Research Article
Hepatic and Biliary Cancer

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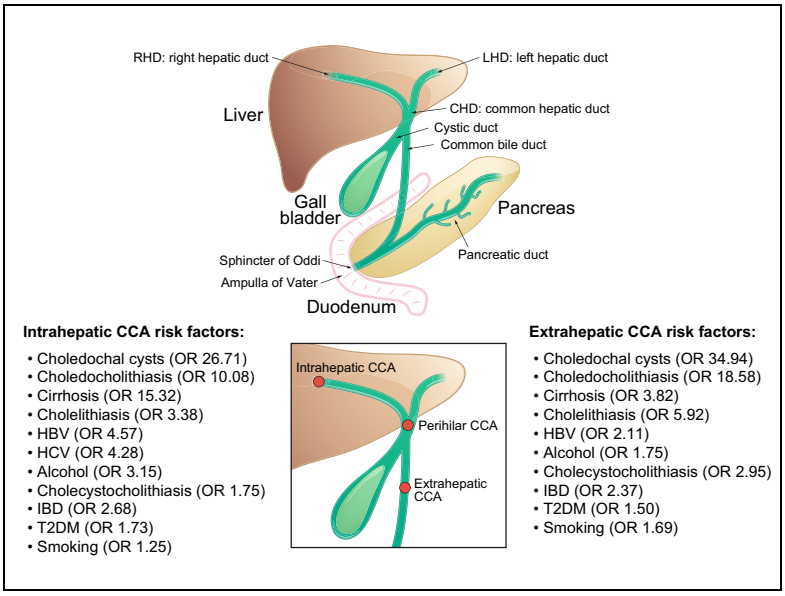
Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis

Graphical abstract



Highlights

- Choledochal cysts were found to be most strongly associated with both iCCA and eCCA.
- Cirrhosis was a significant CCA risk, with a stronger association with iCCA than eCCA.
- Choledocholithiasis had a stronger association with eCCA than iCCA.
- In Eastern countries, cirrhosis and HBV conferred a greater risk of iCCA than in Western countries.
- Rising global incidence of iCCA may be linked to increases in T2DM, cirrhosis, alcoholic liver disease and cholelithiasis.

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Lay summary

Cholangiocarcinoma (CCA) is a cancer arising in the bile ducts inside (intrahepatic CCA) and connected to the liver (extrahepatic CCA). It is a very aggressive cancer: 95% of patients die within 5 years. CCA rates are increasing globally, but the causes of CCA are poorly understood. The few risk factors that are known account for only a minority of cases. In this study, we found that the strongest risk factors for both intrahepatic and extrahepatic CCA are cysts and stones in the bile ducts, cirrhosis, and hepatitis B and C viruses. Some risk factors for CCA, such as diabetes, although less strong, are increasing globally and may be contributing to rising rates of CCA.

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Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis

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Background & Aims: Cholangiocarcinoma (CCA) carries a poor prognosis, is increasing in incidence and its causes are poorly understood. Although some risk factors are known, they vary globally and collectively account for a minority of cases. The aim of this study was to perform a comprehensive meta-analysis of risk factors for intrahepatic (iCCA) and extrahepatic cholangiocarcinoma (eCCA), from Eastern and Western world studies.

Methods: A literature search of case-control studies was performed to identify potential risk factors for iCCA and eCCA. Pooled odds ratios (ORs) with 95% CIs and heterogeneity were calculated. Funnel plots were used to assess publication bias, and meta-regression was used to select risk factors for comparison between Eastern and Western studies.

Results: A total of 13 risk factors were selected from 25 case-control studies in 7 geographically diverse countries. The strongest risk factors for both iCCA and eCCA were biliary cysts and stones, cirrhosis, hepatitis B and hepatitis C. Choledochal cysts conferred the greatest risk of both iCCA and eCCA with pooled ORs of 26.71 (95% CI 15.80–45.16) and 34.94 (24.36–50.12), respectively. No significant associations were found between hypertension and obesity for either iCCA or eCCA. Comparing Eastern and Western populations, there was a difference for the association of hepatitis B with iCCA (coefficient = −0.15195; 95% CI −0.278 to −0.025; $p = 0.022$).

Conclusion: This is the most comprehensive meta-analysis of CCA risk factors to date. Some risk factors, such as diabetes, although less strong, are increasing globally and may be contributing to rising rates of this cancer.

Lay summary: Cholangiocarcinoma (CCA) is a cancer arising in the bile ducts inside (intrahepatic CCA) and connected to the liver (extrahepatic CCA). It is a very aggressive cancer: 95% of patients die within 5 years. CCA rates are increasing globally, but the causes of CCA are poorly understood. The few risk factors that are known account for only a minority of cases. In this study, we found that the strongest risk factors for both intrahepatic and extrahepatic CCA are cysts and stones in the bile ducts, cirrhosis, and hepatitis B and C viruses. Some risk factors for CCA, such as diabetes, although less strong, are increasing globally and may be contributing to rising rates of CCA.

