Epidemiology of Cholangiocarcinoma and Gallbladder Carcinoma

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Contents

Abstract

Cholangiocarcinoma (CCA) and gallbladder carcinoma (GBCA) are rare but lethal cancers of the liver and biliary tract. While surgical resection offers the best chance for cure, many cancers present late in the disease course when surgery does not alter patient survival or quality of life and is often unable to achieve a margin-negative (R0) resection. Despite advances in imaging and diagnostic modalities, appropriate screening protocols are yet to be developed due to the lack of known and modifiable risk factors. This chapter describes the epidemiology of cholangiocarcinoma and gallbladder carcinoma across world populations. Special attention is paid to describing the incidence, prevalence, and mortality of cholangiocarcinoma in the high-risk populations from Thailand, Japan, Korea, and China where infection with the liver flukes, *O. viverrini* and *C. sinensis*, and positive Hepatitis B and C infection are strongly implicated in CCA development. Intrahepatic stones, primary sclerosing cholangitis (PSC), biliary tree infection, and altered bilio-pancreatic anatomy may contribute to a chronic inflammatory state that promotes biliary epithelial metaplasia and CCA. In the last 10 – 15 years, there has been a trend of increased intrahepatic cholangiocarcinoma (ICC) and concurrent decreased extrahepatic cholangiocarcinoma (ECC) incidence, especially in low-risk populations of the United States, Europe, and Scandinavia. Gallbladder carcinoma incidence and mortality continues to be high in populations from northern India, Pakistan, and Eastern Europe, and is disproportionally higher in women. While the overall recent trend of GBCA incidence and mortality is on the decline, it remains high in women of high Amerindian ethnicity in South America and the United States. The differential decreased mortality in populations from the United States, Europe, and Scandinavia compared to South America and Asia is attributed to differential access and utilization of cholecystectomy. Specific risk factors for GBCA include longstanding cholelithiasis,

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J. M. Herman et al. (eds.), *Biliary Tract and Gallbladder Cancer*, Medical Radiology. Radiation Oncology,
DOI: 10.1007/978-3-642-40558-7_1,

S. typhi infection / chronic carrier state, and polypoid lesions of the gallbladder. However, these are not sensitive or specific modifiable risk factors are limited, thereby restricting the ability to design a screening protocol or mandate prophylactic surgery to protect against GBCA. Ongoing research efforts are focusing on the multifactorial contributions of environmental toxins, diet, obesity, and molecular mechanisms of CCA and GBCA development to improve early diagnosis and develop targeted therapies to complement surgical resection.

1 Cholangiocarcinoma

Cholangiocarcinoma is a rare cancer of the biliary tract that develops from the epithelial cholangiocyte cells [1]. It is the second most common form of primary liver cancer, representing 10–25 % of cases, and the third most common gastrointestinal malignancy [2–4]. Worldwide, the highest incidence of cholangiocarcinoma is found in males and in Asians in Thailand, Korea, China and Japan, and individuals of Asian descent in the United States [5–7].

Cholangiocarcinomas are described as intrahepatic (ICC) or extrahepatic (ECC) based on their location along the biliary tree. The World Health Organization (WHO) and International Agency for Research on Cancer (IARC) assign intrahepatic cholangiocarcinoma the International Classification of Diseases-Oncology (ICD-O) morphology code ICD-O 8160/3 which aligns topographically with other primary tumors of the liver (C22.0, C22.1), such as hepatocellular carcinoma (HCC) [8–10]. Furthermore, molecular research also supports this topographic grouping based on a common hepatic stem/pluripotent cell origin for ICC and HCC [11, 12]. Intrahepatic cholangiocarcinomas typically are mass-forming and contiguous with the ductal system. Intrahepatic tumor metastases in advanced stages are common, as is infiltrative spread along the portal tracts. Extrahepatic cholangiocarcinomas are assigned the morphology code ICD-O 8140/3 and are topographically described with gallbladder carcinomas (C23) and other tumors of the biliary tree (C24) [8, 9, 13].

ECCs can be polypoid, nodular, scirrhous, or diffusely infiltrating. Hilar cholangiocarcinomas, or Klatskin tumors, (ICD-O 8162/3) have largely been studied, treated, and reported as a separate entity from both ICC and ECC, but originate from the same cell type [14]. The assignment of a unique ICD-O code to Klatskin tumors in its second edition introduced additional difficulty with classifying and reporting, as hilar cholangiocarcinomas are now cross-referenced topographically to both intra- and extrahepatic locations in edition 3 in comparison with being aligned with the intrahepatic location in edition 2 [15–18].

In its recent usage, cholangiocarcinoma (CCA) frequently refers to both carcinomas of the intrahepatic and extrahepatic (hilar, mid, and distal) biliary tree [1, 19]. The division of tumors in this manner dictates the approach to surgical resection. Historically, distribution of cholangiocarcinoma has been reported as perihilar in 50–70 %, intrahepatic in 6–10 %, and distal in 25–27 % [1, 19]. This distribution, however, has recently been called into question given the concern for underestimation of ECC and overclassification of ICC that occurred with adding a specific ICD-O-2 code for Klatskin tumors [15–18]. Re-analysis of 3,350 CCA cases in the United States (US) Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2000 suggests that the errant ICD classification overestimates the incidence of ICC by 13 % and underestimates that of ECC by 15 % [17].

Within the published literature, ICC and ECC may not be distinguished from each other or may be reported in conjunction with either HCC or gallbladder carcinomas, respectively. Without the accompanying histopathology of the tumors, documenting and reporting the true incidence, prevalence, and risk factors associated with cholangiocarcinoma are fraught with uncertainty. Known risk factors for CCA include liver fluke infection, primary sclerosing cholangitis, and hepatolithiasis [20–24]. Chronic inflammatory biliary conditions causing a repetitive cholangiocyte injury and repair cycle, such as hepatitis B or C virus infection, cirrhosis, alcohol use, obesity, non-alcoholic fatty liver disease (NAFLD), and exposure to certain carcinogens are also implicated in CCA pathogenesis [2, 25–27].

Publications from large, population-based registries provide the best national and regional epidemiologic data on cholangiocarcinoma. There continues to be increasing support for differential risk factors in developing ICC versus ECC [7]. Certainly, there is wide demographic and geographic variability in the development of cholangiocarcinoma as reflected in the regularly updated WHO/IARC publication, *Cancer Incidence in Five Continents* (Fig. 1a, b). Differential outcomes following surgical resection for ICC versus ECC have also been reported [28]. The incidence of ICC continues to rise while that of ECC is relatively static or minimally decreasing [29–31].

Although significant progress has been made in the diagnosis and treatment of CCA in the last two decades, mortality continues to rise in low-prevalence areas of the United States, Europe, United Kingdom, and the non-high-risk areas of Asia and the Middle East [29, 30]. This chapter describes the incidence, risk factors, and mortality associated with cholangiocarcinoma.

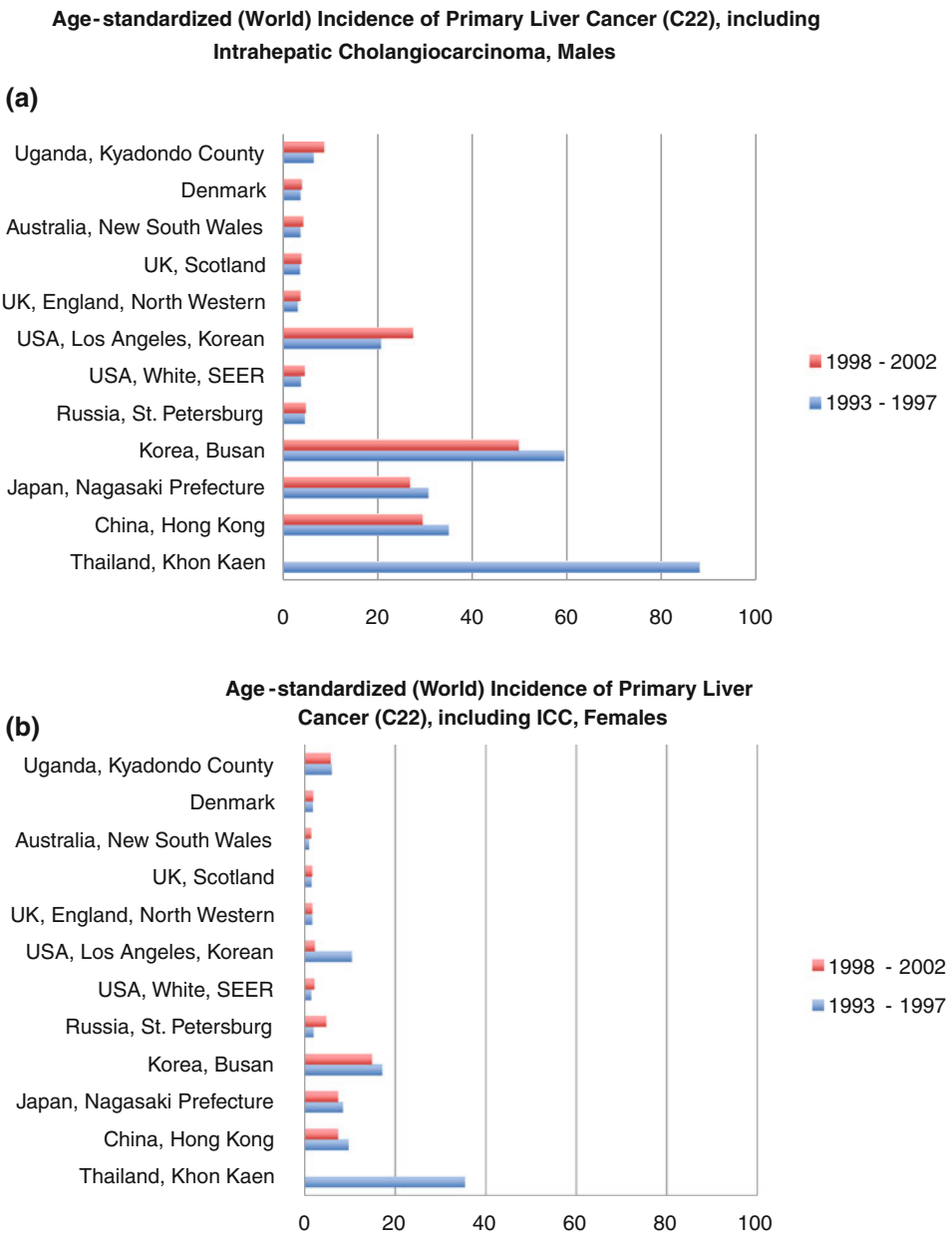


Fig. 1 Age-standardized (World) incidence (per 100,000) of primary liver cancer (C22) including ICC (C22.1) in high-risk, low-risk and endemic population areas, **a** males, **b** females. Rates shown on *x*-axis are per 100,000 person-years. *Source* WHO IARC [5, 6]

1.1 Incidence and Mortality Trends: United States of America

In the US for the year 2012, there were 2,580 cases of ICC and 7,410 'other biliary,' mostly ECC, cancers reported, amounting to approximately 3 % of total gastrointestinal malignancies using the US SEER program. SEER cancer statistics predict national incidence rates for cancer based on aggregate information from the North American Association of Cancer Registries (NAACR), which represents approximately 95 % of the US population. In 2013, it is estimated that there will be a total of 30,640 cases of ICC and primary liver cancer [3, 4]. The SEER Cancer Statistics Review (1975–2009) covers 18 designated areas and approximately 26 % of the US population, and reported a total age-adjusted incidence for ICC as 0.7 per 100,000 males and 0.6 per 100,000 females for 2005–2009. These latest incidence figures reflect a 1.5 % annual percentage change (APC) decline in males and a 0.6 % APC decrease in females between 2000 and 2009 [3, 4]. The overall trend for all US race and ethnicities (white, black, Hispanics, Native Americans, and Asian-Pacific Islanders) shows an increase in ICC from initial data collected in 1973–1975 (Table 1a and b). The age-adjusted incidence rates are highest in Hispanic Americans (1.22 per 100,000) and lowest in African-American males and females (0.3 per 100,000) [32].

Mortality rates have increased across all racial and ethnic groups by at least 3.5 % annual percentage per year, except

Table 1 SEER incidence, US mortality and survival percent for all and selected races in (*a*) ICC, and (*b*) ECC

	Incidence	Mortality	Survival (%)
(a) *SEER incidence, US mortality and survival for ICC, 2005–2009*			
All races, total	0.6	1.2	6.6
All races, male	0.7	1.4	6.0
All race, female	0.6	1.1	7.1
Whites, total	0.6	1.2	6.4
Whites, male	0.7	1.4	6.4
Whites, female	0.5	1.1	6.3
Blacks, total	0.5	1.1	7.9
Blacks, male	0.5	1.3	0.0
Blacks, female	0.5	1.0	9.7
(b) *SEER incidence, US mortality and survival for ECC, 2005–2009*			
All races, total	1.8	0.4	15.7
All races, male	2.2	0.5	16.9
All race, female	1.5	0.4	14.4
Whites, total	1.8	0.5	15.6
Whites, male	2.2	0.5	17.1
Whites, female	1.5	0.4	14.4
Blacks, total	1.7	0.4	13.3
Blacks, male	2.1	0.4	14.1
Blacks, female	1.5	0.3	12.7

Incidence and death rates are per 100,000 and are age-adjusted to the 2000 US Standard population. Mortality data are derived from US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention (CDC). Surveillance, Epidemiology, and End Results (SEER) data is from 18 US areas. Survival data (2002–2008) is based on follow-up of patients into 2009. *Source* SEER Cancer Statistics Review, 1975–2009 [3]

Table 2 Incidence rates (per 100,00) of extrahepatic bile duct cancers, including ECC in the United States, 1997–2002 age-standardized to the US 2000 standard population

Age-standardized incidence rates of extrahepatic bile duct cancers, United States, 1997–2002		
	Male	Female
All races/ethnicities	0.93	0.61
American Indian/Alaska Native	0.90	0.76
White	0.91	0.60
Black	0.82	0.55
Asian-Pacific Islander	1.50	0.92
Hispanic	1.14	0.87
Non-hispanic	0.92	0.60

Source Goodman, 2007 [7]

in Asian/Pacific Islander women in whom mortality rates have decreased at a rate of 0.2 % per year [32]. The age-specific distribution of ICC and ECC peaks between the ages of 65–84 years and is relatively uncommon below age 45 and above age 85 [3, 4, 32]. The SEER-reported incidence of ECC, reported as 'other biliary cancers,' incorporates other non-epithelial tumors, though a similar age distribution and male preponderance for ICC is seen. Using cumulative SEER data from 13 sites registered from 1992 to 2009, there has been a 3.5 % APC increase in incidence of primary liver cancer and ICC. Recent United States data corroborate a continued trend of an increasing incidence of ICC from 0.13 per 100,000 in 1973 to 0.67 per 100,000 in 1997 [31].

In a review of the 30-year trend in SEER mortality since 1973, Nathan et al. demonstrated improved survival for both ICC and ECC. Five-year survival for resected ICC in the period 1973–1992 when compared to 1993–2002 demonstrated a significant improvement to 22.9 % from 16.5 % [29]. Their model reported yearly increased survival from 1992 onwards, resulting in a 34.4 % improvement through all three decades. Improved survival was more marked in ECC where multivariate modeling demonstrated a 23.3 % increase in adjusted survival per decade and a cumulative improved survival of 53.7 % from 1973 to 2002 [29].

