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GALLSTONES AND CHOLECYSTECTOMY IN RELATION TO RISK OF LIVER CANCER: A META- ANALYSIS STUDY

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Abstract:
Background: *The association between gallstones or cholecystectomy and the incidence risk of liver cancer is controversial. This is a meta-analysis of observational studies on the role of gallstones or cholecystectomy in primary liver cancer.*
Method: *Relevant studies were identified after the literature search via electronic databases until 2018.* ***Results:*** *A random effects model was used to generate pooled multivariable adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity among studies was evaluated using Cochran's Q and I 2 statistics. A total of 14 studies (four case–control, 10 cohort) were included in this study. Our study showed the pooled OR was 2.66 (95% CI: 2.05–3.28) for gallstones with liver cancer risk and OR was 1.47 (95% CI: 1.24–1.71) for cholecystectomy. Though there was obvious heterogeneity among these studies, the risk of incidence was consistent in the subgroup analyses and sensitivity analysis.*
Conclusion: *This meta-analysis showed that gallstones and cholecystectomy was associated with risk of liver cancer. The findings should be confirmed by future studies with validated questionnaires, well designed studies and strict control of confounders.*
Key Words: *cholecystectomy, gallstone, liver cancer, meta-analysis.*

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INTRODUCTION:

Primary liver cancer mainly includes hepatocellular carcinoma (HCC), which originates in liver cells, and intrahepatic cholangiocarcinoma (ICC), which arises from the intrahepatic bile duct [1]. Estimated 782,000 new cancer cases was the worldwide burden of primary liver cancer for 2012 [2]. It ranks as the fifth most common incident cancer in men and the ninth in women [2]. Owing to its poor prognosis, it is the second commonest cause of death from cancer worldwide. The above data highlight the importance of a better understanding of risk factors related to liver cancer development. However, the etiology of this disease remains largely elusive, apart from known relationships with hepatitis B or C virus infection, alcohol, aflatoxins, liver cirrhosis, and diabetes [3, 4]. It has been hypothesized that gallstones (i.e., cholelithiasis) and cholecystectomy are associated with an increased risk of several cancers, especially the risk of rectal cancer [5], pancreatic cancer [6], and colorectal cancer [7, 8]. Gallstones are known to induce biliary inflammation, and cholecystectomy is typically followed by dilation of the common bile ducts and elevated bile duct pressure, which also results in chronic inflammation [9]. The relationship between chronic inflammation and cancer is well recognized[10]. It has also been proposed that gallstones and cholecystectomy result in the accumulation of bile and secondary bile acids, in particular, deoxycholic acid [11–15], and that bile acids can act as carcinogens. Several epidemiological studies have investigated the association between gallstones, cholecystectomy, and liver cancer. However, the existing results are controversial. Most studies have reported a positive relationship between gallstones and liver cancer, but one failed to demonstrate a significant association. With regard to cholecystectomy, several studies suggested a significant increased risk of liver cancer, whereas others demonstrated a no significant adverse effect. No meta-analysis has previously been published on the relationship between gallstones or cholecystectomy and the incidence risk of liver cancer. The aim of this study is to find out the association between cholecystectomy, gallstones, and the risk of developing liver cancer in observational studies. A better understanding of these relationships may highlight the need to consider additional intervention methods in this area.

METHODOLOGY:

Search Strategy: A literature search of related studies was conducted in the databases of PubMed (Medline), Web of Science and EMBASE from 1995 to 2018, using the following key words or MeSH terms: ('cholecystectomy' or 'gallstone' or 'cholelithiasis' or 'gallbladder surgery') combined with ('liver cancer' or 'liver tumor' or 'liver neoplasms' or 'hepatic tumor' or 'hepatic neoplasms'). In addition, find additional relevant studies, reference list was also retrieved.

