



Systematic review and meta-analysis of the association between gallstones and cholecystectomy with liver cancer

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Abstract

Introduction: Cholelithiasis and related treatments are associated with several gastrointestinal cancers. Thus, the present systematic review and meta-analysis aimed to investigate the relationship between cholelithiasis and cholecystectomy with the risk of liver cancer.

Materials and Methods: The present study is a systematic review and meta-analysis conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We performed a search on the databases of Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar until January 21, 2024. Moreover, the statistical analysis was performed using the STATA 14, and the significance level was set at $P < 0.05$.

Results: The present meta-analysis included 15 studies with a total sample size of 1426704 participants. According to our results, a significant association between cholelithiasis and liver cancer (OR: 1.76, 95% CI: 1.52, 2.03), as well as cholecystectomy and liver cancer (OR: 1.55, 95% CI: 1.29, 1.87) were detected. Moreover, the relationship between cholelithiasis and liver cancer was significant in cohort studies (OR: 1.76, 95% CI: 1.51, 2.04) and insignificant in case-control studies (OR: 1.69, 95% CI: 0.86). However, there was a significant relationship between cholecystectomy and liver cancer in both the cohort (OR: 1.62, 95% CI: 1.29, 2.04) and case-control studies (OR: 1.26, 95% CI: 1.12, 1.41).

Conclusion: In conclusion, cholelithiasis and cholecystectomy increased the risk of liver cancer by 76% and 55%, respectively. Thus, they can be considered as risk factors for liver cancer.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024508640) and Research Registry (UIN: reviewregistry1787) website.

Introduction

Cholelithiasis is one of the most common gastrointestinal diseases, with an estimated prevalence of 10% in Europe and the United States and 5%-10% in Asia (1,2). The disease usually manifests itself with nausea, diarrhea, anorexia, and other gastrointestinal symptoms (3). Moreover, the related risk factors include age, gender, race, family history of cholelithiasis, and metabolic disorders, such as obesity, hypertension, and type 2 diabetes mellitus (4). Cholelithiasis is a common gastrointestinal cause of

hospitalization, causing a considerable economic and healthcare-related burden (5,6). According to studies on the Western populations, it has been associated with an elevated risk of gastrointestinal malignancies, including colon, liver, pancreatic, gallbladder, and biliary tract cancers (7).

Defined as the removal of the gallbladder, cholecystectomy is one of the most common surgical procedures (8). However, it can be associated with several complications that impose serious threats on the patients' health and quality of life (9). For example,



Key point

In a meta-analysis, we found that cholelithiasis and cholecystectomy both increased the risk of liver cancer by 76% and 55%, respectively, and they can be considered risk factors for liver cancer. Therefore, it is crucial for healthcare providers to closely monitor patients who have a history of cholelithiasis or cholecystectomy for signs of liver cancer. Early detection and intervention can significantly improve outcomes for these individuals. Additionally, more research is needed to fully understand the relationship between these conditions and liver cancer development. By increasing awareness and conducting further studies, we can better prevent and manage this serious health concern.

cholecystectomy is usually associated with bile duct dilation and increased bile duct pressure, causing chronic inflammation (10). In addition, cholelithiasis and related therapies are associated with the development of multiple gastrointestinal cancers (11).

As a prevalent type of malignancy, primary liver cancer is the fifth cause of global cancer-related mortality, showing a growing incidence and mortality (12). According to the latest reports in 2020, it is estimated that the related incidence and mortality will increase by more than 55% by 2040 (13). Therefore, the present meta-analysis and systematic review intended to investigate the association of cholelithiasis and/or cholecystectomy with liver cancer.

Materials and Methods

The present study is a systematic review and meta-analysis conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14). In addition, the related protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

We performed a search on the databases of Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar until January 21, 2024, without any location-related filters. The search was performed using the following Medical Subject Heading (MeSH) terms and their equivalents: "Gallstones", "Common Bile Duct Gall Stone", "Biliary Calculi", "Cholecystectomy", "Liver Neoplasms", and "Liver Cancer". The keywords were combined using the "AND" and "OR" operators. The references of the included studies were investigated as well. For example, the search strategy in the Web of Science database was as follows; "Gallstones" OR "Common Bile Duct Gall Stone" OR "Biliary Calculi" OR "Cholecystectomy" (Title) AND "Liver Neoplasms" OR "Liver Cancer" (Topic).

