Cholecystectomy and the risk of esophageal and gastric cancer

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ABSTRACT

الأهداف: دراسة العلاقة بين استئصال المرارة وزيادة خطر الإصابة بسرطان المعدة (GC) والبلعوم (EC) وذلك من خلال عمل تحليل بعدي لمجموعة من الدراسات الاستطلاعية.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في مستشفى الشعب الأول التابع لنانتونغ جيانغسو، الصين وذلك خلال الفترة من يناير إلى إبريل 2012م. لقد قمنا بتجميع الدراسات عن طريق عمل بحث في قاعدة بيانات ميدلاين وإمبيس خلال شهر مارس 2012م، وأيضاً من خلال البحث في قائمة المراجع للدراسات التي تضمنها البحث. لقد قمنا بعمل خلاصة لعوامل الخطر النسبية (SRRs) ومدى الأمان الإحصائي 95% باستخدام نموذج الآثار العشوائية.

النتائج: لقد قمنا بجمع 12 تقدير من أصل 6 دراسات مستقلة (شملت 1622 حالة مصابة بسرطان البلعوم، و2314 حالة مصابة بسرطان المعدة). ولم يكن هناك علاقة بين استئصال المرارة وزيادة خطر الإصابة بسرطان المعدة والبلعوم (EC: SRRs 1.03, CI 0.94–1.13, heterogeneity p=0.496, I^2=0) (GC: SRRs 1.03, CI 0.93–1.13, heterogeneity p=0.652, I^2=0). وقد أظهر تحليل مجموعات الدراسات الفرعية بأن العلاقة الباطلة كانت بعيدة عن الموقع الجغرافي وتصميم الدراسة. وقد وجدنا في دراستين بأن هناك مرضى قد خضعوا لعملية استئصال المرارة قبل 10 سنوات على الأقل من زيادة خطر الإصابة بسرطان البلعوم الغدي.

خاتمة: أظهر هذا التحليل البعدي بأن استئصال المرارة لم يؤدي إلى زيادة خطر الإصابة بسرطان الخلايا الحرشفية في البلعوم وسرطان المعدة، غير أنه قد يؤدي إلى زيادة خطر الإصابة بسرطان البلعوم الغدي. ونحن بحاجة إلى من المزيد من البحث حول وبائيات هذه المرض وعمل الدراسات الاستطلاعية.

Objective: To conduct a meta-analysis of observational studies to explore the relationships between cholecystectomy and the risk of esophageal and gastric cancer (GC).

Methods: The study design was retrospective, and carried out in the First People's Hospital of Nantong, Jiangsu, China from January 2012 to April 2012. Studies were identified by a literature search of MEDLINE and EMBASE through March 31, 2012, and by manually searching the reference lists of pertinent articles. The summary relative risks (SRRs) with their 95% confidence intervals (CIs) were calculated with a random-effects model.

Results: A total of 12 estimates from 6 independent studies (including 1,622 esophageal cancer [EC] cases and 2,314 GC cases) were included in this meta-analysis. We found that cholecystectomy was not associated with risk of EC and GC (EC: SRRs - 1.03; 95% CI: 0.94-1.13; heterogeneity: p=0.496; I^2=0; n=4 studies; [GC: SRRs - 1.03; 95% CI: 0.93-1.13; heterogeneity: p=0.652; I^2=0; n=5 studies]). Sub-grouped analyses revealed that these null associations were independent of geographic location and study design. Based on 2 studies, we found patients undergoing cholecystectomy at least 10 years before had an elevated risk of esophageal adenocarcinoma (EAC).

Conclusion: The results of this meta-analysis suggest that cholecystectomy does not increase the risk of esophageal squamous cell carcinoma and GC development, but may increase EAC risk. More epidemiological research of a prospective design is needed to further clarify these associations in the future.

