Original Article

The association between cholecystectomy and the risk of colorectal cancer: an updated systematic review and meta-analysis of cohort studies

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Background: The effect of cholecystectomy on the development of colorectal cancer (CRC) has prompted a large number of population-based studies. However, the results of these studies are debatable and inconclusive. Our aim in the present study was to conduct an updated systematic review and meta-analysis to explore the causality between cholecystectomy and CRC.

Methods: Cohort studies published in the PubMed, Web of Science, Embase, Medline, and Cochrane databases up to May 2022 were retrieved. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were analyzed using a random effects model.

Results: Eighteen studies, involving 1,469,880 cholecystectomy and 2,356,238 non-cholecystectomy cases, were eligible for the final analysis. Cholecystectomy was not associated with the development of CRC (P=0.109), colon cancer (P=0.112), or rectal cancer (P=0.184). Subgroup analysis of sex, lag period, geographic region, and study quality revealed no significant differences in the relationship between cholecystectomy and CRC. Interestingly, cholecystectomy was significantly associated with right-sided colon cancer (RR =1.20, 95% CI: 1.04–1.38; P=0.010), especially in the cecum, the ascending colon and/or the hepatic flexure (RR =1.21, 95% CI: 1.05–1.40; P=0.007) but not in the transverse, descending, or sigmoid colon.

Conclusions: Cholecystectomy has no effect on the risk of CRC overall, but a harmful effect on the risk of right-sided colon cancer proximally.

Keywords: Cholecystectomy; colorectal cancer; cohort studies; meta-analysis

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Introduction

Colorectal cancer (CRC) has become the third most common cancer and the second leading cause of malignancy-related deaths worldwide (1). Large-scale epidemiological studies have identified several risk factors associated with CRC, including smoking, alcohol addiction, excessive consumption of red and processed meat, family history of CRC, obesity, male sex, and age (2-6). However, the etiology of CRC remains debatable and obscure. Therefore, a major challenge in current research is to identify the possible causes of the initiation and progression of CRC.

Functions of the gallbladder include storing bile acids (BAs) and regulating the physiological homeostasis and enterohepatic circulation of BAs. For patients with gallstone disease (GSD), cholecystectomy, which is mostly performed laparoscopically, has become the first-line treatment (7). However, surgical removal of the gallbladder can change the secretion rhythm of BAs (8,9). Furthermore, alternations in BA composition and concentration are characterized by the enhancement of bacterial dehydroxylation of cholic acid to deoxycholic acid (DCA), which is considered to be carcinogenic to the colonic epithelium (10,11).

There is controversy surrounding the results of cohort studies focusing on the association between cholecystectomy and CRC. A previous meta-analysis of cohort studies to demonstrate the pooled effect of cholecystectomy on CRC indicated that cholecystectomy carried a high risk of CRC, colon cancer (CC) and ascending CC, especially in Western countries (12). However, previous meta-analysis had several limitations. An appropriate lag period was not taken into consideration and it should be adopted after cholecystectomy since CRC may already exist at the time the surgery is performed. In addition, significant heterogeneity was observed in the whole and subgroup analyses. These limitations resulted in more well-designed, population-based, confounding factors-adjusted cohort studies in recent years, which have added more solid evidence to the issue. Given the controversial results from previous studies and the need for further clarification, we performed an updated systematic review and meta-analysis of cohort studies to explore the association between cholecystectomy and CRC. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2049/rc) (13).

Highlight box

Key findings

- Cholecystectomy has no effect on the overall risk of colorectal cancer (CRC), colon cancer (CC), or rectal cancer (RC), but does have a harmful effect on the risk of right-sided CC, especially in the cecum, ascending colon, and/or hepatic flexure.

What is known and what is new?

- Previous meta-analysis of cohort studies has demonstrated that cholecystectomy carries a high risk of CRC, CC and ascending CC, particularly in Western countries.
- This study indicates that cholecystectomy has a detrimental effect on the risk of right-sided CC, especially in the cecum, ascending colon, and/or hepatic flexure, but not on the risk of CRC, CC, or RC overall.

What is the implication, and what should change now?

- These results have critical implications that may warrant further investigation of colonoscopy surveillance strategies in patients undergoing cholecystectomy.

Methods

Literature search strategy

This meta-analysis was registered on PROSPERO (ID: CRD42022332769). The review protocol was not published or submitted online. Published articles investigating the association between cholecystectomy and CRC published up to May 2022 were retrieved from the PubMed, Web of Science, Embase, Medline, and Cochrane Library databases. The search strategy was restricted to the English language and included the following terms: ("cholecystectomy" OR "cholecystectomies") AND ("colorectal" OR "gastrointestinal") AND ("carcinoma" OR "cancer" OR "neoplasm" OR "adenocarcinoma") AND "cohort study".