PICO component

- Population: The population of the present systematic review included studies investigating the relationship between cholelithiasis and/or cholecystectomy with

liver cancer. Intervention/Exposure: Colelithiasis or cholecystectomy.

- Comparison: healthy population.
- Outcomes: The odds ratio (OR) of the relationship between cholelithiasis and/or cholecystectomy with liver cancer.

Inclusion criteria

The present systematic review included all cohort and case-control studies evaluating the relationship between cholelithiasis and/or cholecystectomy with liver cancer.

Exclusion criteria

The repetitive studies, reviews, low-quality studies, studies with unavailable full texts, those reporting qualitative data, and those lacking the necessary data for data analysis were excluded from the present systematic review.

Quality assessment

The studies underwent quality assessment using the Newcastle-Ottawa Scale (NOS) (15), which included three subscales: participant selection, comparability, and outcome evaluation. The studies with at least 6 stars were considered high-quality studies and were included in the present systematic review. Then, two researchers evaluated the disagreements regarding the answers to the questions and resolved them.

Data extraction

The data extraction was conducted by two researchers, and the data included the authors' names, participants' age, study location and time, study type, sample size, the OR of the relationship between cholelithiasis and/or cholecystectomy with liver cancer, and the related 95% confidence interval (CI). Moreover, a third researcher evaluated the extracted data and corrected the defects.

Statistical analysis

An OR logarithm was assigned to each study, and the inter-study heterogeneity was classified using the I^2 index (less than 25%: low heterogeneity, 25%-75%: moderate heterogeneity, more than 75%: severe heterogeneity). Furthermore, the present systematic review used the random effects model. Finally, the statistical analysis was performed using the STATA 14, and the significance level was set at $P < 0.05$.

Results

A total of 332 studies were obtained by searching the mentioned databases. However, 121 studies were repetitive. Moreover, the abstracts of the studies were evaluated, and nine studies were excluded due to unavailable full texts, while 21 studies were excluded because they lacked the necessary data for data analysis. In addition, 166 studies were excluded because of fulfilling other exclusion criteria.

Finally, 15 studies with the desired quality were included in the final analysis (Figure 1).

The present study evaluated 15 observational studies (13 cohorts and 2 case-control studies) that included 1 426 704 participants and were published during 1996-2022. Moreover, the smallest sample size was 306, while the largest study included 704 437 participants (Table 1).

According to our findings, cholelithiasis increases the risk of liver cancer (OR: 1.76, 95% CI: 1.52, 2.03), as presented in Figure 2. Moreover, subgroup analysis showed that cholelithiasis elevated the risk of liver cancer in cohort studies (OR: 1.76, 95% CI: 1.51, 2.04), while no significant relationship was found between these two variables in case-control studies (OR: 1.69, 95% CI: 0.86, 3.35, Figure 3).

Regarding the location of the study, the relationship between cholelithiasis and the risk of liver cancer was not significant in Denmark (OR: 1.25, 95% CI: 0.63, 2.47), Italy, and Switzerland (OR: 1.17, 95% CI: 0.83, 1.65). However, a significant association was found in the United States (OR: 2.01, 95% CI: 1.39, 2.91), the Republic of China (OR: 1.84, 95% CI: 1.54, 2.20), the Republic of Korea (OR: 2.21, 95% CI: 1.93, 2.54), and Taiwan (OR: 1.90, 95% CI: 1.59, 2.27, Figure 4).

As presented in Figure 5, we found a significant association between cholecystectomy and liver cancer

(OR: 1.55, 95% CI: 1.29, 1.87), which was evident in both the cohort (OR: 1.62, 95% CI: 1.29, 2.04) and case-control studies (OR: 1.26, 95% CI: 1.12, 1.41, Figure 6).