Inclusion Criteria: Inclusion criteria as follows: (i) case–control or cohort studies, (ii) studies with history of gallstones or cholecystectomy, (iii) reported the odds ratio (OR) estimates with the corresponding 95% confidence interval (CI) or sufficient information to calculate them, and (iii) outcome was liver cancer incidence. When several reports were published on the same subject, only the most recent and informative one was included.

Statistical Analysis: All statistical tests were two sided, and all statistical analyses were carried out with SPSS 16.0 and Stata Statistical Software 13.0 (IBM, Chicago, USA). A random-effects model was used to estimate pooled ORs to take into account the heterogeneity of the risk estimates and to provide more conservative estimates compared with the fixed effects model. Statistical heterogeneity between studies was assessed with the $\chi 2$ statistic and quantified by I^2, a statistic that represented the percentage of total variation contributed by between-study variation. To investigate potential sources of between-study heterogeneity, subgroup analysis and meta-regression models were conducted. Also, sensitivity analysis was carried out to assess whether the summary estimates were robust to inclusion of studies. Publication bias was assessed using the tests by Egger et al. (1997), Begg and Mazumdar (1994), and the contour enhanced funnel plots (Peters et al., 2008). The methods were carried out in accordance with the approved guidelines.

RESULTS:

Figure 1 showed the number of studies assessed and excluded through the stages of the meta-analysis. A total of 14 studies (four case–control, 10 cohort) published between 1995 and 2018 were included in this study. Three studies were conducted in the USA, four in China, and seven in Europe (Table 1).

Fig. 1 search strategy

Table 1 Characteristics of studies included in the meta-analysis

References	Region	Design	Duration (years)	Factor and number of factor	Liver cancer patient	Total
Vogtmann et al. (2014)	China	Cohort	10	Gallstones/ holecystectomy (8161/3151)	160	73 209
Vogtmann et al. (2014)	China	Cohort	8	Gallstones/Cholecystectomy (4614/1684)	252	61 337
Nogueira et al. (2014)	USA	Case–control	13	Gallstones/Cholecystectomy (15097/9109)	10219	1 238 390
Nogueira et al. (2014)	USA	Cohort	Unknown	Gallstones/Cholecystectomy (30674/25457)	414	487 207
Kao et al. (2013)	China	Cohort	12	Cholecystectomy (2590)	67	1 002 590
Chen et al. (2014)	China	Cohort	10	Gallstones/Cholecystectomy (15545/5850)	791	77 725
Chang et al. (2013)	China	Case–control	4	Gallstones (1484)	2978	14 890
Tavani et al. (2012)	Europe	Case–control	27	Gallstonesb (206)	684	2640
Nordenstedt et al. (2012)	Europe	Cohort	43	Gallstones/Cholecystectomy (192960/345251)	170	538 211
Lagergren et al. (2011)	Europe	Cohort	43	Cholecystectomy (354251)	333	345 251
Welzel et al. (2007a, 2007b)	Europe	Case–control	13	Gallstones/Cholecystectomy (35/25)	764	3820
Welzel et al. (2007a, 2007b)	USA	Case–control	6	Gallstones/Cholecystectomy (4445/1690)	535	103 317
Goldacre et al. (2005)	Europe	Cohort	36	Cholecystectomy (39254)	344	374 067
Chow et al. (1999)	Europe	Cohort	16	Gallstones/Cholecystectomy (17715/42461)	82	60 176
Johansen et al. (1996)	Europe	Cohort	15	Gallstones (42098)	56	42 098