Selection criteria

The inclusion criteria were as follows: (I) a cohort study with original data provided, including hazard ratio (HR), relative risk (RR), incidence rate ratio, standardized incidence ratio (SIR), and the corresponding 95% confidence intervals (CIs), or data sufficient to compute these measures; (II) explored the effects of cholecystectomy on the development of CRC; (III) the exposure factor was a previous open or laparoscopic cholecystectomy; and (IV) the outcome of interest was the development of CRC. The exclusion criteria were as follows: (I) case reports/series,

letters, reviews, guidelines, protocols, replies and cross-sectional studies; (II) studies which did not precisely report HRs and 95% CIs for the outcome; (III) studies with no original data or whose data were not calculable for the outcome; (IV) studies limited to specific populations, such as patients with inflammatory bowel disease or males or females only.

The titles and abstracts of the selected literature were separately screened by two authors (L Mu and W Li). Discrepancies in the review process were verified by the senior author (D Hu). The remaining articles were separately screened through a comprehensive reading of the full text. The reference lists of articles deemed relevant during the full-text review process were cross-checked to find any relevant studies.

Data extraction and quality assessment

Two researchers conducted the data extraction process independently (Y Song and L Mu). Discrepancies that arose between the two researchers during the data collection process were discussed and resolved through consultation with the senior author (D Hu). The basic features of all the relevant studies were recorded, including the author and publication year, study characteristics, diagnosis of cholecystectomy and CRC, outcome (CRC cases), and adjustments. The Newcastle-Ottawa Scale (NOS) (14) was used to assess the study quality. We judged studies with a score of 7 to 9 to be of high quality, studies with a score of 4 to 6 to be of moderate quality, and studies with a score of 0 to 3 to be of low quality.

Two authors (Y Song and W Li) independently rated the certainty of the evidence using the GRADE system on the online GRADEpro software (https://www.gradepro.org/) (15). The GRADE system evaluates the certainty of a study in the following five dimensions: study limitations, consistency of effect, imprecision, indirectness, and publication bias (16). Using the GRADE system, the certainty of evidence in each dimension is categorized as: high, moderate, low, or very low quality.

Statistical analyses

STATA software 17.0 (StataCorp LLC, College Station, TX, USA) was used to perform all data analyses. Pooled RRs and 95% CIs were computed from SIRs, incidence rate ratios, RRs, HRs, and 95% CIs using the DerSimonian and Laird method. For the studies with a time interval following cholecystectomy, RRs were extracted and computed from data with an appropriate lag period. Subgroup analysis was also conducted. The I^2 statistic was used to analyze heterogeneity (17). Significant heterogeneity was indicated by either $P<0.10$ or an I^2 value >50%. The presence of publication bias was verified by funnel plot and Egger's test (18). A sensitivity analysis was performed by removing each study in sequence to find the possible source of heterogeneity. $P<0.05$ was considered as the significance level.

Results

Study selection and characteristics

The flow diagram for literature selection is displayed in *Figure 1*. In total, 824 articles were identified through the database searches. Of these studies, 329 articles were excluded due to being duplicates. The remaining 495 articles were reviewed by title, and subsequently, 435 records were excluded for the following reasons: study aim not relevant (n=339); records not in English (n=53); case report/series, letter, review, guideline, protocol, or reply (n=34); case-control study (n=5); and basic science research (n=4). After further reading of the abstracts and full texts, 18 studies, involving a total of 1,469,880 cholecystectomy cases and 2,356,238 non-cholecystectomy cases, were eventually deemed eligible for inclusion (19-36).

The main characteristics of the included studies are displayed in *Table 1*. Of the included studies, 11 were from Europe, 6 were from Asia, and 1 was from the USA. Most of the studies recruited cases either from general populations or from inpatient cohorts of individuals from healthcare programs or insurance systems. The identification of cholecystectomy was mostly based on International Classification of Diseases (ICD) codes, hospital medical records, and insurance claim codes, except in 1 study which used questionnaires (23). The diagnosis of CRC was also mainly validated based on ICD codes (C18–C20). The results of data extraction and NOS scoring are displayed in Table S1. The mean NOS score of the 18 studies was 7.11. The quality of 13 studies was high and that of the remaining 5 studies was moderate.

Synthesis of the results

Synthesis of the studies' results was conducted using a random effects model. As shown in *Figure 2*,