However, the relationship between cholecystectomy and liver cancer was not significant in the Republic of China (OR: 2.48, 95% CI: 0.98, 6.28) and Taiwan (OR: 1.96, 95% CI: 0.71, 5.41), while it was significant in the United States (OR: 1.27, 95% CI: 1.13, 1.41), the Republic of Korea (OR: 1.59, 95% CI: 1.26, 2.01), Denmark (OR: 1.40, 95% CI: 1.14, 1.71), Sweden (OR: 1.24, 95% CI: 1.11, 1.38), and the United Kingdom (OR: 1.45, 95% CI: 1.10, 1.91, Figure 7).

Finally, using the meta-regression, we found no significant relationship between the sample size and OR of the relationship between cholelithiasis and liver cancer ($P=0.566$, Figure 8).

Discussion

The present study combined the results of 15 cohort and case-control studies, showing that cholelithiasis and cholecystectomy increased the risk of liver cancer by 76% and 55%, respectively. However, it is necessary to perform further research to confirm these findings.

According to the study by Sun et al, a history of cholecystectomy due to cholelithiasis increases the risk of pancreatic cancer (RR: 1.30, 95% CI: 1.14-1.48) (31), while a meta-analysis by Yang et al, which included 8 studies,

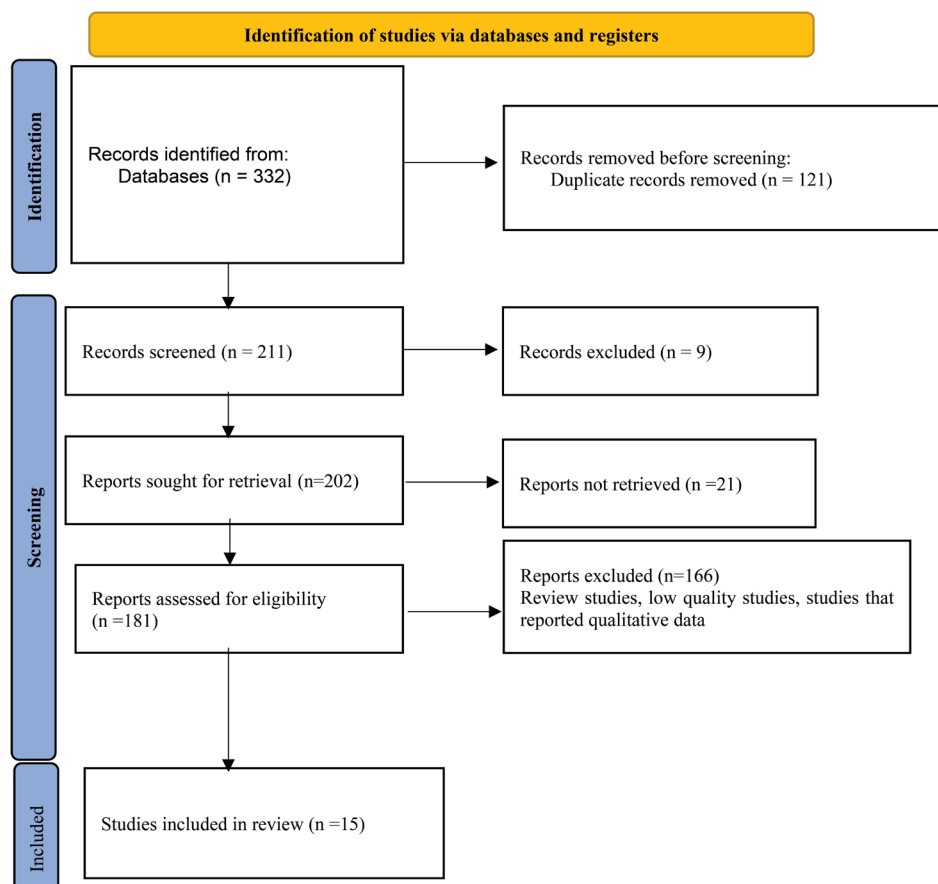


Figure 1. The PRISMA flow chart of study selection.

Figure 1. The PRISMA flow chart of study selection.