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Esophageal cancer (EC) is the sixth leading cause of cancer mortality in the world,[1] with an estimated of 407,000 people dying from this disease annually.[2] It has 2 main histological forms: esophageal squamous cell carcinoma (ESCC), and esophageal adenocarcinoma (EAC), which show marked differences in carcinogenesis, tumor biology, and patient characteristics. In recent years, an increased incidence of EAC and a decreased incidence of ESCC have been seen in the United States and Western Europe.[3-5] The most known risk factors for ESCC are tobacco smoking, dietary carcinogen exposure, and alcohol consumption, while for EAC, symptoms of gastroesophageal reflux (GER), male gender, white race, obesity, and tobacco smoking are consistently identified as established risk factors.[6,7]

Gastric cancer (GC) is the fourth most common cancer type and the second leading cause of death due to cancer in the world.[1] Surgical resection is still the primary curative treatment choice, with a 5-year survival rate ranging from 10-30%.[8] Therefore, the prospect of primary prevention is appealing, but little is known of its etiological factors apart from *Helicobacter pylori* (HP) strains, pickled vegetables, high salt intake, and tobacco smoking.[9-12]

Cholecystectomy has long been introduced for the treatment of uncomplicated gallstone disease over a hundred years ago. Recently, several clinical studies have investigated the relationship between a prior cholecystectomy and the risk of cancer or precancerous lesion development,[13-17] especially the relationship between cholecystectomy and colorectal cancer risk (CRC).[18,19] Patients who have their gallbladder removed would have an increased reflux of bile and pancreatic juice from the duodenum to the stomach and esophagus, which may result in the development of erosive esophagitis and gastritis[20] and intestinal metaplasia of the stomach.[21] Animal and clinical studies have reported that trypsin and bile acids in the duodenal juice are particularly cytotoxic and carcinogenic to the esophageal and gastric mucosa.[22,23]

Several epidemiological studies have evaluated the risk of developing gastric and EC after cholecystectomy for benign gallbladder disease with inconsistent results.[13-15,24-28] To provide overall quantitative estimates of such associations, we combined all available evidence of observational studies on cholecystectomy and esophageal and GC using a method of meta-analysis.

Methods. The study design was retrospective, and carried out in the First People's Hospital of Nantong, Nantong, China from January 2012 to April 2012. Ethical approval was obtained from the medical ethics committee of the First People's Hospital of Nantong.

Data sources and searches. A comprehensive, computerized literature search was conducted in MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974), through March 31, 2012, by 2 independent investigators. We searched the relevant studies with the following text words and/or Medical Subject Heading (MeSH) terms: "cholecystectomy," and "gastric," or "stomach," or "(o)esophag" and "cancer," or "neoplasm", or "carcinoma", or "adenocarcinoma", and "risk" or "incidence" or "mortality". Moreover, we searched for additional studies in the reference lists of the identified articles. Only articles written in English were included.

Study selection. Primary inclusion criteria were case-control and cohort studies published as an original article, which reported relative risk (RR) estimates or raw data for a history of cholecystectomy for benign disease and the risk of esophageal or GC. Ecological studies, case reports, reviews, and editorials were not considered eligible. Two authors independently evaluated all the studies retrieved from the databases. Discrepancies between the 2 reviewers were solved by discussion. In cases of multiple publications drawn from studies of the same population, only the most recent study was included, which resulted in 2 articles being excluded.[24,28]

Data extraction. The following data from each study were abstracted using a standardized data-collection protocol: the first author's last name, country of origin, year of publication, study design, case size, the number of controls or subjects, measurement of exposure and outcome, duration of follow-up in cohort studies, covariates adjusted for in the analysis, and the effect estimates with corresponding 95% confidence intervals (CIs). From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders. When studies provided more than one estimate according to the duration of cholecystectomy before outcome was diagnosed, we extracted and combined the RRs for individuals undergoing cholecystectomy more than one year prior to outcome diagnosis. If studies reported both incidence rate and mortality rate for GC, we extracted the incidence rate, since mortality rate could be confounded by survival related factors. Data abstraction was performed independently by 2 readers and then crosschecked.