Mortality from ECC is also steadily increasing from 0.07 per 100,000 in 1973 to 0.69 per 100,000 in 1997. The incidence of ECC has been otherwise static to slightly decreased in the last few decades. This may be a result of discrepant coding, or the impact of a decreasing incidence of gallbladder cancer [17]. The trend of increasing incidence of ICC and decreasing to static incidence of ECC is preserved even when making allowances for the differential coding that place Klatskin tumors with ICC with ICD-O-2 (1995–2001) and to either ICC or ECC with ICD-O-3 [15, 17, 18, 33].

Within a descriptive study of biliary tract cancers (gallbladder, extrahepatic, ampulla of Vater) from 1997 to 2002, cancers from 11,261 men and 15,722 women were identified from network or US population-based registries and normalized to the US census population in 2000 [7]. Populations of Native Alaskan/Native American and Asian-Pacific Islanders showed significantly higher rates of ECC compared with whites or blacks. Incidence rates for ECC were higher overall in men than women. Incidence rates were comparatively lower in all women with the highest rates in Native Alaskan/Native American and Asian-Pacific Islanders (Table 2).

Age-specific incidence rates in men showed a steady increase in incidence beginning in the early 20s during which the incidence curves for Asian-Pacific Islanders diverged and increased at a dramatically different rate than white or black males after age 50 [7]. Similar divergence was seen with Native Alaskan/Native Americans with the significant divergence occurring after age 75. A recent longitudinal view (1973–2007) of biliary tract cancers (ICC, ECC, and ampulla of Vater) in Native Alaskans established a rate of 2.6 per 100,000 compared to 1.2 per 100,000 and 1.0 per 100,000 in the US white and black populations, respectively, using the age-adjusted rates to the world standard million

population. Remarkably, an increase in the rate of biliary tract cancer in Native Alaskan women from 0.9 per 100,000 (1973–1992) to 2.6 per 100,000 (1993-2007), without a similar increase in the males for the same interval periods (3.5 per 100,000 and 3.4 per 100,000), was noted [34].

Various regional US populations comprised of non-specific risk groups, such as Olmsted County, Minnesota, reported trend results that are consistent with US national incidence and mortality data for biliary tract cancers and CCA. Over the study period of 1976–2008, the age-sex-adjusted incidence of ICC in 116 patients increased from 0.3 to 2.1 per 100,000 person-years with the increased incidence in men accounting for the majority of the change [35]. During this time period, no overall increase in biliary tract cancer was seen, which was ascribed to concomitant decreases in gallbladder cancers, in women predominantly. Other variations within the US population may reflect socioeconomic status, underlying ethnicity, and other environmental factors. In general, Hispanics have a higher prevalence of hepatobiliary cancers and ICC than whites in the US, with a contrastingly higher predominance in females than males [32]. The prevalence of ICC in Asian-Pacific Islanders is not significantly different from other US population groups when reported for cancer cases 1990–2000 [32].

1.2 Incidence and Mortality Trends: United Kingdom, Europe, and Australia

In the United Kingdom, the Office of National Statistics (ONS) capture cancer data for England and Wales. The ONS noted an increase in the age-adjusted incidence and mortality from primary liver cancer, attributable primarily to a rise in HCC. The age-adjusted incidence for ICC (not histologically verified) was lowest in the period 1971–1973 at 0.11 per 100,000 males and 0.09 per 100,000 females, but steadily increased by 12-fold over the next three decades, to 1.33 per 100,000 and 1.06 per 100,000, respectively [36]. The age-adjusted incidence of ECC (separate from gallbladder cancers) declined between 1971–1973 and 1999–2001 in both males and females, although the rates rose in males in the decade between 1971–1973 and 1981–1983, before and then subsequently declining [36]. The mortality rate from primary liver tumors (including ICC) doubled between 1976 and 1994 [37]. Specific morphologic analysis attributed the rise to the increase in ICC rather than HCC [36, 38].

Age-adjusted mortality rates in England and Wales standardized to the European population increased from <0.02 per 100,000 in 1976 to just over 1 per 100,000 in 1994, accounting for differences in coding and uncertainties in death registration. Deaths from ICC reliably exceeded HCC as the most common cause related to a primary liver tumor in 1993 [38]. Gallbladder tumors and ECC were reported together and showed an overall decrease in age-adjusted mortality from 1974 to 1994. In absolute numbers, the total ECC mortality fell from 413 deaths in 1974 to 176 deaths in 1996. Data from Scotland (1968–1997) are consistent with the rest of the United Kingdom data, with a documented dramatic increase in incidence in ICC of 817 and 851 % in males and females, respectively [39]. The incidence of ICC increased to 1.53 per 100,000 in males and 1.24 per 100,000 in females from 1993 to 1997 compared with 0.12 in males and 0.17 in females (1968–1972). These data reflect small sample size with 9 diagnoses in 1968 and 68 diagnoses in 1997.

In a recent analysis of 12,638 biliary tract cancers, including ECC, diagnosed in England and Wales from 1998 to 2007, the median age at diagnosis was 75 years with an incidence of 2 per 100,000 adjusted to the European standard population [40]. The incidence was relatively static over time and between males and females. A further in-depth analysis of the incidence of ICC and ECC in England and Wales for the period of 1990–2008 reported an increase in age-adjusted incidence of ICC for males from 0.43 to 1.84 per 100,000 and 0.27 to 1.51 per 100,000 in females [33]. The trend in ECC declined to 0.51 from 0.78 per 100,000 in males and to 0.39 per 100,000 in females in the same time period. The noted trends in incidence were maintained in the England and Wales populations after addressing possible discrepancies in the coding of 'Klatskin' or 'hilar' tumors, by analyzing the data with Klatskin tumors in both the ICC and ECC groups [33] (Fig. 2).

Comparative incidence reporting in a variety of populations worldwide, using the official WHO-validated mortality database, showed steady age-adjusted increases related to ICC from 1979 to 1997 in the United States, Japan, Australia, England and Wales, and Scotland [41]. The opposite trend was seen for ECC and gallbladder cancers in the same group of nations. Of the countries with complete WHO mortality data that were studied, France displayed no change in age-adjusted mortality for ICC and ECC. Japan and Italy both reported increased mortality for ECC and gallbladder cancers [41] (Fig. 3).

Reports of cancer incidence and survival data from Norway, Sweden, Denmark, Iceland, and Finland is made possible through the NORDCAN collaboration network. Primary liver (including ICC) and gallbladder (including ECC) each represent 1–2 % of the cancer burden within these countries [42, 43]. Specific data extracted from the Danish Cancer Registry shows a decrease in age-adjusted incidence of ICC (1.5 to 0.62 per 100,000) and ECC (1.05 to 0.65 per 100,000) from 1978 to 2002 in both men and women. The highest incidence of ICC and ECC was found in diagnosis groups aged 60–79 and aged 80 and older. The

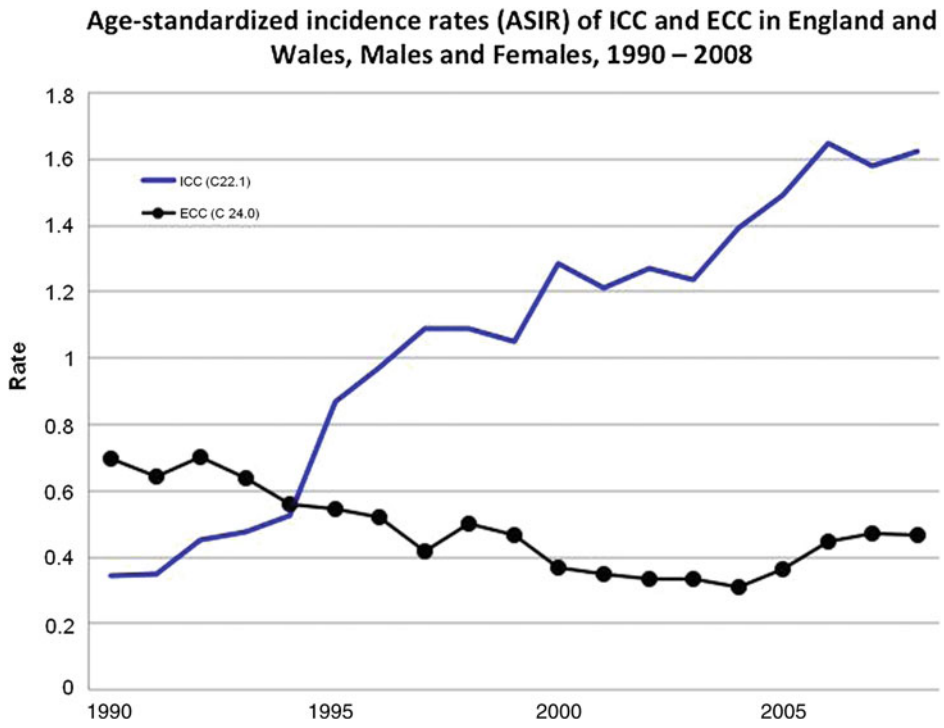


Fig. 2 Age-standardized incidence rates (ASIR) per 100,000 of ICC and ECC in England and Wales, 1990–2008, Males and Females combined. ICC (C22.1), excludes Klatskin tumors (M8162/3). ECC (C24.0), includes Klatskin tumors (M8162.3). Modified and reprinted with permission from Khan et al. 2012 [33]

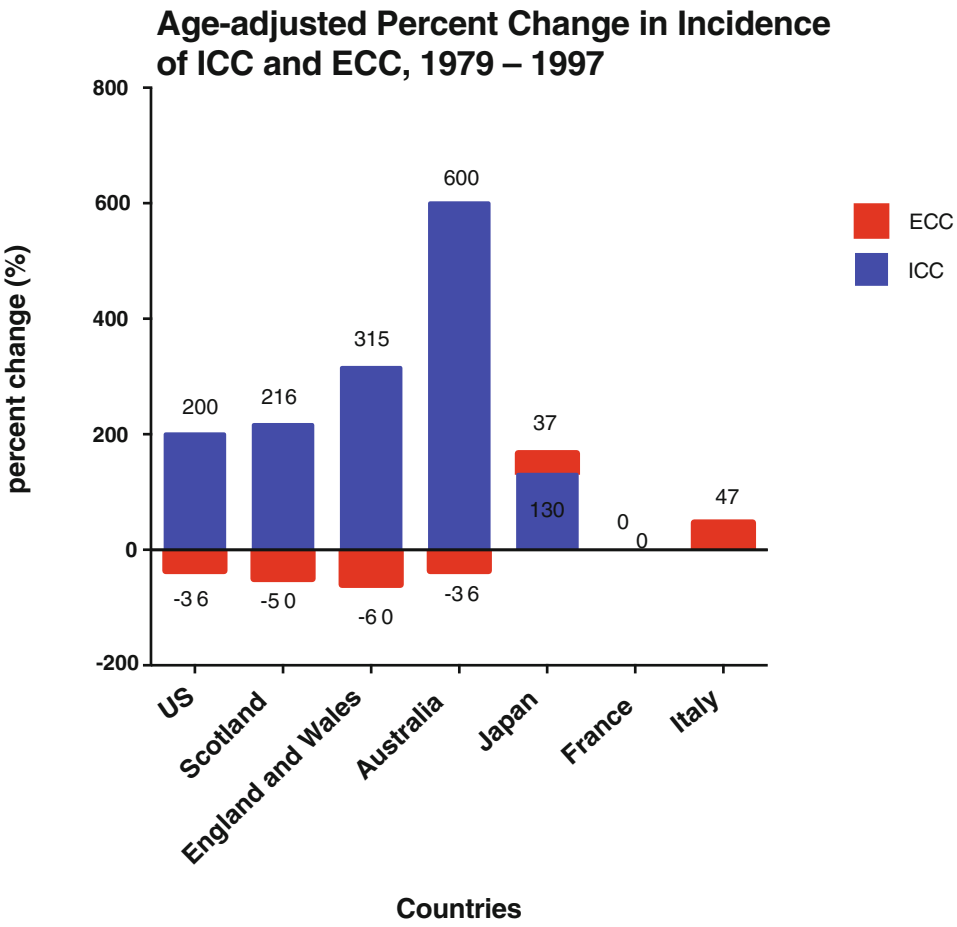


Fig. 3 Age-adjusted percentage change in incidence rate (per 100,000) of ICC and ECC in Select Countries, 1979–1997 [41]. Percent change is shown on *y*-axis and select countries on the *x*-axis. Numerical values for absolute percentage change are shown with the corresponding column

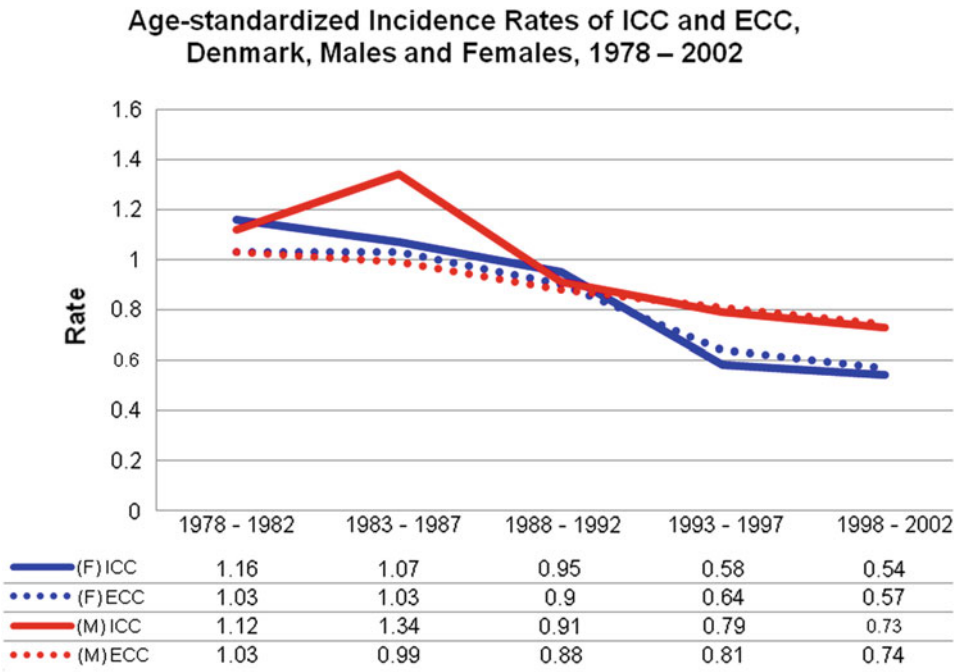


Fig. 4 Age-standardized (US 2000) incidence rates (per 100,000) of intrahepatic cholangiocarcinoma (*ICC*) and extrahepatic cholangiocarcinoma (*ECC*) for Denmark, Males (*M*) and Females (*F*), 1978–2002 [44]. Incidence rate is shown on the *y*-axis and grouped time intervals in years are shown on the *x*-axis with the graphed incidence data shown below in tabular format

overall temporal incidence of ECC was 3.67 per 100,000 and 5.32 per 100,000 in the age division 60–79 and 80 and older, respectively [44] (Fig. 4).