Table 1. A summary of the information extracted from the reviewed articles

First author, year	Place	Design of study	Sample size	Mean age (year)	Duration of study	Odds ratio between gallstones and risk of liver cancer			Odds ratio between cholecystectomy and risk of liver cancer		
						OR	Low	Up	OR	Low	Up
Luo X, 2022 (16)	USA	Cohort	164865	NR	1982-2012	1.6	1.14	2.26	1.33	0.9	1.95
Pang Y, 2021 (17)	China	Cohort	39298	NR	2004–2008	2.01	1.78	2.26	NR	NR	NR
Huang D, 2020 (18)	Korea	Cohort	704437	41.7	Between 2002 and 2015	2.21	1.92	2.53	1.59	1.26	2.01
Liu T, 2020 (19)	China	Cohort	95021	18-98	Between Jun. 2006 to Oct. 2007	1.77	1.05	2.94	5.25	1.95	14.17
Zhao X, 2020 (20)	China	Cohort	81110	NR	2006-2007	2.28	1.2	4.33	2.81	0.68	11.51
Torp NM, 2020 (21)	Denmark	Cohort	132771	>18	1996 to 2015	0.51	0.28	0.93	NR	NR	NR
Nogueira L, 2014 (22)	USA	Case-Control	10219	NR	1992–2005	2.35	2.18	2.54	1.26	1.12	1.41
Vogtmann E, 2014 (23)	China	Cohort	13115	57.7	1996-2010	1.49	1.15	1.94	1.38	0.92	2.07
Chen YK, 2014 (24)	Taiwan	Cohort	77725	55	2000 to 2010	1.9	1.59	2.27	1.17	0.9	1.52
Kao WY, 2013 (25)	Taiwan	Cohort	2590	62.8	1996–2008	NR	NR	NR	3.29	2.55	4.18
Tavani A, 2012 (26)	Italy and Switzerland	Case-Control	2640	NR	1982–2009	1.17	0.83	1.65	NR	NR	NR
Lagergren J, 2011 (27)	Sweden	Cohort	333	52	1965–2008	NR	NR	NR	1.24	1.11	1.38
Goldacre MJ, 2005 (28)	UK	Cohort	306	NR	from 1 Jan. 1963 to 31 Mar. 1999	NR	NR	NR	1.45	1.09	1.9
Chow WH, 1999 (29)	Denmark	Cohort	60176	61	1977 to 1989	2	1.2	3.1	1.4	1.2	1.8
Johansen C, 1996 (30)	Denmark	Cohort	42098	NR	1977-1989	1.7	1.3	2.2	NR	NR	NR

NR: Not reported; OR: Odds ratio.

reported cholecystectomy as a risk factor for gastric cancer (RR: 1.11, 95% CI: 1.03-1.20) (32). Moreover, another meta-analysis by Polychronidis et al showed the dramatically increasing effect of cholelithiasis and cholecystectomy on the risk of colorectal cancer (RR: 1.15, 95% CI: 1.08-1.24) (33). In general, several previous meta-analyses have shown that cholelithiasis and cholecystectomy are risk factors for multiple gastrointestinal malignancies, such as gastric, pancreatic, and colorectal cancers.

However, a meta-analysis by Chen et al, which included 7 studies, showed a reduced risk of colorectal cancer in cholelithiasis patients who had undergone cholecystectomy (RR: 0.80, 95% CI: 0.65-0.99) (11), which was not compatible with our findings. Interestingly, the meta-analysis by Chen et al showed that cholelithiasis and cholecystectomy are not risk factors for cancers and they can even prevent it.

On the other hand, a meta-analysis by Wang et al,

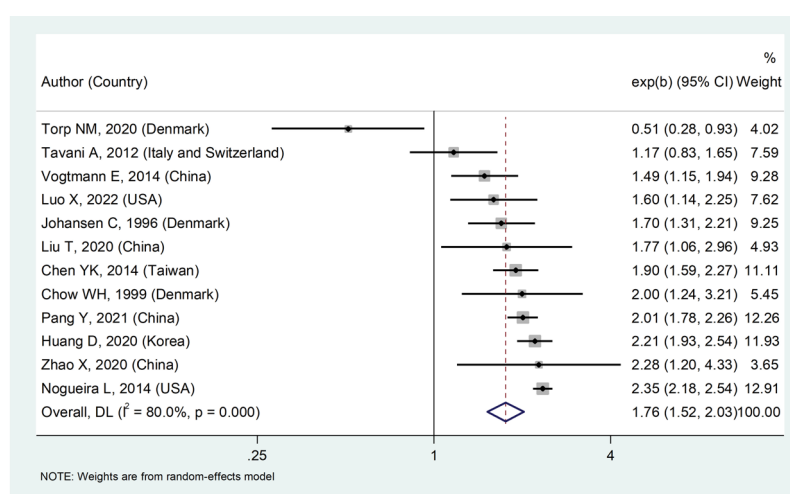


Figure 2. Forest plot of the association between gallstones and liver neoplasms.