Statistical analysis. We divided epidemiological studies of the relationship between cholecystectomy and the risk of esophageal and GC into 3 general types according to design: case-control study; cohort study (rate ratio); and cohort study using external population comparisons (standardized incidence [SIR] /mortality

ratio [SMR]). As esophageal and GCs are relatively rare diseases, we ignored the distinction between the various estimates of RR (namely, OR, rate ratio, SIR, and SMR) and all measures were interpreted as RR for simplicity. The variance of the log RR from each study was calculated by converting the 95% CI to its natural logarithm by taking the width of the CI and then dividing by 3.92. If the variance were unavailable, raw data or χ^2 value or *p*-values were used to estimate the 95% CI. The summary relative risk (SRR) estimates with their corresponding 95% CIs were combined and weighted to produce pooled RRs with the use of a random-effects model, which considers both within- and between-study variation.[29] When subsites/subtype-specific estimates were available, we first analyzed together (as RR estimates for GC and EC) and then separately (as RR estimates for cancer of gastric cardia and distal stomach or for EAC and ESCC).

The homogeneity of the effects across studies was assessed using Cochran Q and I2 statistics,[30] which were used to test the differences obtained between studies due to chance. As the Q statistic has limited power, we considered statistically significant heterogeneity at a *p*-value less than 0.10. The I^2 statistic is the proportion of total variation contributed by between-study variation. It has been suggested that I^2 values of 25%, 50%, and 75% are assigned to low, moderate, and high heterogeneity.[31] Sensitivity analysis was conducted to evaluate the stability of the pooled estimates. We also evaluated the role of several potential sources of heterogeneity by sub-grouped analyses according to study design (case-control versus cohort study) and geographical locations. Studies that reported separate RRs for mutually exclusive categories of duration since gallbladder was removed (for example, 1-4 years, 5-9 years, >10 years) were pooled separately to examine how the strength of the association varied with latency interval after surgery.[15,27] All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX, USA). A 2-tailed *p*-value <0.05 was considered to be significant.

Results. *Eligible studies.* We initially identified 245 studies that reported the association between cholecystectomy and EC and GC. Of those, 239 reports were excluded due to reviews, molecular studies, case reports, reporting the same population, duplicate reports or lack of any informative data. A total of 12 estimates from 6 independent eligible studies (2 case-control and 4 cohort studies) were included (**Figure 1 and Table 1**). Of these 6 studies, 3 studies reported results on both EC and GC;[13,25,27] and 5 were from Europe[13-15,26,27] and one from Japan.[25] The ascertainment of EC and GC outcome was based on cancer/death registry in 4 studies,[13-15,25] and pathological findings in the remaining 2 studies (**Table 1**).[26,27] For research on EC, 4 studies enrolled a total of 1,622 EC cases.[13,15,25,27] Overall, most studies found a null association between risk of EC and cholecystectomy, and only one study found a significantly increased risk of EAC in patients undergoing cholecystectomy.[15] For studies on GC, 5 studies enrolled a total of 2,314 GC cases.[13,14,25-27] Collectively, most studies found a null association between cholecystectomy and risk of GC, and only one study found a significantly increased risk of distal GC following cholecystectomy.[14]