Gallstones and liver cancer risk: Eleven studies investigated the association between gallstones and liver cancer risk, including six cohort studies and five case–control studies. We found that patients with gallstones were significantly more likely to develop liver cancer than without gallstones (OR =2.66, 95% CI: 2.05–3.28) by the random-effects model, with a high heterogeneity (I 2=94.6%, Pheterogeneity< 0.01; Fig. 2). In subgroup analyses, design, location, and quality were carried out to examine the stability of the pooled OR. The results indicated that the association was unchanged by most confounders and heterogeneity was observed in all subgroup analyses (Table 2). We then conducted further meta-regression analysis to find the heterogeneity factors which affected the OR, and we found that design (P=0.31), location (P=0.89), and quality (P=0.78) were not significant sources of heterogeneity. In addition, we performed the sensitivity analysis. When one study was removed, the rest was analyzed sequentially by meta-analysis. Any study was omitted; the pooled ORs were not materially altered with the overall pooled ORs, indicating that our results were statistically robust. Finally, among techniques to minimize the effects of publication bias, we have performed a thorough search for unpublished studies, and to use such analytical tools as a funnel plot to quantify the potential presence of publication bias. Then we created funnel plots by plotting the treatment effect against the reciprocal of the standard error of the treatment effect. Begg's test was carried out to access the publication bias in our studies. In our study, no publication bias (Egger's test P=0.85) was observed (Fig. 3).

Fig 2.

