Cholecystectomy and the risk of esophageal and gastric cancer

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ABSTRACT

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; I²=0; n=4 studies; [GC: SRRs - 1.03; 95% CI: 0.93-1.13; heterogeneity: p=0.652; I²=0; n=5 studies]). Subgroup 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.
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.6–8

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%.6 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 gastritis20 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 gastric 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
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,

5 were from Europe and one from Japan. The ascertainment of EC and GC outcome was based on cancer/death registry in 4 studies and pathological findings in the remaining 2 studies (Table 1). For research on EC, 4 studies enrolled a total of 1,622 EC cases. 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. For studies on GC, 5 studies enrolled a total of 2,314 GC cases. 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.

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 GC (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, 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 risk was found in the remaining 2 studies (SRRs=0.87, 95% CI: 0.65-1.17) 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, 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) to 1.04 (95% CI: 0.94-1.15) (after excluding Goldacre et al), which confirmed the stability of the null association between...
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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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design; no. of cases and controls/subjects</th>
<th>Exposure ascertainment</th>
<th>Outcome ascertainment</th>
<th>Follow-up, years</th>
<th>Effect estimate (95% CI)</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ichimiya et al</td>
<td>1986</td>
<td>Japan</td>
<td>Cohort; 29 EC; 29 GC; 1238 control</td>
<td>Self-reported</td>
<td>Death registry</td>
<td>&lt;31</td>
<td>EC: 0.59 (0.26-1.36)</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Sarli et al</td>
<td>1986</td>
<td>Italy</td>
<td>Case control; 157 GC; 157 control</td>
<td>Surgical and ultrasound</td>
<td>Pathology</td>
<td>-</td>
<td>GC: 0.77 (0.09-6.40)</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Freedman et al</td>
<td>2000</td>
<td>Sweden</td>
<td>Case control; 189 EAC; 167 ESCC; 262 GC; Control: 820</td>
<td>Self-reported</td>
<td>Pathology</td>
<td>-</td>
<td>EC: 0.82 (0.43-1.54)</td>
<td>Age, gender, alcohol, smoking, BMI, physical activity, educational level, intake of fruit and vegetables</td>
</tr>
<tr>
<td>Goldacre et al</td>
<td>2005</td>
<td>UK</td>
<td>Cohort; 894 EC; 1531 GC; 39254; 334813</td>
<td>NA</td>
<td>Cancer registry</td>
<td>NA</td>
<td>GC: 0.98 (0.79-1.21)</td>
<td>Age, gender, calendar year of first recorded admission, residence</td>
</tr>
<tr>
<td>Lagegran et al</td>
<td>2011</td>
<td>Sweden</td>
<td>Cohort; 193 ESCC; 126 EAC; Total N: 345,251</td>
<td>NA</td>
<td>Cancer registry</td>
<td>15</td>
<td>ESCC: 0.93 (0.81-1.08)</td>
<td>Age, gender, and calendar year</td>
</tr>
<tr>
<td>Fall et al</td>
<td>2007</td>
<td>Sweden</td>
<td>Cohort; 854 DGC; 94 GCA; total N: 251,672</td>
<td>Registry</td>
<td>Cancer registry</td>
<td>11.5</td>
<td>DGC: 1.11 (1.04-1.19)</td>
<td>Age, gender, calendar year</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Duration, years</th>
<th>Esophageal adenocarcinoma</th>
<th>P-value heterogeneity; F(%)</th>
<th>Esophageal squamous cell carcinoma</th>
<th>P-value heterogeneity; F(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>1.15 (0.78-1.69)</td>
<td>0.867; 0</td>
<td>0.86 (0.67-1.11)</td>
<td>0.759; 0</td>
</tr>
<tr>
<td>5-9</td>
<td>1.32 (0.94-1.84)</td>
<td>0.782; 0</td>
<td>0.78 (0.62-0.98)</td>
<td>0.418; 0</td>
</tr>
<tr>
<td>≥10</td>
<td>1.38 (1.14-1.67)</td>
<td>0.610; 0</td>
<td>1.01 (0.88-1.15)</td>
<td>0.944; 0</td>
</tr>
</tbody>
</table>

RR - relative risk; CI - confidence interval

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 cancer, 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 reflex (DGR) and the subsequent chronic inflammatory reaction in the gastric mucosa after cholecystectomy is not associated with neoplastic changes. We presume that the reflux...
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. Based on 2 studies, 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. The DGER is strongly associated with the development of EAC. In addition, bile, and pancreatic enzymes may be cytotoxic and carcinogenic to esophageal mucosa, as suggested by experimental animal models of induced bile reflux. 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, however, only one case-control study was controlled for BMI. 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. 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.

References


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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RR (95% CI)</th>
<th>Tests for heterogeneity</th>
<th>I^2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q</td>
<td>P</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographical region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1.04 (0.95-1.14)</td>
<td>0.62</td>
<td>0.733</td>
</tr>
<tr>
<td>Asia</td>
<td>0.59 (0.26-1.35)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case control</td>
<td>0.95 (0.64-1.40)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cohort</td>
<td>1.03 (0.92-1.15)</td>
<td>2.21</td>
<td>0.331</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographical region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1.04 (0.94-1.16)</td>
<td>2.82</td>
<td>0.42</td>
</tr>
<tr>
<td>Asia</td>
<td>0.92 (0.66-1.28)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case control</td>
<td>0.68 (0.40-1.13)</td>
<td>0.02</td>
<td>0.901</td>
</tr>
<tr>
<td>Cohort</td>
<td>1.05 (0.94-1.16)</td>
<td>0.63</td>
<td>0.728</td>
</tr>
</tbody>
</table>

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