In the Netherlands, a different trend was seen than that in Scandinavia. ICC diagnoses corresponding to ICD-O codes C22.1 from 1989 to 2009 were analyzed from the Netherlands Cancer Registry (NCR) data [45]. For both males and females, the three-year moving averages showed a 5 % annual percentage decline in age-adjusted incidence from 1989 to 1998 and a subsequent 9.4 % annual percentage increase from 1998 to 2009. Most marked was a 3 % annual percentage increase in ICC incidence within the group aged 45–49 years, where the increases in age-specific incidence are seen in later years in other low-endemic area studies [3, 34, 46]. Epidemiologic data from Italy reflect a trend most consistent with the UK data for 55,000 patients diagnosed in the period 1998–2005. Similarly, a French population-based study from Burgundy reported stable rates of age-adjusted ICC incidence. The adjusted incidence rates for ICC in 1976–1980 and 2001–2005 were 0.3 per 100,000 and 0.2 per 100,000, respectively, and 1.1 per 100,000 in 1976–1980 and 2001–2005 for ECC [47].

Regional-specific cancer incidence and mortality data across Europe are available in the WHO/IARC publications, *Cancer Incidence in Five Continents, Vol. IX* and Scientific Publication No. 159 [6, 48]. Determining the specific incidence and trend data for ECC and ICC in these aggregated publication is difficult due to the grouping of liver and intrahepatic bile duct tumors, and gallbladder cancers with other biliary tumors. Significant efforts have been made to understand the coding of tumors between ICD-8, 9, and 10 and ICD-O and O-2, in reporting data for ICC and ECC as biliary tract cancers. Notwithstanding this, the data bear out the worldwide trend of increased incidence of ICC and stable to declining incidence of ECC in the low- to normal-risk populations, and select high-risk groups within low-risk populations in North America, Europe, and the United Kingdom, with the exception of Denmark [17, 30, 31, 33, 36, 39, 47, 49].

1.3 Cholangiocarcinoma in Asia and Liver Fluke Infestation

The IARC Working Group on the evaluation of carcinogenic risks to humans formally addressed the association of cholangiocarcinoma to infections with the trematodes, *Opisthorchis viverrini*, and *Clonorchis sinensis* [20, 23, 50–52]. The liver fluke *Opisthorchis viverrini* is endemic to north and northeastern Thailand, western Malaysia, Cambodia, Vietnam, and Laos. Transmission to humans is via consumption of raw fish and water contaminated with sewage and agricultural pollutants [20, 50, 53, 54]. Infection with the trematode, *Clonorchis sinensis*, is the more common infectious agent related to cholangiocarcinoma in China, Korea, Taiwan, and Japan [50]. Cholangiocarcinoma in the Eastern European nations of Kazakhstan, Russia, Siberia, and Ukraine is likely related to transmission of *O. felineus* in freshwater fish and polluted water [50, 52]. The evidence supporting the association of *Schistosomiasis japonicum* with liver cancer and cholangiocarcinoma has been less convincing [20, 55].

The highest national prevalence data for *O. viverrini* infections are found in Laos (37 %) and Thailand (9.4 %) and for *C. sinensis* infections in Hong Kong (5.6 %) by most recent estimation [56]. Of the 35 million people infected with *C.* sinensis worldwide, an estimated 10–15 million live in China [57]. While public health efforts aimed at prevention and treatment are most advanced in these endemic trematode infection areas, the population-at-risk for infection is in excess of 67 million for *O. viverrini* alone [50]. Indeed, despite educational efforts, biliary tract complications related to liver fluke infection include cholestatic damage, inflammatory lesions, cirrhosis, and cholangiocarcinoma. Carcinogenesis is thought to be related to the chronic inflammation and attempts at cholangiocyte repair incited by trematode infection [58–60]. Cholangiocarcinoma related to food-borne trematodiasis is the most common cause of death. The calculated odds ratio (OR) for developing CCA following *C. sinensis* infection is 6.1 and with *O. viverrini* infection is 4.4 [56]. A recent meta-analysis of CCA risk factors in Asian countries calculated an OR of liver fluke infestation (both *C. sinensis* and *O. viverrini)* of 4.8 [61].

The trends in primary liver cell cancer, including ICC, are detailed in Table 3 [5, 6]. While these data do not specifically detail the trends in ICC alone in areas of high-risk and low-risk populations and in endemic areas of cholangiocarcinoma, the data reflect the demonstrated trends in ICC seen in population-based studies given a rather static incidence in HCC [5, 6].

The region of Busan (Pusan) in South Korea continues to have one of the highest areas of primary liver cell cancer worldwide with 1990 incidence rates as high as 74.8 per 100,000 and 15.6 per 100,000 in males and females, respectively, for the age group of 35–64 years [62]. Intrahepatic cholangiocarcinoma is estimated to account for 20 % of total cases. High relative risk (RR) values for *C. sinensis* infection and alcohol consumption were associated with CCA in this population, whereas hepatitis B and C infections were more strongly associated with HCC. Additionally, case-matched studies from a tertiary referral practice demonstrated a high OR of ICC (OR 16.0) and ECC (OR 7.0) with associated *C. sinensis* exposure in cases with at least one of six parameters—history of ingesting raw freshwater fish or evidence of *C. sinensis* infection on stool microscopy, serology, pathology examination, or skin testing [63]. Again, an increased risk of CCA was not seen with concurrent hepatitis B or C infections [63].

The major risk factors for CCA in Asia are male gender, excess alcohol consumption, *C. sinensis* infection, and consumption of raw fresh water fish based on the report published in 2010 from the Korean Multicenter Cancer Cohort [64]. The study, based on 2000–2004 data, demonstrated that incidence and mortality rates closely aligned with the varying incidence rates of *C. sinensis* infection in the studied areas. The low and moderate endemic *C. sinensis* infections areas of Chungju (7.8 %) and Haman (31.3 %) showed age-adjusted incidence rates of 1.8 per 100,000 and 5.5 per 100,000 with corresponding age-adjusted mortality of 1.1 and 2.6 per 100,000, respectively. A further study using the Korean National Cancer Incidence Database (KNCID) from 1995 to 2004 attributes 9.5 % of CCA to liver fluke infection in low- to moderate-risk areas and in up to 22.6 % of CCA cases in high-endemic areas of Korea [65]. Incidence rates in Korean males were more than twice those of females [65]. Incidence rates of 4.1 per 100,000 in males and 1.8 per 100,000 in females were roughly twice those in the United States (1996–2000) and four times those in England and Wales (1991–2001). As outlined in Table 4, the rates of primary liver cancer (HCC and CCA) are decreasing and have been since 1985 [65, 66].

Age-adjusted rates of ICC and ECC in east and south-eastern Asia, using data collected from 18 cancer registries in Asia together with data from US and other Western registries, corroborate the rise in CCA worldwide [66]. Among populations of China, Korea, Japan, and Thailand, regional variations in the incidence of CCA are seen, with the highest rates of ECC noted in Korea. The areas of highest prevalence are concentrated around the Nakdong River and its lower extents [61, 62]. Though the majority of CCA incidence variation is related to varying prevalence of liver fluke infection, there are additional, as yet unknown, environmental, and ethnic factors that may explain the differential presentation of ICC and ECC within a population.

Table 3 Age-standardized world (ASRW) incidence rates (per 100,000) showing trends in incidence of primary liver cancer (C22) including intrahepatic cholangiocarcinoma for high-risk, low-risk and endemic population areas

Age-standardized incidence rates in primary liver ICC in high-risk, low-risk and endemic population areas				
1993–1997		1998–2002		Location
Male	Female	Male	Female	
88.0	35.4	–	–	Thailand (Khon Kaen)
35.0	9.7	29.5	7.3	China (Hong/Kong)
30.7	8.4	26.8	7.3	Japan (Nagasaki Prefecture)
59.4	17.1	49.8	14.9	Korea (Busan)
4.6	2.0	4.8	2.1	Russia (St. Petersburg)
3.8	1.4	6.2	2.2	USA (White SEER)
20.7	10.4	27.5	10.2	USA (Los Angeles, Korean)
3.1	1.7	3.7	1.7	UK, England (North Western)
3.6	1.5	3.9	1.7	UK, Scotland
3.7	1.0	4.3	1.4	Australia (New South Wales)
3.7	1.8	4.0	1.9	Denmark
6.5	6.0	8.7	5.8	Uganda (Kyadondo County)

Source Parkin et al. [5] (1993–1997) and Curado et al. [6] (1998–2002)

Table 4 Age-standardized incidence rates of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) for selected regions in Asia, males and females, 1998–2002

Age-standardized incidence rates of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) for selected regions in Asia, males and females, 1998–2002				
	ICC (C22.1)		ECC (C24)	
	Male	Female	Male	Female
China, Qidong	10.3	4.6	0.0	–
China, Guangzhou	0.3	0.1	1.1	0.8
China, Hong Kong	2.3	1.7	0.3	0.2
China, Shanghai	7.4	4.9	1.4	1.4
Japan, Hiroshima (1996–2000)	1.7	0.8	2.4	1.2
Japan, Osaka	1.7	0.9	2.7	1.5
Korea KCCR (1999–2002)	5.4	2.5	3.3	1.5
Korea, Busan	5.8	3.4	4.2	2.3
Korea, Daegu	5.7	2.6	4.1	2.2
Korea, Daejeon	5.0	2.1	2.8	1.3
Philippines, Manila	1.3	0.9	0.1	0.1
Singapore, Chinese	1.1	1.1	0.4	0.3
Taiwan	4.3	3.9	0.7	0.5
Thailand, Khon Kaen	71.3	31.6	0.4	0.1
Thailand, Chiang Mai	8.2	4.0	0.4	0.2
Thailand, Bangkok	2.5	1.4	0.3	0.1
Thailand, Songkhla	1.6	0.5	0.1	0.2
Viet Nam, Hanoi	0.1	0.1	0.0	0.0

Source Shin et al. [66]

The Khon Kaen region of Thailand accounts for 70–90 % of primary liver tumors, as compared to high-risk areas, like Busan, Korea (20 %), Japan (5 %), and worldwide (10–25 %) [54, 65–67]. The highest prevalence of liver fluke infections occurs in the north (19.3 %), northeast (15.8 %), and central (3.8 %) regions of Thailand [54, 61]. *O. viverinni* infection is the strongest risk factor for developing CCA, and all areas have shown appreciable decreases over the last three decades [61, 68]. The prevalence of *O. viverinni* declined to an overall 9.6 % (6 million people) in 2001 from 14 % (7 million people) in the early 1980s [54, 61]. Average rates of CCA in the Khon Kaen Province area were 118 per 100,000 with an average prevalence of 24.5 % using data from 1990 to 2001 [54].

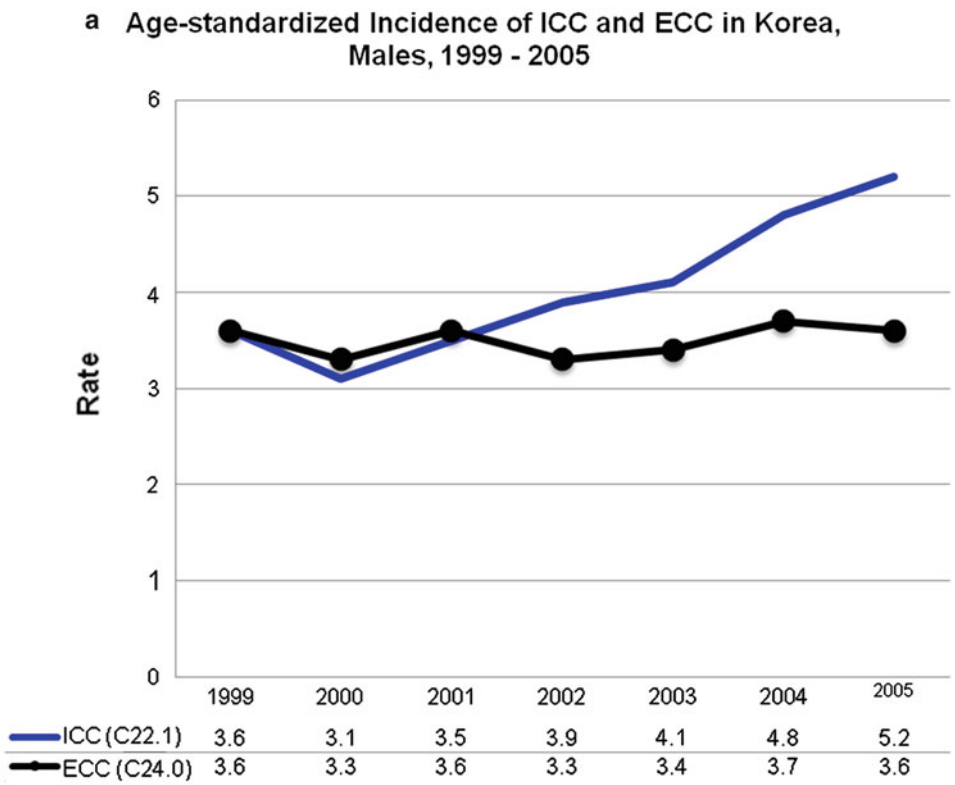
For the rest of Thailand, data in 2002 demonstrated an incidence of 71.4 per 100,000 for ICC in males and 31.6 per 100,000 in females. Corresponding rates of ECC in Korea are dramatically less at 0.4 per 100,000 in males and 0.1 per 100,000 in females [66] (Fig. 5a, b). Recent results documenting the outcomes of resected ECC in a cohort of 58 patients in Khon Kaen, Thailand, reported a 10.8 % 5-year survival rate that is somewhat reflective of the outcomes worldwide [69]. Survival remains poor despite public health education regarding the consumption of raw fish, more rigorous surveillance of at-risk populations, and increased efforts to treat the trematode infections that precede development of cholangiocarcinoma. Studies show similar poor long-term outcomes following surgery in patients resected for cholangiocarcinoma with and without an underlying trematode infection [53, 69, 70].

The island of Japan has a higher risk than the rest of world for CCA, but a lower risk than Korea, China, Japan, and Thailand (Table 1) [5, 6, 41]. Bile duct cancers account for over 45 % of biliary tract cancers studied through the Japanese Biliary Tract Cancer Statistics Registry [71, 72]. The Japan Public Health Center Prospective Study reported outcome data on patients with ECC collected between 1990 and 1994 and found an association of cholelithiasis with the development of ECC in a study limited to gallbladder cancer and ECC [73]. Improvements in diagnostic techniques, patient selection for operation, and safety of extensive resections have improved over the last decade. Even though rates of CCA have declined overall in Asian populations, the overall survival still remains poor for this cancer once it develops.

1.4 Choledochal Cysts, Caroli's Disease, and the Abnormal Pancreatobiliary Junction

Choledochal cysts (Types I–IV) involve the extrahepatic biliary tree, while Caroli's disease (Type V) is defined as cystic dilation of the intrahepatic biliary tree [74]. Choledochal cysts are most common in Asia, particularly in Japan, and account for one-half to two-thirds of reported cases [74–76]. Type 1 choledochal cysts are most common, and there is a 3–4:1 preponderance in females [77–80]. The frequency of choledochal cysts is estimated between 1:13,000 and 1:2 million live births [78, 81].

