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**Cholecystectomy and the risk of alimentary tract cancers: A systematic review**

Coats M *et al*. No association between cholecystectomy and cancers

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**Abstract**

**Aim**: To investigate the association between cholecystectomy and gastro-intestinal tract (GIT) cancers.

**Methods**: We conducted a systematic review according to the PRISMA guidelines. A MEDLINE search was performed with predefined search criteria for English Language articles on the association between cholecystectomt and GIT cancers. Additional articles were retrieved by manual search of references. All relevant articles were accessed in full text. Data on study type; cases; controls; country; effect estimate; adjustments for confounders and quality of publication were extracted. The quality of the publications were scored by adherence to the STROBE checklist. The data for each part of the GIT were presented in separate tables.

**Results**: Seventy-five studies and 5 meta-analyses satisfied the predefined criteria for inclusion and were included in this review. There were inconsistent reports and no strong evidence of an association between cholecystectomy and cancers of the oesophagus (Adenocarcinoma), pancreas, small bowel and right-sided colon cancers. In squamous cancer of the oesophagus, cancers of the stomach, liver, bile ducts, small bowel and left sided colon cancers, good quality studies suggested a lack of association with cholecystectomy. Equally, distal colon and rectal cancers were found not to be associated with cholecystectomy. Several mechanisms for carcinogenesis/promotion of carcinogensis have been proposed. These have focused on a role for bile salts in carcinogenesis with several potential mutagenic molecular events and gut metabolic hormones signaling cell proliferation or initiation of carcinogenesis.

**Conclusion**: This is a comprehensive review of the association between GIT cancers and cholecystectomy. This review found no clear association between cholecystectomy and GIT cancers.

**Key words:** Cholecystectomy; Cancer; gastro-intestinal tract; carcinogenesis

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**Core tip:** This systematic review explores the association between cholecystectomy and individual gastro-intestinal tract cancers and proposed mechanisms of carcinogenesis. The review finds no clear association between cholecystectomy and cancers of the gastro-intestinal tract.

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**INTRODUCTION**

The presence of gallstones increases with age with an estimated median prevalence ranging from 5.9% to 21.9% in large population surveys[1]. Gallstone disease constitutes a significant health problem affecting 10% to 15% of adults in the western world[2-4]. Gallstone related problems such as cholecystitis and choledocholithiasis are becoming the leading cause of inpatient hospital admissions for gastrointestinal problems[5]. Cholecystectomy is the treatment of choice for symptomatic cholelithiasis. Since 1988, laparoscopic cholecystectomy has evolved globally and more than 90% of cholecystectomies are carried out either acutely or electively using laparoscopy. Laparoscopic cholecystectomy has become standard practice for benign gallbladder disease[6]. Several studies have shown an early increase of cholecystectomies after the adoption of laparoscopic cholecystectomy[7-9]. Some studies have shown a sustained increase which is independent of total population growth[6].

Over the past decade, a number of studies have investigated the association between cholecystectomy and/or cholelithiasis with gastro-intestinal tract (GIT) cancers. Although cholelithiasis is reported to be strongly associated with an increased risk of biliary tract cancers[10], the association with other GIT cancers is not established. With regards to cholecystectomy, authors of meta-analysis reported that pooled results from case-control studies had shown a significant elevation of increased cancer risk after cholecystectomy but pooled results from cohort studies had not[11]. However, cohort studies, which are less prone to bias have been less commonly undertaken. Further, the time scale between the exposure and the risk is not always reported. This is important given that GIT cancers and cholelithiasis are common and may arise independently. However, the symptoms of cancer may be misinterpreted to be symptoms of cholelithiasis.

The proposed mechanism for the increased risk of digestive tract cancers after cholecystectomy is through alteration of bile flow[11,12], increased exposure[13], alteration of bile salts[14] or alterations to metabolic hormone levels[15].

Since both cholecystectomy and a diagnosis of cancer of the gastro-intestinal tract are common[6,16,17], the same person could encounter both within a lifetime, by chance alone reasonably frequently. Cancers may be missed at laparoscopic cholecystectomy for gallstones[18]. For these reasons, it is important to establish and quantify the association between cholecystectomy and gastro-intestinal tract cancer risk to aid the informed consent process. If a real relationship exists, every patient consented for cholecystectomy, should have all the established risks explained including the potential for GIT cancers.

The objective of this study is to perform a systematic review of the literature of studies to determine whether or not there is an association between cholecystectomy and the development of GIT cancers.

**MATERIALS AND METHODS**

***Search strategy***

A comprehensive literature search of MEDLINE via the online database pubMED was carried out by two observers to identify all relevant studies for inclusion in this literature review. The search criteria (MeSH headings/index terms) included (1) “cholecystectomy”; (2) “risk of cancer” and one of the following cancer subtypes; (3) “oesophageal”; (4) “gastric”; (5) “pancreatic”; (6) “bile duct”; (7) “liver”; (8) “small intestine”; and (9) “colorectal”. In addition, MeSH headings, index terms of ‘bile salts’, ‘risk of cancer’ and “carcinogenesis” were used to search for the proposed mechanism of action.

Only English language articles were included in the analysis. Review articles, case reports and studies based on autopsy results were excluded. Articles, which combined the risk for cholelithiasis and cancer, were also excluded. Articles with poor study design (*e.g.*, Inappropriate comparisons or without controlling for appropriate confounders) were excluded. No restriction was placed on the journal in which it was published, location or date of the study. Studies should report statistical ratios with 95% confidence intervals (95%CIs) or provide data to enable derivation of rate or risk ratios. Rarely, studies reporting odds ratio (or) with 95%CIs were included if their inclusion was deemed relevant. References from included studies were searched manually to identify missing relevant publications. When data of a study group were used in multiple articles, only the most recent paper was used for this review.

***Data extraction***

Each study was analyzed based on type of methodology (meta-analysis; case control; cohort) and study size indicating the number of GIT cancers and control cases. The data sources were noted for both the exposure and outcome parameters. The number of years follow up as reported in the study was recorded when available and the effect estimate [relative risk (RR); hazard ratio (HR); OR; Incidence rate ratio (IRR)] with its calculated 95%CI was noted. Where risk ratios were adjusted for age, gender and other confounding factors this was recorded. Extracted data were stratified by the site of cancer, year of publication, country where the study was undertaken and any other relevant factors.