Quantitative data synthesis. Meta-analysis of these 4 studies on EC in a random-effects model showed that previous cholecystectomy was not associated with risk of EC (SRRs: 1.03; 95% CIs: 0.94-1.13). There was no significant heterogeneity among studies (*p*-value=0.496, I^2=0) (**Figure 2A**). Combining 2 studies that provided results on risk specific for ESCC and EAC,[15,27] we found cholecystectomy was associated with an increased risk of EAC (SRRs: 1.26; 95% CIs: 1.06-1.49; *p*-value=0.401; I^2=0), but not for ESCC (SRRs: 0.92; 95% CIs: 0.80-1.06; *p*-value=0.706; I^2=0). The 2 studies also presented RR of EAC or ESCC specific for similar duration after cholecystectomy: 1-4 years, 5-9 years, and ≥10 years. Combining these 2 studies according to duration, we found that a longer duration after cholecystectomy appeared to be associated with a greater EAC risk. No association was found during the first 1-9 years after cholecystectomy, whereas an excess 38% (95% CI: 1.14-1.67) of EAC risk was found for persons who had undergone cholecystectomy at least 10 years ago. No association was found between cholecystectomy and ESCC risk in strata of duration (**Table 2**). Combining 5 studies that provided results on the association of cholecystectomy and the risk of GC, we found that prior cholecystectomy was not associated with the risk of GC, with no significant heterogeneity among studies (SRRs: 1.03; 95% CI: 0.93-1.13; *p*-value=0.652; I^2=0). Combining 2 studies specific for gastric cardia cancer,[14,27] we found that cholecystectomy was not associated with risk of gastric cardia cancer (SRRs=0.87, 95% CI: 0.65-1.17) (**Figure 2B**).

In a sensitivity analysis, the overall homogeneity, and effect size were calculated by removing one study at a time. For studies on EC, pooled RRs from the sensitivity analysis ranged from 0.95 (95% CI: 0.77-1.14) (after excluding Lagergren and Mattsson[15]) to 1.04 (95% CI: 0.94-1.15) (after excluding Goldacre et al),[13] which confirmed the stability of the null association between

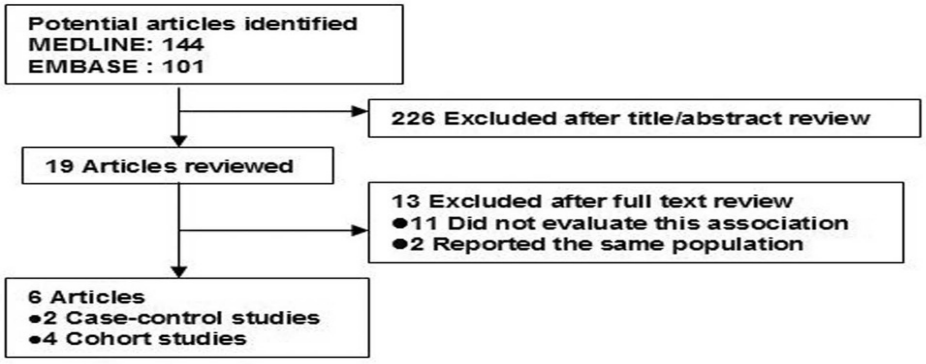

Figure 1 - Flow diagram of study selection for cholecystectomy and the risk of esophageal and gastric cancer.

Table 1 - Characteristics of studies on the association between cholecystectomy and esophageal and gastric cancer.

Author	Year	Country	Study design; no. of cases and controls/subjects	Exposure ascertainment	Outcome ascertainment	Follow-up, years	Effect estimate (95% CI)	Adjustments
Ichimiya et al[25]	1986	Japan	Cohort; 29 EC; 29 GC; 1238 control	Self-reported	Death registry	<31	EC: 0.59 (0.26-1.36)* GC: 0.92 (0.66-1.28)*	Age, gender
Sarli et al[26]	1986	Italy	Case control; 157 GC; 157 control	Surgical and ultrasound	Pathology	-	GC: 0.77 (0.09-6.40)*	Age, gender
Freedman et al[27]	2000	Sweden	Case control; 189 EAC; 167 ESCC; 262 GC; Control: 820	Self-reported	Pathology	-	ESCC: 0.82 (0.43-1.54) EAC: 1.03 (0.63-1.69) GCA: 0.67 (0.39-1.13)	Age, gender, alcohol, smoking, BMI, physical activity, educational level, intake of fruit and vegetables
Goldacre et al[13]	2005	UK	Cohort; 894 EC; 1531 GC;39254; 334813	NA	Cancer registry	NA	EC: 0.98 (0.79 –1.21) GC:1.06 (0.88-1.26)	Age, gender, calendar year of first recorded admission, residence
Lagegran et al[15]	2011	Sweden	Cohort; 193 ESCC; 126 EAC; Total N: 345,251	NA	Cancer registry	15	EAC: 1.29 (1.07-1.53) ESCC: 0.93 (0.81-1.08)	Age, gender, and calendar year
Fall et al[14]	2007	Sweden	Cohort; 854 DGC; 94 GCA; total N: 251,672	Registry	Cancer registry	11.5	DGC: 1.11(1.04–1.19) GCA:0.95 (0.76–1.16)	Age, gender, calendar year