Introduction

Cholangiocarcinoma (CCA) is an exceptionally aggressive cancer arising from the biliary duct epithelium. CCAs represent approximately 3 to 5% of all malignancies of the gastrointestinal system. CCAs are classically sub-divided into 3 groups depending on the anatomical site of origin: intrahepatic CCA (iCCA), perihilar CCA (pCCA) and distal CCA (dCCA). iCCAs classically arise above the second-order bile ducts, whereas the anatomical point of distinction between perihilar cholangiocarcinomas (pCCAs) and distal cholangiocarcinomas (dCCAs) is the cystic duct.[1–5] pCCA account for approximately 50–60% of all CCAs, dCCA 20–30%; and iCCA approximately 10–20%. iCCAs comprise about 10% of all primary liver cancers, making them the second most common primary hepatic malignancy after hepatocellular carcinoma.[4,6] CCA typically presents late with non-specific symptoms. This is compounded by the lack of knowledge of risk factors in most cases and inaccurate screening tools, making the diagnosis of early, resectable disease uncommon. Beyond this stage, CCA is one of the most fatal cancers with a 5-year survival of approximately 5%.[6]

The incidence of CCA varies globally and particularly so between East and West. Northeast Thailand reports the highest age standardised incidence rates of CCA of 113/100,000 in men and 50/100,000 in women, which are approximately 100-fold greater than European and North American rates of around 1–2/100,000.[6] However, several studies report a rising incidence of iCCA in recent decades across diverse geographical regions, in contrast to a stable or declining incidence of eCCA.[5,7–12] The reasons for these trends are unclear, but the ongoing overall increase in the incidence of CCA makes it imperative to understand the disease's aetiology and risk factors.

Presumably, geographical variations in CCA incidence are likely to be due to differences in environmental and genetic risk factors. The most significant known risk factor for the development of CCA in East Asia involves parasitic infection, specifically with *Opisthorchis viverrini* (OV) or *Clonorchis sinensis*.[13,14] OV is endemic in Northeast Thailand with a prevalence of 9.4%.[15] In the West, primary sclerosing cholangitis (PSC) is the most common known risk factor, for example a case-control study by Choi

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and colleagues showing an adjusted odds ratio (OR) of 117.[16] In addition, case-control studies and meta-analyses have proposed other risk factors for CCA, including: hepatitis B and C viruses (HBV, HCV); biliary tract diseases (*e.g.* choledochal cyst, cholelithiasis); cirrhosis and environmental toxins.[17–20] However, the few accepted risk factors account for only a minority of CCA cases, particularly in the Western world. Most cases are sporadic, occurring without any accepted or known risk factors. There are data on other potential and more common risk factors, such as inflammatory bowel disease (IBD), type 2 diabetes mellitus (T2DM), obesity, alcohol/alcohol-related liver disease, smoking and hypertension, but several of these have not been subjected to meta-analyses. Previous meta-analyses have also tended not to distinguish between eCCA and iCCA, which are increasingly recognised as clinically and pathobiologically distinct entities.[5] The 2 most comprehensive meta-analyses of CCA risk factors to date were performed by Palmer and Patel in 2012[17] and Kamsa-ard *et al.* in 2018.[21] The first study quantitatively defined the risk of 7 risk factors, including HBV and HCV, cirrhosis and alcohol, for iCCA only. The second study examined 17 risk factors, but did not distinguish the subtype of CCA. Furthermore, the study by Kamsa-ard only included case-control studies performed in Thailand, and hence several risk factors studied, such as parasitic infection and treatment with the antihelminthic, praziquantel, have local geographical relevance only. The remaining meta-analyses have mainly analysed a single or a few risk factors, and their association with either iCCA or eCCA.[18,22–40] In recent years, newer case-control studies have shown some significant results, several of which have not been meta-analysed. Consequently, there is a need for an updated meta-analysis that includes all recent case-control studies and also examines previously inconclusive risk factors, including their quantifiable effect on both iCCA and eCCA. The aim of this study was to perform the most comprehensive global meta-analysis of risk factors to date, for both iCCA and eCCA, other than the established risk factors of PSC and liver flukes. Furthermore, we aimed to compare the relative importance of shared risk factors between Eastern and Western regions for the first time.

Materials and methods

Literature search

To identify relevant studies for inclusion in the meta-analysis, a search of the National Library of Medicine's MEDLINE database using Ovid was conducted. The following Medical Subject Headings (MeSH) were included: "cholangiocarcinoma", "bile duct neoplasms", "biliary tract neoplasms" and "risk factors". The following terms were also searched as keywords: "bile duct carcinoma", "biliary tract carcinoma", "biliary tree cancer" and "biliary tree carcinoma". The search was not restricted by country or language. Only studies performed after 1990 were included, due to the update in the International Classification Diseases for Oncology (ICD-O), which altered the classification of the CCA subtypes. Furthermore, we performed a manual search of the reference lists of the selected studies.

