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SYSTEMATIC REVIEWS

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

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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 cholecystectomy 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

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

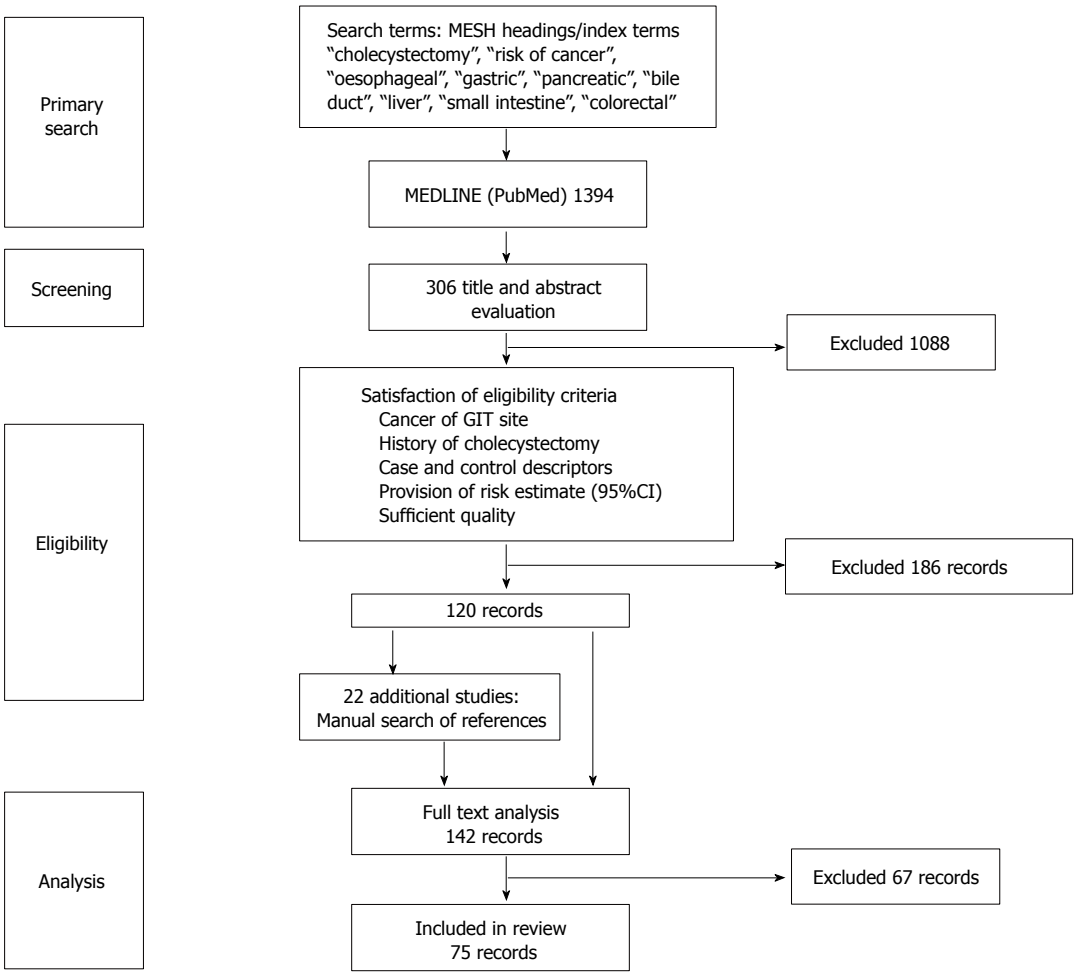

Figure 1 Study flow diagram. GIT: Gastro-intestinal tract.

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 body mass index (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, 95%CI: 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

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

Ref.	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	2572/1000000	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

NA: Not available; BMI: Body mass index.

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

Ref.	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. NA: Not available; BMI: Body mass index.

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

Ref.	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

NA: Not available; BMI: Body mass index.

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].

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

Ref.	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

NA: Not available.

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

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

Ref.	Period of study	Study design	No. of cases	No. of controls	Exposure ascertainment	Outcome ascertainment	Follow-up (yr)	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

[1]RR and 95% confidence intervals were calculated from raw data. NA: Not available; BMI: Body mass index.

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

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

Ref.	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

NA: Not available.

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

Ref.	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

NA: Not available.

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

Ref.	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	148/3694	2572/100000	Medicare database	Cancer registry	> 6	OR = 1.49 (1.26-1.77)	Age, gender	49
Lagergren *et al*[51], 2001	1965-1997	Cohort	68/278460[1]	NA	National registry	National registry	10	1.77 (1.37-2.24)	Age, gender, time aftercholecystectomy	38
Lagergren *et al*[51], 2001	1965-1997	Cohort	98/278460[2]	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

[1]Proximal small bowel adenocarcinoma; [2]Distal small bowel carcinoids. NA: Not available.

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

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

Ref.	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
[1]Weiss *et al*[53], 1982	1976-1977	Case-Control	92	687	Cancer Registry	Self-reporting	⩾ 1	RR = 1.4 (0.7-2.6)		40
[2]Turnbull *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
[2]Hartz *et al*[55], 2012	1993-1998	Cohort	1207/150912	NA	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
[2]Schernhammer *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
[1]Johansen *et al*[64], 1996	1977-1989	Cohort	225/42098	NA	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		[2]RR = 1.3 (0.9-1.9) [3]RR = 1.3 (0.7-2.2)		34

[1]Excluding rectal cancer; [2]Women only; [3]Men only; NA: Not available; BMI: Body mass index; NSAIDs: Nonsteroidal anti-inflammatory drugs.

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].

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

Ref.	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
[1]Schernhammer *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 *et al*[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
[1]Ekbom *et al*[68], 1993	1965-1983	Cohort	633/62615		National registry	National registry	< 23	SIR = 1.24 (1.03-1.48)	Age	46

[1]Women only. NA: Not available; BMI: Body mass index; NSAIDs: Nonsteroidal anti-inflammatory drugs.

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

Ref.	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 *et al*[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

NA: Not available; BMI: Body mass index; NSAIDs: Nonsteroidal anti-inflammatory drugs.

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

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

Ref.	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	NA	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
[1]Schernhammer *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
[2]Johansen *et al*[64], 1996	1977-1989	Cohort	119/42098	NA	Hospital register	Cancer registry	1-16	RR = 1.07 (0.9-1.3)	Age, gender, calendar year	43
Linos *et al*[57], 1981	1950-1969	Cohort	[1]7/1681 [3]4/1681		Hospital database	Hospital records and self reporting		[1]RR = 0.5 (0.1-1.3) [3]RR = 2.3 (0.9-4.8)		34

[1]Women only; [2]Excluding rectal cancer; [3]Men only. NA: Not available; BMI: Body mass index.

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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