From very early reports, an association of cancer concurrent with choledochal cysts was noted [74, 75, 82]. In a large study of 1,433 Japanese patients across all ages, the incidence of cancer related to a choledochal cyst was 3.2 % and predominantly adenocarcinoma, though cases of squamous carcinoma and mucinous adenocarcinoma have been reported. Of all patients in the series, 45 % were 10 years of age or less and the choledochal cyst-related cancers occurred in patients with a mean age of 32 (range, 15 to 66 years) [75]. The prevalence of cancer is <1 % in the first decade of life, increasing to 6.8 % in the second decade of life, and rising to >14.3 % in those over the age of 20 [82, 83]. Adenocarcinoma in patients as young as 12 and 15 years of age has been described [74, 84].



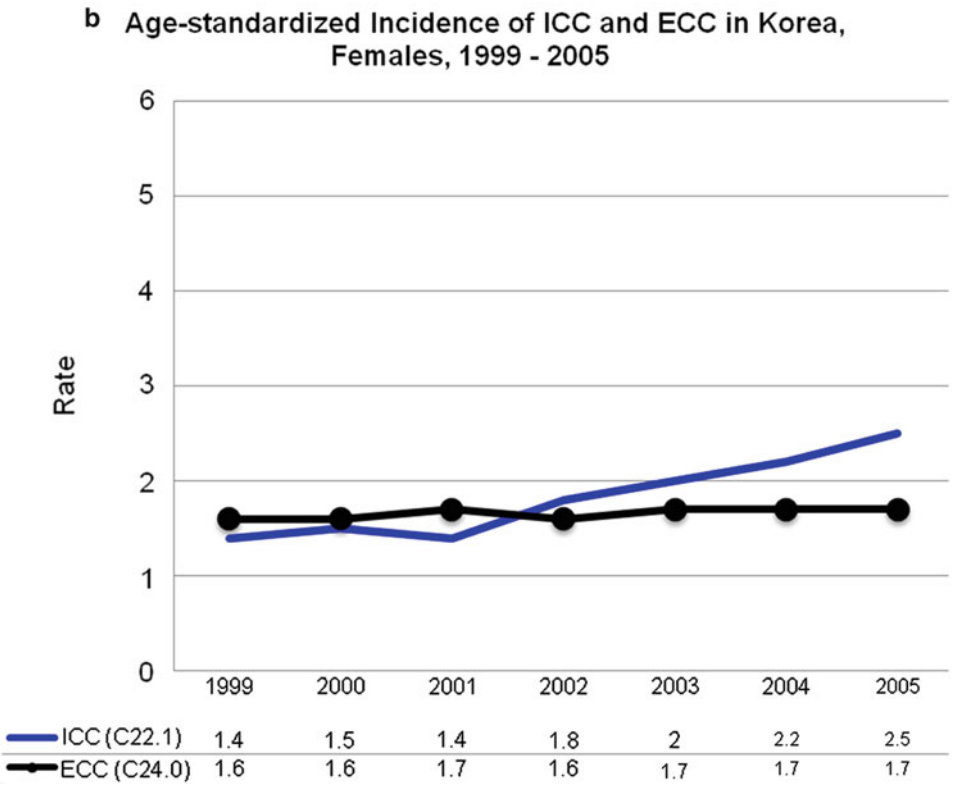


Fig. 5 Age-standardized incidence rates (*ASIR*) of intrahepatic cholangiocarcinoma (C22.1) and extrahepatic cholangiocarcinoma (C24.0) in Korean, **a** males and **b** females. Rates shown on *x*-axis are per 100,000 person-years. Overall rate for ICC is 4.1 males, 1.8 females with a +7.9 % and +10.6 % annual percentage change (*APC*), respectively, for time period. Overall rate for ECC is 3.5 males, 1.7 females with a +0.3 % and +1.3 % APC, respectively, for time period. *Source* Shin et al. 2010 [65]

Cholangiocarcinoma is the most common cancer that occurs with choledochal cysts, and the patient risk is 20–30 times that of the normal population [79]. Gallbladder malignancy comprises 10 % of cancers associated with choledochal cysts, and CCA occurs in about 7 % of patients with Caroli's disease [85, 86]. Synchronous or metachronous identification of CCA with treatment of choledochal cysts is reportedly as high as 20–28 % in Western literature and 8–30 % in reports from Asia [78, 81–83, 87]. More often, the literature describes adult patients who develop cholangiocarcinoma on long-term follow-up after a surgical intervention in infancy or adolescence [85, 88]. In the most recent two decades, published literature has shown a rate of 0–33 % CCA development following excision of choledochal cysts [79].

The theories of CCA pathogenesis in choledochal cysts include biliary stasis, exposure to infected bile and its carcinogenic byproducts, exposure to pancreatic amylase because of an abnormal pancreato-biliary junction (APBJ), and chronic inflammation related to biliary track stones [58, 59, 89, 90]. An APBJ is found concurrently with choledochal cysts in 39–92 % of cases [89]. Manometric studies have demonstrated high pancreatic amylase secretion with the cyst substance and noted pressure changes within the biliary tract system whereby reflux of pancreatic enzymes occurs [91]. The Japanese literature suggests that choledochal cysts do not occur without an APBJ [89]. The biliary tract epithelium may of itself be abnormal and more susceptible to the malignant degeneration that normally occurs in an age-dependent fashion. Mucosal adenomatous hyperplasia of cholangiocytes in response to chronic inflammation initiates the hyperplasia-metaplasia-carcinoma sequence that culminates in carcinogenesis [92, 93].

Other conditions that cause chronic inflammation of the biliary tree predispose patients to cholangiocarcinoma. Prior manipulation of the biliary tree for benign disease is an example of an acquired risk factor for CCA. A 5.5 % increased risk has been reported for patients that have undergone biliary-enteric bypass procedures, usually for choledocholithiasis [94]. The risk of CCA is highest following choledochoduodenostomy (7.6 %) and lowest following Roux-en-Y hepaticojejunostomy (1.9 %) [94].

Transduodenal sphincteroplasty for treatment for sphincter of Oddi dysfunction is also implicated as causative in the development of CCA (7.4 %) [95–97]. Other reported cases indicate that the risk continues to be present as many as 1–40 years following the initial intervention [95, 96]. The proposed mechanism for carcinogenesis is stasis of bile infected with intestinal contents secondary to the new biliary-enteric configuration. Conflicting data suggest that manipulation of the biliary tract for otherwise benign, or non-bile duct cyst disease, is itself a risk factor for cholangiocarcinoma [94, 98], while other reports do not support an increased cancer susceptibility [99]. Secondary stone formation caused by anastomotic stricturing and recurrent cholangitis after biliary-enteric anastomosis is also implicated in CCA metaplasia [100–102]. The constant irritation of the biliary tract by stones, which may be infected, also contribute to cholangiocyte metaplasia [100, 101].

Primary intrahepatic stones, or hepatolithiasis, are common in East Asia and a known risk factor for the development of CCA. Japan and Taiwan have the highest incidence of cholangiocarcinoma complicating long-standing hepatolithiasis at 1.5–9.4 % and 2.4–5.0 %, respectively [21, 103–106]. The overall incidence in the literature is estimated at 4–11 %, but has been reported to be as high as 20 % in a Taiwanese population [104]. Following hepatectomy for stone disease, one series of 29 patients from Japan documented a 17.1 % incidence of ICC. Stone disease predominantly affects the left lobe of the liver, though right-sided and bilateral stone disease is also described [105, 107, 108]. Tumors typically develop first within the intrahepatic ducts in close proximity to where stones are located though hilar tumors and ECC have been described [21, 104, 105, 108].

Survival following surgical resection in patients with hepatolithiasis and CCA is poor and is similar to patients with uncomplicated CCA. The cycle of biliary sepsis requiring drainage can delay and may prevent a patient from presenting for surgical resection. Diagnosing CCA is difficult in the face of hepatolithiasis; however, it should be suspected in patients with long-standing hepatolithiasis (>10 years), deranged liver function tests, age >40–50 years, and lobar atrophy, stricture, or obvious tumor mass on imaging [104, 108, 109]. As such, overall resectability rates may be lower due to advanced disease stage at time of presentation. Favorable long-term survival is associated with completeness of surgical resection rather than any specific impact of hepatolithiasis.

1.5 Primary Sclerosing Cholangitis and Cholangiocarcinoma

The development of CCA in patients with primary sclerosing cholangitis (PSC) is an important risk factor in Western populations. PSC is a chronic cholestatic disease with no optimal liver-directed therapy to appreciably treat disease. Use of ursodeoxycholic acid (UDCA) and immunosuppression with corticosteroids, tacrolimus, cyclosporine, and methotrexate may result in biochemical improvements of liver function tests in affected patients [110]. The natural history of the disease is an insidious onset of intra- and extrahepatic biliary strictures punctuated by bouts of treatment-refractory sepsis [110]. Stenting is used to alleviate biliary obstruction caused by dominant strictures. Cirrhosis, liver failure, CCA, and death are the

most significant complications. In the absence of tumors, the median survival for patients with PSC is between 10 and 12 years, with asymptomatic patient survival of 70 % at 16 years [111–113].

PSC is closely associated with inflammatory bowel disease (IBD) (60–80 %), both ulcerative colitis (UC) (26–68 %) and, to a lesser extent, Crohn's disease (13 %) [1, 22, 67, 114, 115]. The estimated prevalence of IBD with PSC ranges from 60 to 80 % in the United States, Nordic Countries, and Northern European populations with little variation over the last two decades [1, 22, 67, 112, 115]. The annual incidence risk of CCA with PSC ranges from 0.6 to 1.5 % [58, 116–118]. The prevalence of CCA complicating PSC is 7–18 % in the United States and has been reported as 8 and 14.3 % in Sweden and Germany, respectively [112, 114, 119, 120]. On average, patients develop CCA 30–63 months following the diagnosis of PSC [2, 22, 114] with up to 50 % diagnosed with CCA concurrent with their PSC diagnosis [114, 116, 121]. The primary tumor location in PSC-CCA is extrahepatic or hilar in 60–76 % of cases, 16–60 % intrahepatic, and indeterminate or both in 20–35 % [22, 111, 114, 117, 122].

The most complete datasets summarizing the known relationship of PSC with cholangiocarcinoma come from a large referral-based population in Minnesota (USA) and the Nordic Countries (Denmark, Finland, Sweden, Norway, Iceland) [22, 112, 122–125]. The cohort of 604 patients obtained from the Swedish Cancer and Deaths Registry (1970–1998) showed a 13.3 % incidence of patients with PSC developing a malignancy (any cholangiocarcinoma, gallbladder cancer, or HCC). The standardized incidence risk (SIR), adjusted for age and sex, compared to the general population of Sweden was 161 for developing any malignancy [118]. The updated data present information from a specific region of Sweden in patients with PSC who developed CCA between 1992 and 2005 [124]. The incidence of CCA in this cohort was 8.5 % with 5-year and 10-year cumulative incidences of 7 and 11 %, respectively. The SIR for all HPB malignancies was 177 and for CCA was 868 [124]. In the Swedish studies, no influence of duration of PSC to the development of CCA has been documented, in contrast to other Western studies [111, 118, 124]. The literature is relatively sparse on the interaction of PSC and CCA in Eastern populations. After documenting the pattern of PSC in the Japanese population, a further cross-sectional study reported a 3.4 % incidence of CCA in patients with PSC. Approximately 50 % of patients were diagnosed with CCA at the time of the PSC diagnosis. The time to CCA diagnosis was an average of 2.5 years later in the remainder of patients [126].

The gains in improved survival for patients with PSC and CCA have been seen with rapid treatment of sepsis, recognition of and stenting of dominant strictures, and liver transplantation. Using a neoadjuvant chemotherapeutic protocol followed by transplantation, actuarial 5-year survival rates of 82 % with transplantation compared to 21 % with resection alone have been reported [127]. Other series have seen modest survival rates of 35 % at 5 years with liver transplant for PSC without a chemotherapy protocol [117]. Recurrences in the transplant group are also demonstrably lower (13 vs. 27 %). Up to 20 % of patients with PSC on the waiting list may harbor an undiagnosed cholangiocarcinoma, as found on waiting list surveillance testing or in the liver explant [117, 128].

1.6 Hepatitis B, Hepatitis C and the Effect of Chronic Inflammation, Hepatocyte Injury, and Cholangitis

Historically, no association between chronic Hepatitis B (HBV) and Hepatitis C virus (HCV) infections in the pathogenesis of CCA was reported [62, 129], but this has changed in recent years [27]. The IARC linked, with limited supporting evidence, HBV and HCV infections to CCA through a causal mechanism of inflammation, chronic liver disease, cirrhosis, and fibrosis [51]. Chronic HBV infection is responsible for cirrhosis and the progression to HCC in sub-Saharan Africa and in East Asia. Chronic HCV infection is the predominant risk factor for HCC in Japan and Western countries [5, 6]. The influence of HBV and HCV on CCA is multifactorial. In conjunction with other probably contributory risk factors such as alcohol consumption, smoking, and consumption of nitrosamine-preserved foods, it has emerged as a more likely direct influence, though the exact mechanisms are unknown.

Studies from the United States, Japan, and Italy demonstrated an increased risk of ICC with HCV [130–133]. In direct contrast, other studies from the East, in Taiwan, China, and Korea, show a closer association of HBV infection and ICC [134–137]. In a series that published tumor location, the relationship of HBV or HCV infection is more commonly associated with ICC than ECC [130, 133, 135, 136]. The differential findings do correspond with population and geographic areas in which HBV and HCV are endemic. A recent publication from Taiwan, where both HBV and HCV are endemic, reported a significant association of ICC with HBV and HCV [135]. Additionally, co-infection with hepatitis surface antigen (HBsAg) and anti-HCV core antigen (anti-HCV) confers a higher risk of ICC formation than with either HBsAg or anti-HCV alone [135]. The findings of two separate meta-analyses support the view that HCV and HBV infection plays a significant role in the development of CCA, more often ICC than ECC [138, 139].

Although a new risk factor related to CCA has been described, the relative importance of this contribution for CCA pathogenesis is unclear. The HBV and HCV

seropositivity rate in the patient populations from which results derive ranges from 1.6–49 to 1.2–36 %, respectively [131, 132, 137, 140]. In a 4:1 matched case-control study from Korea, an association of HBV (OR = 2.2) to ICC was found with more significant contributions from diabetes (OR = 3.2), hepatolithiasis (OR = 50), choledochal cysts (OR = 10.7), cirrhosis (OR = 13.6), and *C. sinensis* infection (OR = 13.6) [136]. The relationship to other risk factors is supported by other HCV studies with PSC, diabetes playing a stronger role in CCA pathogenesis than HBV or HCV [132, 141]. The RR of HBV pathogenesis in ICC is stronger in reports from Asian populations compared with other nationalities [138].