Inclusion and exclusion criteria

Studies were included if they fulfilled the following criteria: (i) case-control study design, (ii) provided sufficient data to calculate ORs, (iii) specifically defined individual risk factors and (iv) reported outcomes for association between risk factor and iCCA or eCCA or both. Studies were excluded if any of these criteria were unmet and/or for failure to distinguish between tumour subtypes. Studies were selected in an unblinded manner.

Data extraction

The following information was extracted from each study: name of first author, year of publication, country, definition of risk factor and number of individuals and controls with and without the risk factor of interest. The raw data extracted from each study are available in Table 1.

Quality assessment

Study quality and risk of bias were assessed using the Newcastle-Ottawa quality assessment scale (NOS).[41] This scale consists of the following 3 dimensions: selection, comparability and exposure, covered by 8 items. Four points can be scored for selection, 2 for comparability and 3 for exposure. Studies were scored out of 9, with a higher score indicating higher quality. Studies with a score of 1–3 were considered low quality, those with a score of 4–6 were considered intermediate quality and those with a score >7 were considered high quality.

Statistical analysis

Statistical analysis was performed using RevMan 5.3 (Cochrane Community, 2014), which generated a Forest plot, pooled ORs and CIs for each risk factor. Study heterogeneity was assessed using the Cochrane Q test and I^2 test and publication bias was examined using funnel plots. Random-effects meta-analysis (Der Simonian and Laird) was used to pool results from studies looking at risk factors. Meta-regression was used to compare differences between regions for selected risk factors. This was performed using Stata 15 (StataCorp 2017, Dallas, Texas, USA).

Results

Study selection and study characteristics

The literature search of MEDLINE identified a total of 1,487 references, of which 1,445 were excluded for failing to meet the inclusion criteria or lack of relevance, generating 42 references for further screening (Fig. 1). Seventeen were excluded for the following reasons: failure to define tumour subtype, failing to employ a case-control design or the full paper not being available in English. This resulted in 25 studies eligible for inclusion in the meta-analysis (Table 1). A total of 13 risk factors were eligible for meta-analysis: alcohol, choledochal cysts, cholelithiasis, choledocholithiasis, cholecystocholithiasis, cirrhosis, HBV, HCV, hypertension, IBD, obesity, smoking and T2DM.

Meta-analysis was performed using a random-effects model due to heterogeneity between the included studies. Meta-regression was used to compare differences between regions for these 4 risk factors: cirrhosis, HBV, HCV and alcohol, and only for iCCA.

A summary of the pooled ORs for all risk factors is given in Table 2. Forest plots for individual risk factors for iCCA and eCCA are available in Appendix 1 (Figs. S1–13).

Publication bias and study quality

Funnel plots indicated no evidence of potential publication bias (available in Appendix 2). Study quality was assessed using the NOS scale: 21 of the 25 studies were determined to be of high quality and 4 of the 25 were determined to be of intermediate quality. None of the studies was deemed low quality.

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Table 1. Summary of studies (all were case-control studies).

