Gallstones, cholecystectomy and the risk of pancreatic cancer: an updated systematic review and meta-analysis of cohort studies

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The effect of gallstones and cholecystectomy on the development of pancreatic cancer has recently prompted many population-based studies. However, the results are controversial. We conducted an updated systematic review and meta-analysis to explore the causality among gallstones, cholecystectomy and pancreatic cancer. Cohort studies published in the PubMed, Web of Science, Embase, and Cochrane Library databases up to May 2023 were retrieved. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were analyzed using a random-effects model. We screened 1391 articles and included 16 studies. Gallstones were not associated with an increased risk of pancreatic cancer ($P = 0.082$), with only the Asian population ($P = 0.011$) showing an increased risk in the subgroup analysis. A markedly higher risk of pancreatic cancer was observed among patients with cholecystectomy (RR = 1.23; 95% CI, 1.07–1.41; $P = 0.004$; $I^2 = 74.4\%$). The association remained significant in the Asian population ($P = 0.004$), in the subgroup analyses stratified by sex, lag period, and time interval since cholecystectomy, and when the models were adjusted for diabetes, smoking, and BMI. Interestingly, cholecystectomy due to gallstones (RR = 1.30; 95% CI, 1.14–1.48; $P < 0.001$; $I^2 = 30.8\%$), rather than for unspecified reasons ($P = 0.116$), markedly increased the risk of pancreatic cancer. In conclusion, cholecystectomy due to gallstones, rather than gallstone formation, conferred an increased risk for pancreatic cancer. There was a higher risk for the Asian population for both gallstones and cholecystectomy. Eur J Gastroenterol Hepatol 35: 1313–1323

Introduction

Pancreatic cancer is one of the most aggressive digestive malignancies and has become a leading cause of cancer-related mortality [1]. Since patients with pancreatic cancer are usually asymptomatic, this malignant disease is prone to be neglected. Upon diagnosis, the 5-year survival rate was as low as approximately 9% in the USA and Europe in 2019 [2]. Even for surgically resectable patients, the 5-year survival rate is still approximately 15–25% [3]. Thus, studies focusing on risk factors are essential to further elucidate the pathogenesis of pancreatic cancer.

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Gallstone disease (GSD) is a frequently encountered digestive disease worldwide. The prevalence of GSD is approximately 10–15% in adults from the USA [4] and ranges from 4.2 to 23% in China [5]. While most gallstone patients are asymptomatic, a substantial number of patients develop acute or chronic inflammation, with complications such as secondary choledocholithiasis, cholangitis, acute pancreatitis, perforation, internal fistula, gallbladder heart syndrome, liver abscess, and hepatic injury [6]. Cholecystectomy has become a major treatment for gallstone patients and it has been identified to be associated with various malignant diseases, such as liver [7], pancreatic [8], and gastric [9] cancer. Previous meta-analyses indicated that a history of gallstones and cholecystectomy displayed robust positive associations with pancreatic cancer [8,10]. However, there are controversial and unsolved issues regarding this topic. First, the most recent meta-analysis conducted by Fan *et al.* [8] included both case–control and cohort studies. The case–control studies failed to elucidate the causality between cholecystectomy and pancreatic cancer, which made the results less reliable. In addition, the studies conducted by Fan *et al.* [8] and Lin *et al.* [10] both yielded substantial heterogeneity in the overall and subgroup analyses. In addition, since potential pancreatic cancer might coexist with gallstones or cholecystectomy, an appropriate lag period following gallstones or cholecystectomy should be implemented to make the results more precise.

Based on the above disputes, there have been many population-based, confounder-adjusted cohort studies on this issue, with several studies supporting a neutral effect [11–14] and one study showing a decreased risk of pancreatic cancer following gallstones and cholecystectomy [15]. The