***Assessment of study quality***

The quality of the different studies was measured using the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology[19] checklist. Each item on the STROBE checklist was scored by one of the authors as follows: 0, item not reported; 1, item reported but inadequately; 2, item reported adequately. Although there are 22 items on the STROBE checklist, item number 1 was divided into 2 sections, item number 6 was divided into two sections, item number 12 was divided into 5 sections, item number 13 was divided into three sections, item number 14 was divided into two sections and item number 16 was divided into three sections. As such, the maximum score that any publication could achieve was 66. In order to be comprehensive, no minimum score was set for inclusion.

***Statistical analysis***

Descriptive statistics were quoted from the original source where provided. In a few circumstances, it was necessary to derive the OR and 95%CI from the data provided. Statistical analysis was done using IBM SPSS v21 (SPSS, Chicago, IL, United States).

**RESULTS**

***Included studies***

The total number of initial publications retrieved from MEDLINE for the association between cholecystectomy and GIT cancers was 1394 articles. After screening titles and abstracts, 142 were included for full text analysis. After exclusion of studies, which did not meet the selection criteria, 75 studies (cohort and case-control) describing an association between cholecystectomy and a GIT cancer site were included for data extraction. Three meta-analyses were reviewed. A flow chart of the literature search is depicted in Figure 1.

***Oesophageal adenocarcinoma and squamous cell carcinoma***

Two case control studies[20,21] with 321 cases between them and one cohort study[22] based on 91 cases, found that cholecystectomy, despite its effect on gastric juice did not appear to increase the risk of oesophageal adenocarcinoma. By contrast, two cohort studies[23,24] based on 179 cases, found a moderate association between cholecystectomy and subsequent oesophageal adenocarcinoma, however, the absolute risk was found to be small. The results from a meta-analysis[25] suggested that patients who had a cholecystectomy more than 10 years previously are at an increased risk for oesophageal adenocarcinoma (SRRs = 1.26; 95%CI: 1.06–1.49). Descriptive characteristics of studies on the association between cholecystectomy and Oesophageal Adenocarcinoma are shown in Table 1.

Two case control[20,21] and three cohort studies[23,24,26] based on 618 cases found that cholecystectomy was not associated with an increased risk of oesophageal squamous cell carcinoma. The results from a meta-analysis, which included some of these studies, confirmed the null association (SRRs = 0.92; 95%CI: 0.80-1.06), which was independent of study location or study design[25]. Descriptive characteristics of studies on the association between cholecystectomy and Oesophageal squamous cell carcinoma are shown in Table 2.

***Gastric cancer***

Two case control studies[26,27] based on 186 cases found that cholecystectomy did not increase the risk of gastric cancer. However, one case control study[21] and three cohort studies[22,28,29] based on a total of 1491 cases found an increased risk of gastric cancer after a cholecystectomy. The results from a meta-analysis, which included some of these studies, found that prior cholecystectomy was not associated with the risk of gastric cancer (SRRs = 1.03; 95%CI: 0.93–1.13). Descriptive characteristics of studies on the association between cholecystectomy and gastric cancer are shown in Table 3.

Two case control[20,21] and one cohort study[28] based on a total of 478 cases found that prior cholecystectomy was not associated with an increased risk of gastric cardia cancer. The results from a meta-analysis[25] which included two studies specific for gastric cardia cancer[20,28] found that cholecystectomy was not associated with risk of gastric cardia cancer(SRRs = 0.87; 95%CI: 0.65–1.17). Descriptive characteristics of studies on the association between cholecystectomy and gastric cardia cancers are shown in Table 4.

***Pancreatic cancer***

There are at least 23 epidemiological studies investigating the association between cholecystectomy and pancreatic cancer (see table 5). The results obtained from these studies are contradictory. A significantly increased risk between previous cholecystectomy and pancreatic cancer was found in four case control studies[21,30-32] and four cohort studies[33-36]. However, no association was found among nine case-control studies[37-45] and six cohort studies[22,26,29,46-48].

A meta-analysis based on 18 studies (8 cohort studies and 10 case-control studies) reporting a total of 12129 cases of pancreatic cancer found that 9 studies reported a positive (but not significant) association between previous cholecystectomy and risk of pancreatic cancer and 5 studies found a significantly increased risk of pancreatic cancer in patients who had a cholecystectomy[49]. The meta-analysis found that compared with individuals without a history of cholecystectomy, those who had their gallbladder removed had a 23% excess risk of pancreatic adenocarcinoma (SSRs = 1.23; 95%CI: 1.12-1.35). Sub-group analysis revealed that the increased risk was independent of geographic location, gender, study design and confounders including BMI, diabetes and smoking. The risk of pancreatic cancer remained elevated two and five years post cholecystectomy. Descriptive characteristics of studies on the association between cholecystectomy and pancreatic cancer are shown in table 5.

***Extra-hepatic bile duct cancer***

A case control study comparing the incidence of cancers of the extra-hepatic bile duct and ampulla of Vater, before and after the introduction of laparoscopic cholecystectomy, found, no increase in the incidence of these cancers in the short term[50]. The study was based on the observed increase in the rate of laparoscopic cholecystectomy since its introduction in 1990[7-9]. One case-control study[21] and two cohort studies[29,34] based on 143 cases of extra-hepatic bile duct cancer did not find a significant association in cancer risk with a history of cholecystectomy. Descriptive characteristics of studies on the association between cholecystectomy and extra-hepatic bile duct cancers are shown in Table 6.

***Liver cancer***

One case-control study[21] (332 incident cases of cancer of the liver) found a significant association between a previous history of cholecystectomy and an increased risk of liver cancer (OR = 1.26; 95%CI: 1.12–1.41). This significant association was found for hepatocellular carcinoma (OR = 1.34; 95%CI: 1.17–1.52) and not for cholangiocarcinoma (OR = 1.19; 0.98–1.43). However, three cohort studies[22,29,34] based on 173 incident cases of liver cancer in patients who had a previous cholecystectomy did not show an increased risk of liver cancer after cholecystectomy. Descriptive characteristics of studies on the association between cholecystectomy and liver cancer are shown in Table 7.

