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

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Abstract

Background

The incidence of intrahepatic cholangiocarcinoma (ICC) has increased worldwide in recent years, but the risk factors of ICC have not yet been clearly defined. The aim of this study was to identify risk factors for ICC.

Methods

A literature search was conducted in PubMed database for eligible studies published from January 2000 to November 2018. Summary odds ratio (OR) with their corresponding 95% confidence intervals (CI) were calculated using a random-effects model.

Results

Thirty-two studies (5 cohort, 27 case control) were included in this meta-analysis. Pooled estimates indicated that cirrhosis (OR=11.96, 95% CI 7.53-19.00), hepatitis B virus (HBV) infection (OR=4.09, 95% CI 3.13-5.34), hepatitis C virus (HCV) infection (OR=3.94, 95% CI 2.85-5.45), alcohol consumption (OR=2.68, 95% CI 1.97-3.66), hepatolithiasis (OR=14.94, 95% CI 6.41-34.83), choledochal cyst (OR=21.67, 95%CI 10.83-43.36), primary sclerosing cholangitis (PSC) (OR=93.91, 95%CI 43.99-200.47), diabetes mellitus (OR=1.82, 95% CI 1.57-2.11), non-alcoholic fatty liver disease (OR=2.23, 95% CI 1.65-3.02), liver fluke infection (OR=2.28, 95% CI 1.30-4.01) and smoking (OR=1.26, 95% CI 1.07-1.49) were significantly associated with ICC. Non-significant association was found between ICC and history of cholecystectomy, hypertension, coffee and aspirin.

Conclusions

Cirrhosis, HBV infection, HCV infection, alcohol consumption, hepatolithiasis, choledochal cyst, PSC, diabetes mellitus, non-alcoholic fatty liver disease, liver fluke infection and smoking are risk factors for ICC.
Background

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of liver cancer next to hepatocellular carcinoma (HCC), accounting for nearly 3% of all gastrointestinal cancers in the world, and its incidence has been increasing recently in many geographic areas [1, 2]. The prognosis of ICC patients is dismal because most patients are diagnosed late, when curative treatment is not possible [3]. Therefore, early detection of ICC and recognition of risk factors are of great clinical significance.

Liver fluke infestation, primary sclerosing cholangitis (PSC) and hepatolithiasis are established risk factors for ICC [4]. Several recent studies have investigated the association of ICC with hepatitis B virus (HBV)/hepatitis C virus (HCV) infection cirrhosis, choledochal cyst, the history of cholecystectomy, diabetes mellitus (DM), non-alcoholic fatty liver disease (NAFLD) and smoking, but the results are inconclusive, partly due to the relatively low ICC incidence, making it difficult to assemble large enough cohorts to achieve adequate power for statistical analysis. We therefore conducted a systematic review and meta-analysis to identify risk factors for ICC.

Methods

Literature search

Studies were identified by carrying out a systematic review of all relevant published literatures in the PubMed database. The language of studies was limited only for English with studies published from January 2000 to November 2018. We conducted the search in November 2018 using the following key words: risk, “epidemiology, etiology and cholangiocarcinoma. In addition, we manually searched the citations of all retrieved articles for additional studies.

Criteria for inclusion and exclusion
The included studies must meet the following criteria: (a) cohort-based or case-control studies; (b) studies using the defined criteria to examine individual risk factors; and (c) studies providing adequate information for odds ratio (OR) calculation. Abstracts, reviews, expert opinions, animal studies, letters, editorials, and cohort studies involving patients with extra-hepatic cholangiocarcinoma and co-existing hepatocellular-cholangiocarcinoma were excluded.

**Data extraction**

Two reviewers (Shijie Wang and Zhibin Cai) independently the extracted information from each included study using the predefined criteria, including the first author, year of publication, documentation of risk factor, and numbers of individuals with ICC (cases) and without ICC (controls).

**Statistical analysis**

Statistical analyses were performed using Review Manager (RevMan) software 5.3 (Cochrane Collaboration). A pooled OR and 95% confidence interval (CI) were calculated for each risk factor from the crude number of study patients. Subgroup analysis was based on stratification by geographical area. Study heterogeneity was evaluated by $I^2$, and values greater than 50% indicated considerable heterogeneity. The random-effects model was adopted regardless of heterogeneity or not, and funnel plots were used to detect potential publication bias.

**Results**

**Study characteristics**

A total of 1091 publications were identified, including 1088 from Pubmed and 3 from other sources, of which 32 met the selection criteria and were included in the analysis, including 5 cohort-based and 27 case-control studies (Fig. 1). Of the 32 included studies, nine were
conducted in the United States [5-14], eight in China [15-22], four in Taiwan (China) [23-26], three in Korea [27-29], two in Italy [30, 31], three in Japan [32-34], one in Denmark [35], and one in 10 European countries [36]. The characteristics of the 32 included studies are summarized in Table 1.