Study	Country	Nature of study	Risk factors considered	Cholangiocarcinoma subtype studied	Variables used for adjustment	Number of cases		Number of controls		Study quality (NOS)
						Intrahepatic	Extrahepatic	Intrahepatic	Extrahepatic	
Chaiteerakij, 2013	Taiwan	Case-control	HBV, HCV, cirrhosis, choledochal cyst, smoking and obesity	Intrahepatic	Age, gender and ethnicity	612	/	594	/	8
Chang, 2013	Taiwan	Case-control	HBV, HCV, cirrhosis, choledochal cyst, cholelithiasis, choledocholithiasis, IBD, T2DM, alcohol	Intrahepatic and extrahepatic	Age, gender and time of diagnosis	2,978	2,179	11,912	8,716	9
Choi, 2016	US	Case-control	HBV, HCV, cirrhosis, choledochal cyst, IBD, smoking and obesity	Intrahepatic and extrahepatic	Age, gender, ethnicity and residence	1,169	231		4,769	8
Chow, 1994	US	Case-control	Cholelithiasis, smoking, obesity, alcohol	Extrahepatic	Age and gender	/	105	/	255	8
Donato, 2001	Italy	Case-control	HBV, HCV, alcohol	Intrahepatic	Age, gender, date and hospital of admission	26	/	824	/	8
Hsing, 2008	China	Case-control	HBV, HCV, cirrhosis, smoking, obesity, alcohol, hypertension	Extrahepatic	Age, gender and hospital	/	134	/	762	8
Hsing, 2007	China	Case-control	Cirrhosis	Extrahepatic	Age, gender and hospital	/	191	/	959	8
Huang, 2017	Taiwan	Case-control	HBV, HCV, cirrhosis, IBD, T2DM, alcohol	Intrahepatic and extrahepatic	Age and gender	4,695	1,398	46,942	13,964	8
Lee, 2015	South Korea	Case-control	HBV, HCV, choledocholithiasis, cholecystolithiasis, smoking, obesity, alcohol, hypertension	Intrahepatic and extrahepatic	Age, gender and date of diagnosis	83	193	166	386	7
Lee, 2009	Taiwan	Case-control	HBV, HCV, cirrhosis, cholelithiasis	Intrahepatic	Age and gender	160	/	160	/	6
Lee, 2008	South Korea	Case-control	HBV, HCV, cirrhosis, choledochal cyst, smoking, T2DM, alcohol	Intrahepatic	Age and gender	622	/	2,488	/	8
Liu, 2005	China	Case-control	Smoking, obesity, alcohol, hypertension	Extrahepatic	Age, gender, education and biliary stone status	/	191	/	959	8
Peng, 2011	China	Case-control	HBV, cirrhosis, choledocholithiasis, cholecystolithiasis, hypertension	Intrahepatic	Age and gender	98	/	196	/	8
Petrick, 2017	US	Case-control	HBV, HCV, cirrhosis, choledochal cyst, cholelithiasis, choledocholithiasis, IBD, smoking, obesity, T2DM, alcohol, hypertension	Intrahepatic and extrahepatic	Age, ethnicity, region and socioeconomic status	2,092	2,981		323,615	8
Shaib, 2007	US	Case-control	HBV, HCV, smoking, T2DM, alcohol	Intrahepatic and extrahepatic	Age, gender and ethnicity	83	163		236	8
Shaib, 2005	US	Case-control	HBV, HCV, cirrhosis, IBD, smoking, T2DM, alcohol	Intrahepatic	Age, gender, ethnicity and region	625	/	90,834	/	7
Tao, 2010	China	Case-control	HBV, cholecystolithiasis, smoking, T2DM, alcohol, hypertension	Intrahepatic and extrahepatic	Age, gender and year of diagnosis	61	129		380	8
Welzel, 2011	US	Case-control	HBV, HCV, cirrhosis, choledochal cyst, cholelithiasis, IBD, smoking, obesity, T2DM, alcohol, hypertension	Intrahepatic	Age, gender, region and Medicare enrolment	743	/	195,953	/	6
Welzel, 2007	US	Case-control	HCV, cirrhosis, choledochal cyst, cholelithiasis, choledocholithiasis, IBD, smoking, obesity, T2DM, alcohol	Intrahepatic and extrahepatic	Age, gender, ethnicity and region	535	549		102,782	8
Welzel, 2007	Denmark	Case-control	Cirrhosis, IBD, obesity, T2DM, alcohol	Intrahepatic	Age, gender and year of diagnosis	764	/	3,056	/	8
Wu, 2012	China	Case-control	HBV, cirrhosis, hypertension	Intrahepatic and extrahepatic	Age, gender and year of diagnosis	102	86		835	7

(*continued on next page*)

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Table 1 (*continued*)

Study	Country	Nature of study	Risk factors considered	Cholangiocarcinoma subtype studied	Variables used for adjustment	Number of cases		Number of controls		Study quality (NOS)
						Intrahepatic	Extrahepatic	Intrahepatic	Extrahepatic	
Yamamoto, 2004	Japan	Case-control	HBV, HCV, cirrhosis, cholelithiasis, smoking, T2DM, alcohol, hypertension	Intrahepatic	Age and gender	50	/	205	/	6
Zhou, 2013	China	Case-control	HBV, cirrhosis, choledocholithiasis, cholecystolithiasis, smoking, alcohol	Extrahepatic	Age and gender	/	239	/	478	7
Zhou, 2010	China	Case-control	HBV, cirrhosis, choledocholithiasis, cholecystolithiasis, alcohol	Intrahepatic	Age and gender	317	/	634	/	8
Zhou, 2008	China	Case-control	HBV, HCV, smoking, T2DM, alcohol, hypertension	Intrahepatic	Age and gender	312	/	438	/	6

HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; NOS, Newcastle-Ottawa quality assessment scale; T2DM, type 2 diabetes mellitus.

Choledochal cyst

Seven case-control studies were included (4 studies from the US, 2 from Taiwan and 1 from South Korea), comprising 8,751 cases and 642,113 controls, to study the association between choledochal cysts and iCCA from 2007 to 2017.[42–47] Choledochal cysts were diagnosed from radiographic evidence in 1 study; questionnaires in 2 studies or defined by ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 26.71 (95% CI 15.80–45.16).

Four case-control studies were included (3 from the US and 1 from Taiwan), comprising 5,940 cases and 439,882 controls, to analyse the association between choledochal cysts and eCCA from 2007 to 2017.[16,42,43,47] Choledochal cysts were diagnosed from a questionnaire in 1 study or defined by ICD9 coding in 3 studies. Meta-analysis calculated a pooled OR of 34.94 (95% CI 24.36–50.12).

Choledocholithiasis

Six case-control studies were included (2 studies from the US, 1 from Taiwan, 2 from China and 1 from South Korea), comprising 6,103 cases and 43,905 controls, to study the association between choledocholithiasis and iCCA from 2007 to 2017.[19,42,43,48–50] Choledocholithiasis was diagnosed through radiographic evidence in 2 studies, obtained from medical records in 1 study or defined by ICD9 coding in 3 studies. Meta-analysis calculated a pooled OR of 10.08 (95% CI 5.50–18.49).