***Intestinal (small bowel) cancer***

One case control study[21] based on 148 incident cases of small bowel cancer found a significant association between a history of cholecystectomy and an increased risk of carcinoid tumors of the small bowel (OR = 1.78; 95%CI: 1.41–2.25) and a weaker increased risk of adenocarcinoma of the small bowel (OR = 1.34; 95%CI: 1.02–1.76). In addition, two cohort studies[51,52] found a significantly elevated risk of small bowel tumors after cholecystectomy. The risk was found to be elevated for both proximal small bowel adenocarcinoma and for distal small bowel carcinoid tumors. In the first year after cholecystectomy, the age adjusted rate ratios for cancer of the small bowel were significantly high at 10.43; 95%CI: 7.79–13.99. Thereafter, the rate ratio reduced with increasing time since operation. By 8 years and more from cholecystectomy, the rate ratio was not significantly raised at 2.47; 95%CI: 0.82–6.28[52]. Descriptive characteristics of studies on the association between cholecystectomy and small intestine cancers are shown in Table 8.

***Colorectal cancer***

Three case-control studies reporting 132 cases of colorectal cancer found a significant association between cholecystectomy and colorectal cancers[43,53,54]. The highest reported RR was 2.11 (95%CI: 1.19-3.85)[54]. This finding was supported by three cohort studies[29,55,56] suggesting an increased risk of colorectal cancer by up to 56% (RR = 1.56, 95%CI: 1.12-2.17[29]). Similar trends were identified in another four case-control and two cohort studies but these were not statistically significant[57-62]. The largest and most recent study in the literature encompasses 3907 incident cases and, with age and gender adjustments, showed no association (OR = 0.97, 95%CI: 0.92-1.02). This finding is supported by five more studies[63-67]. Descriptive characteristics of studies on the association between cholecystectomy and colorectal cancers are shown in Table 9.

***Proximal colon cancer***

Six studies (4 case-control; 2 cohort) demonstrated a positive association between proximal colon cancer and cholecystectomy[59,62,63,67-79]. An extremely high association (OR = 5.85, 95%CI: 2.13-16.7) was found in one particular Chinese study but 95%CIs were broad and a low quality assessment score indicates these findings are somewhat unreliable[62]. However, a well-designed study scoring highly (57 out of 66) on the STROBE checklist also showed a positive association (RR = 1.35, 95%CI: 0.97-1.88). The study performed a comprehensive statistical analysis to account for several confounding factors (age, smoking, BMI, lifestyle and dietary factors, comorbid disease such as diabetes)[59]. This strengthens the findings of the study considerably. However, this study was based on a female only cohort, which raises the possibility of increased gender-based risk. Two other studies selected for analysis showed no association between proximal colon cancers and cholecystectomy[21,51]. Descriptive characteristics of studies on the association between cholecystectomy and colorectal cancers are shown in Table 10.

***Distal colon cancer***

Subgroup analysis within five of the selected studies showed that there was no association of cholecystectomies with distal colon cancer[21,51,59,67]. However, Zeng *et al*[62] calculated an OR of 1.87 (95%CI: 0.943-8.14) but the design of this study and statistical methodology was poor which renders meaningful interpretation difficult. Descriptive characteristics of studies on the association between cholecystectomy and colorectal cancers are shown in Table 11.

***Rectal cancer***

The rectum lies farthest from the gall bladder in the GI tract and any proposed mechanism relating to altered flow of bile metabolism following cholecystectomy causing cancer would be presumed to have the least effect here. A meta-analysis of 42 studies encompassing 14226 incident cases showed no significant risk of rectal cancer following cholecystectomy (OR = 1.14, 95%CI: 0.92-1.41)[70]. This finding is supported by three other case-control studies[53,62,63,65] and two cohort studies[56,64]. Linos *et al*[57] showed a reduced risk of rectal cancer in women post cholecystectomy (RR = 0.5 95%CI: 0.1-1.3) and an increased risk in men (RR = 2.3 95%CI: 0.9-4.8). These findings are not clinically significant and do not correlate with any other studies. They are most likely artifact due to small sample size and lack of adjustment for confounding factors and the results should be interpreted cautiously. Descriptive characteristics of studies on the association between cholecystectomy and colorectal cancers are shown in Table 12.

***Proposed mechanisms of carcinogenesis***

When the normal gallbladder is in situ, wide physiological fluctuations occur in the bile-emptying rate from the common bile duct (CBD) into the duodenum[71,72]. After cholecystectomy, all the bile secreted from the liver enters the CBD and drains through the sphincter of Oddi into the duodenum, thereby producing a continuous flow. Although the net effect of cholecystectomy on bile secretion is not fully understood, cholecystectomy results in globally increased trans-papillary bile flow and CBD emptying rate[73]. The increased and continuous bile flow into the duodenum can either reflux back into the stomach and oesophagus or proceed cephalad down to the small and large bowel. Increased duodeno-gastro-oesophageal reflux after cholecystectomy is controversial[74-76] and probably relates to the method of measurement[76]. The effects of refluxed bile may be augmented by additional noxious refluxed material such as acid and pancreatic enzymes[77].

Bile acids were initially proposed as carcinogenic. However, later work with rodent models suggested that they should be regarded as cancer promoters (increasing tumorigenesis by other known carcinogens) rather than carcinogens acting independently[78-80]. More recent evidence supports the view that bile acids (primary or secondary) are carcinogens in humans[81,82]. Bile acids cause DNA damage probably indirectly through induction of oxidative stress and production of reactive oxygen species which damage DNA[83]. Repeated DNA damage may increase the mutation rate including that of tumor suppressor genes and oncogenes[84]. Additional reports suggest that bile acids at an increased concentration induce apoptosis and hence select for apoptosis resistant cells[85] with an increased rate of mutation[86].