**Cirrhosis**

Sixteen case-control studies investigated the association between cirrhosis and ICC [5, 6, 9, 10, 12, 13, 16, 18, 19, 22, 23, 25, 26, 29, 34, 35]. Of them, six studies were from the United States, four from China, three from Taiwan (China), and one each was from Japan, Denmark and Korea. These studies included a total case and control population of 801278 participants. All these 16 case-control studies showed that cirrhosis increased the ICC risk. Our meta-analysis further confirmed this significant association with a pooled OR of 11.96 (95% CI 7.53-19.00; $I^2=95\%$) (Fig. 2). The corresponding OR for studies in Eastern and Western countries was 8.97 (95% CI 4.91-16.37; $I^2=93\%$) and 16.38 (95% CI 9.12-29.42; $I^2=93\%$), respectively (Table 2).

**HBV infection**

 Twenty-three studies including 21 case-control and 2 cohort-based studies investigated the association between HBV infection and ICC [5, 6, 9, 10, 13, 15-29, 31, 33, 34]. Of them, five studies were from the United States, weight from China, four from Taiwan (China), three from Korea, two from Japan, and one was from Italy. The research data were collected during the period from 1983 to 2014, involving a total of 2632515 participants. Six of the 23 studies reported no significant association between HBV infection and ICC [5, 10, 15, 27, 31, 34], but the remaining 17 studies showed a significant association [6, 9, 13, 16-26, 28, 29, 33]. Our meta-analysis showed that HBV infection was a risk factor for ICC with a pooled OR of 4.09 (95% CI 3.13-5.34; $I^2=83\%$) (Fig. 3). The corresponding OR
for Eastern and Western countries studies was 4.56 (95% CI 3.33-6.24; $I^2$=87%) and 2.90 (95% CI 1.70-4.97; $I^2$=58%), respectively (Table 2).

**HCV infection**

Twenty-one studies including 19 case-control and 2 cohort-based studies investigated the association between HBV infection and ICC [5-7, 9-13, 15, 19-21, 23, 25-29, 31, 33, 34]. Of them, eight studies were from the United States, four from China, three from Taiwan (China), three from Korea, two from Japan, and one was from Italy. The research data were collected during the period from 1988 to 2014, involving a total of 1669223 participants. Seven studies reported no significant association between HCV infection and ICC [15, 19-21, 27-29], but the remaining 14 studies showed a significant association [5-7, 9-13, 23, 25, 26, 31, 33, 34]. Our meta-analysis showed that HCV infection was a risk factor for ICC with a pooled OR of 3.94 (95% CI 2.85-5.45; $I^2$=80%) (Fig. 4). The corresponding OR for Eastern and Western countries studies was 3.03 (95% CI 1.80-5.10; $I^2$=89%) and 5.13 (95% CI 3.81-6.91; $I^2$=39%), respectively (Table 2).

**Smoking**

Seventeen case-control studies investigated the association between smoking and ICC [5, 6, 9-13, 15, 17, 19-21, 28-30, 32, 34]. Of them, seven studies were from the United States, five from China, two from Korea, two from Japan, and one was from Italy. The research data were collected during the period from 1991 to 2014, involving a total of 731128 participants. Ten studies reported no significant association between smoking and ICC [6, 11, 17, 20, 21, 28-30, 32, 34], but the remaining seven studies showed a significant association [5, 9, 10, 12, 13, 15, 19]. Our meta-analysis showed that smoking was a risk factor for ICC with a pooled OR of 1.26 (95% CI 1.07-1.49; $I^2$=78%) (Fig. 5). The corresponding OR for Eastern and Western countries studies was 1.01 (95% CI 0.74-1.37;
$I^2 = 74\%$) and 1.49 (95% CI 1.21-1.83; $I^2 = 79\%$), respectively (Table 2).

**Alcohol consumption**

Eighteen case-control studies investigated the association between alcohol consumption and ICC [9-13, 15, 17, 19-23, 25, 28, 29, 31, 34, 35]. Of them, five studies were from the United States, six from China, two from Taiwan (China) and Korea, and one each was from Denmark, Japan and Italy. The research data were collected during the period from 1978 and 2013, involving a total of 795889 participants. Six of the 18 studies reported no significant association between alcohol consumption and ICC [15, 17, 21, 28, 31, 34], but the remaining twelve studies showed a significant association [9-13, 19, 20, 22, 23, 25, 29, 35]. Our meta-analysis showed that alcohol consumption was a risk factor for ICC with a pooled OR of 2.68 (95% CI 1.97-3.66; $I^2 = 87\%$) (Fig. 6). The corresponding OR for Eastern and Western countries studies was 1.99 (95% CI 1.30-3.06; $I^2 = 88\%$) and 4.28 (95% CI 2.56-7.15; $I^2 = 83\%$), respectively (Table 2).

**Hepatolithiasis**

Six case-control studies investigated the association between hepatolithiasis and ICC [5, 16, 17, 21, 28, 29]. Of them, one study was from the United States, three were from China and two from Korea. The research data were collected during the period from 1998 to 2013, involving a total of 6560 participants. Five studies performed in Eastern countries indicated a significant association between hepatolithiasis and ICC [16, 17, 21, 28, 29], but the remaining one study performed in the United States did not find such an association [5]. Our meta-analysis showed that hepatolithiasis was a risk factor for ICC with a pooled OR of 14.94 (95% CI 6.41–34.83; $I^2 = 66\%$) (Fig. 7).