Five case-control studies (2 studies from the US and 1 each from China, Taiwan and South Korea), were included, comprising 6,141 cases and 435,977 controls, to study the association between choledocholithiasis and eCCA from 2007 to 2017.[19,42,43,49,51] Choledocholithiasis was diagnosed through radiographic evidence in 1 study, obtained from medical records in 1 study or defined by ICD9 coding in 3 studies. Meta-analysis calculated a pooled OR of 18.58 (95% CI 11.07–31.18).

Cirrhosis

Fourteen case-control studies were included (5 studies from the US, 4 from Taiwan, 2 from China and 1 each from South Korea, Japan and Denmark), comprising 15,455 cases and 783,940 controls, to study the association between cirrhosis and iCCA from 2004 to 2017.[16,19,20,42–48,50,52–54] Cirrhosis was diagnosed via clinical, laboratory, radiographic or pathological evidence in 7 studies or defined by ICD9 coding in 7 studies. Meta-analysis calculated a pooled OR of 15.32 (95% CI 9.33–25.15).

Eight case-control studies were included (3 studies from the US, 3 from China and 2 from Taiwan), comprising 7,902 cases and 179,545 controls, to study the association between cirrhosis and eCCA[16,19,42,43,51,52,55,56] Cirrhosis was diagnosed via clinical, laboratory, radiographic or pathological evidence in 2 studies, obtained from interview of individuals in 2 studies and via ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 3.82 (95% CI 2.58–5.65).

Cholelithiasis

Seven case-control studies were included (3 studies from the US, 1 from China, 2 from Taiwan and 1 from Japan), consisting of 6,600 cases and 635,462 controls, to study the association between cholelithiasis and iCCA from 2004 to 2017.[19,42,43,45,53,54,57] Cholelithiasis was diagnosed from radiographic evidence in 2 studies, obtained from patient medical records in 1 study or defined by ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 3.38 (95% CI 1.93–5.92).

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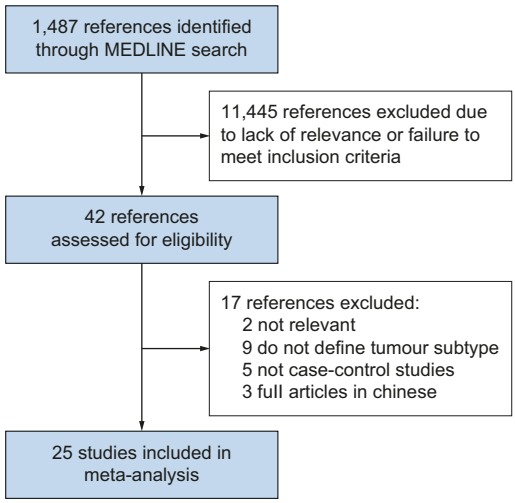

Fig. 1. Process of study selection: A flow diagram demonstrating the process of inclusion and elimination of studies. 25 studies were determined to be eligible for inclusion in the meta-analysis.

Five case-control studies were included (3 studies from the US, 1 from China and 1 from Taiwan), consisting of 5,858 cases and 436,203 controls, to study the association between cholelithiasis and eCCA from 1994 to 2017.[19,42,43,57,58] Cholelithiasis was diagnosed from radiographic evidence in 1 study, obtained from interview in 1 study or defined by ICD9 coding in 3 studies. Meta-analysis calculated a pooled OR of 5.92 (95% CI 3.09–11.32).

Hepatitis B

Eighteen case-control studies were included (5 studies from the US, 5 from China, 4 from Taiwan, 2 from South Korea and 1 each from Japan and Italy), consisting of 14,825 cases and 681,181 controls, to study the association between HBV and iCCA from 2001 to 2017.[16,20,42–46,48–50,52–54,57,59–62] HBV was defined as the presence of HBsAg in 13 studies and defined by ICD9 coding in 5 studies. Meta-analysis calculated a pooled OR of 4.57 (95% CI 3.43–6.09).

Ten case-control studies were included (3 studies from the USA, 4 from China, 2 from Taiwan and 1 from South Korea), consisting of 7,713 cases and 354,141 controls, to study the association between HBV and eCCA from 2007 to 2017.[16,42,43,49,51,52,55,57,59,61] HBV was defined as the presence of HBsAg in 7 studies and defined by ICD9 coding in 3 studies. Meta-analysis calculated a pooled OR of 2.11 (95% CI 1.64–2.73).

Hepatitis C

Fifteen case-control studies were included (6 studies from the US, 4 from Taiwan, 2 from South Korea and 1 each from China, Japan and Italy), consisting of 14,783 cases and 781,918 controls, to study the association between HCV and iCCA from 2001 to 2017.[16,19,20,42–46,49,52–54,60–62] HCV was defined as the presence of HCV RNA in 3 studies, the presence of anti-HCV antibody in 6 studies or defined by ICD9 coding in 6 studies. Meta-analysis calculated a pooled OR of 4.28 (95% CI 2.98–6.16).