BMI - body mass index, NA - not applicable, EC - esophageal cancer, EAC - esophageal adenocarcinoma, ESCC - esophageal squamous cell carcinoma, GC - gastric cancer, DGC - distal gastric cancer, GCA - gastric cardia cancer, *the relative risk and 95% confidence interval (CI) were derived from raw data

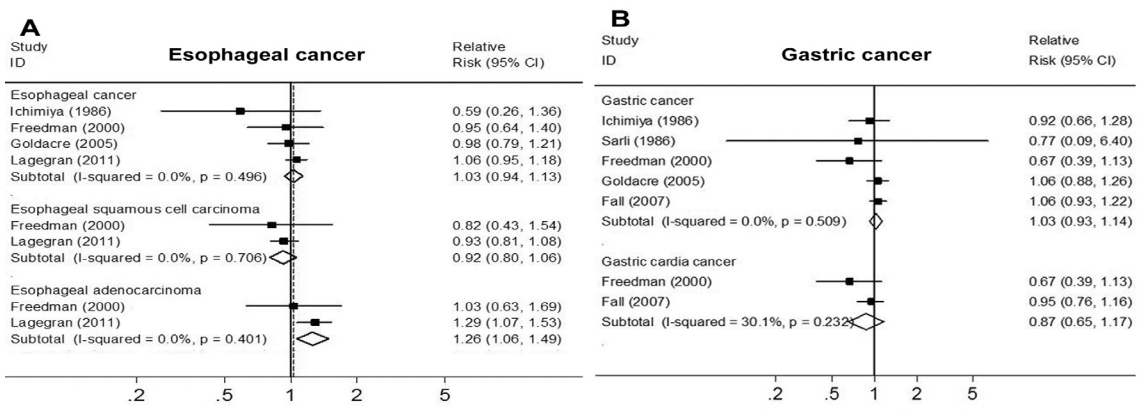

Figure 2 - Forest plots of risk of esophageal (**A**) and gastric cancer (**B**) after cholecystectomy. Squares represent the study-specific relative risk. Diamonds represent the summary relative risks. Horizontal lines represent 95% confidence intervals (CIs).