**Choledochal cyst**

Five case-control studies investigated the association between choledochal cyst and ICC
Of them, three studies were from the United States, and one each was from Korea and Taiwan (China). The research data were collected during the period from 1993 to 2011, involving a total of 541645 participants. All five studies showed that choledochal cyst increased the ICC risk. Our meta-analysis further confirmed this significant association with a pooled OR of 21.67 (95% CI 10.83-43.36; $I^2=76\%$) (Fig. 8). The corresponding OR for studies in Eastern and Western countries was 13.37 (95% CI 4.31-41.50; $I^2=0\%$) and 25.61 (95% CI 11.02-59.50; $I^2=86\%$), respectively (Table 2).

**History of cholecystectomy**

Four case-control studies investigated the association between the history of cholecystectomy and ICC [9, 11, 16, 28]. Of them, two studies were from the United States and one each was from China and Korea. The research data were collected during the period from 1992 to 2013, involving a total of 326605 participants. Three of the four studies reported no significant association between the history of cholecystectomy and ICC [11, 16, 28], and the remaining one showed a significant association [9]. Our meta-analysis showed no significant association between the history of cholecystectomy and ICC with a pooled OR of 2.21 (95% CI 0.69-7.14; $I^2=87\%$) (Fig. 9). The corresponding OR for Eastern and Western countries studies was 1.32 (95% CI 0.60-2.91; $I^2=0\%$) and 3.15 (95% CI 0.45-22.21; $I^2=94\%$), respectively (Table 2).

**PSC**

Two case-control studies investigated the association between PSC and ICC, and both studies were conducted in the United States [5, 6]. The studies included a total case and control population of 7144 participants. Both studies showed that PSC increased the risk of ICC. Our meta-analysis further confirmed this significant association with a pooled OR of 93.91 (95% CI 43.99-200.47; $I^2=0\%$) (Fig. 10).
**DM**

Nineteen case-control studies investigated the association between DM and ICC [6, 9-13, 15-19, 21, 23, 25, 28, 29, 32, 34, 35]. Of them, six studies were from the United States and China, two each from Taiwan (China), Korea and Japan, and one each was from Denmark and other 10 European countries. The research data were collected during the period from 1978 to 2014, involving a total of 800979 participants. Eight studies reported no significant association between DM and ICC [11, 15-17, 32, 34-36], but the remaining 11 studies showed a significant association [6, 9, 10, 12, 13, 18, 19, 23, 25, 28, 29]. Our meta-analysis showed that DM was a risk factor for ICC with a pooled OR of 1.82 (95% CI 1.57-2.11; $I^2=86\%$) (Fig. 11). The corresponding OR for Eastern and Western countries studies was 1.91 (95% CI 1.44-2.54; $I^2=90\%$) and 1.71 (95% CI 1.54-1.89; $I^2=47\%$), respectively (Table 2).

**NAFLD**

Eight case-control studies investigated the association between NAFLD and ICC [6, 9, 12, 22, 23, 25, 32, 36]. Of them, one was from 10 European countries, three were from the United States, two from Taiwan (China), and one each was from China and Japan. The research data were collected during the period from 1992 to 2014, involving a total of 330896 participants. Two studies reported no significant association between NAFLD and ICC [22, 25], but the remaining six studies showed a significant association [6, 9, 12, 23, 32, 36]. Our meta-analysis showed that NAFLD was a risk factor for ICC with pooled OR of 2.23 (95% CI 1.65-3.02; $I^2=76\%$) (Fig. 12). The corresponding OR for Eastern and Western countries studies was 2.15 (95% CI 1.39-3.33; $I^2=64\%$) and 2.33 (95% CI 1.33-4.07; $I^2=86\%$), respectively (Table 2).

**Liver fluke infection**
Four case–control studies investigated the association between liver fluke infection and ICC [15, 16, 23, 28]. All the four studies were conducted in Eastern countries, including two in China, one in Taiwan (China) and one in Korea. The research data were collected during the period from 2000 to 2013, involving a total of 15568 participants. Only one of the four studies indicated a significant association [16], but our the meta-analysis indicated that liver fluke infection is a risk factor for ICC, with pooled OR of 2.28 (95% CI 1.30-4.01; $I^2=0\%$) (Fig. 13).

**Hypertension**

Eleven selective case-control studies investigated the association between hypertension and ICC [5, 9, 13, 15-19, 21, 28, 34]. Of them, three studies were from the United States, six from China, and one each was from Korea and Japan. The research data were collected during the period from 1991 to 2014, involving a total of 527487 participants. Seven studies reported no significant association between hypertension and ICC [15-18, 21, 28, 34], three studies showed an increased risk of ICC [9, 13, 19], and one study showed a reduced risk of ICC [5]. Our meta-analysis indicated no significant association between hypertension and ICC with the pooled OR of 1.01 (95% CI 0.75-1.36; $I^2=88\%$) (Fig. 14). Meanwhile, the corresponding OR for Eastern and Western countries studies was 1.02 (95% CI 0.75-1.38; $I^2=52\%$) and 1.03 (95% CI 0.58-1.81; $I^2=97\%$), respectively (Table 2).