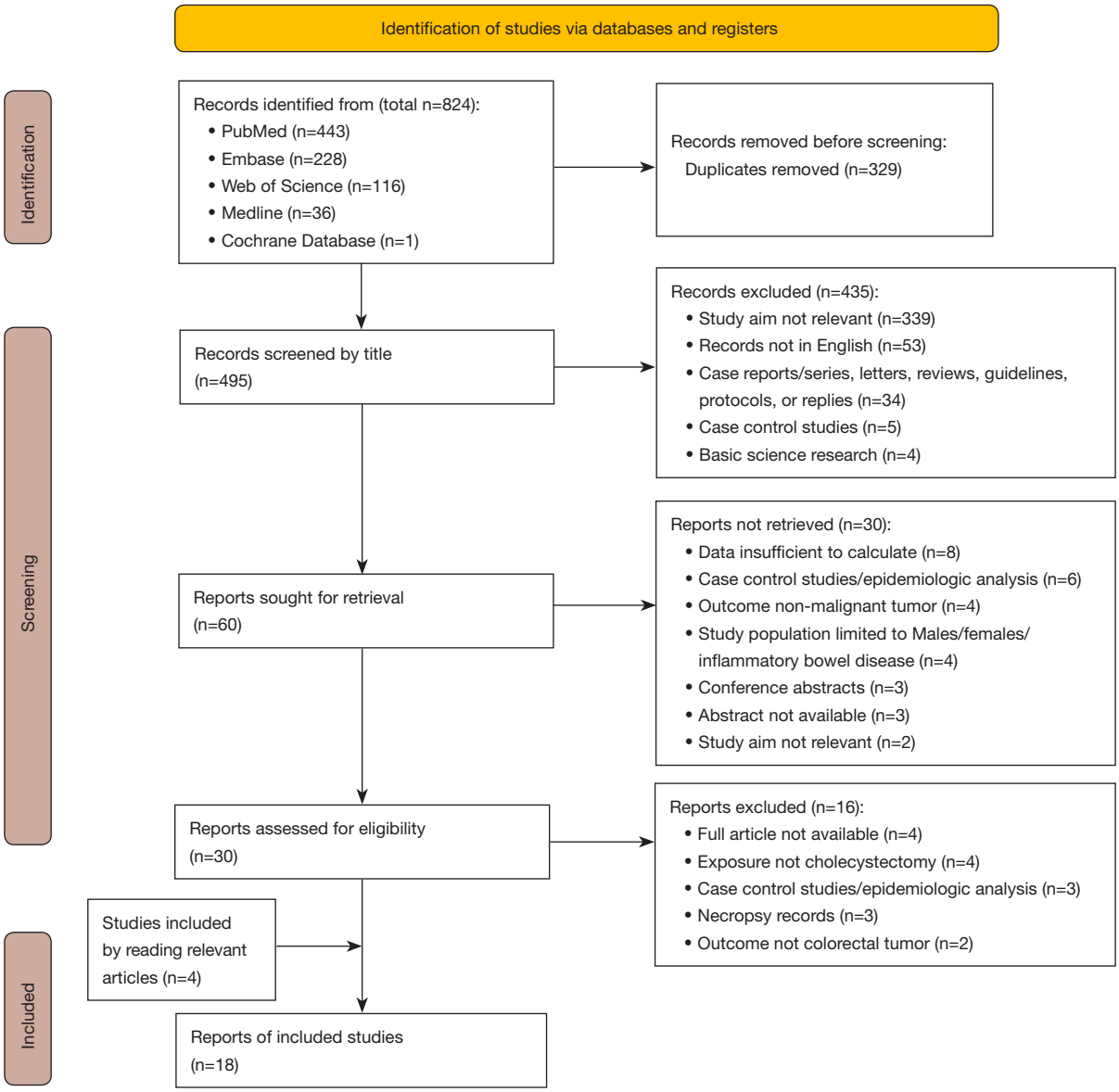

Figure 1 The flow diagram for the search and selection processes of the meta-analysis.

cholecystectomy exhibited no association with CRC (RR =1.12, 95% CI: 0.98–1.29; P=0.109; I^2=95.0%). No statistically significant publication bias was detected through funnel plot analysis and Egger's tests (*Figure 3*, P=0.411). A sensitivity analysis was also conducted, and the result was not affected by the removal of each study in sequence (*Figure 4*).

Subgroup analyses

Subgroup analyses were conducted based on sex, geographic region, lag period, study quality, time interval since cholecystectomy, and tumor location. Subgroup analyses of sex (male: P=0.365; female: P=0.274), geographic region (Europe: P=0.071; Asia: P=0.471; USA: P=0.101), lag period (with lag period: P=0.238; no lag period: P=0.237), study quality (high: P=0.243; moderate or low: P=0.215) showed no significant differences in the relationship between cholecystectomy and CRC (*Table 2*). Regarding the time interval after surgery, cholecystectomy was not associated with CC or rectal cancer (RC) in patients who had undergone cholecystectomy ≤4 years or ≥5 years (*Table 2*).

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Authors, year	Study characteristics	Identification of CS	Diagnosis of CRC	Outcome (CRC cases: CS/non-CS patients)	Adjustment
Linos *et al.*, 1981, (19)	Retrospective cohort study (Rochester-Olmsted Epidemiology Program Project): 1681 CS cases (460 males and 1,221 females) at baseline Follow-up years: 13 years (mean) Lag period: 6 months	Medical records	Medical records	42/–	None
Adami *et al.*, 1983, (20)	Prospective population-based cohort study: 16,773 CS patients (5,095 males and 11,678 females) at baseline Follow-up period: 11–14 completed years Lag period: none	ICD code	ICD code	130/–	None
Adami *et al.*, 1987, (21)	Prospective population-based cohort study: 16,439 CS patients (4,978 males and 11,461 females) at baseline Follow-up period: 14–17 completed years Lag period: none	ICD code	ICD code	150/–	None
Nielsen *et al.*, 1991, (22)	Prospective cohort study: 3,425 CS individuals (857 males and 2,568 females) at baseline Follow-up period: 8–33 years Lag period: none	Icelandic Cancer Registry	Icelandic Cancer Registry	57/–	None
Goldbohm *et al.*, 1993, (23)	Prospective cohort study: 3,500 subjects (men: 1,688, 5.7% of gallstones and 4.7% of CS; women: 1,812, 14.7% of gallstones and 13.3% of CS) at baseline Follow-up years: 3.3 years (mean) Lag period: none	Questionnaire	ICD code	53/408	Age and large-bowel cancer in first-degree relatives
Ekbom *et al.*, 1993, (24)	Retrospective population-based cohort study: 62,615 CS patients (20,745 males and 41,870 females) at baseline Follow-up end: until the end of 1987 Lag period: 1 year	ICD code	ICD code	633/–	None
Johansen *et al.*, 1996, (25)	Retrospective cohort study: 42,098 GSD patients (72.4% with CS) at baseline Follow-up years: 1–16 years Lag period: 1 year	ICD code	Danish Classification of Surgical Procedures and Therapies	344/147	Age, sex, and calendar year