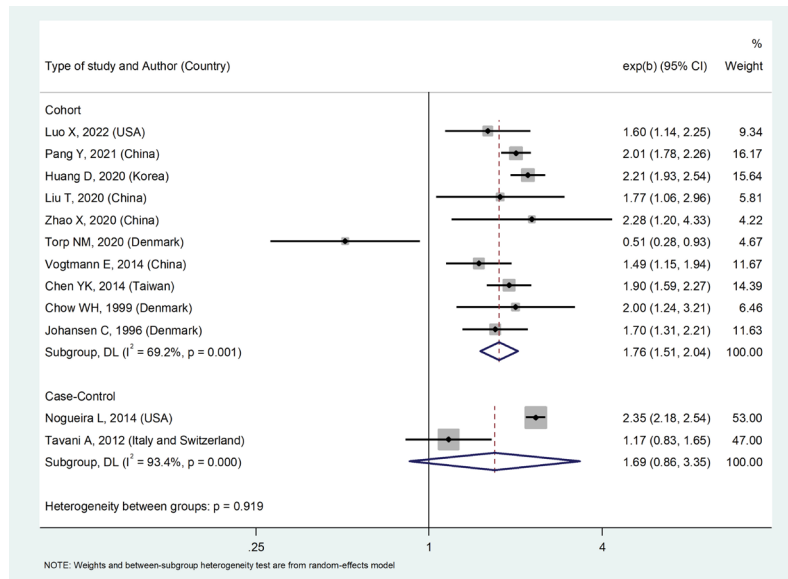


Figure 3. Forest plot of the association between gallstones and liver neoplasms by design of study.

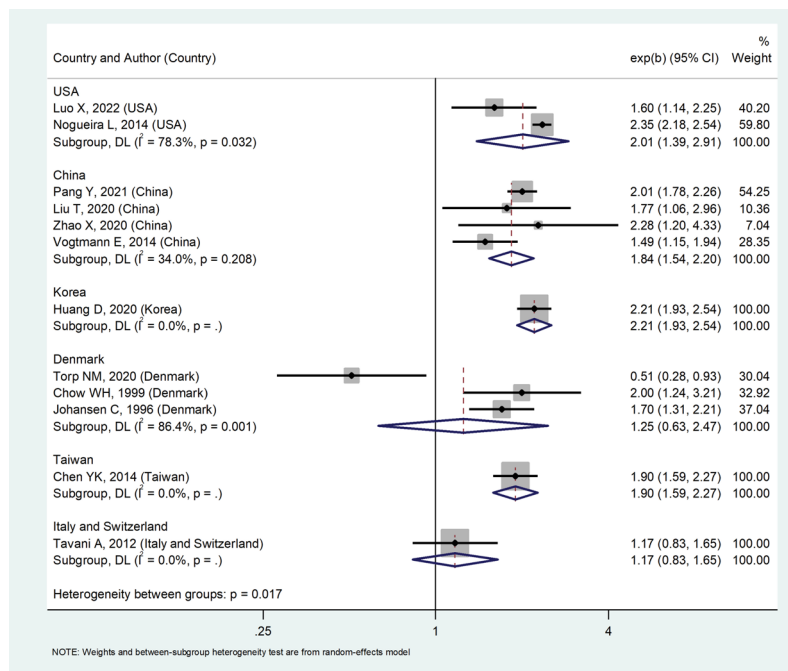


Figure 4. Forest plot of the association between gallstones and liver neoplasms by place of study.

reported ORs of 2.66 (95% CI: 2.05-3.28) and 1.47 (CI: 1.24-1.71) for the relationships between cholelithiasis and cholecystectomy with liver cancer, respectively (34). Moreover, another study by Liu et al reported an increased risk of liver cancer in patients with a history of cholelithiasis (OR: 2.54, 95% CI, 1.71-3.79) or cholecystectomy (OR: 1.62, 95% CI: 1.29-2.02) (35). In addition, Guo et al showed that cholecystectomy (RR: 1.59, 95% CI: 1.01-2.51) and cholelithiasis (RR: 5.40, 95% CI: 3.69-7.89) increased the chance of liver cancer (36). These studies were compatible with our results, showing that cholelithiasis and cholecystectomy are serious risk

factors for liver cancer.