**Aspirin use**

Three studies including two case-control studies and one cohort-based study investigated the association between aspirin use and ICC [6, 8, 25], including two in the United States and one in Taiwan (China). The research data were collected during the period from 2000 to 2014, involving a total of 1141708 participants. All the three studies reported that aspirin use did not increase ICC risk. Our meta-analysis further confirmed this finding with
a pooled OR of 0.74 (95% CI 0.38-1.41; $i^2=98\%$) (Fig. 15).

**Coffee consumption**

Only one study investigated the association between coffee consumption and ICC [14]. The cohort study was conducted in the United States, involving a total of 694,455 participants, with the data collected between 1992 and 2010. According to the study, drinking more than three cups of coffee a day could reduce the risk of HCC (HR=0.73; 95% CI 0.53-0.99), but no significant association was found between coffee consumption and ICC (HR=1.00; 95% CI 0.61-1.63).

**Publication bias and sensitivity analysis**

Risk factor analysis was conducted in more than 10 studies, and publication bias was investigated by funnel plots [37]. The results showed that the funnel plots were generally symmetrical, indicating the absence of publication bias (Supplementary Fig. 1). Sensitivity analysis was performed by removing one study at a time to calculate the pooled ORs of the remaining studies. No significant change was observed in the pooled OR after removing any one single study, demonstrating the reliability and stability of this meta-analysis.

**Discussion**

The incidence of ICC has increased progressively over the past few decades, but the risk factors for ICC have not been clearly defined. Liver fluke infection (Clonorchis sinensis or Opisthorchis viverrini) is regarded as a traditional infectious risk factor. Clonorchis sinensis and Opisthorchis viverrini infections are mainly prevalent in Southeast Asia, Far East and Eastern Europe [38]. Liver fluke infection was previously reported as a major risk affecting Eastern countries rather than Western countries [39]. The prevalence of some risk factors for ICC in these Eastern countries is the main reason for geographic disparity
Risk factors for ICC differ between Eastern and Western countries [41]. It is therefore important to define risk factors for better prevention of ICC in different geographic areas. Most studies appear to indicate HBV/HCV infection as an important risk factor for ICC, knowing that HBV/HCV infection can lead to chronic inflammation of the liver over time, while hepatolithiasis and liver fluke infection are also common causes of chronic inflammation. Similarly, our meta-analysis showed that these risk factors may increase the risk of ICC. In the 9th century, Rudolph Virchow, a Prussian scientist, first proposed the association of inflammation with the development of malignancies [42]. Molecular links between inflammation and tumors have also been reported in recent years. The expression of cycloxygenase 2 (COX2) is increased in chronic liver inflammation and found to be involved in hepatocarcinogenesis. Inflammatory mediator prostaglandin E 2 (PGE2) was found to be highly expressed in liver cancer cells. In addition, COX2 inhibitors were reported to inhibit the growth of liver cancer cells [43]. A previous study [6] reported that aspirin, as an effective non-steroidal anti-inflammatory drug (NSAID), was associated with decreased risk of ICC. However, our meta-analysis involving three relevant studies failed to find this correlation, possibly because of the limited number of the studies.

Increasing evidence has shown that cirrhosis increases the risk of ICC [44-47]. Further animal studies revealed that p53 deficiency, chronic bile duct injury and the fibrotic matrix microenvironment may work together to increase the risk of ICC [48], which is consistent with the finding of the present meta analysis. Meanwhile, our meta-analysis found that NAFLD was significantly associated with an increased risk of ICC, though the underlying mechanism remains unclear. Biologically, NAFLD promotes cholangiocarcinogenesis by inducing hepatic inflammation directly, or cirrhosis indirectly [49].

Several previous studies reported an association between choledochal cyst and
cholangiocarcinoma [50, 51]. Repeated damage and restoration of the biliary epithelium by regurgitation of pancreatic juice into the biliary system is presumed to be the cause of carcinogenesis [52]. Our meta-analysis showed that choledochal cyst is a strong risk factor for ICC.

Smoking has been shown to be associated with most known malignancies, such as lung cancer [53], breast cancer [54] and colorectal cancer [55]. Our meta-analysis also showed a significant association between smoking and ICC in studies performed in Western countries, but not in studies performed in Eastern countries. The significant geographical variations may be due to differences in genes and environments. Alcohol consumption is a known risk factor for ICC, knowing that alcohol can induce oxidative stress, ultimately causing liver parenchyma damage [56]. This significant association between alcohol consumption and ICC was also observed in our meta-analysis.

DM is a chronic disease with a high prevalence and highly suspected to increase the risk of several malignancies [57]. Our meta-analysis consistently showed that DM is a risk factor for ICC. The underlying biological mechanism is probably associated with the up-regulation of insulin-like growth factor-1 (IGF-1), which is known to promote the progression of malignancies [58]. As for the common chronic disease hypertension, our analysis failed to find a significant association with the increased risk of ICC.

It was found in our meta-analysis that ICC shares certain risk factors with HCC, such as cirrhosis, HBV/HCV infection [59, 60]. In addition, bile duct cells and hepatocytes differentiate from the same hepatic progenitor cells in both HBV-associated ICC and HBV-associated HCC, which is known as a common disease process for carcinogenesis [17]. Awareness of these similar risk factors may help understand the pathogenesis of ICC and the origin of ICC cells.