Molecular pathologic analysis of tissue samples has found HBV DNA and HCV RNA within the biliary epithelium and has been proposed this as a possible mechanistic theory for tumor growth [142]. The chronic inflammatory process incited by HCV core protein contributes to cellular proliferation of a damaged biliary epithelium [143]. The initiating events of cholangiocarcinoma involve cytokine activation of inflammatory cells and induce nitric oxide synthase (iNOS) within damaged biliary epithelia. DNA damage occurs in conjunction with nitrosylation of thiol and tyrosine residues to propagate further damage [2, 144]. iNOS-damaged DNA contributes to tumor suppressor *p53* upregulation and may also induce damage that renders the *p53*-mediated DNA repair mechanism inactive [92]. This inflammatory cycle is better described in patients with PSC and CCA, and liver fluke infestation and CCA [2, 59]. However, HBV and HCV infection, as an example of a chronic inflammatory process, is a suitable mechanism for induction of the nitric oxide synthase process and its pleiotropic effects on biliary tract carcinogenesis [10]. While HBV and HCV primarily affect hepatocytes, research evidence supports a common hepatocyte progenitor cell origin for hepatocytes and cholangiocytes [11, 12, 145, 146]. Carcinogenic processes within the liver may thus affect susceptible cholangiocytes in close proximity, perhaps also explaining the increased association of HBV and HCV infection with ICC rather than ECC.

1.7 Environmental Factors

Thorotrast, discontinued as a colloidal intravenous contrast agent after 1955, derived from thorium-232, is recognized as a Class I carcinogen by the IARC [67]. Preferential deposition was seen within the substance of the liver (60–70 %), but its affinity was also for the reticuloendothelial system, the spleen and bone marrow. Historically, tumors of the liver presented as HCC or hepatic angiosarcoma, 10–12 years following the exposure [67, 147]. Dysplasia, or abnormal proliferation of bile ducts, was seen in Thorotrast-induced cases of liver cancer [67]. ECC was the more common of the biliary tract tumors. The IARC drew several conclusions regarding Thorotrast exposure and cholangiocarcinoma from initial data and follow-up of large cohort series from the United States, Germany, Denmark, Japan, and Sweden [148–153]. Thorotrast exposure caused an excess cancer (liver and bile duct) risk of 97 % persisting for up to 50 years, increasing risk and mortality from liver cancer with increasing amount of injected Thorotrast, and an increasing standardized mortality rate (SMR) and RR compared to controls as more time elapsed from first exposure to Thorotrast. One proposed mechanism of pathogenesis is alpha-ionizing radiation particles inducing instability in human mismatch repair genes [154].

1.8 Emerging and Other Risk Factors

Obesity and diabetes as elements of the metabolic syndrome are gaining increasing attention in the pathogenesis of CCA. Both are known risk factors for HCC in NAFLD and other gastrointestinal cancers (esophagus, pancreas, gallbladder, stomach) [155]. In one population case-control study from China, the risk of ECC and other biliary tract cancers increased with the increasing number of diagnostic components of the metabolic syndrome [156]. The increased risk profile persisted for patients with body mass index (BMI) <25 and non-diabetics with three other elements of the metabolic syndrome. Interestingly, high high-density lipoprotein (HDL) (OR = 8.17) and high triglyceride levels (OR = 5.28), additional elements of the metabolic syndrome, gave a higher OR for ECC than for metabolic syndrome as a single risk factor. In a low-risk population from Denmark (1978–1991), diabetes, but not obesity was significantly associated with ICC [157]. Data from the United Kingdom (1987–2002), another low-risk population, also showed a positive association with obesity (BMI $\geq$ 30) and conferred a 1.5-fold increased risk of developing CCA [158].

The relationship of obesity to CCA is not clearly defined and contradictory associations have emerged. Some reports postulate a carcinogenic mechanism based on the pro-inflammatory and carcinogenic components of bile when bile flow is impaired, as in obesity [73]. Still other less well-delineated risk factors for CCA may include heavy alcohol consumption, *H. pylori* infection, smoking, cholelithiasis, thyrotoxicosis, cirrhosis from all causes, and human immunodeficiency virus (HIV) [25–27, 132, 141, 157, 159].

1.9 Summary

Accurate morphologic and histologic tissue sub-typing will facilitate better classification of this disease and allow more precise calculations of incidence and risk factors. Strategies to attempt the cure of CCA include extensive surgical resection and or transplantation. However, the underlying liver disease, as in PSC, HBV, HCV, cirrhosis, and hepatolithiasis may complicate timely diagnosis of the tumor. Diagnostic tools and imaging have improved over the last few decades, though overall resectability remains low. Resection with negative margins remains the best predictor of long-term survival given the lack of suitable adjuvant therapeutic options. Major survival gains with CCA may be made by targeting prevention of the disease and modification of definite risk factors. Public health education to dissuade raw fish consumption and treatment of liver fluke infection in endemic areas are examples of what can be done to reduce the development of this tumor. Continued widespread HBV vaccination and HCV surveillance efforts should help address early CCA recognition in at risk population groups. Given the emerging risk factors for ICC and ECC, general lifestyle modification toward increased health and wellness may minimize the impact of obesity, diabetes and insulin resistance, smoking, and excess alcohol consumption. Further research into the molecular mechanisms of CCA development may be fruitful in developing tailored diagnostic, prognostic and treatment efforts [160].

2 Gallbladder Carcinoma

Gallbladder carcinoma (GBCA) is an epithelial tumor of the gallbladder, which is part of the extrahepatic biliary tract. The majority of tumors described in the literature are adenocarcinoma, but the category includes squamous, adenosquamous, neuroendocrine, and other mixed or undifferentiated malignant neoplasms of biliary, intestinal or foveolar features [8, 13]. The WHO and IARC assigns intrahepatic cholangiocarcinoma the ICD-O morphology code ICD-O 8140/3, 8144/3, 8310/3, 8480/3, 8490/3, 8560/3, 8503/3, 8470/3, 8070/3,8020/3, which corresponds topographically to gallbladder cancer (C23.0). [8–10]. ECC share the same morphologic codes as gallbladder carcinomas (*see above*), and are topographically described with gallbladder carcinomas (C23) and other tumors of the biliary tree (C24) [8, 9, 13]. In the reporting of outcomes, GBCA outcomes are sometimes grouped with other tumors of the extrahepatic bile duct (EHBD), such as ECC. Data trends, and risk factors for GBCA will be discussed in this chapter and where there is overlap with EHBD tumors or ECC, this will be specifically mentioned.

Table 5 Age-standardized world incidence rates (ASR-W) for GBCA, 1998–2002

	ASR-W	Cases
(a) *Age-standardized incidence rates of GBCA, World, Males, 1998–2002*		
Japan, Yamagata prefecture	5.7	335
US, California, Los Angeles: Korean	4.8	24
Ecuador, Quito	3.4	78
Czech Republic	3.2	1,072
Italy, Torino	2.8	114
Slovakia	2.7	389
Slovenia	2.6	175
USA, Connecticut: Black	2.5	15
Italy, Ragusa Province	2.4	29
Brazil, Goiana	2.4	37
China, Shanghai	2.3	493
Poland, Warsaw City	2.3	132
(b) *Age-standardized incidence rates of GBCA, World, females, 1998–2002*		
Ecuador, Quito	5.8	152
Slovakia	4.5	364
Colombia, Cali	4.4	164
Czech Republic	4.3	1,821
Spain, Granada	3.3	109
US, California, Los Angeles: Hispanic White	3.2	218
Japan, 3 registries	3.1	1,787
China, 2 registries	2.9	1,279
Poland, 2 registries	2.9	326
Italy, Torino	2.5	121
US, California, Los Angeles: Korean	2.4	16
Costa Rica	2.4	167
Slovenia	2.4	205

Shown are the highest rates reported to the IARC publication with associated cases for *a* males, *b* females. Representative data from both population registry data and individual regions within a country

The incidence, prevalence, and geographic distribution GBCA vary widely with differential susceptibility based on gender, infectious exposure, ethnicity and genetics or family history, but correlate with the incidence and prevalence of cholelithiasis. Worldwide incidence ratios are difficult to parse out from ECC and other EHBD tumors; however, given the poor survival with this tumor, incidence rates generally follow mortality rates. Consistently high ASR-W incidence areas for GBCA are in India and Chile with rates in women of 8.6 and 27.3, respectively, and rates in men of 3.9 and 12.3, respectively, for ages 0–74 years [6]. Table 5 details the highest and lowest incidence rates of GBCA worldwide based on the most recent last IARC *Cancer*

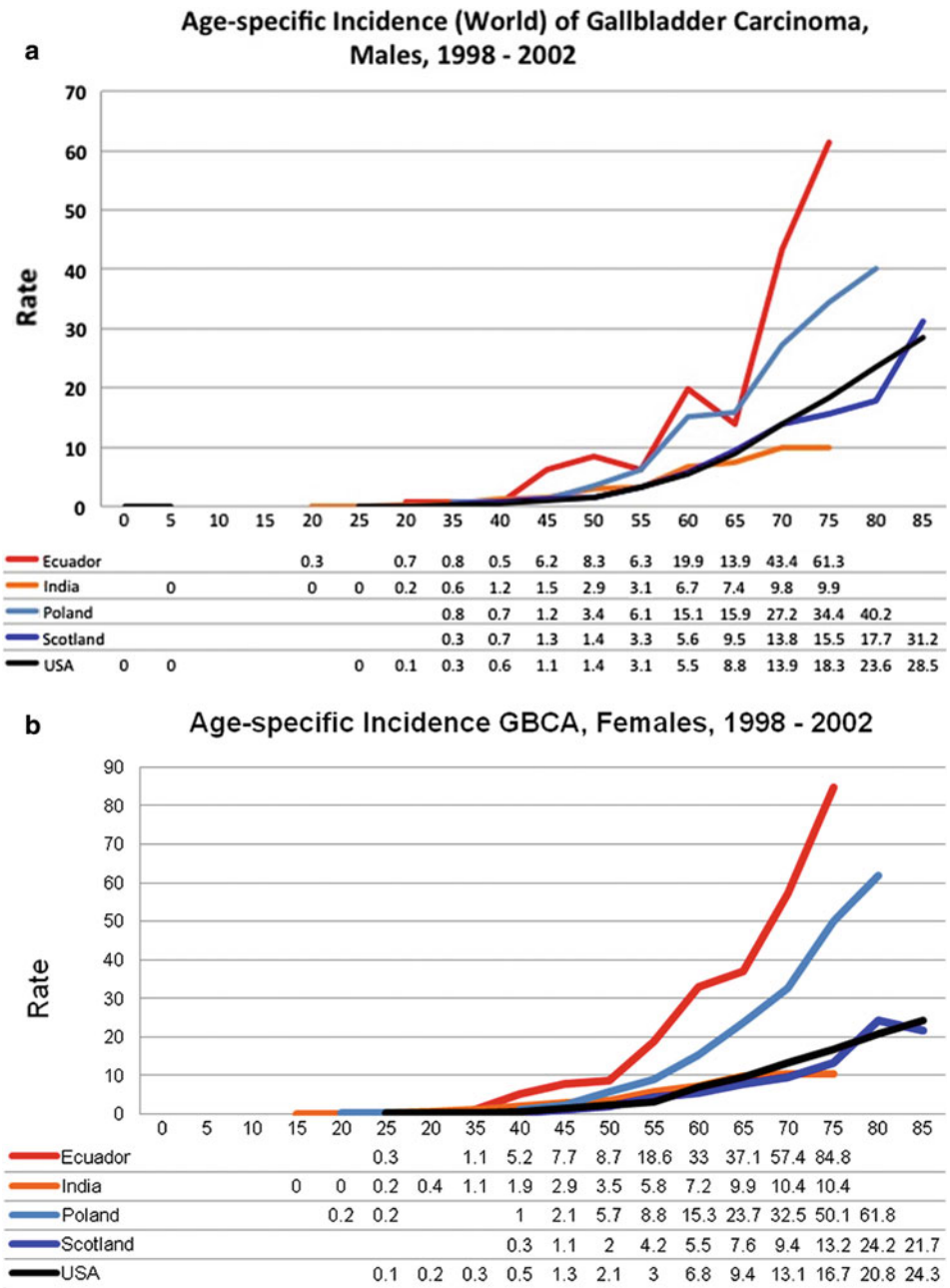


Fig. 6 Age-specific incidence world rates (*ASRW*) per 100,000 of GBCA in, **a** males and **b** females, 1992–2009 [195]. Rates shown are per 100,000 person-years on the *y*-axis. Patient age in years are shown on the *x*-axis

Incidence in Five Continents, Vol. IX publication covering data from 1998 to 2002 [6, 161]. Trends in GBCA show an overall declining mortality over the last 2 decades, although increases have been noted in Italy, Iceland, Korea and Costa Rica [5, 6, 41, 48, 162, 163]. Few reports regarding the prevalence and incidence of GBCA in Africa are published in the literature.

Individuals in their late fifth to seventh decades of life are more commonly afflicted with GBCA [5, 6, 164] (Fig. 6). The female to male ratio of GBCA is generally 3:1 in the United States, Australia, Europe, and Asia, and as high as 5:1 in India, Pakistan, Ecuador, and Israel [5, 6, 163–165]. Geographic areas of high prevalence include populations in India, Ecuador, Chile, Pakistan, and Japan [5, 6, 166]. High prevalence rates occur in specific populations in low-risk nations, like the Pima Indians, Hispanics, and Alaska Natives in the United States [3, 4]. The Mapuche Indians in the high-risk nation of Chile, and women in India and Pakistan, have some of the highest incidence of GBCA worldwide [5, 6, 167].

Risk factors for the development of GBCA include long-standing gallstones and the inflammatory changes that may impact the progression to carcinoma [168, 169]. The overall incidence of GBCA in the presence of cholelithiasis is <0.2 and greater than 80 % of patients with GBCA have gallstones [8, 168]. GBCA may also progress through an

adenoma-carcinoma sequence or a dysplasia-carcinoma sequence [170]. In either case, the evidence supports an increased risk of GBCA with increasing number and size of gallstones, and other polypoid lesions of the gallbladder. Both theories of GBCA pathogenesis are plausible [170–173]. Additional risk factors for GBCA include multiparity, obesity, and biliary tract infections with *S. typhi* and *Helicobacter* spp. [174–180]. Many studies support an increased risk of GBCA in women with more childbirths (>3) and pregnancies [166, 178, 179]. The association of age at first birth, age at last birth, use of the oral contraceptive pill, menopausal status, and use of hormone-replacement therapy (HRT) with GBCA is less well-defined [164, 178, 179, 181].

Current data point to increasing cholecystectomy rates, especially since the introduction of laparoscopic cholecystectomy, are partially responsible for the improved incidence and survival trends in this rare and often deadly cancer [182–186]. Aggressive surgical resection remains the best option for cure [187–189]. Even with high-quality and advanced imaging and diagnostic techniques, patients with GBCA present late, given the lack of specific signs and symptoms early in the disease. Once GBCA achieves regional and/or nodal spread, there are few efficacious chemotherapeutic or radiotherapeutic options that improve prognosis, with 5-year survival rates <10 % in Stage II and <3 % in Stage IV disease [190–194].