Eight case-control studies were included (4 studies from the US, 2 from Taiwan and 1 from both China and South Korea), consisting of 8,456 cases and 454,602 controls, to study the association between HCV and eCCA from 2007 to 2017.[16,19,42,43,49,52,55,61] HCV was defined as the presence of HCV RNA in 2 studies, the presence of anti-HCV antibody in 2 studies and defined by ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 1.51 (95% CI 0.96–2.36).

Alcohol

Fifteen case-control studies were included (5 studies from US, 3 from China, 2 from Taiwan, 2 from South Korea and 1 each from Denmark, Italy and Japan), consisting of 13,986 cases and 780,565 controls, to study the association between alcohol exposure and iCCA from 2004 to 2017.[19,20,42,43,45–47,49,50,52,54,59–62] Alcohol exposure was defined as >80 g/day in 4 studies, any history of exposure in 1 study, 1 day/week for >6 months in 1 study, >5 g consumed (135 ml)/day for >10 years in 1 study, or through the presence of alcohol-related liver disease or ICD9 coding in 8 studies. Meta-analysis calculated a pooled OR of 3.15 (95% CI 2.24–4.41).

Eleven case-control studies were included (4 studies from China, 2 from Taiwan and 1 from South Korea), consisting of 8,293 cases and 452,450 controls, to study the association between alcohol exposure and eCCA from 1994 to 2017.[19,42,43,49,51,52,55,58,59,61,63] Alcohol exposure was defined as >80 g/day in 2 studies, any history of exposure in 4 studies, >15 alcoholic beverages/week in 1 study or through ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 1.75 (95% CI 1.20–2.55).

Table 2. Summary of pooled odds ratios for all risk factors.

Risk factor	Number of studies		Odds ratio (95% CI)	
	Intrahepatic	Extrahepatic	Intrahepatic	Extrahepatic
Choledochal cyst	7	4	26.71 (15.80–45.16)	34.94 (24.36–50.12)
Choledocholithiasis	6	5	10.08 (5.50–18.49)	18.58 (11.07–31.18)
Cirrhosis	14	8	15.32 (9.33–25.15)	3.82 (2.58–5.65)
Cholelithiasis	7	5	3.38 (1.93–5.92)	5.92 (3.09–11.32)
HBV	18	10	4.57 (3.43–6.09)	2.11 (1.64–2.73)
HCV	15	8	4.28 (2.98– 6.16)	1.98 (1.33–2.94)
Alcohol	15	11	3.15 (2.24– 4.41)	1.75 (1.20–2.55)
Cholecystolithiasis	4	3	1.75 (0.97–3.16)	2.94 (2.10–4.11)
IBD	8	5	2.68 (1.79–4.01)	2.37 (1.34– 4.22)
T2DM	12	6	1.73 (1.47–2.04)	1.50 (1.31–1.71)
Smoking	12	10	1.25 (1.05–1.49)	1.69 (1.28–2.22)
Hypertension	8	6	1.10 (0.89–1.37)	1.21 (0.77–1.90)
Obesity	7	7	1.14 (0.93–1.39)	1.20 (0.84–1.70)

HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; T2DM, type 2 diabetes mellitus.

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Cholecystocholithiasis

Four case-control studies were included (3 studies from China and 1 from South Korea), consisting of 559 cases and 1,376 controls, to study the association between cholecystocholithiasis and iCCA from 2010 to 2017.[48–50,59] Cholecystocholithiasis was diagnosed from radiographic evidence in 2 studies or obtained from medical records in 2 studies. Meta-analysis calculated a pooled OR of 1.75 (95% CI 1.97–3.16).

Three case-control studies were included (2 studies from China and 1 from South Korea), consisting of 561 cases and 1,244 controls, to study the association between cholecystocholithiasis and eCCA from 2010 to 2015.[49,51,59] Cholecystocholithiasis was diagnosed from radiographic evidence in 1 study or obtained from medical records in 2 studies. Meta-analysis calculated a pooled OR of 2.95 (95% CI 2.11–4.12).

Inflammatory bowel disease

Eight case-control studies were included (5 studies from the US, 2 from Taiwan and 1 from Denmark), consisting of 13,601 cases and 779,863 controls, to study the association between IBD and iCCA from 2005 to 2017.[16,19,20,42,43,45,47,52] IBD was diagnosed from histopathology or endoscopic evidence in 1 study or defined by ICD9 coding in 7 studies. Meta-analysis calculated a pooled OR of 2.68 (95% CI 1.79–4.01).

Five case-control studies were included (3 studies from the US and 2 from Taiwan), consisting of 7,338 cases and 453,846 controls, to study the association between IBD and eCCA from 2007 to 2017.[16,19,42,43,52] IBD was diagnosed from histopathology or endoscopic evidence in 1 study or defined by ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 2.37 (95% CI 1.34–4.22).

Type 2 diabetes

Twelve case-control studies were included (5 studies from the US, 2 from China, 2 from Taiwan and 1 each from Denmark, Japan and South Korea), consisting of 13,560 cases and 778,841 controls, to study the association between T2DM and iCCA from 2004 to 2017.[19,20,42,43,45–47,52,54,59–61] A diagnosis of T2DM was made from patient medical records in 3 studies, patient medications in 1 study, according to WHO criteria in 1 study or defined by ICD9 coding in 7 studies. Meta-analysis calculated a pooled OR of 1.73 (95% CI 1.47–2.04).