This review of ICC risks included 31 studies involving a large number of cases throughout
the world. However, there are still some limitations in this meta-analysis. First, we did not conduct separate analyses on liver fluke infection, PSC, hepatolithiasis, coffee and aspirin because of the limited number of studies. Second, we did not conduct separate meta-analyses for risk by gender, although there may be differences between different genders. The main reason is that most studies did not classify cases by sex. Finally, although we revealed a relationship between ICC and smoking, alcohol consumption and aspirin use, the duration of exposure to these risk factors varies with individual studies, and therefore future studies are required to focus on the association between the duration of exposure to these risk factors and ICC.

Conclusions

Our meta-analysis indicates that cirrhosis, HBV/HCV infection, alcohol consumption, hepatolithiasis, choledochal cyst, PSC, DM, NAFLD, liver fluke infection and smoking are significantly associated with the increased risk for ICC. A non-significant association was found with hypertension, the history of cholecystectomy, coffee and aspirin, which needs to be verified by further study. As for PSC, liver fluke infection and smoking, geographic and ethnic differences may play a role in the development of ICC.

Abbreviations

**ICC:** intrahepatic cholangiocarcinoma  
**HCC:** hepatocellular carcinoma  
**PRISMA:** Preferred reporting items for systematic reviews and meta-analyses  
**OR:** odds ratio  
**CI:** confidence intervals;  
**HBV:** hepatitis B virus  
**HCV:** hepatitis C virus;  
**PSC:** primary sclerosing cholangitis  
**DM:** diabetes mellitus  
**NAFLD:** non-alcoholic fatty liver disease

Declarations
Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Input data for the analyses are available from the corresponding author on request.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

WS, HB and ZY participated in the design and coordination of the study, carried out the critical appraisal of studies and wrote the manuscript. HB, LY, and CZ developed the literature search, carried out the extraction of data, assisted in the critical appraisal of included studies and assisted in writing up, WS and YZ carried out the statistical analysis of studies. All authors read and approved the final manuscript.

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**Tables**

**Table 1: Characteristics of included trials.**

| Risk factor | Author/year of publication | Region | Dates       | Total |
|-------------|-----------------------------|--------|-------------|-------|
| HBV         | Chaiteerakij, 2013           | US     | 2000-2010   | 612   |
|             | Chang,2013                   | Taiwan | 2004-2008   | 2978  |
|             | Choi,2006                    | Korea  | 2003-2004   | 51    |
|             | Choi,2016                    | US     | 2000-2014   | 1169  |
|             | Donato,2001                  | Italy  | 1995-2000   | 23    |
| Year      | Country | Time Period | Sample Size |
|-----------|---------|-------------|-------------|
| 2003-2009 | Taiwan  |             | 4695        |
| 2000-2004 | Korea   |             | 622         |
| 1991-2005 | Taiwan  |             | 160         |
| 2007-2013 | Korea   |             | 83          |
| 2000-2008 | China   |             | 87          |
| 2002-2009 | China   |             | 98          |
| 2000-2011 | US      |             | 2092        |
| 1993-1999 | US      |             | 625         |
| 1998-2008 | China   |             | 102         |
| 2002-2014 | China   |             | 136         |
| 1991-2002 | Japan   |             | 50          |
| 1993-2013 | China   |             | 127         |
| 2004-2006 | China   |             | 312         |
| 2000-2006 | Japan   |             | 317         |
| 1991-2000 | Korea   |             | HBV cohort 2519 |
| 1983-2000 | Taiwan  |             | HBV cohort 289992 |

### HCV

- Chang, 2013: Taiwan (2000-2010, 612)
- Choi, 2006: Korea (2003-2004, 51)
- Choi, 2016: US (2000-2014, 1169)
- Donato, 2001: Italy (1995-2000, 24)
- Hu, 2017: Taiwan (2003-2009, 4695)
- Lee, 2008: Korea (2000-2004, 622)
- Lee, 2009: Taiwan (1991-2005, 160)
- Lee, 2015: Korea (2007-2013, 83)
- Liu, 2011: China (2000-2008, 87)
- Paetnick, 2017: US (2000-2011, 2092)
- Shaib, 2005: US (1993-1999, 625)
- Welzel, 2007: US (1993-1999, 535)
- Welzel, 2011: US (1993-2005, 743)
- Xiong, 2018: China (2002-2014, 136)
- Yamamoto, 2004: Japan (1991-2002, 50)
- Zhang, 2014: China (1993-2013, 127)
- Zhou, 2008: China (2004-2006, 312)
- El-Serag, 2009: US (1988-2004, HCV cohort 146394)
- Tanaka, 2010: Japan (1991-2000, HCV cohort 1927)