2.1 Incidence and Mortality Trends: United States of America

In the United States, it is estimated that there will be about 10,310 cancers of the gallbladder and biliary tract per annum [4]. GBCA accounts for 3.5 % of all digestive system cancers and is currently the 7th most common cancer with 4,740 cancers in men and 5,570 cancers women (includes cancers of the biliary tree and EHBD). Deaths from this cancer remain high with an estimated 1,260 and 1,970 deaths expected for males and females in 2013, respectively. These data represent an increased total number of cases from 2012 ($n = 9{,}810$) spread evenly between men and women, with a similar mortality rate in males and females [3]. As of 2009, GBCA was not in the top 5 causes of cancer-related death for the United States population [4].

Using the SEER program population-based cancer registry results, age-adjusted GBCA incidence per 100,000 fell from 1.8 in 1993 to 1.5 in 2009 for White females. Corresponding GBCA incidence rates per 100,000 for Hispanic females ranged from 2.8 in 2006 and 2008 to a maximum of 5.8 in 1993, with the most recent incidence rate reported as 3.2 per 100,000 [3, 195]. GBCA incidence rates over the same time period in males were comparatively lower than in females with 2009 incidence rates per 100,000 of 1.1 in Hispanic males and 0.8 in White males, representing a slight decrease over the 1992–2009 time period [3, 195]. The SEER program reports are a collaborative effort of the National Cancer Institute (NCI), the Center for Disease Control (CDC) and the North American Association of Central Cancer Registries (NAACR) to collect and publish incidence and mortality data for cancer in the United States. SEER 13 represents data from 26 % of the United States population while the current version SEER 18 collects between 87 and 93 % of the US population. The most robust longitudinal data use SEER incidence data from 1992 to 2009 [3] (Fig. 7).

In a study using United States SEER data to review the incidence and management of GBCA over 10,000 cases across 2 time periods from 1973 to 1992 and 1993 to 2002, the gender distribution of GBCA remained the same with women accounting for 73 and 72.1 % of cancers, respectively [196]. The study noted a gradual reduction in the incidence of GBCA during the second time period, and most notably in patients aged 50 years or older. More Black patients were diagnosed with GBCA during the second time period, which reflected an increase from 5.3 to 8 % of 5,918 and 4,179 total patients, respectively. Regional data from a large epidemiology project in Minnesota (USA) reporting from 1976 to 2008, support the decreasing trend in GBCA overall, and in women [35]. Within this cohort, 81 % reported a history of cholelithiasis. During the study time period, the overall age-sex-adjusted incidence per 100,000 declined from 4.0 to 2.2, with the decrease in female incidence rates from 5.0 (1976–1990) to 1.6 (2001–2008) per 100,000 accounting for the significant difference [35]. The mean/median age at diagnosis of 72 in this study is consistent with the age of diagnosis between 72 and 73 reported in other US data sources [193, 197].

The ratio of GBCA in females to males in the United States was roughly 2–2.5:1 from 1992 to 2009 and closer to 1.2–1.3:1 in recent years (Fig. 8) [3, 4, 193, 195, 197]. Approximately 70 % of cancers were found in White or White Hispanic women and this remains unchanged in published data over the last 30 years [194, 196, 197]. Ethnic and racial differences in GBCA exist within the US population. The age-adjusted incidence rates per 100,000 for Black American males and females (2009) are 1.4 and 1.5, respectively [195]. Since the 1990s, the incidence rates of GBCA in Black American males and females have surpassed that of White males and females though the prevalence of gallstone and gallbladder disease is lower in this group [161, 198]. The APC in incidence and mortality for American Whites has declined at a faster rate than in American Blacks (Table 6) [3, 161, 195, 198].

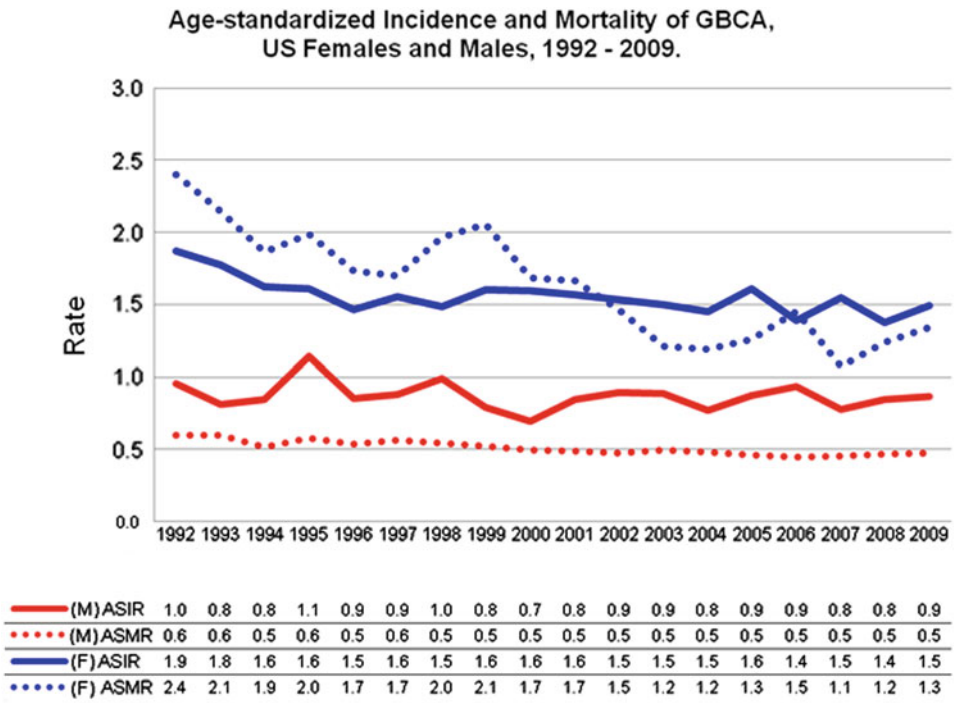


Fig. 7 Age-standardized (US 2000 Standard Population) incidence rates (per 100,000) of GBCA in the United States. Incidence rate is shown on the *y*-axis and grouped time intervals in years are shown on the *x*-axis with the graphed incidence data shown below in tabular format. *ASIR* age-standardized incidence rate. *ASMR* age-standardized mortality rate [3]

The highest US incidence rates for GBCA are found in those with Hispanic, American Indian and/or Native Alaskan heritage. Trend outcomes report that Hispanic females have the highest age-adjusted incidence of GBCA in the United States, followed next by American Indian and Native Alaskan females [7]. Hispanic males have a higher incidence of GBCA than White males, but it is still half that of Hispanic females. One recent comprehensive review of GBCA in 189 American Indian/Alaskan Native (AIAN) Americans (1999–2004) found wide geographic variation in the GBCA incidence rate of 0.5 (East) to 5.5 (Alaska) per 100,000 [199]. Incidence rates were consistently higher in AIAN and non-Hispanic White females than males. In comparison to non-Hispanic Whites, many more in the AIAN population were diagnosed with GBCA at an earlier age [199]. These results hold over a longer time period (1973–2007) in a study of 213 AN (only), 73 of whom developed GBCA [34]. AIAN, Hispanics and Chileans present with GBCA at 61–63 years of age, a stage that is 1–1.5 decades earlier than in low-prevalence populations [169, 200].

2.2 Incidence and Mortality Trends: United Kingdom and Europe

Incidence and mortality trends for GBCA in Europe are comparable to those of the US population [6, 161, 162, 201]. Decreased mortality for GBCA is seen through most northern European countries except for high incidence areas of Poland, Italy, Spain and France in Central and Eastern Europe [5, 6, 162, 164, 165]. Mortality of GBCA across Europe declined by as much as 30 % in women and 10 % in men in the time period 1980–1999 [162]. For females, ASR-W incidence ratios per 100,000 in 2001–2002 for France (1), Denmark (1.1), the Netherlands (1.54), United Kingdom (0.74), and Scotland (1.1) were similar to figures from the United States [5, 6, 161]. Higher incidence rates for females were found in Poland (4.2), Spain (2.05) and Italy (2). The ASR-W for males in Europe were low in 2001–2002 in Denmark (0.9), France (1.25), Switzerland (1), the Netherlands (1.1), United Kingdom (0.6) and Scotland (1.23), with higher incidence rates in Italy, Poland and Slovakia, but not Spain [5, 6, 161].

The high incidence rates of GBCA seen in Central European countries, including Hungary, Poland, Czech Republic, and Slovakia is not associated with any specific known etiology such as a higher incidence of gallstones nor a decreased cholecystectomy rate [163, 202]. Though ASR-W rates of GBCA remained stable across Europe from 1992 to 2002, appreciable declining mortality trends were noted in Slovenia, Hungary, the Czech Republic and Slovakia [163, 202].

The Nordic countries, Finland, Sweden, Denmark, Iceland and Norway, produced a 30-year review of cancer, and reported declines in GBCA and ECC incidence and mortality from the late 1980s, and notably in Denmark since the 1970s [43]. Iceland did show a significant increased GBCA mortality rate in males during the period 1992–2002, but a similar trend was not noted for women [163]. The decreased mortality from GBCA was significant for both sexes in Denmark and Sweden, and in females only in Finland [163].

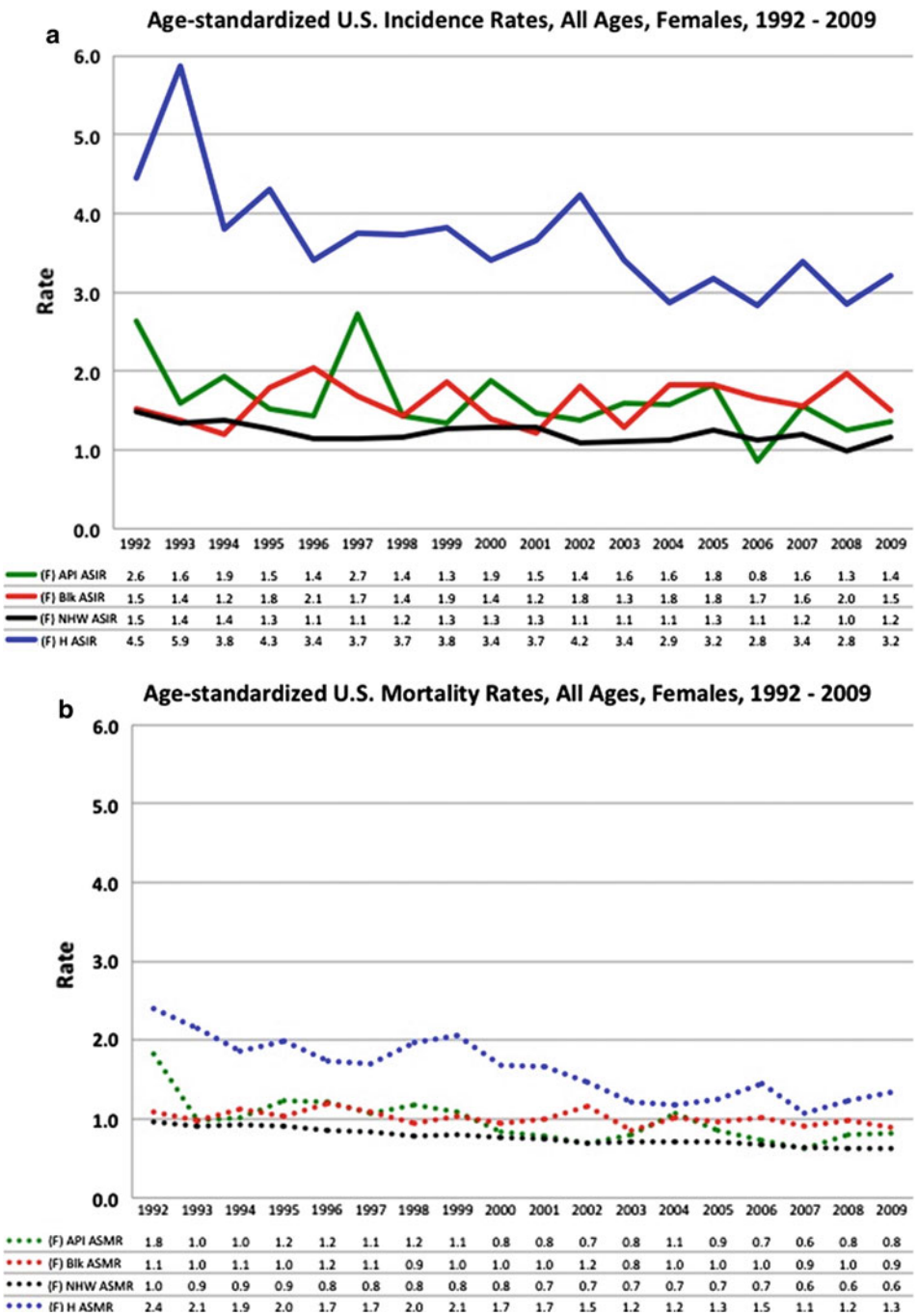


Fig. 8 Age-standardized (US Census 2000) **a** incidence and **b** mortality of gallbladder carcinoma in the United States, all females, 1992–2009. Rates shown are per 100,000 person-years. ASIR, age-standardized incidence ratio. *ASMR* age-standardized mortality ratio. *F* females. *API* Asian/Pacific Islander. *Blk* black. *NHW* non-Hispanic white. *H* Hispanic (inclusive of all races). Trends are significant for incidence in all groups. API, −2.7. Blk, −0.6. NHW −1.0. H, −2.7 Trends are significant for mortality in all groups. API, −13.5. Blk, +0.9. NHW −2.2. H, −3.7. *Source* US SEER Data [3, 195, 265, 266]

Trends in excess mortality in the month following initial diagnosis of GBCA showed a modest improvement in survival, however, 5-year survival in the Nordic countries is still 10–40 %, as seen worldwide [43]. A historic multicontinent, case-controlled study conducted in Canada, the Netherlands, Australia, and Poland provided supportive evidence implicating a history of gallstones and previous cholecystectomy in the pathogenesis of gallbladder cancer [167]. In England, similar to the United States, the median age at diagnosis for GBCA is 73 years, 70 % of the diagnoses are in women and 75 % of patients are diagnosed between the ages of 65–85 years [40]. The incidence rate of GBCA from 1998 to 2007 was stable in comparison to a declining rate seen from 1971 to 2001 [36, 40]. The mortality rate for GBCA in the United Kingdom declined significantly from 1992 to 2002 in both sexes [163]. Longitudinal incidence and mortality data in Scotland from 2001 to 2010 show ASIR and ASMR data for GBCA are shown in Fig. 9.