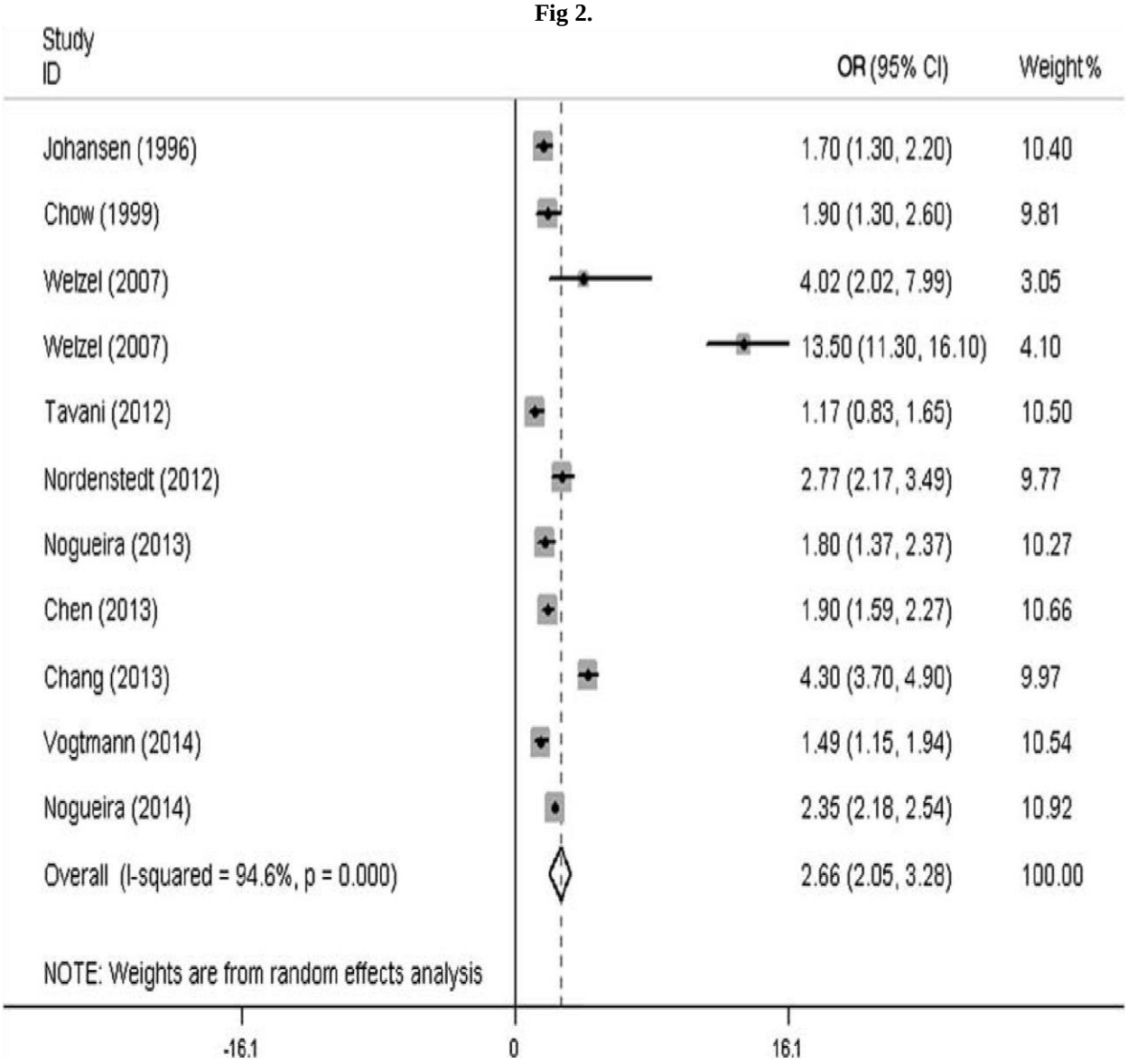
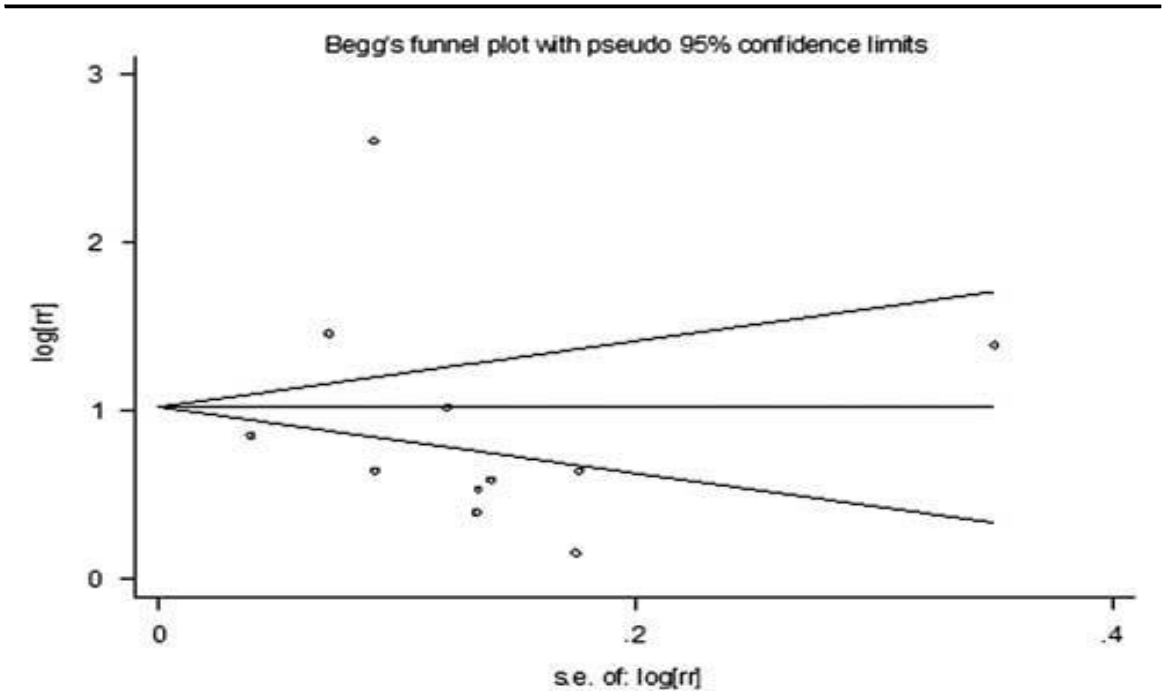