### Cirrhosis

- Chaiteerakij, 2013: US (2000-2010, 612)
- Chang, 2013: Taiwan (2004-2008, 2978)
- Choi, 2016: US (2000-2014, 1169)
- Hu, 2017: Taiwan (2003-2009, 4695)
- Lee, 2008: Korea (2000-2004, 622)
- Lee, 2009: Taiwan (1991-2005, 160)
- Peng, 2011: China (2002-2009, 98)
- Paetnick, 2017: US (2000-2011, 2092)
- Shaib, 2005: US (1993-1999, 625)
- Welzel, 2011: US (1993-2005, 743)
- Welzel, 2006: Denmark (1978-1991, 764)
- Welzel, 2007: US (1993-1999, 535)
- Wu, 2012: China (1998-2010, 102)
- Xiong, 2018: China (2002-2014, 136)
- Yamamoto, 2004: Japan (1991-2002, 50)
- Zhou, 2010: China (2003-2006, 317)
- Brand, 2013: Italy (2006-2010, 41)

### Smoking

- Chaiteerakij, 2013: US (2000-2010, 612)
- Choi, 2016: US (2000-2014, 1169)
- Kinoshita, 2016: Japan (1995-2014, 34)
- Lee, 2008: Korea (2000-2004, 622)
- Lee, 2015: Korea (2007-2013, 83)
- Liu, 2011: China (2000-2008, 87)
- Paetnick, 2017: US (2000-2011, 2092)
- Shaib, 2005: US (1993-1999, 625)
- Shaib, 2007: US (1992-2002, 83)
- Tao, 2010: China (1998-2008, 61)
- Welzel, 2007: US (1993-1999, 535)
- Welzel, 2011: US (1993-2005, 743)
- Xiong, 2018: China (2002-2014, 136)
- Yamamoto, 2004: Japan (1991-2002, 50)
- Zhang, 2014: China (1993-2013, 127)
- Zhou, 2008: China (2004-2006, 312)
- Zhou, 2010: China (2003-2006, 317)
- Tanaka, 2010: Japan (1991-2000, HBV cohort 2519)