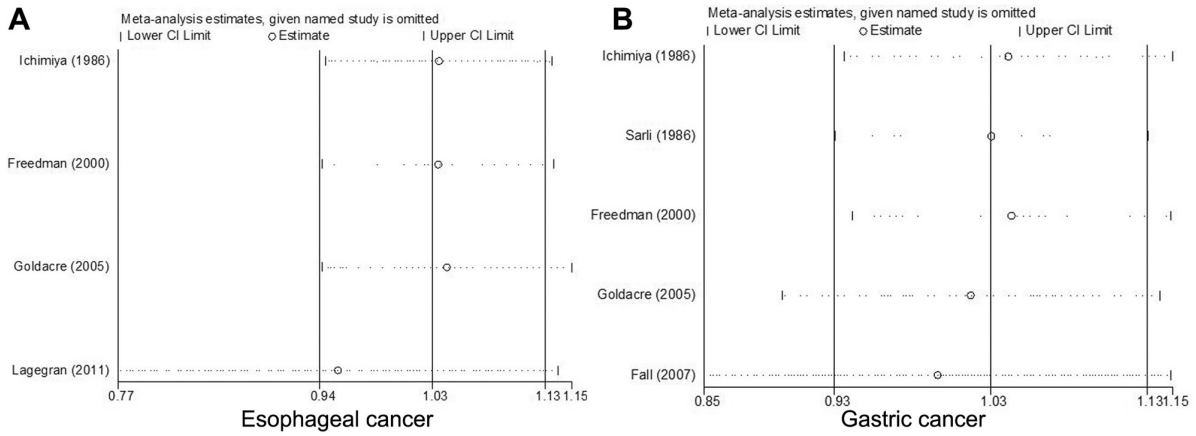

Figure 3 - Influence of removing studies one by one on effect estimates of esophageal (**A**) and gastric cancer (**B**). Circles are effect estimates and horizontal dotted lines were 95% confidence intervals for meta-analysis of the remained studies; the vertical line in the center is the pooled effect estimate for all studies.

Table 2 - Pooled relative risk of esophageal cancer according to duration of cholecystectomy from 2 studies.[15, 27]

Duration, years	Esophageal adenocarcinoma		Esophageal squamous cell carcinoma	
	RR (95% CI)	*P*-value heterogeneity; I^2 (%)	RR (95% CI)	*P*-value heterogeneity; I^2 (%)
1-4	1.15 (0.78-1.69)	0.867; 0	0.86 (0.67-1.11)	0.759; 0
5-9	1.32 (0.94-1.84)	0.782; 0	0.78 (0.62-0.98)	0.418; 0
≥10	1.38 (1.14-1.67)	0.610; 0	1.01 (0.88-1.15)	0.944; 0

RR - relative risk; CI - confidence interval

cholecystectomy and the risk of EC. For studies on GC, pooled RRs ranged from 1.00 (95% CI: 0.85-1.15) after excluding Fall et al[14] to 1.04 (95% CI: 0.94-1.15) after excluding Freedman et al,[27] which confirmed the stability of the null association between cholecystectomy and the risk of GC (**Figure 3**).

We then conducted a subgroup meta-analyses by geographical location and study design. We obtained non-significant associations between cholecystectomy and EC risk for studies conducted in both Asia (SRRs= 0.59, 95% CI: 0.26-1.35) and Europe (SRRs=1.04, 95% CI: 0.95-1.14). Also, non-significant associations between cholecystectomy and GC risk were also found in both Asian and European studies. In addition, the summary estimates for EC associated with a history of cholecystectomy were not statistically significant in both case-control (SRRs=0.95, 95% CI: 0.64-1.40) and cohort studies (SRRs=1.03, 95% CI: 0.92-1.15). Similarly, the association between cholecystectomy and GC risk was also not significant in both case-control (SRRs=0.68, 95% CI: 0.40-1.13) and cohort studies (SRRs=1.05, 95% CI: 0.94-1.16) (**Table 3**).

Discussion. In the comprehensive meta-analysis, we find that cholecystectomy does not increase the overall risk of EC and GC. However, an excess EAC risk was found in subjects who have undergone cholecystectomy before more than 10 years. Most of the studies on the association between cholecystectomy and risk of cancer are research of colorectal caner, including 2 published meta-analyses, which indicated an increased risk of CRC following cholecystectomy.[19,32] The mechanisms for such a positive link are that the continuous flow of bile and enhanced secondary bile acids (particularly deoxycholic acid) or metabolites are secreted into the gut after cholecystectomy, which may enhance the colon exposure to bile salts, lead to damage of the colonic mucosa, increase cellular proliferation, and therefore, have a carcinogenic effect on the colonic mucosa.[33-35] In the present study, no association between cholecystectomy, and the risk of EC and GC was found. The absence of a positive link might imply that the duodenogastric reflux (DGR) and the subsequent chronic inflammatory reaction in the gastric mucosa after cholecystectomy is not associated with neoplastic changes. We presume that the reflux

Table 3 - Subgroup analysis of relative risks (RR) for the association between cholecystectomy and esophageal and gastric cancer.