Six case-control studies were included (3 studies from the US, 2 from Taiwan and 1 from China), consisting of 7,399 cases and 449,693 controls, to study the association between T2DM and eCCA from 2007 to 2017.[19,42,43,52,59,61] T2DM was diagnosed from patient medical records in 2 studies or through ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 1.50 (95% CI 1.31–1.71).

Smoking

Twelve case-control studies were included (6 studies from the US, 2 from China, 2 from South Korea and 1 each from Japan and Taiwan), consisting of 6,987 cases and 722,460 controls, to study the association between smoking and iCCA from 2004 to 2017.[16,19,20,42,44–46,49,54,59–61] Smoking was defined as any history of tobacco use in 5 studies, by pack years in 2 studies (>20 or >25), by duration in 1 study (>4 days/week for >6 months) or via ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 1.25 (95% CI 1.05–1.49).

Ten case-control studies were included (5 studies from the US, 4 from China and 1 from South Korea), consisting of 4,874 cases and 434,622 controls, to study the association between smoking and eCCA from 1994 to 2017.[16,19,42,49,51,55,58,59,61,63] Smoking was defined by any history of tobacco use in 5 studies, by pack years in 3 studies (>20, >25 or >51) or defined by ICD9 coding in 2 studies. Meta-analysis calculated a pooled OR of 1.69 (95% CI 1.28–2.22).

Hypertension

Eight case-control studies were included (2 studies from the US, 4 from China and 1 each from Japan and South Korea), consisting of 3,541 cases and 521,788 controls, to study the association between hypertension and iCCA from 2004 to 2017.[42,45,48,49,54,57,59,60] Hypertension was diagnosed from patient medical records in 5 studies, patients requiring medication in 1 study or through ICD9 coding in 2 studies. Meta-analysis calculated a pooled OR of 1.10 (95% CI 0.89–1.37).

Six case-control studies were included (1 study from the US, 4 from China and 1 from South Korea), consisting of 3,714 cases and 326,937 controls, to study the association between hypertension and eCCA from 2005 to 2017.[42,49,55,57,59,63] Hypertension was diagnosed from patient medical records in 5 studies or defined by ICD9 coding in 1 study. Meta-analysis calculated a pooled OR of 1.21 (95% CI 0.77–1.90).

Obesity

Seven case-control studies were included (4 studies from the US and 1 each from Denmark, Taiwan and South Korea), consisting of 5,998 cases and 630,935 controls, to study the association between obesity and iCCA from 2007 to 2017.[16,19,42,44,45,47,49] Obesity was defined by body mass index (BMI) in 3 studies (>25 or >30) or listed by ICD9 coding in 4 studies. Meta-analysis calculated a pooled OR of 1.14 (95% CI 0.93–1.39).

Seven case-control studies were included (4 studies from the US, 2 from China and 1 from South Korea), consisting of 4,343 cases and 433,528 controls, to study the association between obesity and eCCA from 2007 to 2017.[16,19,42,49,55,58,63] Obesity was defined by BMI in 5 studies (>25 or >30) or via ICD9 coding in 2 studies. Meta-analysis calculated a pooled OR of 1.20 (95% CI 0.84–1.70).

Comparison of differences in risk for selected risk factors between studies from Western and Eastern countries using meta-regression analysis

Comparison between studies from Western (US, Denmark and Italy) and Eastern countries (China, Taiwan, Japan and South Korea) found a marginal difference for cirrhosis as a risk factor iCCA (coefficient = −0.077; 95% CI −0.168 to 0.015; $p = 0.092$), some evidence of a difference for HBV (-0.151; −0.278 to −0.025; $p = 0.022$), no significant difference for HCV (-0.009; −0.043 to 0.026; $p = 0.602$) and no significant difference for alcohol (-0.0002; −0.063 to 0.637; $p = 0.994$).

Discussion

This is the most comprehensive systematic review and meta-analysis to date, which studied the association between risk factors and both iCCA and eCCA within both the Eastern and Western hemispheres. This meta-analysis was the first to show that choledochal cysts, which are congenital cystic dilatations of the biliary tree,[64] were most strongly associated with both iCCA and eCCA (OR 26.71 and 34.94, respectively). Cirrhosis was found to confer a significant CCA risk, with a stronger

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association with iCCA than eCCA (OR 15.32 and 3.82, respectively). Choledocholithiasis was also observed to be a prominent risk factor, with a greater association with eCCA than iCCA (OR 18.58 and 10.08, respectively). Neither hypertension nor obesity had a statistically significant association with iCCA (OR 1.1, 95% CI 0.89–13.7 and OR 1.14, 95% CI 0.93–1.39, respectively) or eCCA, (OR 1.21, 95% CI 0.77–1.90 and OR 1.20, 95% CI 0.84–1.70, respectively). This is the first meta-analysis to examine the association between cirrhosis, choledocholithiasis, cholecystocholithiasis, cholelithiasis and hypertension with eCCA, as well as the association between hypertension and iCCA. Meta-regression revealed that in Eastern countries, cirrhosis and HBV conferred a greater risk of iCCA than in Western countries. However, there was no statistically significant geographical difference for HCV and alcohol. These geographical differences are interesting to observe and may be explained by the difference of risk exposure from both genetic variations and environmental factors.

