, 104]. Biliary malignancy has been reported with choledochal cysts of

virtually all types [106–108]. In small cohort series, the incidence of CCA in individuals with choledochal cysts is generally 14% to 15% [109, 110]. The risk of CCA is thought to increase with increasing age [101].

Choledochal cysts are thought to be associated in particular with an increased risk for extrahepatic CCA [101, 106–110]. Except for the type III cysts (choledochocele), the lifetime risk of CCA for unresected choledochal cysts is thought to range between 3% and 15% [103, 111]. The vast majority of the literature suggests that the risk of a biliary malignancy in Todani Type III cysts or choledochocele is extremely low.

Abnormal pancreaticobiliary duct junction or pancreaticobiliary maljunction, most prevalent in Asian populations such as Japanese [112, 113], is thought to predispose to pancreaticobiliary reflux, biliary epithelial damage and inflammation, and appears to increase the risk of biliary malignancy [114–116]. GBC is the most common malignancy seen in patients with anomalous pancreaticobiliary duct junction. As a result, prophylactic cholecystectomy is recommended in affected patients.

Primary Sclerosing Cholangitis

Both intrahepatic CCA and extrahepatic CCA are well-known complications of PSC in Western countries [117]. PSC is strongly associated with ulcerative colitis (UC); approximately 40% to 50% of patients have symptomatic colitis, while the incidence of colitis is around 90% in patients with PSC [41]. Nearly 30% of CCAs are diagnosed in patients with PSC with or without UC. The incidence of CCA in patients with PSC has been estimated to be between 0.6% and 1.5% per year, with a lifetime risk of 10% to 15% [118–124]. The existing literature suggests that the majority of biliary malignancies in patients with PSC occur in the first 18–24 months and that the risk is much lower after the first 2 years. In contrast, the incidence has been shown to be much higher (30% or more) in some autopsy series [125].

CCA develops at a significantly younger age (between the ages of 30 and 50) in patients with PSC than in patients without this condition. Over one-third of these cases are diagnosed within 2 years of the initial diagnosis of PSC, and the risk appears unrelated to the duration of the inflammatory disease [122, 125, 126]. Smokers or former smokers are significantly more likely to develop this cancer [127]. Alcohol consumption has also been suggested to be a risk factor for the development of CCA in patients with PSC (odds ratio of 2.95; 95% CI of 1.04 to 8.3) [122].

As shown above, PSC is strongly associated with inflammatory bowel disease in the West; nearly three quarters of individuals with PSC also have UC, whereas a smaller percentage of patients have Crohn's disease [126]. Instances of biliary malignancy developing in individuals with UC were reported as early as the 1960s [128, 129]. Large series from Sweden with extended follow-up have reported a lifetime risk of CCA between 8% and 11% in individuals with PSC [126, 130]. In comparison, a lifetime CCA incidence of 6.8% was reported in a recent study from Mayo Clinic [120]. Although there is no clear correlation between the duration of PSC and development of CCA, the presence of cirrhosis is associated with an increased risk for CCA [131].

Miscellaneous Risk Factors

Obesity has been consistently associated with an increased risk for GBC [35, 62], and has also been linked to extrahepatic CCA in a population-based case–control study [53]. A meta-analysis of eight cohort studies and three case–control studies, with a total of 3,288 cases, confirmed the association between excess body weight and risk of GBC [132]. Compared with individuals of "normal weight", the summary relative risk of GBC for those who were overweight or obese was found to be 1.15 (95% CI, 1.01–1.30) and 1.66 (95% CI, 1.47–1.88), respectively. The association between obesity and GBC risk was stronger for women (relative risk, 1.88; 95% CI, 1.66–2.13) than for men (relative risk, 1.35; 95% CI, 1.09–1.68) in this meta-analysis [132].

Similarly, several epidemiological studies worldwide have implicated dietary factors in the pathogenesis of GBC, and it is suggested that the variations in GBC incidence of different populations might be in part determined by their dietary variations [133]. An increased risk has been observed with high intake of calorie, high carbohydrate, red meat, and greater preference for oily foods [133, 134]. Risk of GBC has also been associated with high consumption of red chili pepper [133, 135]. Vegetables, particularly green leafy vegetables, and fruits may have a protective effect and there has been a suggestion of inverse association with fiber intake, vitamin C, and vitamin E [133, 134, 136]. The importance of other dietary factors such as egg, proteins, cholesterol, tea and coffee is not yet clear due to insufficient evidence and inconsistent results [133].