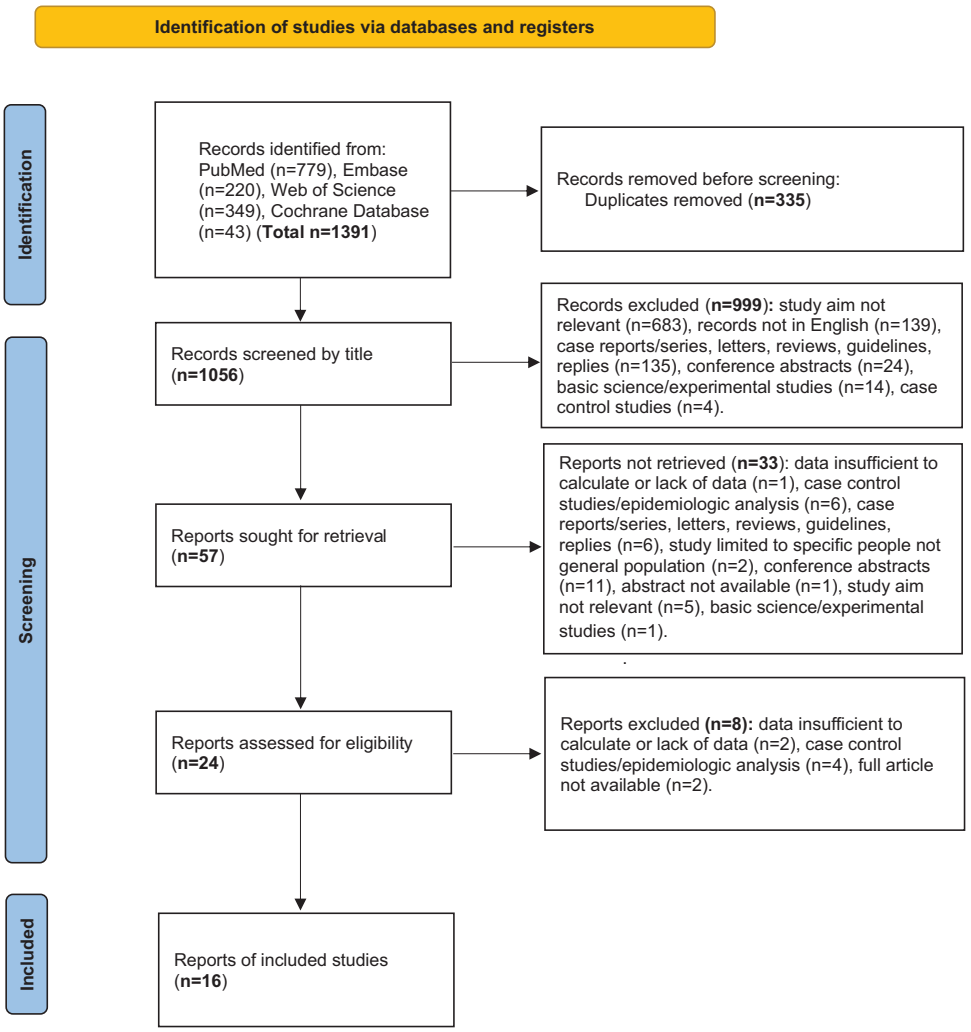

Fig. 1 Flow diagram of study inclusion.

addition of this new research indicates the need for a new meta-analysis to explore the causality of the relationships among gallstones, cholecystectomy and pancreatic cancer.

This systematic review and meta-analysis aimed to update the current understanding of pancreatic cancer risk following gallstone and cholecystectomy.

Methods

Literature search strategy

This meta-analysis was registered on PROSPERO (ID: CRD42022382221). The review protocol was not published or submitted online. We present the article in accordance with the PRISMA reporting checklist. Published articles investigating the association among gallstones, cholecystectomy and pancreatic cancer up to May 2023 were retrieved from the PubMed, Web of Science, Embase, Medline, and Cochrane Library databases. The search strategy was restricted to the English language and included the following terms: ('cholecystectomy' OR 'cholecystectomies' OR 'gallstone') AND ('pancreatic' OR 'pancreas') AND ('carcinoma' OR 'cancer' OR 'neoplasm').

Selection criteria

The inclusion criteria were as follows: (a) a cohort study with original data provided, including hazard ratio (HR), relative risk (RR), incidence rate ratio (IRR), standardized incidence ratio (SIR), and the corresponding 95% confidence intervals (CIs), or data sufficient to compute these measures; (b) the exposure factor was gallstones or cholecystectomy; and (c) the outcome of interest was the development of pancreatic cancer. The exclusion criteria were as follows: (a) case reports/series, letters, reviews, guidelines, protocols, replies and cross-sectional studies; (b) studies that did not precisely report HRs, RRs, IRRs, SIRs and 95% CIs for the outcome; (c) studies with no original data or whose data were not calculable for the outcome; and (d) studies limited to specific populations, such as males or females only or diabetes patients.

The titles and abstracts of the selected literature were separately screened by two authors (Na Sun and Jichao Wei). Discrepancies in the review process were verified by the senior author (Jichao Wei). The remaining articles were separately screened through a comprehensive reading of the full text. The reference lists of articles deemed relevant

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Authors, year	Study Characteristics	Diagnosis of CS/gallstones	Diagnosis of pancreatic cancer	Outcome (pancreatic cancer cases, total)	Adjustment
Shibata *et al*. 1994 [21]	Prospective cohort study: 13 979 participants at baseline Follow-up years: 9 years Lag period: no	Health questionnaires	Pathology reports	65	Sex, age and cigarette smoking
Ekbom *et al*. 1996 [22]	Prospective cohort study: 62 615 CS patients at baseline Follow-up end: until the date of cancer diagnosis, emigration, death, or the end of the observation period (31 December 1987) Lag period: no	ICD code	ICD code	261	None
Johansen *et al*. 1996 [23]	Prospective population-based cohort study: 42 098 gallstone patients at baseline Follow-up years: 7.4 years (mean) Lag period: 1 year	Danish Classification of Surgical Procedures and Therapies/ICD code	ICD code	145	Age, sex, and calendar year
Chow *et al*. 1999 [24]	Prospective cohort study: 42 461 CS and 17 715 gallstone patients at baseline Follow-up years: 6.1 years (mean) Lag period: 1 year	Danish Classification of Surgical Procedures/ICD code	ICD code	264	Age and gender
Ye *et al*. 2001 [25]	Retrospective cohort study: 268 312 CS patients (87 263 men, 181 049 women) at baseline Follow-up period: until a diagnosis of any cancer, death, emigration, or the end of follow-up, 31 December 1997, whichever occurred first Lag period: no	ICD code	ICD code	730	None
Schernhammer *et al*. 2002 [26]	Prospective cohort study: 11 495 CS and/or gallstone patients and 142 289 with no CS or gallstones at baseline Follow-up end: the date of diagnosis of pancreatic cancer, death from any cause, or to the end of the study period (June 1, 1998, for women, and February 1, 1998, for men) whichever occurred first. Lag period: no	Questionnaires	Medical records	349	Age in months, follow-up cycle, history of DM, smoking status, nonvigorous physical activity METs/week, in quintiles, cohort baseline, and baseline BMI
Stolzenberg-Solomon *et al*. 2002 [32]	Retrospective cohort study: 29 048 smoking subjects at baseline Follow-up end: until diagnosis of pancreatic cancer, death, or November 1997 Lag period: no	Questionnaires	Medical records (Finnish Cancer Registry)	172	Age at randomization, years smoked, cigarettes smoked per day, self-reported history of DM and bronchial asthma, occupational activity, and measured high blood pressure
Goldacre *et al*. 2005 [27]	Retrospective cohort study: 39 254 CS individuals and 334 813 reference controls at baseline Follow-up end: the date of subsequent admission for the cancer, or death, or 31 March 1999 Lag period: 2 years	Hospital records	Hospital records	918	None
Eijgenraam *et al*. 2013 [28]	Prospective cohort study: 5000 subjects at baseline Follow-up years: 16.3 years (mean) Lag period: no	Questionnaires	ICD code	448	Age, sex, smoking, BMI, level of education, alcohol, T2DM, and family history of pancreatic cancer
Chen *et al*. 2014 [29]	Retrospective cohort study: 5850 cholelithiasis patients with CS and 62 180 controls at baseline Follow-up years: not mentioned. Lag period: no	ICD code	Registry for Catastrophic Illness Patient Database	41	Sex, age and comorbidities, such as DM, hyperlipidemia, hepatitis B, hepatitis C, menopause, and cirrhosis
Huang *et al*. 2020 [30]	Retrospective cohort study: 9910 CS patients and 687 270 patients with no gallstones Follow-up years: 7.4 years (mean) Lag period: 1 year	Procedure code	ICD code	67	Sex, diabetes, liver cirrhosis
Zhao *et al*. 2020 [12]	Prospective cohort study: 148 CS, 1857 gallstone and 77 804 non-gallstone patients at baseline Follow-up years: 11.0 years (mean) Lag period: 1 year	Ultrasonography	ICD code	94	Education, smoking status, drinking status, diabetes, fatty liver levels, and BMI