A previous meta-analysis by Luo et al showed that cholecystectomy could increase the risk of hepatic disease (OR: 1.63, 95% CI: 1.34-1.98), non-alcoholic fatty liver disease (NAFLD) (OR: 1.54, 95% CI: 1.18-2.01), hepatic cirrhosis (OR: 2.73, 95% CI: 1.81-4.12), and primary liver cancer (OR: 1.46, 95% CI: 1.18-1.82) (37). Moreover, another meta-analysis by Jaruvongvanich et al reported a higher risk of NAFLD in patients suffering from cholelithiasis (OR: 1.55, 95% CI: 1.31-1.82) (38). These studies have shown that cholelithiasis can increase the risk of diseases other than liver cancer, such as NAFLD and

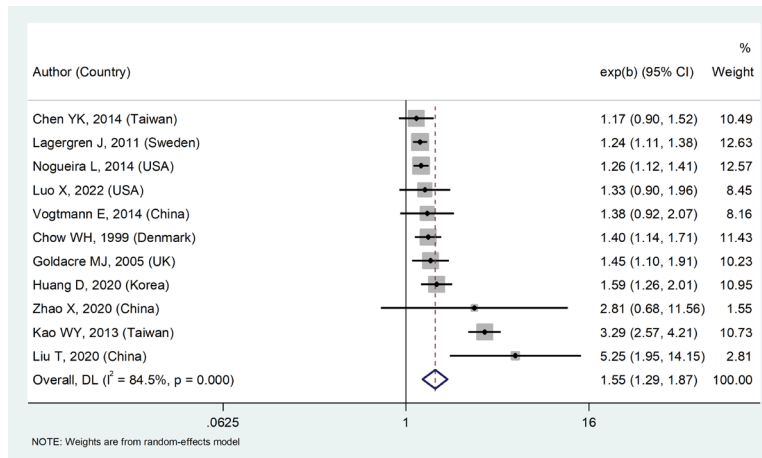


Figure 5. Forest plot of the association between cholecystectomy and liver neoplasms.

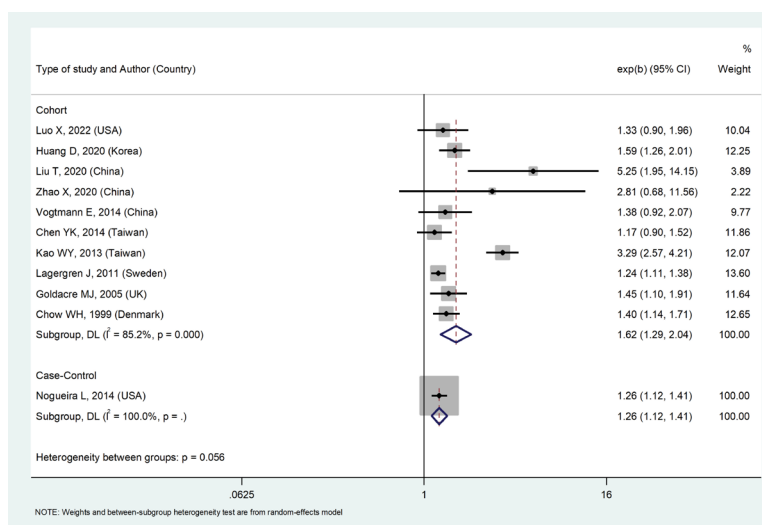


Figure 6. Forest plot of the association between cholecystectomy and liver neoplasms by design of study.