Table 6 SEER incidence, US mortality and survival percent for all and selected races in GBCA

	Incidence	Mortality	Survival (%)
SEER incidence, US mortality and survival for GBCA, 2005–2009			
All races, total	1.2	0.6	16.6
All races, male	0.8	0.5	14.8
All race, female	1.4	0.8	17.3
Whites, total	1.1	0.6	16.9
Whites, male	0.8	0.4	14.5
Whites, female	1.4	0.7	17.8
Blacks, total	1.5	0.8	12.8
Blacks, male	1.3	0.7	15.8
Blacks, female	1.7	1.0	13.0

Incidence and death rates are per 100,000 and are age-adjusted to the 2000 US standard population. Mortality data are derived from US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention (CDC). Surveillance, Epidemiology, and End Results (SEER) data is from 18 US areas. Survival data (2002–2008) is based on follow-up of patients into 2009. *Source* SEER Cancer Statistics Review, 1975–2009 [3]

2.3 Incidence and Mortality Trends: Asia

The populations in North India, including neighboring Pakistan, have high incidence rates of GBCA compared to other parts of the world and to Indians in the southern part of the continent [164, 203–205]. The ASIR in Delhi, India, a high prevalence area, was 8.6 per 100,000 in females and 3.9 per 100,000 for males from 1998 to 2002 and relatively unchanged (9.4 and 3.9, respectively) since the 1993–1997 evaluation, for ages 0–74 years. GBCA is the leading cause of death for women in North India [206]. In stark contrast, the GBCA incidence rate in females from South India ranges from 0 to 0.7 per 100,000, for ages 0–74 years [5, 6, 164].

The Japanese Public Health Center-based prospective study (JPHC) launched from 1990 to 1994 examined over 100,000 Japanese people and the impact of known and likely risk factors on the biliary tract cancers, GBCA and ECC [73]. The major advantage of this study was that it separately analyzed GBCA and ECC with associated risk factors. The cohort analysis of the Japanese population followed through 2004 found a strong association (hazard ratio, HR 3.10) of cholelithiasis with GBCA that was stronger for men (HR 4.28) than women (HR 2.38). In a previous study from the Japan Collaborative Cohort Study for the Evaluation of Cancer (JACC Study) of over 113,000 Japanese enrolled from 1988 to 1990 and studied for a median of 13 years, the strong association of cholelithiasis with GBCA was not seen [207]. In Japan, the development of GBCA and other biliary tract cancers may be related to an abnormal pancreatobiliary junction (APBJ). This developmental abnormality of the biliary tract is found in 17 % of Japanese with GBCA, and may represent a separate pathway from the association with cholelithiasis and typhoid infection seen in other countries [204, 208, 209]. However, it still remains unclear as to the etiology of the recent trends in increased incidence and mortality of GBCA in Japan.

2.4 Gallbladder Cancer in Africa

Few reports on the incidence and prevalence of GBCA in Africa are published in the literature. The 20-year findings in 30 patients from a tertiary referral center in Nigeria suggested an 87 % preponderance of GBCA in women, and 40 % of cases were associated with gallstones [210]. The mean age at diagnosis was 58 years of age and over 80 % presented with jaundice, an adverse prognostic factor [211]. WHO/IARC data for 1998–2002 reported a high ASR-W incidence of GBCA in females from Algeria (10.0 per 100,000) and Tunisia (3.1 per 100,000) [6]. The incidence rates from the remainder of reported nations (Egypt, Uganda, and Zimbabwe) were otherwise low, ranging from 0.4 per 100,000 in Ugandan females to 1.9 per 100,000 in Tunisian men, placing Africa as a continent of otherwise low prevalence using the available limited data [6].

2.5 Incidence and Mortality Trends: South America

In South America, similar to the United States American Indians, the incidence of GBCA varies with the degree of Amerindian admixture in the population. Again, a higher degree of Amerindian admixture, as is seen in Chile, Bolivia, Ecuador and Bolivia, closely follows a higher incidence of GBCA, than would be seen in Argentina and Brazil [181, 204, 208]. The decreased cholecystectomy rate in Chile in the 1980s coupled with a low rate of cholecystectomy in the high prevalence Mapuche Indians of South Chile led to the higher mortality rate of GBCA [204, 208]. Recent age and sex-adjusted mortality estimates from 333 counties in Chile range from 8.2 to 12.4 per 100,000 for the population from 1985 to 2002, with a higher risk in inland (10-fold) and southern-inland counties (26-fold) [212]. Trends in incidence and mortality rates for GBCA from Chile, 1985–2002, are shown in Fig. 10. Rates of GBCA were higher in counties with more Mapuche Indians in the population [212]. For female Chilean Mapuche Indians, 50 % of females older than aged 50 years harbor gallstones [213].

Differential susceptibility to gallstone formation may be a primary reason for the increased incidence of gallbladder cancer in South American, Hispanic and AIAN populations. The National Health and Nutritional Examination Survey

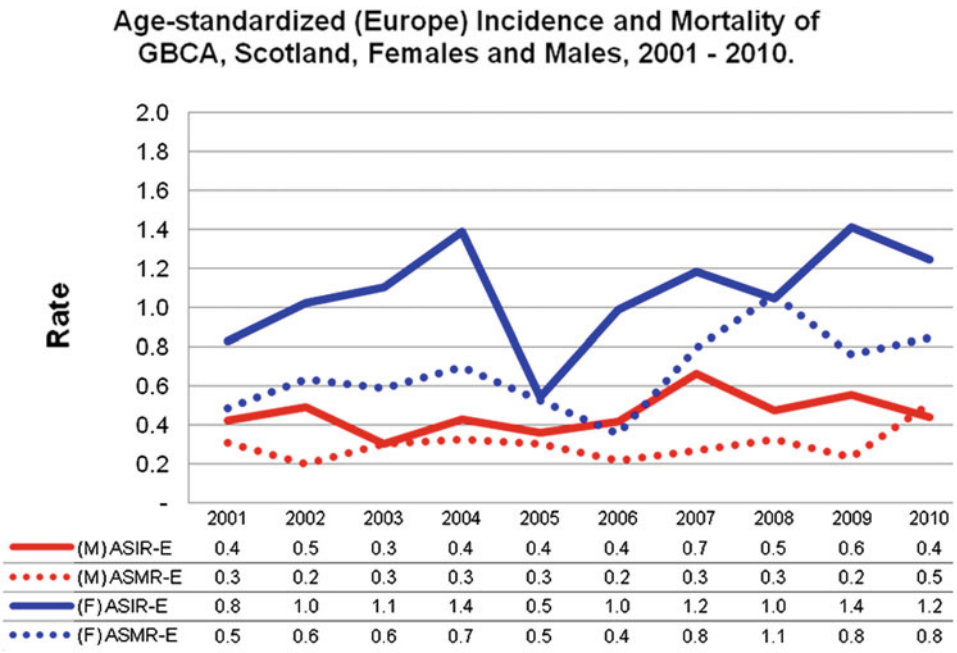


Fig. 9 Age-standardized (Europe) incidence and mortality of gallbladder carcinoma in Scotland, males and females, 2001–2010. Rates shown are per 100,000 person-years. *ASIR-E* age-standardized incidence ratio, Europe. *ASMR-E* age-standardized mortality ratio, Europe. *M* males. *F* females. *Source* Information Services Division (*ISD*) Scotland and NHS National Services Division [267]

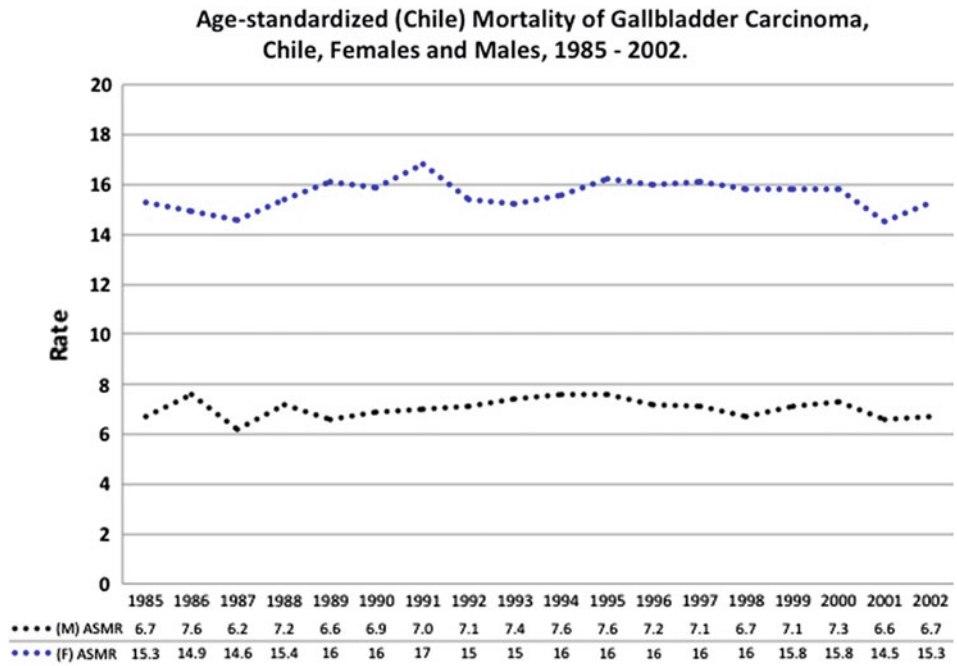


Fig. 10 Age-standardized (Chile) mortality rates (per 100,000) of GBCA, Chile, both sexes, 1985–2002 [268]. *ASMR* age-standardized mortality rate. *M* males. *F* females

(NHANES) III study established the incidence of gallbladder disease (GBD), as defined by the presence of gallstones or a history of cholecystectomy [214]. The report estimated that 20 million people in the United States had GBD. The study found a 12.8 % prevalence rate of gallstones in Mexican–American women, and a nadir of 3.9 % in American Black males, corresponding to a 26.7 and 5.3 % incidence of GBD, respectively.

There is a high incidence of larger gallstone formation at younger ages in populations with a significant Amerindian ethnic admixture, as low as 8.3 years of age in females and 10.8 years of age in males. There is a dramatic increase in the size and number of stones beginning after age 20 [169, 213]. The incidence of GBD is as high as 76 % in AIAN females aged 65 and older in the Southwestern United States, in Pima Indians older than

45 years of age, and in New Mexico Native Americans [213, 215]. However, the increased gallstone formation rates in both males and females with Amerindian ethnicity does not translate into significantly increased GBCA incidence rates for Hispanic males as compared to Hispanic females [199, 213, 216]. In the Mexican–American population, the Amerindian admixture is estimated at 30–50 % [199, 213, 216].

2.6 Cholelithiasis and Chronic Inflammation

Multiple reviews have confirmed the association of the presence of gallstones as an important risk for development of GBCA, and are present in up to 80 % of patients with this cancer [8, 168, 200, 208, 217, 218]. Worldwide, the prevalence of gallstones varies dramatically [208, 219, 220]. The prevalence of GBD, defined as the presence of gallstones or patients undergoing cholecystectomy in a population, can be as high as 64 % in American Indian Tribes of the United States, 61 % in Montreal, and 15–30 % in select areas of India, Italy and Poland [220]. The lowest prevalence areas for gallstones are in Africa (<5 %), while Asia (5–20 %) ranks as an intermediate prevalence area. Approximately 1–3 % of people harboring gallstones develop GBCA [208]. In the presence of gallstones, the odds ratio (OR) for developing GBCA was 2.4 for stones 2–2.9 cm in diameter compared to stones <1 cm, but was as high as 10.1 for stones >3 cm in diameter [168]. In a population-based study from China, the presence of gallstones was associated with a 23-fold increased risk in developing GBCA [221, 222]. Stones in this GBCA group were heavier than in the gallstone alone group [221].

The impact of gallstone size on GBCA is pronounced in American Indians, Alaskan Natives and Hispanics. In a United States study of Blacks and Whites (low prevalence) and American Indians (high prevalence) with gallstones, the age-adjusted OR for GBCA in patients with stones >2 cm in diameter was 1.5 for Indian populations and for the American Indian group, the OR for patients with stones >3 cm was 9.1. The mean gallstone size in patients with cancer compared to those who did not have GBCA was 2.5 cm versus 1.5 cm, respectively [169]. In a prospective study of 600 females with gallstones in Chile, single gallstones with a mean size of 2.5 cm were significantly associated with GBCA [200]. Patients with asymptomatic stones are more likely to have singular stones, however symptomatology and incidence of GBCA increase with greater than six gallstones [200].

The risk of GBCA in the presence of cholelithiasis may be related to the duration of stones within the gallbladder and their secondary impact as a chronic, inflammatory stimulus on the gallbladder epithelium. In populations at risk for GBCA, the increased incidence and early age at presentation of GBCA may be related to larger stones developing earlier in life, given the similar growth rate (2.0 mm/year) across many different populations [169, 213, 216]. GBCA may proceed through a metaplasia-dysplasia-carcinoma sequence in which the chronic irritation by gallstones contributes to biliary epithelial metaplasia [170, 204, 208, 217]. The pathogenic pathway to GBCA in the presence of cholelithiasis (whether cholesterol, brown or black pigment stones) is due to alteration of the chemical composition of bile and alteration of the gallbladder wall to promote stone formation [223]. Genetic analysis of stone formation in high prevalence areas of North and South America have identified genetic predispositions to 'lithogenic bile' and a potential causal relationship with GBCA [208, 223, 224].

2.7 The Porcelain Gallbladder and Polypoid Lesions

The porcelain, or calcified, gallbladder confers a higher risk of GBCA, in the range of 10–60 % (Fig. 11). The risk of GBCA is higher in a partially calcified gallbladder [217, 225]. The gallbladder mucosa undergoes intestinal or biliary metaplasia prior to proceeding toward carcinoma [223].

Initial reports established a risk of GBCA in resected gallbladders with a solitary polypoid lesions of the gallbladder (PLG) >1 cm in males and in females older than 60 years of age [171, 226]. The estimated prevalence of PLG is 3–8 %, on ultrasound scanning and 2–12 % in gallbladder specimens following cholecystectomy [171]. Worrisome imaging findings include growth over an interval observation period, vascularity within the polyp, and obliteration of the fat plane between the gallbladder and liver bed, or symptomatic polyps are an indication for cholecystectomy [227] (Fig. 11). Additional reports have corroborated these findings in an attempt to stratify patients for operative resection. One recent study based on ultrasound findings suggests that cholecystectomy is indicated for PLG greater than or equal to 6 mm, and that show vascularity, growth, invasion, or cause symptoms, after reporting cancer findings in 7.4 % of their cohort [172]. Consistent high-risk features for cancer in PLG include age 50–60 years, solitary polyp, >1 cm, sessile, symptomatic, or with evidence of liver parenchymal invasion [173, 228–230].