(*Continued*)

Table 1
(*Continued*)

Authors, year	Study Characteristics	Diagnosis of CS/gallstones	Diagnosis of pancreatic cancer	Outcome (pancreatic cancer cases, total)	Adjustment
Wang *et al*. 2021 [13]	Retrospective cohort study: 3518 CS individuals and 3787 no intervention controls at baseline Follow time: 48.87 months for CS group and 38.25 months for no intervention group Lag period: 6 months	ICD code	ICD code	8	Chronic pancreatitis, and pancreatic cystic diseases
Shabanzadeh *et al*. 2022 [15]	Prospective cohort study: 4 465 962 subjects at baseline Follow-up end: until occurrence of upper gastrointestinal cancer, death, hepatic metastasis, or were censored if moving out of the country, whichever came first Lag period: 2 years	ICD code	ICD code	13 928	Sex, socioeconomic status, civil status, level of education, vocational training, personal annual income
Choi *et al*. 2022 [31]	Retrospective cohort study: a total of 123 295 patients who underwent cholecystectomy and 123 295 matched comparison subjects at baseline Follow-up years: 4.59 years (mean) Lag period: 1 year	Insurance claims code	ICD code	845	Age, sex, diabetes, BMI, and current smoking
Luo *et al*. 2022 [14]	Prospective cohort study: 153 306 subjects with no gallstones and 11 559 gallstone patients (9848 CS patients and 1711 non-CS subjects) at baseline Follow-up years: 26 years (mean) Lag period: 2 years	Questionnaires and medical records	State Cancer Registries and the National Death Index	1147	Age, study period, cohort, with additional adjustment for the race, aspirin use, smoking status, total calorie intake, alcohol intake, coffee consumption, physical activity, AHEI-2010, BMI, hypercholesterolemia and T2DM

AHEI-2010, Alternate Healthy Eating Index-2010;CS, cholecystectomy; DM, diabetes mellitus; ICD, International Classification of Diseases; GSD, gallstone disease; MET–h/week, sum of the average time/week spent in each activity by its typical energy-expenditure requirements expressed in metabolic equivalents (METs), MET, caloric need per kilogram of body weight per hour activity, divided by the caloric need per kg per h at rest.