Previously reported risk factors including choledocholithiasis, cirrhosis, HBV and HCV were found to be significant and the ORs were generally comparable to those reported in prior literature. However, the varying definition of cholelithiasis in the literature leads to uncertainty as to the true risk of CCA, requiring further studies to quantify choledolithiasis, cholecystolithiasis, hepatolithiasis and cholelithiasis definitively. The less established risk factors were all associated with significant risk for iCCA and eCCA, including alcohol (OR 3.15 and 1.75, respectively), IBD (OR 2.68 and 2.37, respectively), T2DM (OR 1.73 and 1.5, respectively) and smoking (OR 1.25 and 1.69, respectively).

One of the key findings is the difference in the degree to which these risk factors are associated with iCCA and eCCA (Table 2). Cirrhosis, HBV, HCV, IBD and T2DM were found to have a greater association with iCCA, in contrast to choledochal cysts, choledocholithiasis cholelithiasis, cholecystolithiasis and smoking, which conferred a greater risk of eCCA. The findings are concordant with the primary locations that are targeted by the specific factors. Viral hepatitis and cirrhosis primarily affect the intrahepatic bile ducts, whereas cholelithiasis, choledocholithiasis and cholecystolithiasis affect the extrahepatic bile ducts. The risk factors associated with both iCCA and eCCA are T2DM, alcohol and smoking, which are likely to be general risk factors for malignancy; while choledochal cyst develops in both the intrahepatic and extrahepatic bile ducts.[65]

Choledochal cysts are very rare in the Western world with an incidence of 1/100,000–150,000, a stark contrast to Asia where the incidence is 1/1,000.[66] Despite the greater burden of CCA in the East, multiple studies have identified increasing iCCA incidence and mortality in Western countries. Bertuccio and colleagues reported an increase of incidence and mortality in 12 European countries, with the highest increases occurring in Germany, France and the UK.[11] Interestingly, there is mounting evidence for an upward trend in the incidence of IBD, T2DM, cirrhosis, alcohol-related liver disease and cholelithiasis in the US and Europe,[67–72] which appear to correspond to the rising incidence of iCCA. The results of this meta-analysis show that the increasing incidence of these risk factors may be contributing to the increasing incidence of iCCA, but clearly further cohort studies are required to confirm a causal relationship. However, there is still no clear explanation for the stable/declining incidence of eCCA through the same period. Although the association between the aforementioned risk factors and eCCA are weaker than iCCA, the association remains significant and is likely contributed to by other undiscovered risk factors of eCCA.

In future studies, other potential risk factors that have been suggested in case-control studies may be suitable for meta-analysis, such as chronic pancreatitis, peptic ulcer disease and haemochromatosis.[43,49,52] Furthermore, studies exploring potentially protective factors such as aspirin, would be of interest.[16,73,74]

There is a paucity of data on the risk factors for pCCA. This is particularly important as pCCA comprises 50–60% of CCA cases, and its epidemiology and aetiopathogenesis are debated as a result of ICD coding not distinguishing between pCCA and eCCA until now.[4,5] Additionally, the fact that all CCA cases cannot be explained by the currently identifiable and established risk factors may mean a significant genetic component to CCA pathogenesis, which will require identification via whole genome sequencing.[75] Further evidence for this comes from case-control studies showing that family history may confer a disease risk.[54] Finally, it will be interesting to execute a comprehensive meta-regression comparing the relative strength of various risk factors for iCCA and eCCA in different parts of the world, once there are sufficient case-control data to power such analyses.

In conclusion, this systematic review and meta-analysis has found choledochal cysts to be the most significant risk factor for both sporadic iCCA and eCCA, followed by choledocholithiasis and cirrhosis. Previously inconclusive risk factors have been confirmed and could feasibly be contributory to the increasing trend in iCCA, but further investigation is required to verify this relationship and explore other aspects of the aetiopathogenesis of CCA.

Abbreviations

BMI, body mass index; CCA, cholangiocarcinoma; dCCA, distal CCA; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; iCCA, intrahepatic CCA; NOS, Newcastle-Ottawa quality assessment scale; OR, odds ratio; OV, Opisthorchis viverrini; pCCA, perihilar CCA; PSC, primary sclerosing cholangitis; T2DM, type 2 diabetes mellitus.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

O. Clements: collected data, performed statistical analyses, wrote the manuscript with support from other authors. *J.* Eliahoo: performed statistical analyses. *J.U. Kim and S.D. Taylor-Robinson*: critically appraised study design and results. *S.A. Khan*: designed, supervised and implemented the research. All authors discussed the results and contributed to the final manuscript.

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Supplementary data

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