Pathologic assessment of gallbladder specimens has clarified a decreased risk of developing GBCA from adenomas due to the low incidence of adenomas (0.14 %) in cholecystectomy specimens [170]. There is limited evidence for the progression of GBCA through an adenoma-carcinoma sequence similar to colon cancer [208]. Generally, a high index of suspicion regarding abnormalities in the gallbladder should prompt interval reassessment by ultrasound for small

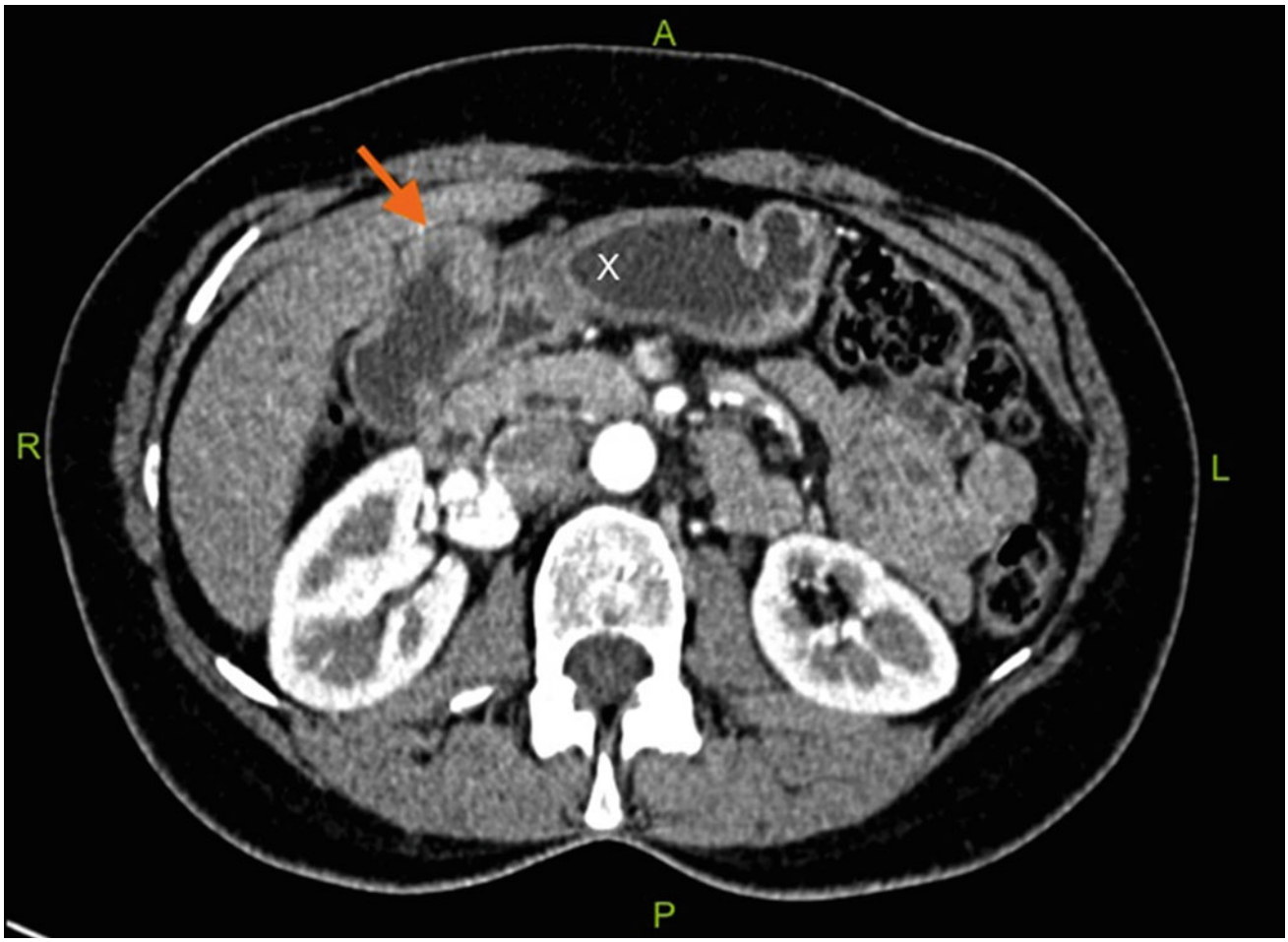


Fig. 11 **a** Ultrasound image of polypoid lesion of the gallbladder. 2.7 cm exophytic, mucosal enhancing polypoid lesion in fundus of gallbladder. pT2 Nx GBCA with lymphatic and vascular invasion at histologic analysis of cholecystectomy specimen. **b** Axial contrast-enhanced CT image of gallbladder with lesion in fundus (*arrow*) adjacent to duodenum (*X*). Orientation is marked, *A* anterior, *P* posterior, *R* right and *L* left. Images: *Royal Infirmary of Edinburgh, NHS Lothian* ©

lesions or referral for cholecystectomy for larger lesions. Cholesterolosis has not been demonstrated to have an association with GBCA in analysis from Chile [231].

2.8 The Impact of Cholecystectomy and Incidental Gallbladder Cancers

Decreased GBCA mortality of 22–30 % in Scotland, England, Wales, and in the United States during the 1970s was attributed to peaks of increased cholecystectomy rates in these countries [182, 183]. Contrastingly, excess deaths due to GBCA were reported during this time in Sweden with falling cholecystectomy rates. The data estimated that 1 in 63 excess deaths in England and Wales, and 1 in 115 excess deaths in the United States and Sweden from GBCA were prevented due to the previous year's cholecystectomies [182]. In Scotland, using the 30-year (1968–1998) GBCA incidence ($n = 1736$) and mortality ($n = 1546$) data from Scotland, declining rates were seen in females since the 1960s and in males since the 1980s [185]. Mortality rates for GBCA closely follow incidence rates. The steeper decline in mortality realized from 1990 to 1991 and onwards coincides with the start of a second peak of increased cholecystectomy rates in Scotland and the introduction of laparoscopic cholecystectomy in Western countries [36, 185, 197].

Laparoscopic cholecystectomy accounted for a 30–60 % increased rate of cholecystectomy with the largest increases seen in women aged 45–65 years of age when it was introduced [197, 232]. Using diagnosis, treatment and survival data from the United States National Cancer Database (NCDB), patient cohorts in 1989–1990 and 1994–1995, notably before and after the introduction of laparoscopic cholecystectomy, did not show increased numbers of early stage (Stage 0, I) cancers [197]. The declining incidence in GBCA is matched by decreasing mortality, and is most marked in women. For the time period 1979–1998, the major declines in ASMR-W occurred in Scotland (41 %), England

and Wales (45 %), the United States (35 %), and France (22 %) [41]. In contrast, the ASMR rose in Japan (16 %) and Italy during the same time period (28 %) [41]. The incidence and mortality rates of GBCA and ECC have continued to fall in the last 2 decades; the etiology is likely multifactorial related to changes in lifestyle, diet, cholecystectomy rates, genetic, and other nuances. Many incidence and mortality figures report GBCA and ECC topographic codes (C23, C24) in a combined manner causing difficulty in separating which cancer accounts for the major declines noted in men and women. However, given the greater propensity of GBCA for women, and ECC for men, each cancer contributes to the steady declines seen in both sexes.

The incidental finding of GBCA, however, has become more common since the advent of laparoscopic cholecystectomy, though this has not dramatically altered incidence and prevalence data [189, 233, 234]. The impact of cholecystectomy rates on GBCA incidence rates, viewed as increasing numbers of early cancers, or incidental cancers found at cholecystectomy, for another indication has not been seen. Intestinal metaplasia, a precancerous lesion, can be seen in 10–76 % of gallbladder specimens [203]. The rate of finding an incidental gallbladder cancer is 1–10 % [235–238]. In Chile, where incidence rates are one of the highest, up to 74 % of specimens harbor a gallbladder cancer [234]. Patient survival outcomes are not adversely affected in patients with early stage tumors who have had laparoscopic cholecystectomy initially [197, 233, 234].

Major surgical resection of the liver and bile duct may be required for advanced staged tumors in order properly stage and treat patients, and guide adjuvant therapy [186, 193, 234, 235, 239–241]. Some groups have found improved survival after re-resection for T2 and T3 GBCA found in the resected pathology specimen. Modest survival benefits are seen in patients with limited nodal and regional spread in Stage III or greater GBCA [238, 241]. Interestingly, while the risk of GBCA declines with cholecystectomy, risks of liver and other biliary tract cancers increase, and the risk of EHBDcancers decreases after cholecystectomy [184, 242, 243].

2.9 The Abnormal Pancreatobiliary Junction

Biliary tract cancers, including those of the gallbladder, are demonstrably higher in the presence of an APBJ [244–246]. The estimated frequency of APBJ with GBCA ranges from 5 to 25 % [247–249]. Endoscopic retrograde cholangiopancreatography (ERCP) reports estimate the prevalence of APBJ as 0.9–2.6 % of the world's population [247, 250]. The APBJ commonly occurs associated with the development of choledochal cysts. The literature discussing these and the incidence of related biliary tract cancers originate in Asia, namely China and Japan. The association of choledochal cysts, APBJ and biliary tract cancer are described in the section on cholangiocarcinoma. Gallbladder carcinoma is frequently encountered in APBJ with or without an associated cystic dilation of the biliary tree, and may occur more commonly in the absence of a choledochal cyst [246, 248]. The long length of the shared 'common channel' of the pancreatic and bile ducts, without a controlling sphincter mechanism, exposes the biliary epithelium to pancreatic amylase, intestinal bacteria and other factors that create an altered bile milieu [247, 251].

Secondary bile acids, lithocholate and deoxycholate, derived from the breakdown of bile by deconjugation, dehydroxylation, and intestinal bacteria, are considered mutagenic [223, 227, 245, 246, 248]. The gallbladder epithelium is affected by altered bile as demonstrated by increased secondary bile acid and pancreatic amylase concentrations in cholecystectomy specimens that differ from patients without an APBJ [223, 245, 246, 248].

2.10 Infectious Agents

Typhoid fever, caused by infection with *Salmonella typhi* and *S. paratyphi*, was common at the turn of the twentieth century in the United States and other developed nations, and remains an important cause of the disease in nations with poor sanitation. The history of typhoid infection or a typhoid carrier state imparts a 6-fold increased risk of death from hepatobiliary cancers as reported in 471 cases from New York (USA) in a case-control study [174]. The increased risk of death from hepatobiliary cancers was most significant in men and those who were foreign-born (67.8 %) [174]. Analysis of deaths in chronic typhoid and paratyphoid carriers in Scotland (UK) from the late 1960s confirmed the excess risk of death from hepatobiliary, or 'bile-related' cancers [175]. The excess risk of GBCA was most pronounced in women and was related to patients who developed a chronic typhoid carrier state rather than acute infection alone. Similar studies in high (Bolivia and Mexico) and low (Denmark) prevalence areas, also found a high incidence of the typhoid carrier state with GBCA [181, 212, 252]. In patients with gallstones, positive typhoid carrier status confers an additional increased risk factor for developing GBCA [253]. High prevalence areas for GBCA across the world (Chile, Bolivia, North India, Ecuador) are also high prevalence areas for gallstones and typhoid. The typhoid bacillus resides in the gallbladder mucosa in chronic infection [174, 212]. The chronic inflammatory environment, creation of mutagenic secondary bile acids and the relative biliary tree obstruction from stasis are postulated mechanisms of hepatobiliary cancer pathogenesis with *S. typhi*.

Bacterial DNA isolates of *Helicobacter* spp. have been retrieved from gallbladder, bile and serum specimens after cholecystectomy, with *Helicobacter pylori* more commonly found than *H. bilis* [254–256]. The role of *Helicobacter* spp. in the pathogenesis of GBCA has been looked at given its close association with bile duct injury, chronic inflammation and proliferation caused by *H. hepaticus* in the liver [257] and the role *H. pylori* plays in gastric inflammation and ulceration. Due to the high prevalence of *Helicobacter*-associated chronic cholecystitis in Chileans, it is postulated as a participatory event in gallstone formation and a possible inciting event in gallbladder epithelial metaplasia [255].

2.11 Emerging and Other Risk Factors

Quantitative summary analysis of the role of obesity, defined by the WHO as overweight (BMI 25–30) and obese (BMI $\geq$ 30), compared to normal weight adults (BMI 18.5–24.9) showed a 66 % increased risk of GBCA with a summary RR of 15 [180]. The report derived data from studies of populations in Chile, Bolivia, United States, Korea, Norway, Sweden, Japan, Denmark and Poland published from 1992 to 2006 demonstrated no statistically significant heterogeneity. The relationship of obesity with GBCA was stronger in women in the majority of studies. In one population-based study from China, using WHO definitions for overweight (BMI 23.0–24.9), obese (BMI $\geq$ 25) and normal weight (BMI 18.5–22.9) adults in Asian populations, reported a 12.6–fold increased risk of GBCA with a BMI $\geq$25 [258]. The study introduced the association of abdominal obesity with GBCA after demonstrating an increased waist-to-hip ratio was more significantly associated with GBCA for any given BMI. The WHO parameters for BMI in Asians attempt to better stratify the impact of BMI-related diseases in Asians given the demonstrated increased prevalence of BMI-related comorbidities at a lower BMI [259]. In population-based studies of biliary tract cancer in China, a significant close association of GBCA with women, diabetes, and BMI >25 has been shown [221, 260].

The familial association of GBCA was initially described in a few short reports on families from New Mexico (USA) and Brazil [166]. The Swedish Family Cancer Database provides more robust contemporary data on the impact of familial relationships on liver and biliary tract cancer [261]. From 1961 to 1998, the database contained data on 10 offspring-parent families from 1,121 offspring and over 17,000 parent cases. The standardized incidence ratio (SIR) of GBCA was increased at 3.13 in offspring from parents with liver or pancreatic cancer. The SIR of gallbladder cancer was increased in parents by offspring with liver or biliary tract cancer at 1.93. For both parents and offspring, the SIR was highest for offspring and parents at 5.05 and 4.09, respectively, for concordant gallbladder sites. The risk of GBCA has been shown to be 57-fold higher for cholelithiasis and a family history cholelithiasis (in first-degree relatives) than the 21-fold increased risk with cholelithiasis alone for the affected patient [222]. Earlier studies on populations in Mexico and Bolivia showed the same close association of GBCA in an affected patient with a first-degree relative who had a history of cholelithiasis [181].

Additional ‘lifestyle’ and related factors such as low socioeconomic status/degrees of deprivation [185, 262, 263], alcohol consumption [207], smoking [207, 264], diets high in chili peppers [263], fried foods [263], foods baked in pork fat [181], and in patients with loose stools, more than 2 bowel movements per day or infrequent weekly stools [167], have all been associated with GBCA in populations worldwide. The association of GBCA with occupational exposure to carcinogens and toxic byproducts of industry are not clearly defined.

2.12 Summary

For the known risk factor of cholelithiasis in the development of GBCA, continued prompt treatment of gallbladder disease and symptomatic cholelithiasis should remove a known risk factor for developing GBCA. Differential availability and access to cholecystectomy (laparoscopic or open) throughout the world makes this a challenging strategy to universally implement. Controversy exists regarding the role of prophylactic cholecystectomy and cholecystectomy for asymptomatic disease due to concern for GBCA in high-risk populations [218]. Gallstones are more prevalent in populations with high Amerindian heritage in North and South America and in India, suggesting evidence of a genetic susceptibility to gallstone formation. The studies analyzing the potentially contributory lifestyle factors, such as alcohol consumption, poverty, smoking, dietary and weight factors suggest that consequences of exposure to environmental or metabolic byproducts contribute to a chronic inflammatory state that initiates gallbladder metaplasia. Indeed, the association of *S. typhi* and *Helicobacter* spp. infection with GBCA supports the pathway of chronic inflammation leading to invasive carcinoma. In areas of Asia, developmental abnormalities may play a stronger role than gallstones in the development of GBCA. Early diagnosis of gallbladder carcinoma based on a high index of suspicion still provides the best opportunity to cure the disease by surgical resection. Current studies demonstrate that cholecystectomy alone is sufficient treatment for early stage tumors, while radical surgical resection of the gallbladder, liver and extrahepatic biliary tree do little to improve survival for advanced-stage GBCA.

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