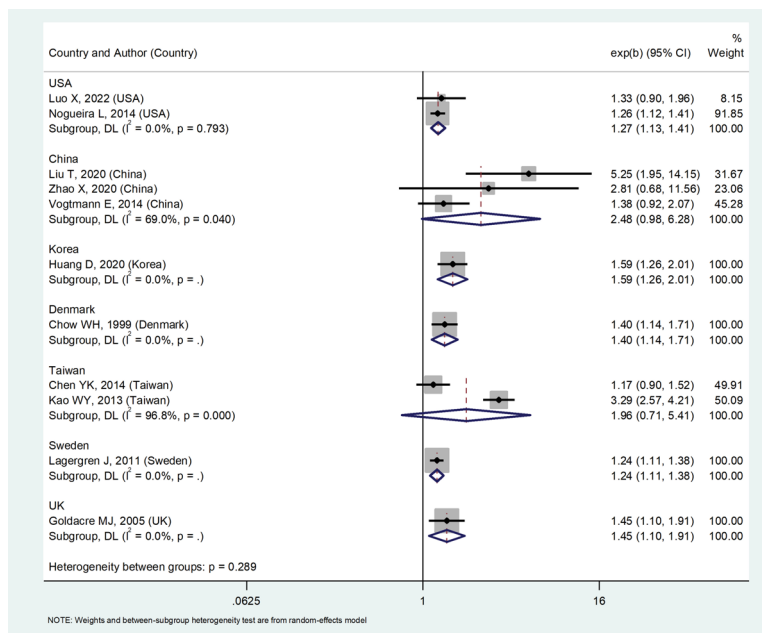


Figure 7. Forest plot of the association between cholecystectomy and liver neoplasms by place of study.

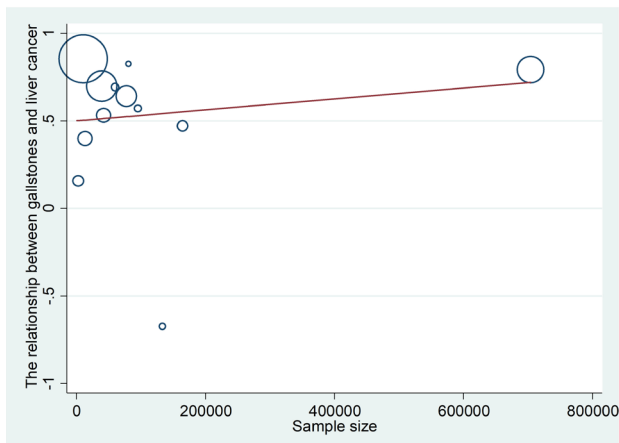


Figure 8. The meta-regression diagram showing the association between gallstones and liver neoplasms by sample size.

hepatic cirrhosis. Thus, cholelithiasis and cholecystectomy can impose a serious threat to liver health, and it is recommended to follow and screen patients with a history of cholelithiasis or cholecystectomy for liver cancer.

Conclusion

In conclusion, cholelithiasis and cholecystectomy can be considered risk factors for liver cancer, increasing the risk of liver cancer development. Thus, it is recommended to perform future studies investigating the underlying mechanism of the effect of cholelithiasis and cholecystectomy on the risk of liver cancer.

Limitations of the study

We did not investigate the effect of gender and age on the relationship between cholelithiasis and cholecystectomy with liver cancer because some of the included studies had not mentioned the gender and age distribution of the participants. Moreover, there were a limited number of case-control studies investigating the relationship between cholelithiasis and cholecystectomy with liver cancer. Finally, the included studies did not show a homogenous geographical distribution. Thus, it is recommended to perform further research on this topic in various parts of the world.

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Authors' contribution

Conceptualization: Shahrzad Ghaffariyan and Shahab Emamieh.

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Formal analysis: Mayyadah Hameed Rashid and Hossein Mardanparvar.

Investigation: Anna Ghorbani Doshantapeh and Anahid Cheraghalian.

Methodology: Mayyadah Hameed Rashid.

Project management: Shahrzad Ghaffariyan.

Resources: All authors.

Supervision: Anna Ghorbani Doshantapeh.

Validation: Raed Muslim Mhaibes and Nazaninfatemeh Hasheminezhad.

Visualization: Anahid Cheraghalian.

Writing—original draft: All authors.

Writing—reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42024508640) and Research Registry website (Unique Identifying Number (UIN) reviewregistry1787). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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