Table 1 (*continued*)

Table 1 (*continued*)

Authors, year	Study characteristics	Identification of CS	Diagnosis of CRC	Outcome (CRC cases: CS/non-CS patients)	Adjustment
Lagergren *et al.*, 2001, (26)	Retrospective cohort study: 278,460 CS patients (90,987 males and 187,473 females) at baseline Follow-up years: 12.1 years (mean) Lag period: 1 year	ICD code	Swedish Classification of Operations and Major Procedures	3,425/–	None
Shao *et al.*, 2005, (27)	Retrospective cohort study: 55,960 CS patients and 574,668 randomly selected controls at baseline Follow-up end: the first diagnosis of CRC, death, dropout, or the end of database entry (i.e., April 2002) Lag period: 1 year	General Practice Research Database	General Practice Research Database	297/2,218	Age
Goldacre *et al.*, 2005, (28)	Retrospective cohort study: 39,254 CS individuals and 334,813 reference controls at baseline Follow-up end: the date of admission for cancer, or death, or March 31, 1999 Lag period: 2 years	Hospital records	Hospital records	505/3,731	None
Goldacre *et al.*, 2012, (29)	Retrospective cohort study: 327,460 CS individuals, 133,114 gallbladder disease individuals, and 3 million controls at baseline Follow-up end: the date of the first record of colon cancer, death, or the end of the data file (March 31, 2008), whichever was the earliest Lag period: 1 year	ICD code	ICD code	2,245/3,622	Age in 5-year bands, sex, time period in single calendar years, area deprivation score in quintiles, and region of residence
Chen *et al.*, 2014, (30)	Retrospective cohort study: 5,850 cholelithiasis patients with CS and 62,180 controls at baseline Follow-up years: not mentioned Lag period: none	ICD code	Registry for Catastrophic Illness Patient Database	67/76	Sex, age, and comorbidities, such as diabetes mellitus, hyperlipidemia, hepatitis B infection, hepatitis C infection, menopause, and cirrhosis
Shabanzadeh *et al.*, 2017, (31)	Retrospective cohort study: 187 CS patients and 5,327 controls at baseline Follow up years: 24.7 years (mean) Lag period: no	ICD code	ICD code	11/183	Age and sex

Table 1 (*continued*)

Table 1 (*continued*)

Authors, year	Study characteristics	Identification of CS	Diagnosis of CRC	Outcome (CRC cases: CS/non-CS patients)	Adjustment
Lee *et al.*, 2018, (32)	Retrospective cohort study: 11,362 CS patients and 696,301 non-CS controls at baseline Follow up years: 13.66 years (mean) Lag period: 1 year	ICD code	ICD code	34/4,276	Sex, diabetes mellitus, and inflammatory bowel disease
Chen *et al.*, 2020, (33)	Retrospective cohort study: 83,963 CS patients and 83,963 control subjects at baseline Follow-up end: the development of CRC, death, withdrawal from the National Health Insurance program due to emigration or death, or 31 December, 2011 Lag period: 6 months	ICD code	ICD code	638/1,170	Age, gender, comorbidities of hypertension, diabetes mellitus, chronic kidney diseases, stroke, coronary artery disease, colorectal adenomas, and chronic obstructive pulmonary disease
Kim *et al.*, 2020, (34)	Retrospective cohort study: 3,588 CS patients at baseline Follow-up years: 15.0 (range, 0–146) months Lag period: 1 year	Single hospital records	Single hospital records	21/–	None
Jung *et al.*, 2021, (35)	Retrospective cohort study: 408,769 CS patients at baseline Follow-up years: 4.7 years (mean) Lag period: 1 year	Insurance claims codes	ICD code	1,773/–	None
Choi *et al.*, 2022, (36)	Retrospective cohort study: A total of 123,295 control subjects and 123,925 age and sex-matched CS subjects at baseline Follow-up years: 4.59 years (mean) Lag period: 1 year	Insurance claims codes	ICD code	1,078/1,003	Age, sex, smoking status, body mass index, hypertension, diabetes mellitus, and dyslipidemia

CS, cholecystectomy; CRC, colorectal cancer; ICD, International Classification of Diseases; GSD, gallstone disease.