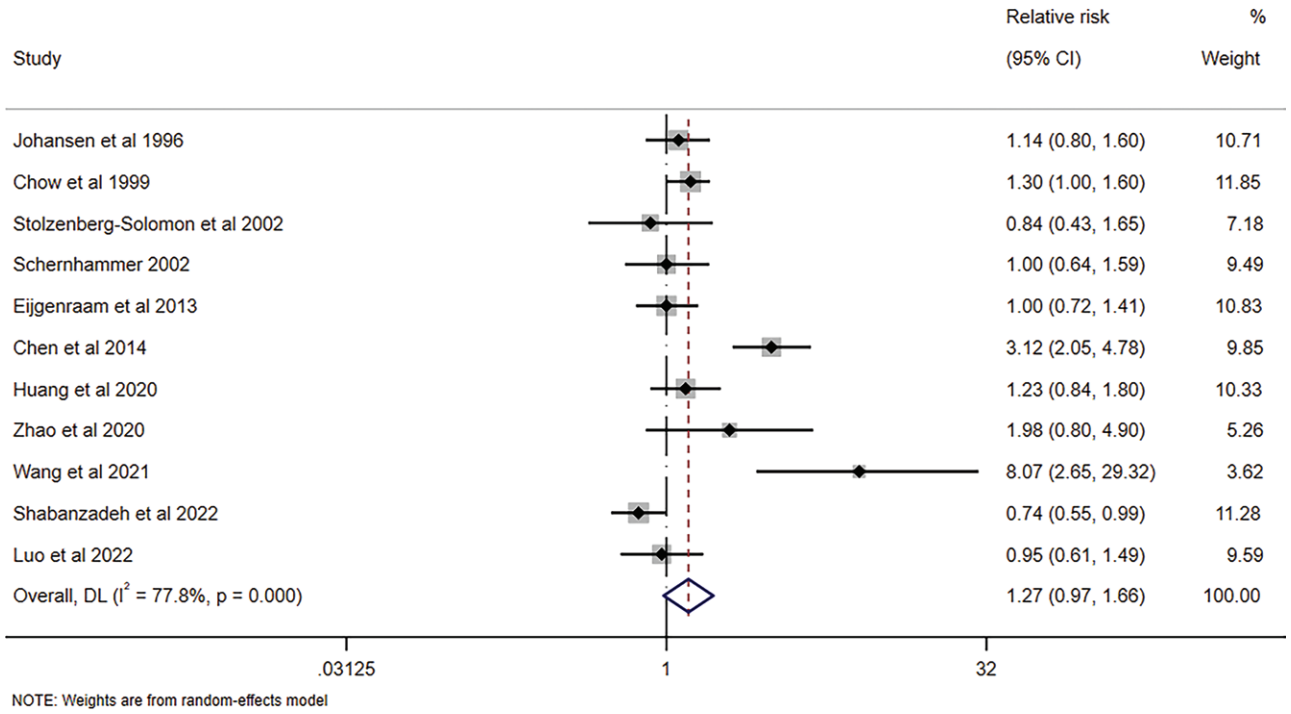

Fig. 2 Forest plot of relative risk between gallstones and pancreatic cancer.

during the full-text review process were cross-checked to identify any additional relevant studies.

Data extraction and quality assessment

Two researchers conducted the data extraction process independently (Xudong Wang and Na Sun). Discrepancies that arose between the two researchers during the data collection process were discussed and resolved through consultation with the senior author (Jichao Wei). The basic features of all the relevant studies were recorded, including the author and publication year, study characteristics, diagnosis of gallstones, cholecystectomy and pancreatic cancer, outcome (pancreatic cancer cases), and adjustments. The Newcastle–Ottawa Scale (NOS) [16] was used to assess the study quality. We judged studies with a score of 7 to 9 to be of high quality, studies with a score of 4 to 6 to be of moderate quality, and studies with a score of 0 to 3 to be of low quality.

Two authors (Na Sun and Jichao Wei) independently rated the certainty of the evidence using the GRADE system on the online GRADEpro software (https://www.gradepro.org/) [17]. The GRADE system evaluates the certainty of a study in the following five dimensions: study limitations, consistency of effect, imprecision, indirectness, and publication bias [18]. Using the GRADE system, the certainty of evidence in each dimension is categorized as high, moderate, low, or very low quality.

STATA software 17.0 (College Station, TX: StataCorp LLC) was used to perform all data analyses. Pooled RRs and 95% CIs were computed from SIRs, IRRs, RRs, HRs, and 95% CIs using the DerSimonian and Laird method. If a study adopted a lag period, data with an appropriate lag period were extracted and computed. Subgroup analysis was also conducted. The I^2 statistic was used to analyze heterogeneity [19]. Significant heterogeneity was indicated by either $P < 0.10$ or an I^2 value>50%. The presence of publication bias was verified by a funnel plot and Egger's test [20]. A sensitivity analysis was performed by removing each study in sequence to find the possible source of heterogeneity. The significance level was $\alpha = 0.05$.

Results

Study selection and characteristics

The flow diagram for literature selection is displayed in Fig. 1. In total, 1391 articles were identified through database searches. Of these studies, 335 articles were excluded due to being duplicates. The remaining 1056 articles were reviewed by title, and subsequently, 999 records were excluded for the following reasons: study aim not relevant (n = 683), records not in English (n = 139), case reports/series, letters, reviews, guidelines, replies (n = 135), conference abstracts (n = 24), basic science/experimental studies (n = 14), and case-control studies (n = 4). After further reading of the abstracts and full texts, 16 studies were eventually deemed eligible for inclusion [12–15,21–32].

The main characteristics of the included studies are displayed in Table 1. Of the included studies, 8 were from Europe, 5 were from Asia, and 3 studies were from America. Most of the studies recruited cases either from general populations or from inpatient cohorts of individuals from health care programs or insurance systems. The identification of cholecystectomy or gallstones was mostly based on ICD (International Classification of Diseases) codes, hospital medical records, or insurance claim codes.