### Alcohol use

- Chang, 2013: Taiwan (2004-2008, 2978)
- Donato, 2001: Italy (1995-2000, 26)
| Year   | Author | Country | Start Year | End Year | Count |
|--------|--------|---------|------------|----------|-------|
| 2017   | Huang  | Taiwan  | 2003-2009  | 4695     |       |
| 2008   | Lee    | Korea   | 2000-2004  | 622      |       |
| 2015   | Lee    | Korea   | 2007-2013  | 83       |       |
| 2011   | Liu    | China   | 2000-2008  | 87       |       |
| 2017   | Petrick| US      | 2000-2011  | 2092     |       |
| 2005   | Shiba  | US      | 1993-1999  | 625      |       |
| 2007   | Shiba  | US      | 1992-2002  | 83       |       |
| 2010   | Tao    | China   | 1998-2008  | 61       |       |
| 2007   | Welzel | US      | 1993-1999  | 535      |       |
| 2011   | Welzel | US      | 1993-2005  | 743      |       |
| 2006   | Welzel | Denmark | 1978-1991  | 764      |       |
| 2018   | Xiong  | China   | 2002-2014  | 136      |       |
| 2004   | Yamamoto| Japan  | 1991-2002  | 50       |       |
| 2014   | Zhang  | China   | 1993-2013  | 127      |       |
| 2008   | Zhou   | China   | 2004-2006  | 312      |       |
| 2010   | Zhou   | China   | 2003-2006  | 317      |       |
| 2015   | Chang  | Korea   | 2007-2013  | 83       |       |
| 2008   | Shaib  | US      | 1993-1999  | 535      |       |
| 2007   | Shaib  | US      | 1992-2002  | 83       |       |
| 2016   | Kinoshita| Japan  | 1995-2014  | 34       |       |
| 2016   | Choi   | US      | 2000-2014  | 1169     |       |
| 2016   | Stepien| 10 European countries | 1992-2000 | 34       |       |
| 2017   | Huang  | Taiwan  | 2003-2009  | 4695     |       |
| 2017   | Petrick| US      | 2000-2011  | 2092     |       |
| 2008   | Zhou   | Korea   | 2000-2004  | 622      |       |
| 2010   | Tao    | China   | 2004-2006  | 312      |       |
| 2011   | Peng   | China   | 2002-2009  | 98       |       |
| 2012   | Chaiteerakij | US   | 2000-2010  | 612      |       |
| 2015   | Lee    | Korea   | 2007-2013  | 83       |       |
| 2008   | Lee    | Korea   | 2000-2004  | 622      |       |
| 2011   | Lee    | US      | 1993-2005  | 743      |       |
| 2017   | Welzel | US      | 2000-2011  | 2092     |       |
| 2012   | Chaiteerakij | US   | 2000-2010  | 612      |       |
| 2013   | Chang  | Taiwan  | 2004-2008  | 2978     |       |
| 2017   | Petrick| US      | 2000-2011  | 2092     |       |
| 2007   | Shaib  | US      | 1992-2002  | 83       |       |
| 2016   | Peng   | China   | 2002-2009  | 98       |       |
| 2015   | Lee    | Korea   | 2007-2013  | 83       |       |
| 2008   | Peng   | China   | 2002-2009  | 98       |       |
| 2017   | Petrick| US      | 2000-2011  | 2092     |       |
| 2016   | Shaib  | US      | 1993-1999  | 625      |       |
| 2007   | Shaib  | US      | 1992-2002  | 83       |       |
| 2010   | Tao    | China   | 1998-2008  | 61       |       |
| 2006   | Welzel | Denmark | 1978-1991  | 764      |       |
| 2007   | Welzel | US      | 1993-1999  | 535      |       |
| 2011   | Welzel | US      | 1993-2005  | 743      |       |
| 2012   | Wu     | China   | 1998-2010  | 102      |       |
| 2018   | Xiong  | China   | 2002-2014  | 136      |       |
| 2004   | Yamamoto| Japan  | 1991-2002  | 50       |       |
| 2006   | Zhou   | China   | 2004-2006  | 312      |       |
| 2013   | Chang  | Korea   | 2007-2013  | 83       |       |
| 2015   | Lee    | Korea   | 2000-2008  | 87       |       |
| 2011   | Liu    | China   | 2002-2009  | 87       |       |
| 2011   | Peng   | US      | 2000-2011  | 2092     |       |
| 2010   | Tao    | China   | 1998-2008  | 61       |       |
| 2011   | Welzel | US      | 1993-2005  | 743      |       |
| 2012   | Wu     | China   | 1998-2010  | 835      |       |
| 2018   | Xiong  | China   | 2002-2014  | 136      |       |
| 2004   | Yamamoto| Japan  | 1991-2002  | 50       |       |
| 2008   | Zhou   | China   | 2004-2006  | 312      |       |
| 2013   | Chang  | Taiwan  | 2004-2008  | 2798     |       |
| 2015   | Lee    | Korea   | 2007-2013  | 83       |       |
| 2011   | Liu    | China   | 2000-2008  | 87       |       |
| 2011   | Peng   | China   | 2002-2009  | 98       |       |
| Risk Factor                  | Region   | Number of studies | Number of participants | OR   | 95% CI     |
|-----------------------------|----------|-------------------|------------------------|------|------------|
| HBV infection               | East     | 16                | 2010560                | 4.56 | 3.33-6.24  |
|                             | West     | 7                 | 621955                 | 2.90 | 1.70-4.97  |
| HCV infection               | East     | 11                | 224944                 | 3.12 | 1.84-5.18  |
|                             | West     | 10                | 1444279                | 5.04 | 3.74-6.98  |
| Cirrhosis                   | East     | 9                 | 73135                  | 8.97 | 4.91-16.1  |
|                             | West     | 7                 | 728144                 | 16.38| 9.12-30.1  |
| Smoking                     | East     | 9                 | 6296                   | 1.01 | 0.74-1.37  |
|                             | West     | 8                 | 724632                 | 1.49 | 1.21-1.85  |
| Alcohol use                 | East     | 11                | 73721                  | 1.99 | 1.30-2.90  |
|                             | West     | 7                 | 722168                 | 4.28 | 2.56-7.10  |
| choledochal cyst            | East     | 2                 | 18000                  | 13.37| 4.31-44.2  |
|                             | West     | 3                 | 523645                 | 25.61| 11.03-57.7 |
| History of cholecystectomy  | East     | 2                 | 543                    | 1.32 | 0.60-2.68  |
|                             | West     | 2                 | 326062                 | 3.15 | 0.45-22.4  |
| Diabetes mellitus           | East     | 12                | 73723                  | 1.91 | 1.44-2.54  |
|                             | West     | 7                 | 727256                 | 1.71 | 1.54-1.89  |
| Hypertension                | East     | 8                 | 3878                   | 1.02 | 0.75-1.42  |
|                             | West     | 3                 | 523609                 | 1.03 | 0.58-1.85  |
| NAFLD                       | East     | 4                 | 67581                  | 2.15 | 1.39-3.30  |
|                             | West     | 4                 | 435099                 | 2.33 | 1.33-4.07  |

HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence intervals
Figure 1

Flowchart of study selection.
**Figure 2**

Forest plots of studies evaluating the association between cirrhosis and ICC.

**Figure 3**

Forest plots of studies evaluating the association between HBV infection and ICC.
### Figure 4

Forest plots of studies evaluating the association between HCV infection and ICC.