The subgroup analysis of tumor location revealed no association of cholecystectomy with CC overall (P=0.112), RC (P=0.184) or left-sided CC (P=0.836) (*Table 3*; *Figure 5A*). However, the association was significant for the risk of right-sided CC (RR =1.20; 95% CI: 1.04–1.38; P=0.010; I^2=64.6%; *Figure 5B*), especially in the cecum, the ascending colon, and/or the hepatic flexure (RR =1.21; 95% CI: 1.05–1.40; P=0.007; I^2=49.3%), but not in the transverse (P=0.397), descending (P=0.769), or sigmoid (P=0.635) colon (*Table 3*).

Discussion

In the current study, we explored the association of cholecystectomy with the development of CRC. The results show that the overall risk of CRC was comparable between patients with cholecystectomy and those without in the general population, as well as in subgroup analysis for sex, lag period, study quality, and geographic origin. However, a positive association was identified between cholecystectomy and the risk of right-sided CC, especially in the cecum, the ascending colon, and/or the hepatic flexure. These

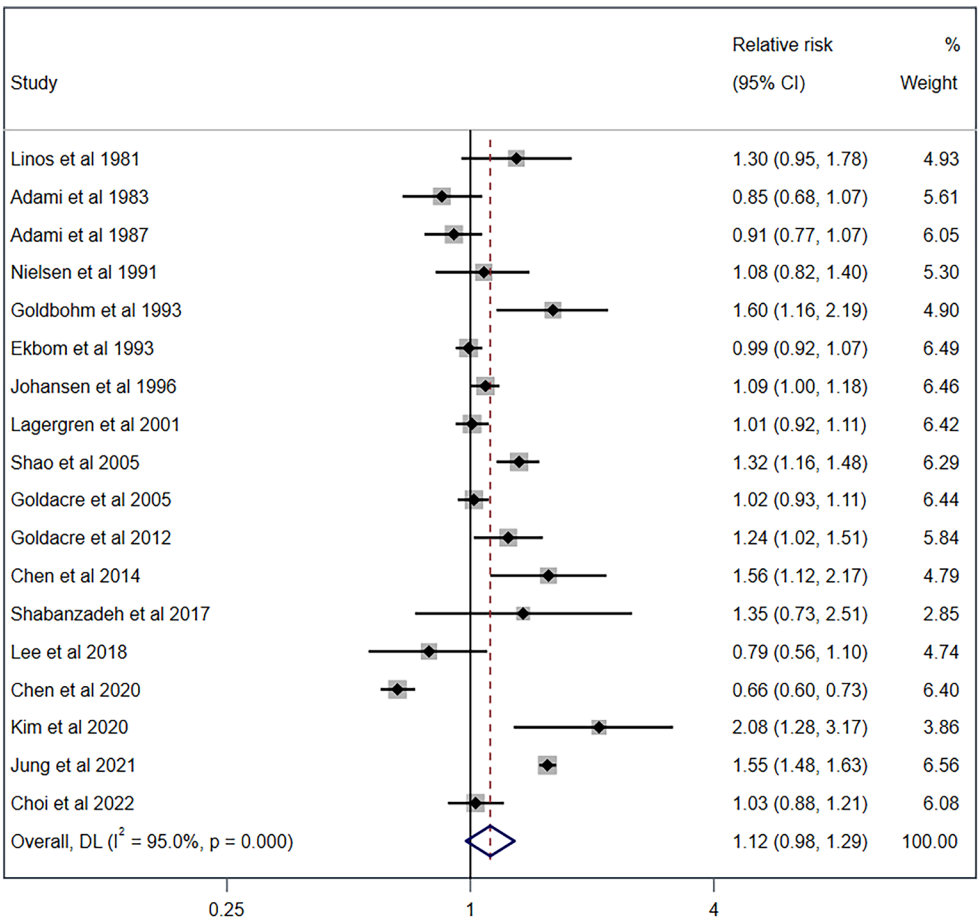

Figure 2 Forest plot and pooled estimates of the effect of cholecystectomy on the risk of colorectal cancer. Weights are from a random effects model. CI, confidence interval; DL, DerSimonian and Laird.

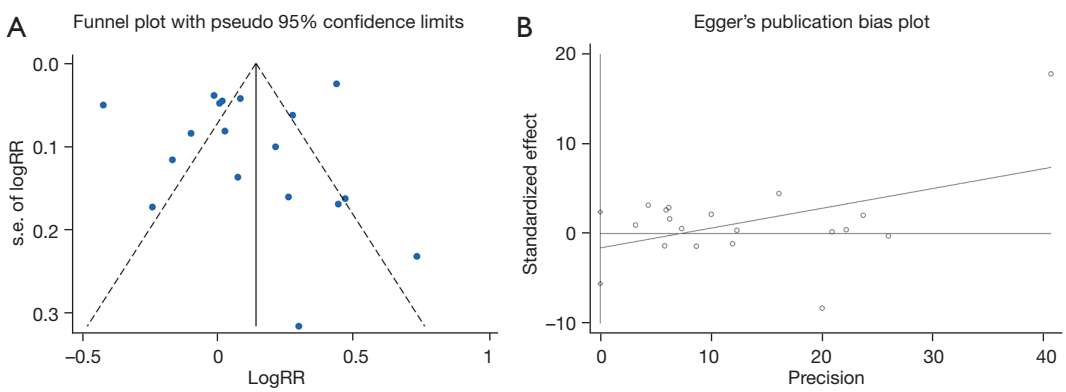

Figure 3 Publication bias of the included studies. (A) Funnel plot for publication bias. (B) Egger's test results. RR, relative risk; s.e., standard error.