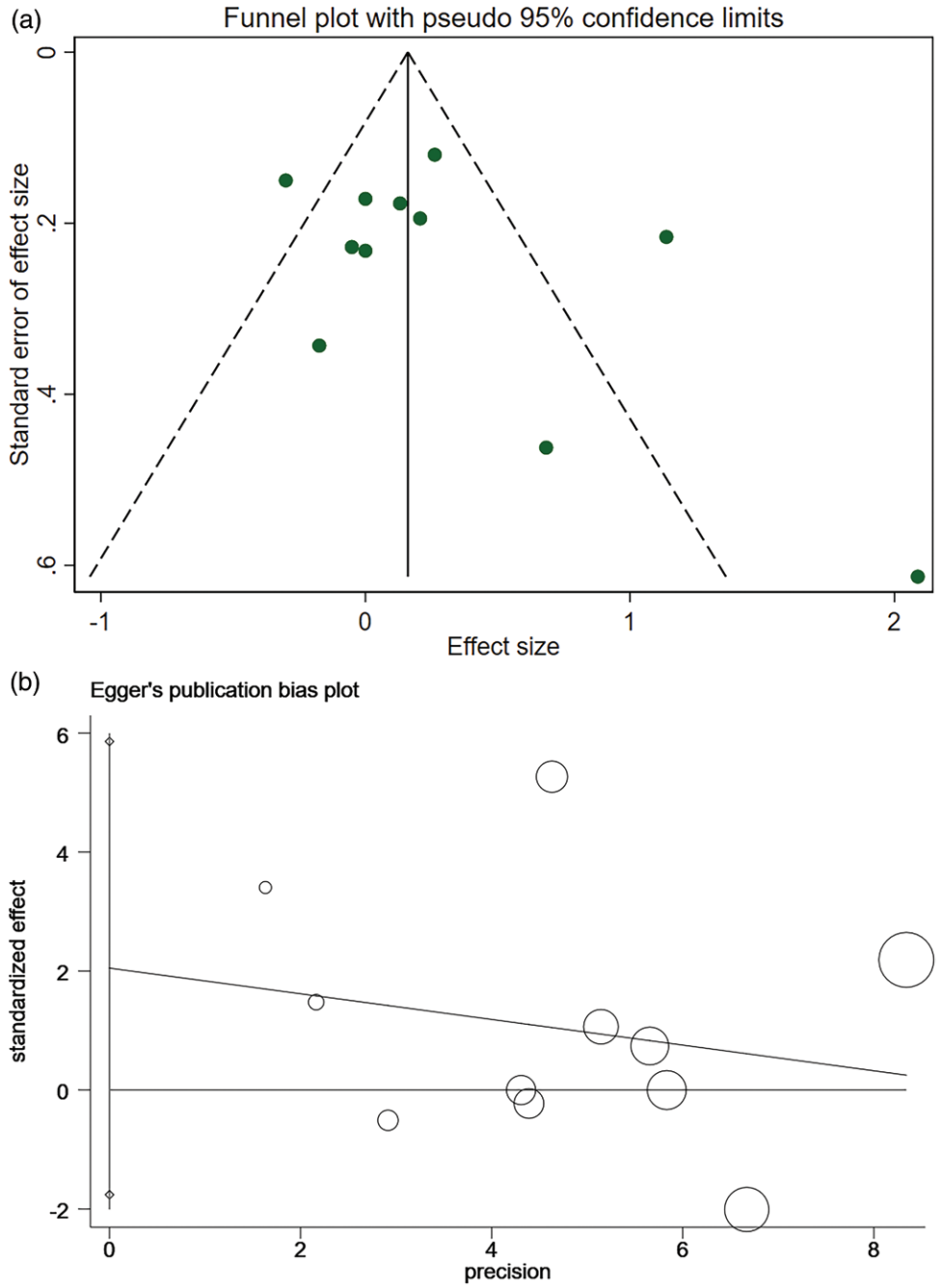

Fig. 3 Publication bias of the included studies. (a) Funnel plot for publication bias. (b) Egger's test results.

The diagnosis of pancreatic cancer was also mainly validated based on ICD codes or medical records. The results of data extraction and NOS scoring were displayed in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A923* (for cholecystectomy) and Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/EJGH/A924* (for gallstones). The mean NOS score was 6.93 for studies with cholecystectomy and 7.18 for studies with gallstones.

Pancreatic cancer risk for gallstone patients

Eleven studies reported data on the development of pancreatic cancer during the follow-up of gallstone patients. The RR of pancreatic cancer with gallstones was 1.27 (95% CI 0.97–1.66, $P = 0.082$) (Fig. 2), with heterogeneity between studies ($I^2 = 77.8\%$). No statistically significant publication bias was detected through funnel plot analysis and Egger's tests (Fig. 3). The results were proven stable through sensitivity analysis (Fig. 4).

Subgroup analysis for gallstone patients

Subgroup analyses were conducted based on geographic region, lag period, and adjustment [diabetes, smoking, BMI], as shown in Table 2. Only Asian subjects showed an increased risk of pancreatic cancer following gallstones (RR = 2.49; 95% CI, 1.24–5.02; $P = 0.011$; $I^2 = 80.8\%$).

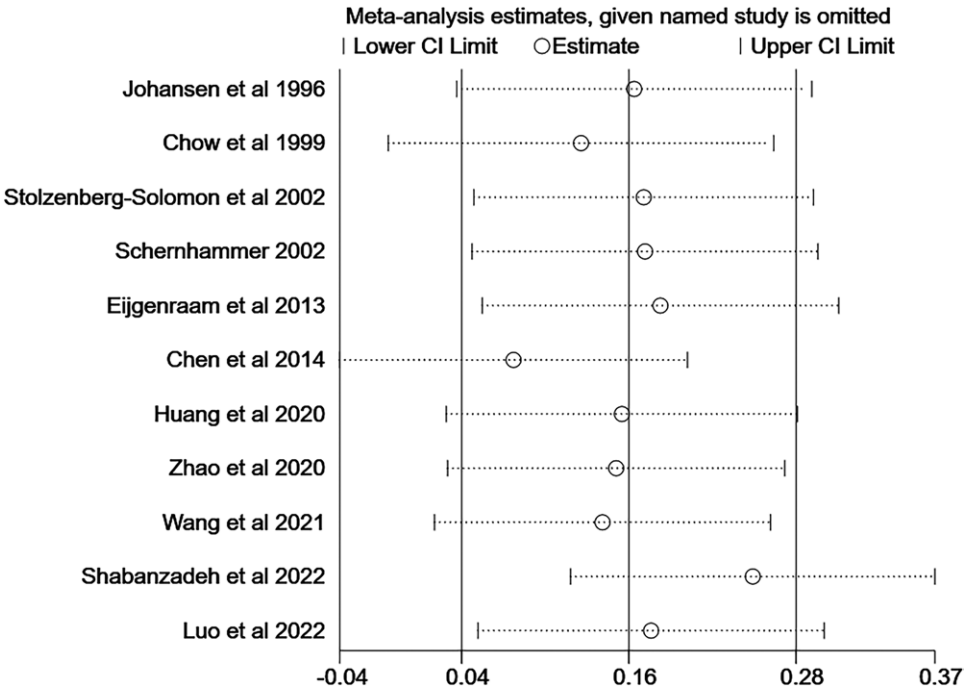

Fig. 4 Sensitivity analysis of all included studies for gallstones.