More than 95% of the bile salts synthesized in the liver are reabsorbed either by passive diffusion in the proximal jejunum, or by active transport in the distal ileum. The bile salts are then transported via the portal vein back to the liver where they are absorbed by hepatic cells and again secreted as bile. The enterohepatic recirculation of bile salts recycles about 6–8 times daily[87]. The bile salts are the ionized form of the bile acid molecule. The carboxyl group in the side chain of the bile salt molecule when activated can react with glycine or taurine forming amides known as conjugated bile salts. Intestinal anaerobic bacteria, for example species of the Bacteroides fragilis group, deconjugate and dehydroxylate the bile salts by removing glycine and taurine residues and the hydroxyl group at position 7[14]. The primary bile salts are then biochemically transformed into the secondary bile acids, deoxycholic acid and lithocholic acid. The deconjugated and dehydroxylated bile salts are less soluble in intestinal chyme and are therefore less readily absorbed from the intestinal lumen than the bile salts that have not been subjected to bacterial metabolism. Based on both experimental and observational epidemiologic studies, deoxycholic acid has been classified as a potential tumor promoter in conjunction with other genotoxic agents[88-90]. Studies of concentration levels of deoxycholic acid in both fecal and serum samples have been associated with colorectal adenomas and cancer[91-93]. The relatively prominent distribution of adenocarcinoma in the duodenum and proximal jejunum, particularly after cholecystectomy, has been attributed to proximity to the juncture of the common bile duct[51].

The other culprits in this scenario include gut metabolic hormones. As an illustrative example, elevated circulating levels of Cholecystokinin (CCK) have been found after cholecystectomy[94]. Normal human pancreas and pancreatic cancer have been found to possess receptors for CCK. CCK has been shown to stimulate the growth of human pancreatic cancer cell lines[95] and initiate pancreatic carcinogenesis in rodents[96].

**DISCUSSION**

This systematic review has found inconclusive evidence for an association between a history of cholecystectomy and cancers of the Gastro-intestinal tract at each site. The contradictory evidence was found both in case-control studies and in cohort studies. The same level of inconsistency was noted by meta-analyses in individual cancer sites. The most likely explanation for this level of inconsistency is the quality of studies. In general, case-control studies are more susceptible to selection bias than are cohort studies. This is mainly due to the increased surveillance of patients in cohort studies which is less likely to distort the true effect[31]. Secondly, the majority of studies did not stipulate or report criteria for disease ascertainment. This was based mainly on cancer or death registry data which are subject to errors. Thirdly, Adjustment for confounding factors has been variable amongst the studies but inadequate in the majority. It is very likely that the same risk factors for cholelithiasis and cancer such as obesity, diet, ethnicity, family history, cigarette smoking, education and physical activity co-exist. Unless such confounders are adjusted for it is difficult to conclude that the risk is purely a cholecystectomy effect.

It is established that early manifestations of abdominal cancers are sometimes misdiagnosed as gallstones and treated with cholecystectomy. Some studies have shown that a not uncommon cause of readmission after laparoscopic cholecystectomy is colon cancer[18,97,98]. As such, all short term studies which did not adjust for the period between cholecystectomy and the incident cancer must be viewed with caution. Further, if there is a causal relationship between cholecystectomy and cancer, the rate ratio, representing the rate in the cholecystectomy cohort relative to that in the comparison cohort, should increase over time (due to the latent period required for the development of a cancer) and the risk should remain at long time intervals. This has not been shown with any consistency in the reported studies.

Cholecystectomy is a common procedure throughout the world[6-9]. The necessity for cholecystectomy has arisen mainly due to symptomatic gallstone disease which is age related[2]. Equally, gastro-intestinal cancers are common and increase with increasing age[81,99]. The association between cancers of the gastro-intestinal tract is more likely to be a casual rather than a causal. In order to establish a causal association, the criteria of Sackett’s modification of the Bradford-Hill criteria would need to be applied on epidemiological research[100]. There are to-date no Randomised controlled trials which have arisen to confirm nature of the association nor is it feasible to conduct such trials in the short term. The strength of the association appears weak at best, particularly when taking into account the almost universal lack of adjustment for all necessary confounders. There is lack of consistency of the association in several cohort studies with some showing an association in a positive direction and others confirming the null hypothesis of an association. Although all the studies show a temporal relationship between cholecystectomy and cancer, there is an equal temporal relationship with the gallstones phenotype. In terms of the plausibility of the association, a number of studies have proposed mechanisms for carcinogenesis by either bile salts or enteric hormones. These studies are based on *in-vitro* or animal experiments and have concluded that bile salts are either promoters increasing tumorigenesis by other known carcinogens[79,80] or carcinogens acting independently[82]. A possible objection to the contention that bile acids could be carcinogenic is based on evolutionary grounds. For a natural substance produced by the body, to be carcinogenic is counter intuitive. Hence the emphasis on bile acids being promoters of other known carcinogens or acting in high physiologic concentrations in certain individuals after high fat intake[101]. With regards to enteric hormones, the evidence was based mainly on *in-vitro* experiments. In terms of biological plausibility, it seems contrary to our understanding of how natural selection operates, that a natural substance produced by the body for a beneficial purpose could be carcinogenic. On the basis that none of the criteria have been to-date satisfactorily satisfied that no such causal relationship exists between cholecystectomy and gastro-intestinal tract cancers. It seems more likely that some of the gallstone producing phenotype, develop gastro-intestinal tract cancers as they age.

This review has several potential limitations. Although an extensive search was made of all the available literature, it is possible that some articles were accidentally missed. However, having captured the majority if not all of the available articles on the subject, it seems less likely that any missed articles would alter the conclusions made. Although it is difficult to rule out publication bias, there appears to be a reasonable number of epidemiological studies from different parts of the world, which encompass the cholecystectomy cohort with no significant differences between populations. Thirdly, a number of the publications reported in this review are of moderate quality but a reasonable number are of sufficiently higher quality. In addition, the majority of reported studies suffer from heterogeneity.

This review has included a number of historical articles on the subject. In a subject with so few articles on each of the components of the GIT, it was important to include such historic articles to avoid bias acknowledging that the inclusion of such articles would not alter the conclusion. It is reasonable to conclude that if a real effect were apparent, it would have manifested more strongly.

In conclusion, this systematic review has found contradictory evidence of an association between a history of cholecystectomy and gastro-intestinal tract cancers. Based on current evidence, there is no clear association between cholecystectomy and cancers of the gastro-intestinal tract. Additional robust, scientific studies are warranted.

**COMMENTS**

***Background***

Cholecystectomy for gallstone disease is a common operation. A number of studies have investigated the association between cholecystectomy and/or cholelithiasis with gastro-intestinal tract cancers with contradictory results.