Subgroup	References number	RR (95% CI)	Tests for heterogeneity		
			Q	P	I^2 (%)
Esophageal cancer					
Geographical region					
Europe	3	1.04 (0.95-1.14)	0.62	0.733	0
Asia	1	0.59 (0.26-1.35)	-	-	-
Study design					
Case control	1	0.95 (0.64-1.40)	-	-	-
Cohort	3	1.03 (0.92-1.15)	2.21	0.331	9.6
Gastric cancer					
Geographical region					
Europe	4	1.04 (0.94-1.16)	2.82	0.42	0
Asia	1	0.92 (0.66-1.28)	-	-	-
Study design					
Case control	2	0.68 (0.40-1.13)	0.02	0.901	0
Cohort	3	1.05 (0.94-1.16)	0.63	0.728	0

I^2= 100%×(Q-df)/Q, where Q is Cochran's heterogeneity statistic; df - degrees of freedom; P - probability; I - inconsistency; CI - confidence interval

following cholecystectomy is only transient, and the possible change in bile composition towards bile with a carcinogenic potentiality following cholecystectomy does not result in clinically significant tumors in the stomach. In the present study, we also explored the relationship between cholecystectomy and the risk of EAC, the incidence of which has increased rapidly over the last 3 decades in Western countries.[4] Based on 2 studies,[15,27] we found that patients had a 26% increased risk for EAC development after cholecystectomy. Furthermore, we found patients who had their gallbladder removed at least 10 years ago (but not 1-9 years ago) would have enhanced risk of EAC. The exact reasons for this positive association are not well known now, but we assume that this may be due to an increased prevalence of duodenal-gastro-esophageal reflux after cholecystectomy, which has been reported in animal and human studies.[21,36] The DGER is strongly associated with the development of EAC.[37] In addition, bile, and pancreatic enzymes may be cytotoxic and carcinogenic to esophageal mucosa, as suggested by experimental animal models of induced bile reflux.[38] However, this positive association was only based on 2 studies conducted in Sweden. We should caution that this positive relationship was only due to chance, because we could not exclude a type I error.

There are several potential limitations in this meta-analysis, which should be discussed. First, 2 of the 6 studies included in this meta-analysis used a case-control design, which is more susceptible to recall and selection biases than a cohort design. Cohort studies might be affected by detection bias, because patients undergoing cholecystectomy are under increased medical surveillance and thus might be more likely to be diagnosed with EC and GC at an early stage. These biases may distort the true effects. Second, most studies included in this meta-analysis have no information on the criteria used for cancer diagnosis, especially in cohort studies where disease ascertainment were all based on cancer or death registry. These would introduce potential measurement error into our meta-analysis. Third, residual confounding is likely to be present. Obesity is one of the important risk factors for both gall bladder disease and EAC,[39] however, only one case-control study was controlled for BMI.[27] Similarly, In addition, HP infection is one of the most important risk factors for GC, however, the risk estimates from all the included studies were not adjusted for this. Finally, the possibility of publication bias is of concern, because studies with small sample size or null results tend not to be published. We cannot assess publication bias of the current analysis due to only 4 studies included for EC, and 5 for GC. We tried to identify all relevant data and retrieve additional published information, but some missing data were unavoidable. Cholecystectomy is an important surgical procedure with an approximate incidence of 200 operations per 100,000 inhabitants per year in Western countries.[40] In the present meta-analysis, we found a weak association between cholecystectomy and EAC risk. However, the individuals' increased risk of developing EAC is negligible owing to the rarity and the small absolute risk of EAC. So, we should not restrict the indications for cholecystectomy or delay the operation because complications to symptomatic gallstone disease are potentially harmful.

In conclusion, this meta-analysis shows no association between a previous cholecystectomy and the risk of GC and ESCC development. However, based on 2 studies we found that patients undergoing cholecystectomy more than 10 years before would have elevated risk of EAC. Further epidemiological research of a prospective design is needed to further clarify these associations in the future.

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