Table 2. Subgroup analyses of the association between gallstones and risk of pancreatic cancer, stratified by geographic region, lag period, and adjustment

Group	Subgroup	RR (95% CI)	Test for overall effect (*P* value)	No. of studies	Heterogeneity *I2*, %
Geographic region					
	America	0.97 (0.71–1.34)	0.872	2	0.0%
	Europe	1.01 (0.80–1.28)	0.924	5	57.1%
	Asia	**2.49 (1.24–5.02)**	**0.011**	4	80.8%
Lag period	Lag period	1.18 (0.90–1.53)	0.225	8	68.3%
	No lag period	1.40 (0.61–3.21)	0.424	3	89.9%
Adjustment	For diabetes, yes	1.28 (0.89–1.83)	0.183	7	75.3%
	For smoking, yes	1.01 (0.82–1.25)	0.937	5	0.0%
	For BMI, yes	1.03 (0.82–1.29)	0.801	4	0.0%
	For diabetes, smoking and BMI, yes	1.03 (0.82–1.29)	0.801	4	0.0%

CI, confidential interval; RR, relative risk; BMI, body mass index.

No associations were found among European ($P = 0.924$) and American ($P = 0.872$) populations or among studies with ($P = 0.225$) or without ($P = 0.424$) lag periods. The results remained consistent when the studies were adjusted for diabetes ($P = 0.183$), smoking ($P = 0.937$), BMI ($P = 0.801$), and the combination of all three confounders ($P = 0.801$).

Pancreatic risk for patients with cholecystectomy

Fifteen studies reported the risk of pancreatic cancer following cholecystectomy. As shown in Supplementary Fig. 1, Supplemental digital content 3, *http://links.lww.com/EJGH/A925* cholecystectomy was significantly associated with an increased risk of pancreatic cancer (RR = 1.21; 95% CI, 1.07–1.36; $P = 0.003$; $I^2 = 76.5\%$). Publication bias was not detected through funnel plot analysis and Egger's tests (Supplementary Fig. 2, Supplemental digital content 4, *http://links.lww.com/EJGH/A926*). Sensitivity analysis was performed (Supplementary Fig. 3, Supplemental digital content 5, *http://links.lww.com/EJGH/A927*), and the result remained unchanged (RR = 1.23; 95% CI, 1.07–1.41; $P = 0.004$; $I^2 = 74.4\%$, Fig. 5), even after removal of one study [25], which might have caused instability of the meta-analysis.

Subgroup analysis for patients with cholecystectomy

Subgroup analyses were conducted based on sex, geographic region, lag period, time interval since cholecystectomy, and reason for cholecystectomy (Table 3). In subgroup analyses for sex and the time interval since cholecystectomy, the results all supported an increased risk among males ($P < 0.001$) or females ($P = 0.043$) and among participants of studies with follow-up periods ≤4 years ($P < 0.001$) or ≥5 years ($P < 0.001$). For geographic region, there was an increased risk in the Asian population (RR = 1.66; 95% CI, 1.05–2.63; $P = 0.004$; $I^2 = 72.0\%$), but there was no excessive risk in European ($P = 0.467$) or American ($P = 0.081$) subjects. In addition,