***Research frontiers***

To the best of our knowledge, no such comprehensive systematic review of the association between cholecystectomy and gastro-intestinal tract (GIT) cancers has previously been published. The objective of this study was to review systematically all the studies which have investigated the association between cholecystectomy and GIT cancers.

***Innovations and breakthroughs***

A number of systematic reviews have been published which were focused on one or other type of GIT cancers, this is the first comprehensive systematic review which have addressed all GIT cancers and have added comments on mechanisms of carcinogenesis in different parts of the GIT.

***Applications***

Based on the lack of clear association between cholecystectomy and GIT cancers, clinicians can be assured of the benefits of cholecystectomy without the risk of GIT cancer. In consenting patients for cholecystectomy, clinicians can assure patients that no causal risk of GIT cancers after cholecystectomy was demonstrated.

***Terminology***

Carcinogenesis is the formation of cancer driven either by direct carcinogens which act independently to cause mutations or by promoters which drive cellular proliferation without causing mutations themselves. As such promoters require the field to have been exposed to a tumor initiator which could be mutagenic.

***Peer-review***

This is a comprehensive review of the world's literature highlighting the relationship between prior cholecystectomy and gastro-intestinal malignancies by site as well as proposed mechanism/pathogenesis.

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Analysis

Eligibility

Screening

Primary Search

120 records

Excluded

186 records

Excluded

67 records

Excluded

1088

Satisfaction of eligibility criteria

Cancer of GIT site

History of cholecystectomy

Case and control descriptors

Provision of risk estimate (95%CI)

Sufficient quality

306 Title and abstract evaluation

MEDLINE (Pubmed) 1394

Full text analysis

142 records

22 additional studies: Manual search of references

Included in review

75 records

**Search terms**: MeSH headings/Index terms

“cholecystectomy”, “risk of cancer”, “oesophageal”, “gastric”, “pancreatic”, “bile duct”, “liver”, “small intestine”, “colorectal”

**Figure 1 Study flow diagram.** GIT: gastro-intestinal tract.

**Table 1 Descriptive characteristics of studies on the association between cholecystectomy and oesophageal adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Freedman *et al*[20], 2000 | 1994-1997 | Case-Control | 189 | 820 | Self report | Pathology records | \_ | RR = 1.03 (0.63-1.69) | Age, gender, alcohol, smoking, BMI, physical activity, education, diet. | 37 |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 132/5488 | 2,572/1000000 | Medicare database | Cancer registry | > 6 | OR = 0.95 (0.80-1.14) | Age, gender, diabetes | 49 |
| Freedman *et al*[23], 2001 | 1965-1997 | Cohort | 53/268312 |  | National registry | Cancer registry | > 10 | SIR = 1.3 (1.0-1.8) | Age, gender | 38 |
| Goldacre *et al*[22], 2005 | 1963-1999 | Cohort | 91/39245 | 803/334813 | NHS database | Cancer registry | NA | RR = 0.98 (0.79-1.21) | Age, gender, calendar year, residence. | 36 |
| Lagergren and Mattsson[24], 2011 | 1965-2008 | Cohort | 126 | 345251 | NA | Cancer registry | 15 | RR = 1.29 (1.07-1.53) | Age, gender, Calendar Year | 40 |

**Table 2 Descriptive characteristics of studies on the association between cholecystectomy and oesophageal squamous cell cancer**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Freedman *et al*[20], 2000 | 1994-1997 | Case-control | 167 | 820 | | Self-report | Pathology records |  | OR = 0.82 (0.43-1.54) | Age, gender, alcohol, smoking, BMI, physical activity, education, diet. | 37 |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 100/4732 | 2572/100000 | | Medicare database | Cancer registry | > 6 | OR = 0.85 (0.69-1.04) | Age, gender, diabetes | 49 |
| Ichimiya *et al*[26], 1986 | 1953-1984 | Cohort | 29 | | 1238 | Self report | Death registry | < 31 | 0.59 (0.26-1.36 | Age, gender | 48 |
| Freedman *et al*[23], 2001 | 1965-1997 | Cohort | 129/268312 | NA | | National registry | Cancer registry | > 10 | SIR = 0.9 (0.7-1.1) | Age, gender | 38 |
| Lagergren and Mattsson[24], 2011 | 1965-2008 | Cohort | 193/345251 |  | | NA | Cancer registry | 15 | SIR 0.93 (0.81-1.08) | Age, gender, calendar year | 40 |

Ichimiya *et al*[26], 1986, reported on oesophageal cancer without specifying pathology of cancer.

**Table 3 Descriptive characteristics of studies on the association between cholecystectomy and gastric cardia cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Freedman *et al*[20], 2000 | 1994-1997 | Case-Control | 262 | 820 | Self-report | Pathology | \_ | RR = 0.67 (0.39-1.13) | Age, gender, alcohol, smoking, BMI, physical activity, education, diet. | 37 |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 122/5579 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 0.88 (0.73-1.06) | Age, gender, diabetes | 49 |
| Fall *et al*[28], 2007 | 1970-1997 | Cohort | 94/251672 | NA | National registry | Cancer registry | 11.5 | RR = 0.95  (0.76-1.16) | Age, gender, surgical procedure | 42 |

**Table 4 Descriptive characteristics of studies on the association between cholecystectomy and gastric cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Sarli *et al[27]*, 1986 | 1980-1984 | Case control | 157 | 157 | Surgical and database | Pathology | NA | 0.77  (0.09-6.40) | Age, gender | 26 |
| Ichimiya *et al*[26], 1986 | 1953-1984 | Cohort | 29 | 1238 | Self report | Death registry | NA | 0.92 (0.66-1.28) | Age, gender | 33 |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 429/12925 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 1.26 (1.13-1.40) | Age, gender, diabetes | 49 |
| Goldacre *et al*[22], 2005 | 1963-1999 | Cohort | 177/39254 | 1354/334813 | NHS database | Cancer registry | NA | 1.06 (0.88-1.26) | Age, gender, calendar year, residence. | 36 |
| Fall *et al*[28], 2007 | 1970-1997 | Cohort | 854/251672 | NA | National registry | Cancer registry | 11.5 | 1.11 (1.04-1.19) | Age, gender, surgical procedure | 42 |
| Chen *et al*[29], 2014 | 2000-2010 | Cohort | 31/5850 |  | National database | Cancer registry | 10 | 1.81 (1.09-3.02) | Age, gender, comorbidities | 53 |