| Study or Subgroup   | ICC Events | No ICC Events | Total Events | Total Weight | Odds Ratio M-H, Random, 95% CI |
|---------------------|------------|---------------|--------------|--------------|-------------------------------|
| Chaiterakij, 2013   | 13         | 612           | 2            | 594          | 3.0% [1.44, 28.59]             |
| Chang, 2013         | 193        | 2978          | 138          | 11912        | 8.2% [4.73, 7.38]              |
| Choi, 2006          | 1          | 51            | 1            | 51           | 1.2% [0.06, 16.43]             |
| Donato, 2001        | 6          | 24            | 50           | 824          | 4.8% [1.96, 13.57]             |
| El-Serag, 2009      | 14         | 146394        | 23           | 572293       | 6.3% [1.22, 4.62]              |
| Huang, 2017         | 112        | 4695          | 541          | 46942        | 8.2% [1.71, 2.57]              |
| Lee, 2008           | 12         | 622           | 47           | 2488         | 6.4% [0.54, 1.94]              |
| Lee, 2009           | 21         | 160           | 10           | 160          | 5.6% [1.03, 4.98]              |
| Lee, 2015           | 5          | 83            | 3            | 166          | 3.1% [0.81, 14.95]             |
| Liu, 2011           | 1          | 87            | 3            | 228          | 1.6% [0.09, 8.50]              |
| Petrick, 2017       | 58         | 2092          | 2161         | 323615       | 8.0% [3.26, 5.53]              |
| Shaib, 2005         | 5          | 625           | 161          | 90834        | 5.2% [1.86, 11.10]             |
| Shaib, 2007         | 5          | 83            | 236          | 2.8% [1.43, 39.43] |
| Tanaka, 2010        | 1          | 1927          | 8            | 150368       | 1.9% [1.22, 78.06]             |
| Welzel, 2007        | 5          | 535           | 142          | 102792       | 5.1% [2.76, 16.70]             |
| Welzel, 2011        | 20         | 743           | 616          | 195953       | 7.3% [5.59, 13.77]             |
| Xiong, 2018         | 5          | 136           | 8            | 606          | 4.2% [0.92, 8.86]              |
| Yamamoto, 2004      | 18         | 50            | 7            | 205          | 4.9% [1.61, 41.12]             |
| Zhang, 2014         | 2          | 127           | 1            | 254          | 1.5% [0.36, 45.07]             |
| Zhou, 2008          | 9          | 312           | 6            | 438          | 4.5% [0.75, 6.07]              |

Total (95% CI): 163505 / 1505718; 100.0% 3.94 [2.85, 5.45]

Total events: 529 / 3947

Heterogeneity: Tau² = 0.32; Chi² = 100.02; df = 20 (P < 0.00001); I² = 80%

Test for overall effect: Z = 8.32 (P < 0.00001)

### Figure 5

Forest plots of studies evaluating the association between smoking and ICC.

| Study or Subgroup   | ICC Events | No ICC Events | Total Events | Total Weight | Odds Ratio M-H, Random, 95% CI |
|---------------------|------------|---------------|--------------|--------------|-------------------------------|
| Brand, 2013         | 21         | 41            | 71           | 149          | 3.7% [0.58, 2.30]             |
| Chaiterakij, 2013   | 308        | 612           | 255          | 594          | 8.3% [1.07, 1.69]             |
| Choi, 2016          | 499        | 1169          | 1929         | 4769         | 9.2% [1.06, 1.25]             |
| Knoshita, 2016      | 11         | 34            | 35           | 69           | 2.8% [0.20, 11.10]            |
| Lee, 2008           | 293        | 622           | 1135         | 2488         | 8.8% [0.89, 1.27]             |
| Lee, 2015           | 16         | 83            | 43           | 116          | 3.9% [0.21, 0.79]             |
| Liu, 2011           | 20         | 87            | 29           | 228          | 4.1% [1.09, 3.86]             |
| Petrick, 2017       | 268        | 2092          | 33789        | 323615       | 9.3% [1.11, 1.43]             |
| Shaib, 2005         | 24         | 625           | 1927         | 90834        | 6.2% [1.22, 2.78]             |
| Shaib, 2007         | 20         | 83            | 37           | 236          | 4.3% [0.92, 3.15]             |
| Tao, 2010           | 18         | 61            | 122          | 380          | 4.5% [0.49, 1.60]             |
| Welzel, 2007        | 12         | 535           | 1212         | 102782       | 4.6% [1.08, 3.42]             |
| Welzel, 2011        | 78         | 743           | 9647         | 195953       | 8.2% [1.79, 2.87]             |
| Xiong, 2018         | 42         | 136           | 105          | 606          | 6.1% [1.40, 3.25]             |
| Yamamoto, 2004      | 17         | 50            | 90           | 205          | 4.0% [0.34, 1.26]             |
| Zhang, 2014         | 83         | 127           | 145          | 254          | 5.9% [0.91, 2.21]             |
| Zhou, 2008          | 43         | 312           | 67           | 438          | 6.2% [0.59, 1.34]             |

Total (95% CI): 7412 / 723716; 100.0% 1.26 [1.07, 1.49]

Total events: 1773 / 50638

Heterogeneity: Tau² = 0.08; Chi² = 71.99; df = 16 (P < 0.00001); I² = 78%

Test for overall effect: Z = 2.70 (P = 0.007)
Figure 6

Forest plots of studies evaluating the association between alcohol consumption and ICC.

Figure 7

Forest plots of studies evaluating the association between hepatolithiasis and ICC.
Figure 8

Forest plots of studies evaluating the association between choledochal cyst and ICC.

Figure 9

Forest plots of studies evaluating the association between history of cholecystectomy and ICC.

Figure 10

Forest plots of studies evaluating the association between PSC and ICC.
Figure 11

Forest plots of studies evaluating the association between diabetes mellitus and ICC.

Figure 12

Forest plots of studies evaluating the association between non-alcoholic fatty liver disease and ICC.
Figure 13

Forest plots of studies evaluating the association between liver fluke infection and ICC.

Figure 14

Forest plots of studies evaluating the association between hypertension and ICC.

Figure 15

Forest plots of studies evaluating the association between aspirin use and ICC.

Additional file 1: Data S1. Funnel plots demonstrate symmetry for risk factor analysis was conducted in more than 10 studies.
Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Additional file 2.docx
Additional file 1.docx