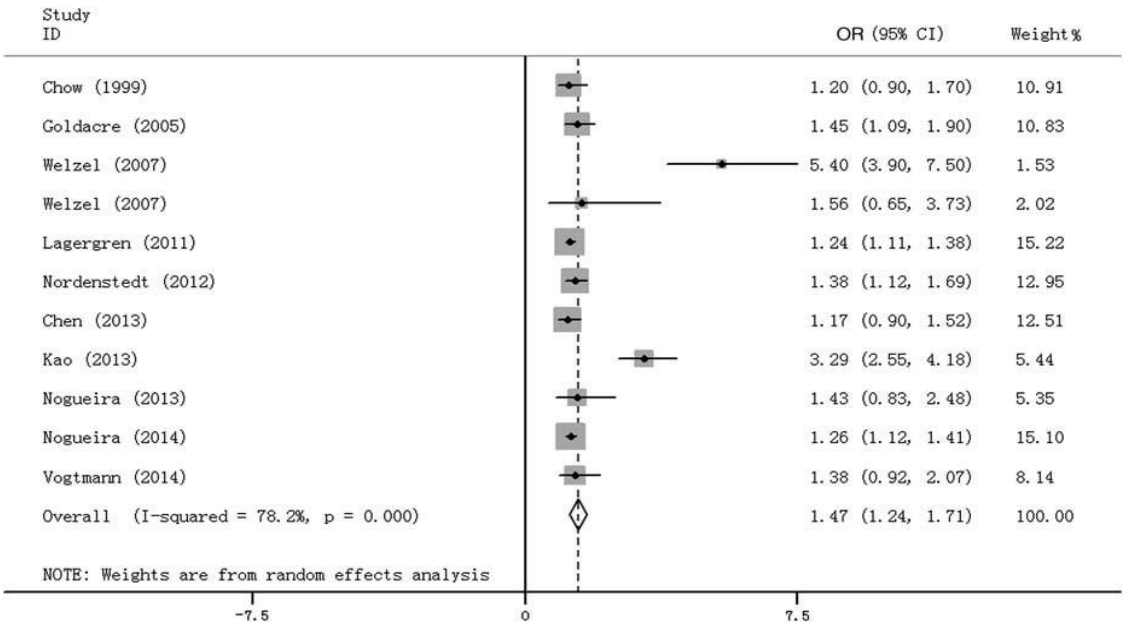
Table 2 Subgroup analysis of odds ratio				
Study characteristics	**Number of studies**	**OR (95% CI)**	**P value**	**Heterogeneity I^2**
Gallstones Study design	11	2.66 (2.05–3.28)	< 0.01	94.6
Case–control studies	5	4.77 (2.89–6.05)	< 0.01	97.4
Cohort studies Study location	6	1.87 (1.58–2.16)	< 0.01	55.3
USA	3	4.96 (2.87–7.06)	0.03	97.7
Europe	5	1.93 (1.30–2.57)	< 0.01	79.2
China Study quality	3	2.54 (1.16–3.92)	0.01	96.8
High	4	3.12 (1.82–4.41)	< 0.01	89.9
Moderate or low Sex	7	2.39 (1.70–3.08)	< 0.01	95.3
Male	3	2.34 (2.00–2.69)	< 0.01	94.1
Female	3	3.29 (1.25–5.33)	0.04	95.8
Cholecystectomy Study design	11	1.47 (1.24–1.71)	< 0.01	78.2
Case–control studies	3	2.61 (0.41–4.80)	0.16	90.2
Cohort studies Study location	8	1.43 (1.18–1.68)	< 0.01	72.6
USA	3	2.35 (0.89–3.80)	0.14	90.1
Europe	5	1.28 (1.16–1.39)	< 0.01	0
China Study quality	3	1.89 (0.83–2.94)	0.12	91.2
High	4	1.25 (1.12–1.37)	0.02	92.8
Moderate or low Sex	7	1.74 (1.32–2.17)	< 0.01	0
Male	4	1.26 (1.14–1.38)	0.03	78.2
Female	4	1.29 (1.09–)	0.04	93

Fig 3: Funnel plot of gallstones and liver cancer risk.