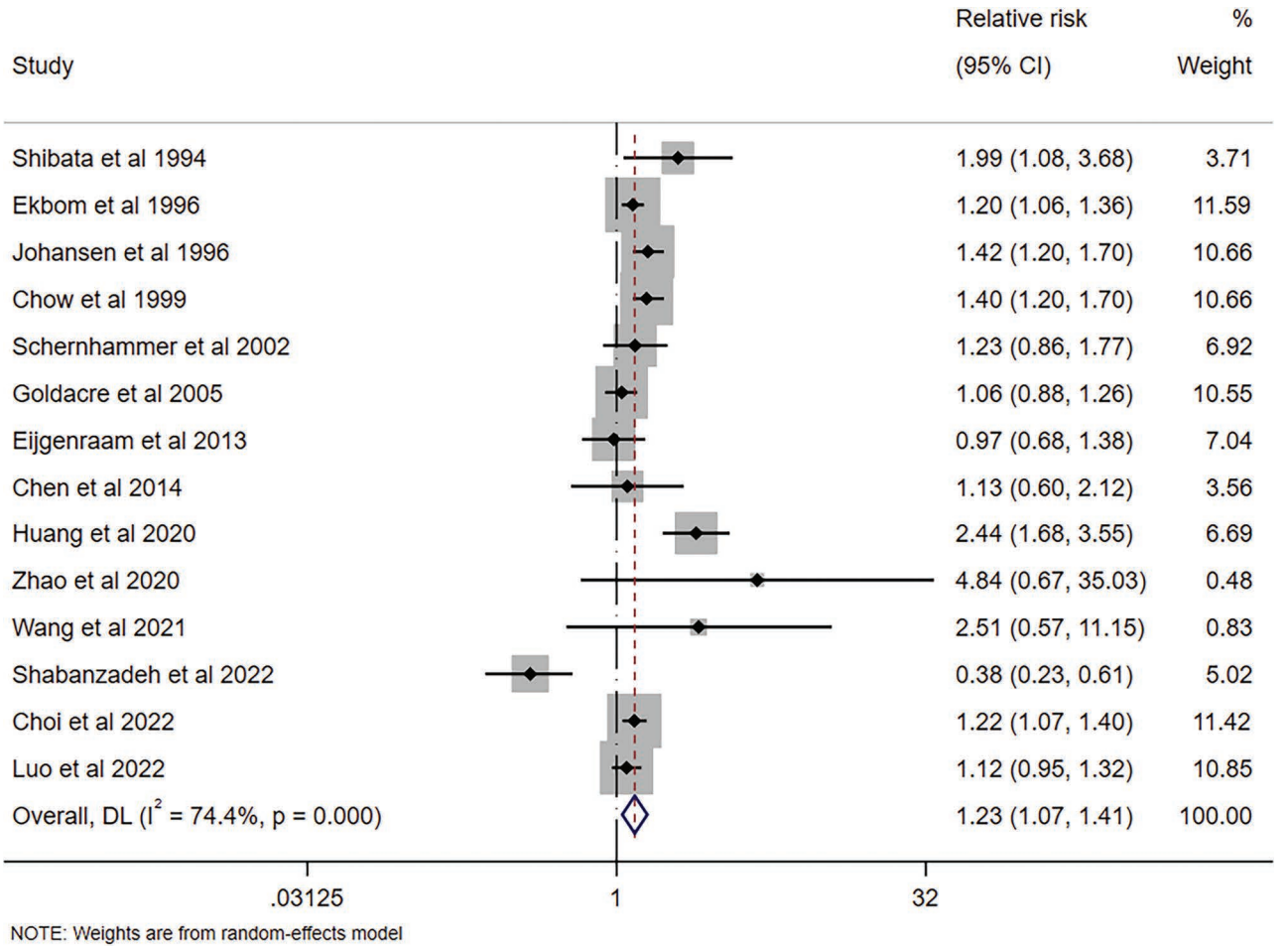

Fig. 5 Forest plot of relative risk between cholecystectomy and pancreatic cancer with stable results.

Table 3 Subgroup analyses of the association between cholecystectomy and the risk of pancreatic cancer, stratified by sex, geographic region, lag period, interval since cholecystectomy, and reason for cholecystectomy

Group	Subgroup	RR (95% CI)	Test for overall effect (*P* value)	No. of studies	Heterogeneity *I2*, %
Sex					
	Male	**1.30 (1.15–1.47)**	**<0.001**	5	0.0%
	Female	**1.58 (1.02–2.45)**	**0.043**	5	87.2%
Geographic region	America	1.24 (0.97–1.58)	0.081	3	38.0%
	Europe	1.08 (0.88–1.33)	0.467	6	84.0%
	Asia	**1.66 (1.05–2.63)**	**0.004**	5	72.0%
Lag period	Lag period	**1.23 (1.02–1.48)**	**0.028**	10	80.6%
	No lag period	1.19 (0.98–1.44)	0.073	4	25.5%
Time interval since cholecystectomy	≤4 years	**1.69 (1.42–2.02)**	**<0.001**	3	0.0%
	≥5 years	**1.34 (1.15–1.56)**	**<0.001**	3	0.0%
Adjustment	For diabetes, yes	**1.29 (1.05–1.58)**	**0.015**	7	66.2%
	For smoking, yes	**1.19 (1.04–1.35)**	**0.009**	6	24.2%
	For BMI, yes	**1.17 (1.06–1.29)**	**0.001**	5	0.0%
	For diabetes, smoking and BMI, yes	**1.17 (1.06–1.29)**	**0.001**	5	0.0%
Reason for cholecystectomy	Not specified	1.19 (0.96–1.47)	0.116	9	81.3%
	Gallstones	**1.30 (1.14–1.48)**	**<0.001**	5	30.8%

CI, confidential interval; RR, relative risk.

cholecystectomy increased the risk of pancreatic cancer for studies with lag periods (RR = 1.23; 95% CI, 1.02–1.48; $P = 0.028$; $I^2 = 80.6\%$) but not for studies without lag periods ($P = 0.073$).

We wondered whether the reason for cholecystectomy influenced the risk for pancreatic cancer. Subgroup analysis demonstrated that only cholecystectomy for gallstones was associated with an increased risk of pancreatic cancer (RR = 1.30; 95% CI, 1.14–1.48; $P < 0.001$; $I^2 = 30.8\%$, Table 3 and Fig. 6), with little heterogeneity. The association of cholecystectomy for unspecified reasons with the risk of pancreatic cancer