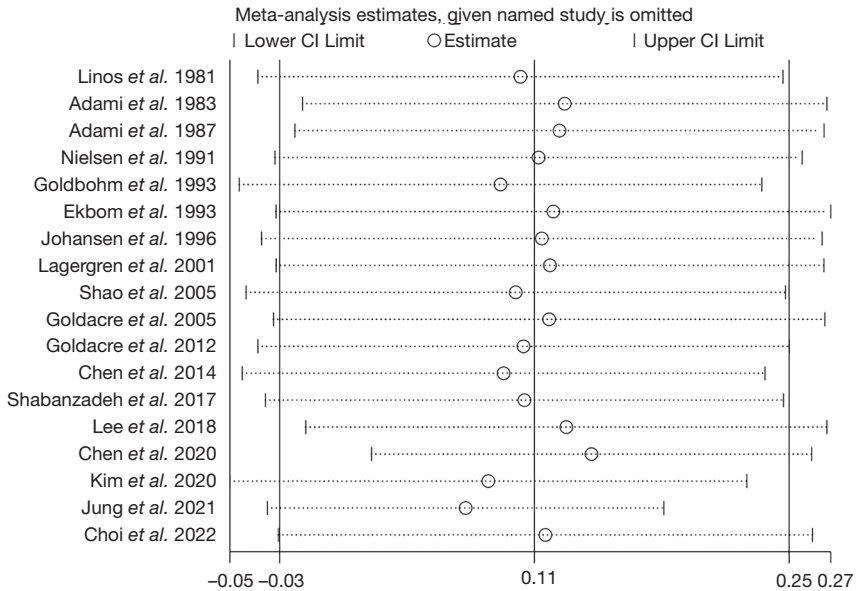

Figure 4 Sensitivity analysis of the colorectal cancer risk associated with cholecystectomy. CI, confidence interval.

Table 2 Subgroup analyses of the association between cholecystectomy and the risk of colorectal cancer, stratified by sex, geographic region, lag period, study quality, and time interval since cholecystectomy

Group	Subgroup	RR (95% CI)	Test for overall effect (P value)	No. of studies	Heterogeneity I^2, %
Sex	Male	1.13 (0.87–1.46)	0.365	10	94.9
	Female	1.13 (0.91–1.41)	0.274	10	92.8
Geographic region	USA	1.30 (0.95–1.78)	0.101	1	0.0
	Europe	1.07 (0.99–1.16)	0.071	11	70.7
	Asia	1.16 (0.77–1.76)	0.471	6	98.0
Lag period	Lag period	1.11 (0.94–1.31)	0.238	12	96.6
	No lag period	1.14 (0.92–1.43)	0.237	6	73.9
Study quality	High	1.09 (0.94–1.26)	0.243	13	90.0
	Moderate or low	1.18 (0.91–1.55)	0.215	5	97.3
Time interval since cholecystectomy					
1–4 years	CC	1.25 (0.90–1.73)	0.178	3	91.5
	RC	1.28 (0.94–1.73)	0.112	3	84.4
≥5 years	CC	1.06 (0.98–1.15)	0.124	3	0.0
	RC	0.96 (0.82–1.12)	0.572	3	44.1

RR, relative risk; CI, confidential interval; CC, colon cancer; RC, rectal cancer.