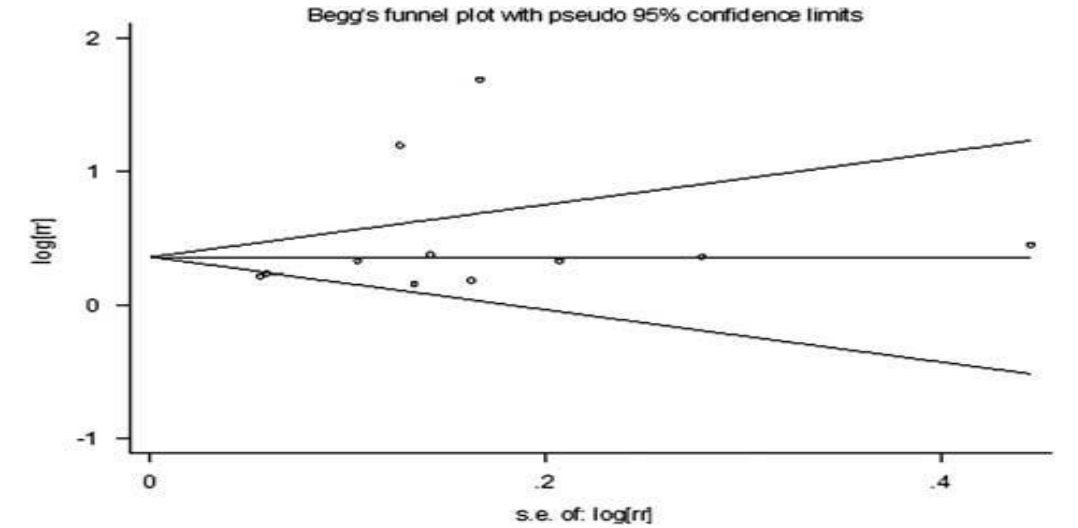


Cholecystectomy and liver cancer risk: Eight cohort studies and three case–control studies were included in the analysis for cholecystectomy with liver cancer risk. An obvious heterogeneity (I 2=78.22%, P effects pooled analysis suggested that cholecystectomy was associated with liver cancer risk (OR =1.47; 95% CI: 1.24–1.71) (Fig. 4). Subgroup analysis showed that there was no relationship between cholecystectomy and liver cancer risk in case–control studies (OR = 2.61; 95% CI: 0.41–4.80); however, the association was inversely significant in cohort studies (OR = 1.43; 95% CI: 1.18–1.68). After stratifying by geographic location, the OR was 1.89 (95% CI: 0.83–2.94) for studies conducted in China, 1.28 (95% CI: 1.16–1.39) in Europe, and 2.35 (95% CI: 0.89–3.80) for studies from the USA. The association also existed in studies with high quality (OR = 1.25, 95% CI: 1.12–1.37). No differences were observed when stratified by sex (Table 2). In the meta-regression analysis, we found that location (P = 0.03) and quality (P =0.04) were significant sources of heterogeneity. The two confounders combined could explain most of heterogeneity in a multivariate model. The stability of the association between cholecystectomy and liver cancer risk was confirmed by the sensitivity analysis. No significant publication bias was detected, either from Egger's test (P =0.23) or from Begg's test (P = 0.04) (Fig. 5).

Fig. 4



Funnel plot of cholecystectomy and liver cancer risk: fig 5



DISCUSSION:

We had systematically reviewed published studies on the association, and then got the conclusion that gallstones or cholecystectomy was positively associated with the risk of liver cancer. The association was similar in cohort and case–control studies, and across study design, study location, studies quality and sex categories. Sensitivity analysis, subgroup as well as meta-regression analysis of potential moderating variables, confirmed that the association between gallstones or cholecystectomy and the risk of liver cancer was robust.

CONCLUSION:

This meta-analysis showed that gallstones and cholecystectomy was associated with risk of liver cancer. The findings should be confirmed by future studies with validated questionnaires, well designed studies and strict control of confounders.

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