Gallbladder polyps have been increasingly recognized as a predisposing factor for GBC. Several studies have shown that the size, number, shape (sessile vs pedunculated), and echogenicity of the polyps, as well as associated gallstones and the patient's age, may be important risk factors for GBC [137]. The prevalence of cancer in polyps less than 10 mm in size is low (0–5%); for polyps 1–1.5 cm and more than 1.5 cm, it is 11–13% and 46–70%, respectively [137]. The majority of malignant lesions are solitary (80–100%). In fact,

up to 18% of single lesions are cancerous. The patients with gallbladder polyps more than 10 mm in size that are single, sessile, or echopenic are at most risk for developing GBC [137]. Similarly, several case reports also suggest that adenomyomatosis may be a risk factor for GBC, though the magnitude of risk for GBC in patients with this finding has not been clearly established. Adenomyomas located in the fundus of the gallbladder, those with a diameter of 1–2 cm, or with a small central ulceration tend to be malignant [137].

Porcelain gallbladder is an uncommon manifestation of chronic cholecystitis that is characterized by extensive intramural calcification of the gallbladder wall. The prevalence of porcelain gallbladder in cholecystectomy specimens has ranged from 0.06% to 0.8% [138]. It is associated with cholelithiasis in more than 95% of cases and is five times as common in women as in men [138]. As with other gallstone-related conditions, these patients are at increased risk of GBC. The incidence of gallbladder cancer in porcelain gallbladder was reported to be 12–61% in an early 1960s series, but more recent studies have suggested that this incidence is less than 10% [44, 138–140]. Two studies in 2001 showed a lower incidence of gallbladder cancer in porcelain gallbladder (0% and 5%) [138–140].

As with hepatocellular carcinoma, chronic liver disease of nonviral etiology also appears to be associated with intrahepatic CCA [10, 17, 24, 53, 67, 80, 141]. In a case–control study, risk factors that were significantly more prevalent among patients with intrahepatic CCA included liver cirrhosis (adjusted OR=27.2) and alcoholic liver disease (adjusted OR=7.4) [17]. A Danish cohort study that followed 11,605 persons with cirrhosis from any cause for an average of approximately 2 years found a tenfold higher risk for intrahepatic CCA among these patients compared to the general population [141]. Some data suggests that insulin resistance and NAFLD may also be risk factors for cholangiocarcinoma, though larger studies are needed to support this statement.

An association between diabetes mellitus and cancer of the biliary tract has been suggested in several studies [17, 142, 143]. The risk was increased by approximately twofold in a population-based case–control study [17]. Whether diabetes itself or other associated conditions (e.g., obesity, hyperlipidemia, etc.) are the true risk factors for intrahepatic CCA is not clear at present time.

Pathogenetic Considerations

Conversion from normal to malignant bile epithelium likely requires a stepwise accumulation of successive genetic abnormalities, similar to the sequence of events that underlies colorectal carcinogenesis. These genetic changes are likely favored by some of the etiologic factors mentioned above. However, the current level of understanding of the molecular pathogenesis of GBC and CCA is significantly lower than that of other gastrointestinal cancers.

In patients with cholelithiasis and chronic cholecystitis that develop GBC, K-ras mutations are rare, while p53 mutations arise early during multistage pathogenesis [144, 145]. GBC arising in the setting of an anomalous pancreaticobiliary duct junction are characterized by K-ras mutations and relatively late onset of p53 mutations [146–148].

A variety of molecular defects involving both oncogenes (K-ras, c-myc, c-neu, c-erbB-2, and c-met) [149–152] and tumor suppressor genes (p53, SMAD4) [153–157] have been described in CCA. Between 37% and 80% of tumors over-express p53, while abnormal expression of K-ras is found in 21% to 100% of cases. These genetic alterations are associated with a more aggressive tumor phenotype [149, 158]. Some data suggest that p16INK4, a promoter point mutations contribute to initiation and progression of CCA in the setting of PSC [159, 160]. Intrahepatic CCA might share some common carcinogenic steps with hepatocellular carcinoma such as loss of heterozygosity of chromosomes 4q and 6q, and/or inactivation of tumor suppressor genes on chromosome 1p [161].

Conclusions

The wide variation in the incidence of the two main biliary cancers, GBC and CCA, in different geographic areas may reflect the distribution of risk factors for these tumors. Each of the two main biliary cancers has a characteristic geographic distribution. Established risk factors for GBC include cholelithiasis, advanced age and salmonella infection. PSC, *C. sinensis*, *O. viverrini*, nitrosamine exposure, and choledochal cysts represent major risk factors CCA, although a specific risk factor cannot be identified in many patients. While both cancers affect mostly individuals over 50 years of age, GBC has a female predominance and CCA—a predilection for males. The current level of understanding of the molecular pathogenesis of GBC and CCA and its interplay with specific risk factors is significantly lower than for other gastrointestinal malignancies, yet it continues to improve in parallel with the contemporary medico-biological scientific advances of the mankind.

Conflicts of Interest None

Financial Disclosure None.

Grant Support None

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