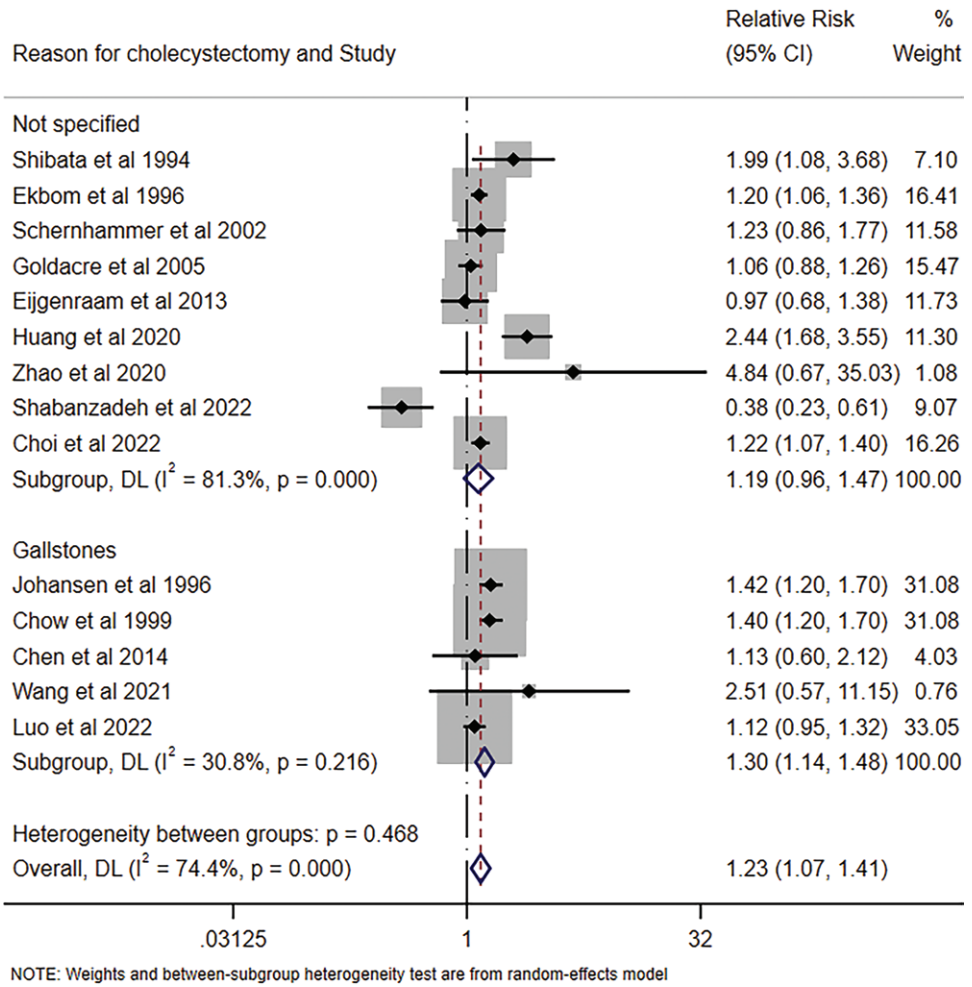

Fig. 6 Forest plot of relative risk between cholecystectomy and pancreatic cancer in subgroup analysis stratified by reason for cholecystectomy.

was NS (RR = 1.19; 95% CI, 0.96–1.47; $P = 0.116$; $I^2 = 81.3\%$, Table 3 and Fig. 6).

Discussion

In this latest and updated meta-analysis, we demonstrated that gallstones were not associated with an increased risk of pancreatic cancer, with only the Asian population being at risk. A higher risk of pancreatic cancer was observed among patients with cholecystectomy. The association remained significant in the Asian population and in the subgroup analyses stratified by sex, lag period, time interval since cholecystectomy and adjustment for diabetes, smoking, and BMI. Interestingly, cholecystectomy due to gallstones, rather than for unspecified reasons, markedly increased the risk of pancreatic cancer.

Numerous case–control and cohort studies have explored the association between gallstones and the risk of pancreatic cancer. These studies resulted in a previous meta-analysis which demonstrated that a history of gallstones was a robust risk factor for pancreatic cancer [8]. With more cohort studies included in our meta-analysis, we found that gallstones alone were insufficient to increase the risk of pancreatic cancer, with only 3 studies showing increased risk among the 11 studies. The results were stable even with studies adjusted for confounders such as diabetes, smoking, and obesity. We postulated that the reasons might be as follows. First, the previous meta-analysis included both case–control and cohort studies. Since the included case–control studies failed to elucidate the causality of the relationships and may have even shown inverse correlations, the real association may have been concealed. In addition, several studies, including the study showing the highest IRR [13], were limited by a small number of clinical cases, which may cause unstable results. In addition, several studies in previous meta-analyses were not adjusted for important confounders, such as diabetes, smoking, and BMI [24,33,34], which made the results less reliable. In our study, only the Asian population showed an increased risk of pancreatic cancer following gallstones, but with significant heterogeneity. The mechanism for the racial preference in our analysis was still obscure. The above controversy and additional risk for Asian subjects indicates the need for more well-designed, population-based studies to confirm this association.

In our study, cholecystectomy was still associated with an increased risk of pancreatic cancer in the general population, which coincided with a previous meta-analysis [8,10], supported by animal studies showing pancreatic hypertrophy, hyperplasia [35] and carcinogenesis [36,37]

of the pancreas following cholecystectomy intervention. The potential mechanism could be that increased circulating levels of cholecystokinin stimulated pancreatic cancer cell growth and initiated pancreatic carcinogenesis [38]. The conclusion that cholecystectomy, instead of gallstone formation, is the more important risk factor for pancreatic cancer seems plausible, as proposed by Chow *et al* [24]. While the possible mechanism remains unknown, further studies might focus on potential reasons, such as genetic susceptibility, inflammatory status, bile acid composition and concentrations, and other mechanisms involving gallstones with or without surgical intervention.

Our meta-analysis has several limitations that warrant consideration. First, the certainty of the evidence was low according to the assessment of limitations, indirectness, and imprecision. For several studies included in this meta-analysis, the evidence was downgraded due to, for example, the risk of selection bias or suspected potential reporting bias. When considering possible biases, imbalances between study groups, such as genetic differences and environmental and lifestyle-related factors, may represent potential sources of biases in this study. In addition, the high heterogeneity in this study, especially in Asian populations, aroused the need for more studies to confirm these associations. In addition, symptomatic cholelithiasis indicates prolonged inflammation of the gallbladder and bile duct, which could be different from asymptomatic gallstones. Whether cholecystectomy due to different gallstone statuses could have different impacts on the risk of pancreatic cancer also needs further validation.

Conclusion

This meta-analysis showed that cholecystectomy, rather than gallstone formation, conferred an increased risk for pancreatic cancer. There was a higher risk for the Asian population in subgroup analyses both for gallstones and cholecystectomy. Cholecystectomy due to gallstones, rather than for unspecified reasons, markedly increased the risk of pancreatic cancer. These findings should be further validated in large, prospective cohort studies, and they may have vital implications for pancreatic cancer screening and surveillance among patients with GSD.

Acknowledgements

The data in this study was available from the corresponding author upon reasonable request.

All analyses were based on previous published studies and no ethical approval and patient consent were required.

Conflicts of interest

There are no conflicts of interest.

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