**Table 5 Descriptive characteristics of studies on the association between cholecystectomy and pancreatic cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of Controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (years)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Wynder *et al*[37], 1973 | 1950-1964 | Case-control | 11/142 | 16/307 | Hospital records | NA | > 2 | 1.57 (0.76-3.24)1 | Age, gender, race, hospital | 28 |
| Haines *et al*[38], 1982 | 1973-1978 | Case-control | 8/116 | 18/232 | Hospital records | Medical records | ≥ 5 | 0.89 (0.40-1.98)1 | Age, gender, race, year of admission | 27 |
| Mack *et al*[39], 1986 | 1976-1981 | Case-control | 38/490 | 44/490 | Hospital records | Pathology records | > 1 | 0.8 (0.5-1.4) | Age, gender, Race | 27 |
| Cuzick and Babiker[40] 1989 | 1983-1986 | Case-control | 14/216 | 7/279 | Hospital records | Medical records | NA | 2.43 (0.91-7.12 | Age, gender | 29 |
| Farrow and Davis[41] 1990 | 1982-1986 | Case-control | 8/218 | 6/188 | Hospital records | Cancer registry | ≥ 3 | 1.1 (0.3-3.4) | Age | 29 |
| Bueno de mesquite *et al*[42], 1992 | 1984-1988 | Case-control | 24/176 | 44/487 | Hospital records | Medical records | > 5 | 1.15 (0.55-2.40) | Age, response status, smoking | 31 |
| Lee *et al*[43], 1996 | 1989-1994 | Case-control | 12/282 | 6/282 | Hospital records | Medical records | NA | 2.04 (0.76-6.21) | Age, gender | 43 |
| Gullo *et al*[45], 1996 | 1987-1992 | Case-Control | 93/720 | 71/720 | Hospital records | Medical records | > 1 | 1.00 (0.70-1.43) | Age, gender | 34 |
| Silverman *et al*[30], 2001 | 1986-1989 | Case-Control | 132/484 | 150/2099 | Hospital records | Pathology records | > 2 | 1.77 (1.26-2.48)1 | Age, race, gender, smoking, alcohol consumption, BMI, Calorie intake. | 31 |
| Ko *et al*[32], 2007 | 1995-1999 | Case-control | 75/532 | 155/1701 | Hospital records | SEER abstracts | NA | 1.73 (1.29-2.33)1 | Ag, gender, BMI, smoking, diabetes | 36 |
| Hassan *et al*[44], 2007 | 2000-2006 | Case-Control | 808 | 808 | Hospital records | Self reported | > 2 | OR = 1.1 (0.9-1.8) | Age, gender, smoking, comorbidities | 35 |
| Zhang *et al*[31], 2014 | 1994-1998 | Case-Control | 215 | 676 | Self report | Pathology reports | > 2 | 2.11 (1.32-3.35) | Age, gender, race, smoking, physical activity, diabetes | 51 |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 1106/33280 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 1.23 (1.15-1.33) | Age, gender, diabetes | 49 | |
| Ichimiya *et al*[26], 1986 | 1953-1984 | Cohort | 3/1238 | NA | National registry | Death registry | NA | SMR = 0.86 (0.33-2.25)1 | Age, gender | 33 | |
| Shibata *et al*[46], 1994 | 1981-1990 | Cohort | 65/13979 | NA | Hospital records | NA | > 4 | RR = 2.09 (0.99-4.39) | Age, gender, smoking | 32 | |
| Ekbom *et al*[33], 1996 | 1965-1987 | Cohort | 261/62615 | NA | National registry | Cancer registry | > 1 | 1.20 (1.06-1.36) | Age, gender | 28 |
| Chow *et al*[34], 1999 | 1977-1993 | Cohort | 184/42461 | NA | National registry | Cancer registry | ≥ 4 | 1.3 (1.1-1.6) | Age, gender, obesity, years of follow-up, other comorbidities | 33 |
| Coughlin *et al*[35], 2000 | 1982-1996 | Cohort | 3751/1.2 M | NA | Study database | Cancer registry | 14 | RR = 1.2 (1.0-1.5) | Age, gender, smoking, race, education, BMI, diet. | 31 |
| Ye *et al*[48], 2001 | 1965-1997 | Cohort | 730/268312 | NA | National database | Cancer registry | ≥ 2 | SIR = 1.06 (0.98-1.14) | Age, gender, calendar year | 35 | |
| Schernhammer *et al*[47], 2002 | 1976-1986 | Cohort | 37/145927 | 256/1675355 | Self-report | Self report and death registry | > 10 | 1.23 (0.86-1.77) | Age, gender, BMI, Physical activity, diabetes | 34 |
| Goldacre *et al*[22], 2005 | 1963-1999 | Cohort | 127/39254 | 791/334813 | NHS database | Cancer registry | ≥ 2 | 1.06 (0.88-1.26) | Age, gender, calendar year, residence. | 36 | |
| Arnold *et al*[36], 2009 | 1984-2004 | Cohort | 6243/1060389 | NA | Hospital records | Death registry | NA | HR = 1.62 (1.02-2.55) black  HR = 1.10 (1.0-1.22) white | Age, gender, BMI, smoking, FH of pancreatic Cancer, diabetes. | 41 | |
| Chen *et al*[29], 2014 | 2000-2010 | Cohort | 16/5850 |  | National database | Cancer registry | 10 | 1.13 (0.60-2.12) | Age, gender, comorbidities | 53 | |

1RR and 95% confidence intervals were calculated from raw data.