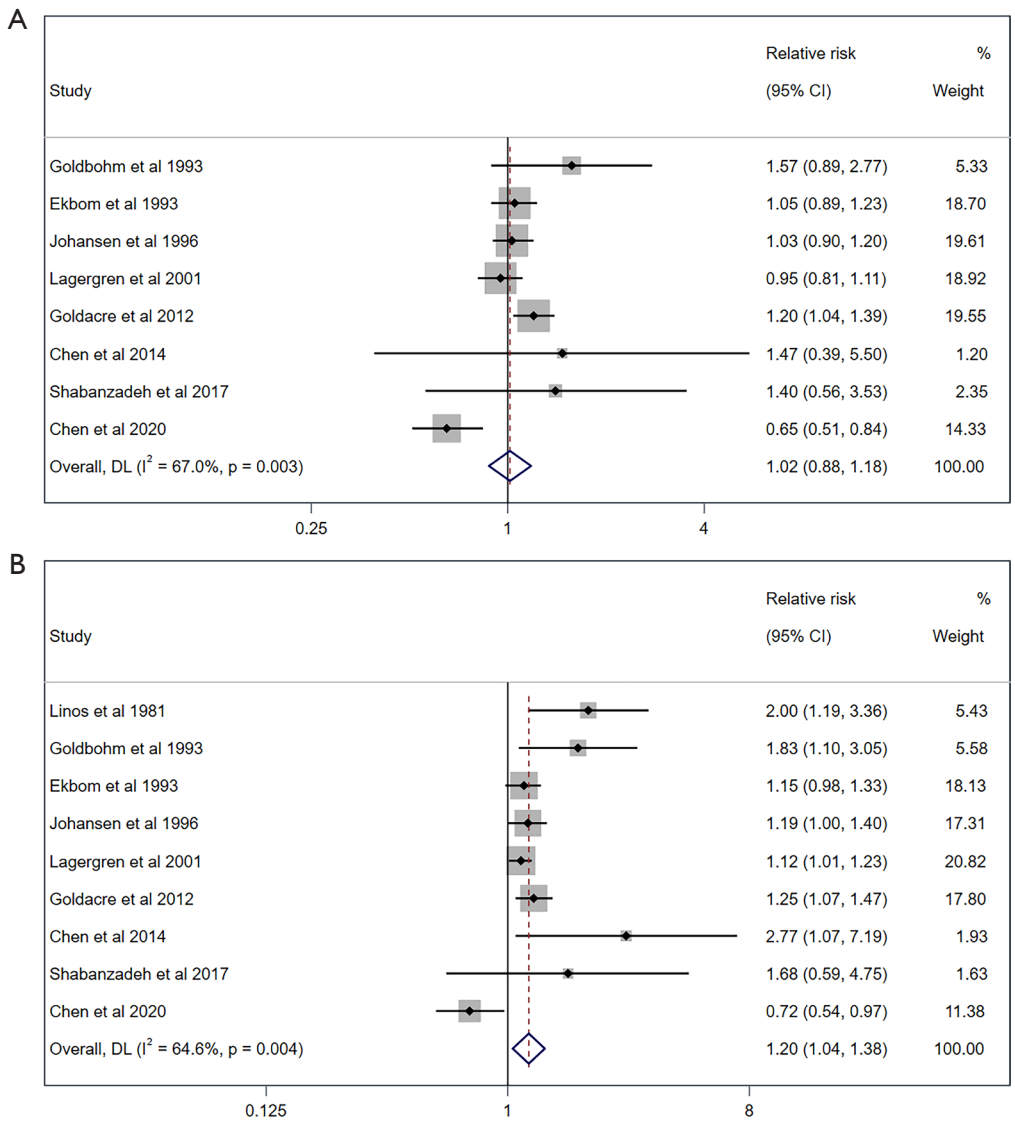

Figure 5 Forest plot and pooled estimates of the effect of cholecystectomy on the risk of left-sided colon cancer (A) and right-sided colon cancer (B). Weights are from a random effects model. CI, confidence interval; DL, DerSimonian and Laird.

results have critical implications that may warrant further investigation for colonoscopy surveillance strategies in individuals who undergo cholecystectomy.

Cholecystectomy has remained one of the most frequently performed and effective treatments for gallbladder diseases, especially symptomatic GSD. However, increasing concern has been raised regarding the long-term risks of cholecystectomy, such as the development of CRC. Numerous case-control and cohort studies, as well as a previous meta-analysis, have provided substantial evidence of an increased CRC risk following cholecystectomy. Several mechanisms may account for this possible association. First, the circadian rhythmicity of BAs after cholecystectomy is diminished, resulting in continuous bile secretion into the bowel (9,37). Second, patients who undergo cholecystectomy have been found to exhibit higher concentrations of total fecal BA and DCA (38). Third, constant exposure to high levels of BAs might cause DNA damage, such as oxidative stress, oncogene mutations, and microsatellite instability (39). Fourth, the composition and abundance of gut microbiota becomes altered after cholecystectomy, which is characterized by an elevated

Table 3 Subgroup analyses of the association between cholecystectomy and the risk of colorectal cancer, stratified by tumor location

Subgroup	RR (95% CI)	Test for overall effect (P value)	No. of studies	Heterogeneity I^2, %
CC	1.08 (0.98–1.19)	0.112	16	76.5
Left-sided	1.02 (0.88–1.18)	0.836	8	67.0
Right-sided	1.20 (1.04–1.38)	0.010	9	64.6
Cecum/ascending colon/hepatic flexure	1.21 (1.05–1.40)	0.007	3	49.3
Transverse	1.05 (0.94–1.18)	0.397	2	0
Descending	1.08 (0.64–1.85)	0.769	2	83.7
Sigmoid	1.02 (0.94–1.10)	0.635	3	0
RC	0.94 (0.86–1.03)	0.184	16	56.7

CC, colon cancer; RC, rectal cancer; RR, relative risk; CI, confidential interval.

abundance of the *Bacteroidetes* phylum, specifically members of the *Bacteroidaceae* family and the genus *Bacteroides* (40), as well as *Blautia obeum* and *Veillonella parvula* (41).

However, the results of studies regarding the above mechanisms remain disputable. For example, several studies have concluded that cholecystectomy has no prominent effect on the concentration and composition of BAs (10,40). This controversy may be attributable to differences in subjects in the control group. In some studies, the control group, namely non-cholecystectomy group, is composed of individuals with normal gallbladder, patients with asymptomatic gall stones, gallbladder polyps, etc. Keren *et al.* reported that cholecystectomy-treated patients exhibited higher levels of BAs than the controls without GSD or cholecystectomy, but had comparable concentrations to patients with GSD (40). Further analysis indicated that levels of primary and secondary BAs did not differ among the three groups (40). Furthermore, as for microbiota change in relation to cholecystectomy, current studies mainly focused on the analysis limited to phylum and genus, while the real pro-carcinogenic influence of microbiota should be ascribed to specific species, such as the pro-carcinogenic effect of enterotoxigenic *Bacteroides fragilis* in CRC (42,43).

The main findings of the current study were that cholecystectomy was only associated with an increased risk of right-sided CC, especially in the cecum, the ascending colon, and/or the hepatic flexure, but not with the overall risk of CRC, CC, RC, or cancers in other segments of the colon. These findings represent interesting results which differ from those of a previous meta-analysis of cohort studies (12). The preference of right-sided CC after cholecystectomy partially coincided with previous descriptive analysis indicating that highest proportion of ascending CC (10.5%) was observed following cholecystectomy (44), and with results of previous meta-analyses of case-control studies (45,46). One possible explanation for these findings is that the absorption of secondary BAs is more significant proximally than distally (19). The distribution of BA in different segments of the colon might be another possible explanation. In a human study, the levels of total tissue-bound BA, especially chenodeoxycholic acid, were found to be higher in the ascending colon than in other parts of the colon (47). In animal studies, the levels of DCA and hyodeoxycholic acid in the cecum (16% and 21%, respectively) were higher than those in the colon (8% and 17%, respectively) (48). Based on the pro-carcinogenic effect of DCA on CRC (49,50), it was postulated that the proximal part of the large intestine was continuously exposed to higher concentrations of deleterious BAs, which may account for the predilection of right-sided CC.

Our meta-analysis has several limitations that warrant consideration. First, the certainty of the evidence was low according to assessment of several limitations, indirectness, and imprecision. For several study limitations, the evidence was downgraded due to, for example, the risk of selection bias or suspected potential reporting bias. When considering possible biases, imbalances between study groups, such as genetic differences that may lead to susceptibility to CRC and environmental and lifestyle-related factors, may represent potential sources of biases in this study. In addition, in some studies, the definition of the non-cholecystectomized group was unclear. Since patients with GSD and non-cholecystectomized individuals without GSD showed distinctions in BA concentration and

composition, as well as other differences, discrepancies may have existed during the comparison.

Conclusions

This updated meta-analysis shows that while cholecystectomy has no effect on the overall risk of CRC, CC, and RC, it does have a harmful effect on the risk of right-sided CC, especially in the cecum, the ascending colon, and/or the hepatic flexure. However, additional evidence is needed to elucidate this complex association.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2049/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2049/prf

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2049/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2049/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Data extraction and quality assessment of studies by NOS

Study	RR	95% CI		Selection	Comparability	Outcome	Total NOS
		Lower limit	Upper limit				
Linos *et al.*, 1981	1.30	0.95	1.78	★★★★	–	★★★	7
Adami *et al.*, 1983	0.85	0.68	1.07	★★★★	–	★★	6
Adami *et al.*, 1987	0.91	0.77	1.07	★★★★	–	★★★	7
Nielsen *et al.*, 1991	1.08	0.82	1.40	★★★★	–	★★★	7
Goldbohm *et al.*, 1993	1.60	1.16	2.19	★★★	★★	★★★	8
Ekbom *et al.*, 1993	0.99	0.92	1.07	★★★★	–	★★	6
Johansen *et al.*, 1996	1.09	1.00	1.18	★★★★	★	★★	7
Lagergren *et al.*, 2001	1.01	0.92	1.11	★★★★	–	★★★	7
Shao *et al.*, 2005	1.32	1.16	1.48	★★★★	★	★★	7
Goldacre *et al.*, 2005	1.02	0.93	1.11	★★★★	–	★★	6
Goldacre *et al.*, 2012	1.24	1.02	1.51	★★★★	★★	★★	8
Chen *et al.*, 2014	1.56	1.12	2.17	★★★★	★★	★	7
Shabanzadeh *et al.*, 2017	1.35	0.73	2.51	★★★★	★	★★★	8
Lee *et al.*, 2018	0.79	0.56	1.10	★★★★	★★	★★	8
Chen *et al.*, 2020	0.66	0.6	0.73	★★★★	★★	★★★	9
Kim *et al.*, 2020	2.08	1.28	3.17	★★★★	–	★★	6
Jung *et al.*, 2021	1.55	1.48	1.63	★★★★	–	★★	6
Choi *et al.*, 2022	1.03	0.88	1.21	★★★★	★★	★★	8

★ represents one point in Newcastle-Ottawa Scale scoring system. RR, relative risk; CI, confidential interval; NOS, Newcastle-Ottawa Scale.

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