**Table 6 Descriptive characteristics of studies on the association between cholecystectomy and extrahepatic bile duct cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of Controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 118/3681 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 1.19 (0.98-1.43) | Age, gender, diabetes | 49 |
| Chow *et al*[34], 1999 | 1977-1993 | Cohort | 16/42461 | NA | National registry | Cancer registry | ≥ 4 | 0.7 (0.3-1.4) | Age, gender, obesity, years of follow-up, other comorbidities | 33 |
| Chen *et al*[29], 2014 | 2000-2010 | Cohort | 9/5850 |  | National database | Cancer registry | 10 | 2.22 (0.91-5.41) | Age, gender, comorbidities | 53 |

**Table 7 Descriptive characteristics of studies on the association between cholecystectomy and liver cancer**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 332/10219 | 2572/100000 | Medicare database | Cancer registry | > 6 | | OR = 1.23 (1.15-1.33) | Age, gender, diabetes | 49 |
| Chow *et al*[34], 1999 | 1977-1993 | Cohort | 48/42461 | NA | National registry | Cancer registry | ≥ 4 | | 1.1 (0.7-1.5) | Age, gender, obesity, years of follow-up, other comorbidities | 33 |
| Goldacre *et al*[22], 2005 | 1963-1999 | Cohort | 38/39245 | 306/334813 | NHS database | Cancer registry | | NA | 0.91 (0.64-1.25) | Age, gender, calendar year, residence. | 36 |
| Chen *et al*[29], 2014 | 2000-2010 | Cohort | 87/5850 | 163/5850 | National database | Cancer Registry | 10 | | 1.17 (0.90-1.52) | Age, gender, comorbidities | 53 |

**Table 8 Descriptive characteristics of studies on the association between cholecystectomy and small intestinal cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of Syudy** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 148/3694 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 1.49 (1.26-1.77) | Age, gender | 49 |
| Lagergren and Ekbom[51], 2001 | 1965-1997 | Cohort | 68/2784601 | NA | National registry | National registry | 10 | 1.77 (1.37-2.24) | Age, gender, time aftercholecystectomy | 38 |
| Lagergren and Ekbom[51], 2001 | 1965-1997 | Cohort | 98/2784602 | NA | National registry | National registry | 10 | 1.71 (1.39-2.08) | Age, gender, time aftercholecystectomy | 38 |
| Goldacre *et al*[52], 2012 | 1998-2008 | Cohort | NA | 327460/3M | HES database | Cancer registry | 10 | 2.47 (0.82—6.28) | Age, gender, period since cholecystectomy | 45 |

1Proximal small bowel adenocarcinoma; 2Distal small bowel carcinoids.

**Table 9 Descriptive characteristics of studies on the association between cholecystectomy and colorectal cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Period of study | Study design | No of cases | No of controls | Exposure ascertainment | Outcome ascertainment | Follow-up (yr) | Effect estimate | Adjustments | Quality of publication |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 3907/150045 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 0.97 (0.92-1.02) | Age, gender | 49 |
| Schmidt *et al*[60], 2012 | 1992 -1994 | Case-Control | 10/254 | 0/1043 | National database | Cancer Registry | 24 | HR = 1.20 (0.85-1.70) | Age, gender | 41 |
| Todoroki *et al*[67], 1999 | 1991-1994 | Case-Control | 226/1982 | 270/2129 | Medicare database and self report | Cancer registry | ≥ 2 | OR = 1.1 (0.9-1.3) | Age, gender, Family history, BMI, diet, NSAIDs | 48 |
| Zeng *et al*[62], 1993 | 1965-1986 | Case-Control | 8/503 | 18/2188 | Hospital records | Hospital records | ≥ 2.5 | OR = 1.95 (0.84-4.51) |  | 26 |
| Neugut *et al*[66], 1991 | 1986-1988 | Case-Control | 11/106 | 41/507 | Hospital Records | Self-report | 2 | OR = 0.96 (0.46-1.98) | Age, gender | 34 |
| Lee *et al*[54], 1989 | 1980-1987 | Case-Control | 40/165 | 19/165 | Hospital Records | Hospital Records | ≥ 2 | RR = 2.11 (1.19-3.85) |  | 30 |
| Kune *et al*[65], 1988 | 1980-1981 | Case-Control | 35/715 | 57/727 | Hospital Records | Self-reporting and hospital records |  | RR = 1.10 (0.7-1.1) |  | 36 |
| Neugut *et al*[58], 1988 | 1983-1985 | Case-Control | 11/56 | 10/84 | Hospital records | Self-reporting |  | OR 1.8 (0.6-5.4) | Age, socioeconomic status | 38 |
| Friedman *et al*[63], 1987 | 1971-1984 | Case-Control | 174/5898 | 773/27687 | Medicare Database | Cancer Registry | ≥ 2 | OR = 1.1 (0.9-1.2) | Age, gender, geographical area, calendar year | 47 |
| 2Weiss *et al*[53], 1982 | 1976-1977 | Case-Control | 92 | 687 | Cancer Registry | Self-reporting | ≥ 1 | RR = 1.4 (0.7-2.6) |  | 40 |
| 1Turnbull *et al*[61], 1981 | 1972-1976 | Case-Control | 20/305 | 5 | Hospital records | Hospital records | >5 | RR = 2.7 |  | 33 |
| Chen *et al*[29], 2014 | 2000-2010 | Cohort | 67/5850 | 76/5850 | National database | Cancer Registry | 10 | HR = 1.56 (1.12-2.17) | Age, gender, comorbidities | 53 |
| 1Hartz *et al*[55], 2012 | 1993-1998 | Cohort | 1207/150912 | N/A | National database | Self-report | 8 | HR = 1.36 (1.13-1.64) | Age, smoking, obesity, Family history, comorbidities | 48 |
| Shao *et al*[56], 2005 | 1987-2002 | Cohort | 297/55960 | 574668 | National database | National database |  | IRR = 1.32 (1.16-1.48 | Age, gender | 54 |
| 1Schernhammer *et al*[59], 2003 | 1982-1998 | Cohort | 133/6669 | 78515 | National database of nurses | Self-Report and National death registry | 16 | RR = 1.21 (1.01-1.46) | Age, smoking, BMI, lifestyle factors, comorbidities | 57 |
| 2Johansen *et al*[64], 1996 | 1977-1989 | Cohort | 225/42098 | N/A | Hospital database | Cancer Registry | 1-16 | RR = 1.09 (1.0-1.2) | Age, gender, calendar year | 43 |
| Linos *et al*[57], 1981 | 1950-1969 | Cohort | 42/1681 |  | Hospital database | Hospital records and self reporting |  | 1RR = 1.3 (0.9-1.9)  3RR = 1.3 (0.7-2.2) |  | 34 |

1Women only; 2Excluding rectal cancer; 3Men only.

**Table 10 Descriptive characteristics of studies on the association between cholecystectomy and proximal colon cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 1963/66740 | 2,572/100000 | Medicare database | Cancer registry | > 6 | OR = 1.06 (0.99-1.12) | Age, gender | 49 |
| Todoroki *et al*[67], 1999 | 1991-1994 | Case-Control | 134/967 | 270/2129 | Medicare database and self report | Cancer registry | ≥ 2 | OR = 1.3 (1.0-1.6) | Age, gender, Family history, BMI, diet, NSAID use | 48 |
| Zeng *et al*[62], 1993 | 1965-1986 | Case-Control | 5/108 | 18/2188 | Hospital records | Hospital records | ≥ 2.5 | OR = 5.85 (2.13-16.7) |  | 26 |
| Friedman *et al*[63], 1987 | 1971-1984 | Case-Control | 70/1925 | 773/27687 | Medicare Database | Cancer Registry | ≥ 2 | OR = 1.2 (0.9-1.5) | Age, gender, geographical area, calendar year | 47 |
| Vernick *et al*[69], 1981 | 1975-1978 | Case-Control | 21/150 | 23/250 | National database | Self-report and hospital records |  | RR = 1.77 (0.95-3.3) |  | 44 |
| 1Schernhammer *et al*[59], 2003 | 1982-1998 | Cohort | 46/6669 | 78515 | National database of nurses | Self-Report and National death registry | 16 | RR = 1.35 (0.97-1.88) | Age, smoking, BMI, lifestyle factors, comorbidities | 57 |
| Lagergren and Ekbom[51], 2001 | 1965-1997 | Cohort | 861/278460 | NA | National registry | National registry | 10 | SIR = 1.16 (1.08-1.24) | Age, gender, time after cholecystectomy | 35 |
| 1Ekbom *et al*[68], 1993 | 1965-1983 | Cohort | 633/62615 |  | National Registry | National Registry | < 23 | SIR = 1.24 (1.03-1.48) | Age | 46 |

1Women only.

**Table 11 Descriptive characteristics of studies on the association between cholecystectomy and distal colon cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Nogueira *et al*[21], 2014 | 1992-2005 | Case-control | 986/40996 | 2572/100000 | Medicare database | Cancer registry | > 6 | OR = 0.93 (0.86-1.00) | Age, gender | 49 |
| Todoroki *et al*[67], 1999 | 1991-1994 | Case-Control | 87/965 | 270/2129 | Medicare database and self report | Cancer registry | ≥ 2 | OR = 0.8 (0.6-1.1) | Age, gender, Family history, BMI, diet, NSAID use | 48 |
| Zeng *et al*[62], 1993 | 1965-1986 | Case-Control | 2/131 | 18/2188 | Hospital records | Hospital records | ≥ 2.5 | OR = 1.87 (0.43-8.14) |  | 26 |
| Friedman *et al*[63], 1987 | 1971-1984 | Case-Control | 60/1963 | 773/27687 | Medicare Database | Cancer Registry | ≥ 2 | OR = 1.2 (0.9-1.6) | Age, gender, geographical area, calendar year | 47 |
| Schernhammer *et al*[59], 2003 | 1982-1998 | Cohort | 28/6669 | 78515 | National database of nurses | Self-Report and National death registry | 16 | RR = 0.95 (0.64-1.43) | Age, smoking, BMI, lifestyle factors, comorbidities | 57 |
| Lagergren and Ekbom[51], 2001 | 1965-1997 | Cohort | 2564/278460 | NA | National registry | National registry | 10 | SIR = 0.98 (0.94-1.02) | Age, gender, time after cholecystectomy | 35 |

**Table 12 Descriptive characteristics of studies on the association between cholecystectomy and rectal cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Period of study** | **Study design** | **No of cases** | **No of controls** | **Exposure ascertainment** | **Outcome ascertainment** | **Follow-up (yr)** | **Effect estimate** | **Adjustments** | **Quality of publication** |
| Chiong *et al*[70], 2012 | 1950-2012 | Meta-Analysis | 14226/460262 | N/A | Mixed Sources | Mixed Sources | Variable | OR = 1.14 (0.92-1.41) | Age, gender | 54 |
| Zeng *et al*[62], 1993 | 1965-1986 | Case-Control | 1/264 | 18/2188 | Hospital records | Hospital records | ≥ 2.5 | OR = 0.46 (0.06-3.45) |  | 26 |
| Kune *et al*[65], 1988 | 1980-1981 | Case-Control | 29/715 | 57/727 | Hospital Records | Self-reporting and hospital records |  | RR = 1.22 (0.7-2.0) |  | 36 |
| Friedman *et al*[63], 1987 | 1971-1984 | Case-Control | 43/1921 | 773/27687 | Medicare Database | Cancer Registry | ≥ 2 | OR = 0.9 (0.6-1.2) | Age, gender, geographical area, calendar year | 47 |
| Weiss *et al*[53], 1982 | 1976-1977 | Case-Control | 49 | 687 | Cancer Registry | Self-reporting | ≥ 1 | RR = 1.0 (0.4-2.4) | Age | 40 |
| Shao *et al*[56], 2005 | 1987-2002 | Cohort | 83/55960 | 574668 | National database | National database |  | IRR = 1.00 (0.85-1.17) | Age, gender | 54 |
| 1Schernhammer *et al*[59], 2003 | 1982-1998 | Cohort | 32/6669 | 78515 | National database of nurses | Self-Report and National death registry | 16 | RR = 1.58 (1.05-2.36) | Age, smoking, BMI, lifestyle factors, comorbidities | 57 |
| 2Johansen *et al*[64], 1996 | 1977-1989 | Cohort | 119/42098 | N/A | Hospital Register | Cancer Registry | 1-16 | RR = 1.07 (0.9-1.3) | Age, gender, calendar year | 43 |
| Linos *et a*l[57*]*, 1981 | 1950-1969 | Cohort | 17/1681  34/1681 |  | Hospital database | Hospital records and self reporting |  | 1RR = 0.5 (0.1-1.3)  3RR = 2.3 (0.9-4.8) |  | 34 |

1Women only; 2Excluding rectal cancer; 3Men only.