Clinical Research

Meta-analysis on the correlation of cholecystectomy or cholecystolithiasis to risk of colorectal cancer in Chinese population

Yi-Ke Xu,¹ Feng-Lan Zhang,² Tao Feng,¹ Jin Li¹ and Yun-Hai Wang¹

[Abstract] Background and Objective: It is reported that the incidence of colorectal cancer is higher in patients receiving cholecystectomy (CHE) than in those who did not. However, the correlation of CHE and cholecystolithiasis (CHO) to colorectal cancer is unclear. This study was to investigate the correlation of CHE or CHO to risk of colorectal cancer in Chinese population. Methods: A meta-analysis was conducted according to the guidelines set forth by the meta-analysis of observational studies in epidemiology (MOOSE statement). A manual and computer search of literature was performed. Included literatures were evaluated using the Newcastle-Ottawa Scale. Original data were extracted, pooled odd ratio (OR) and 95% confidence intervals (CI) were calculated using revman 5.0. Results: In total 26 studies were included. The pooled OR between CHO or CHE, CHE alone, CHO alone and colorectal cancer were 3.00 (95%IC 2.30-3.91), 2.85 (95%IC 2.13-3.81) and 2.68 (95%IC 1.93-3.72), respectively. Sub-group analysis in sex and position of tumors revealed obvious correlation of CHE or CHO to colorectal cancer except for the men’s subgroup. Conclusion: CHE or CHO may be associated with colorectal cancer in Chinese population.

Key words: cholecystectomy, cholecystolithiasis, gallstones, colorectal neoplasm, meta-analysis, MOOSE statement, Newcastle-Ottawa scale

In relevant researches on gallbladder diseases and colorectal cancer, long time ago, there were reports suggested that the ratio of the incidence of colorectal cancer in patients who underwent gallbladder excision was higher than that in normal people. In 1978, Capron et al.¹ and Hage et al.² reported that people received cholecystectomy were more susceptible to colorectal cancer. In later 30 years, there were many basic researches and epidemiological studies, which attempted to found the correlation of cholecystectomy or cholecystolithiasis to risk of colorectal cancer, but no common recognition was achieved.³ Some researches found that, the correlation of cholecystectomy or cholecystolithiasis and colorectal cancer was different because of the difference in geographical location and country of the population.⁴ Chinese scholars have also performed many researches on it. However owing to the different methods and population, there was not any consistent conclusion.

This study was conducted according to the guidelines set forth
by the meta-analysis of observational studies in epidemiology (MOOSE statement), systematically evaluated the research evidence of the correlation of gallbladder diseases and colorectal cancer in Chinese population, comprehensively summarized these results, determined whether the correlation exist or not and quantified the correlation.

Materials and Methods

Criteria of including and excluding literatures. Research object was observational research articles based on Chinese population. Exposure factors were cholecystectomy or cholecystolithiasis caused by various factors. Ending index was whether colorectal cancer occurs or not.

Including criteria: (1) Cohort study or case-control study about cholecystectomy or cholecystolithiasis and colorectal cancer. (2) Research object was Chinese population. (3) There were complete four tables material that could be extracted. (4) The hypothesis of each literature was similar. Excluding criteria: (1) Simple case series studies or cross-sectional studies. (2) The same group was reported repeatedly. (3) Data was not provided for calculating RR or OR. (4) Literature had been published for several times.

Literature retrieval strategies. Literature retrieval staff (Xu, Fen) had had regular literature retrieval knowledge and evidence-based medicine training, both were able to use the medicine database skillfully. They did the job respectively. A controversial literature will be discussed between them or be sent for the third researcher (Wang) to determine whether to be included after discussion.


Chinese searching keywords or free words included: 结直肠癌, 结直肠肿瘤, 结肠癌, 直肠癌, 胆结石, 胆囊结石病, 胆囊切除术.

English searching keywords or free words included: colorectal neoplasms, cholecystectomy, gallstones, Cholecystolithiasis.

Full-texts included authors personal correspondences were obtained as many as possible. References of literature were retrieved manually. After initial screening by reading topics and abstracts, we tried to obtain the original literatures for second screening if literatures were going to be included.

Disposition of literatures included. After primary screening, literatures were printed, name of the magazine, author, and the authors department were hided, then be bound again. Literature evaluators did blind evaluation as they didn’t know the name of the magazine, the author, and the authors department. Two researchers evaluated literatures and extracted data independently. Data included about authors, time, research site, designing type, control group, adjustment of confounding factors, exposures and non-exposures, the number of cases group and control group, intervention types and so on.

Evaluation of the quality of literatures. Included literatures were evaluated using the Newcastle-Ottawa Scale. The full score was 9, about three aspects, the definition and choosing of cases group and control group, the comparable between them, the certainty of exposures.

Statistical analysis method. Revman 5.0.14 were used to merge data and inspect heterogeneity. Test statistics was P, P>0. 05
means heterogeneity was not statistically significant. P > 0.05 means heterogeneity was statistically significant. If not statistically significant, fixed effects model will be used, or else random effects model will be used. Pooled odd ratio (OR) and 95% confidence intervals (CI) were calculated, sub-group analysis in sex and position of tumors was done.

Results

**Process.** In total 1639 literatures were found, 693 literatures were eliminated as the research object was not Chinese population, 708 literatures not qualified were eliminated when reading topics and abstracts, 28 literatures suitable were left for meta-analysis. After reading the full-text, two repeated literatures were eliminated. Twenty-six literatures were left at last.

**Features of literatures included.** Twenty-six literatures included at last were from 15 provinces or municipalities in China. Release time was from 1993 to 2008. They were all case-control studies. The total number of cases was 11502. The total number of controls was 15565. Matched design was used in four articles. Group design was used in the other 22. Two were grey literatures, one was masters thesis, the other was the abstract of a piece of conference paper. Two literatures hadn’t got the full-text. From specific problems in literatures, 21 discussed the correlation of cholecystectomy and colorectal cancer. 14 in them discussed the correlation of cystic calculus and colorectal cancer meantime. The other 4 only discussed the correlation of cholecystolithiasis and colorectal cancer. The last 1 didn’t discuss cholecystolithiasis and cholecystectomy separately. Further researches found that 5 literatures had data to be extracted separately according to gender, 10 had data to be extracted according to position of tumor.

<table>
<thead>
<tr>
<th>Study</th>
<th>Province</th>
<th>Disease (CHO/CHE)</th>
<th>NOS</th>
<th>Design (group/paired)</th>
<th>Selection of control</th>
<th>Compatibility</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu 2002</td>
<td>Shanghai</td>
<td>CHO</td>
<td>4</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Age, sex</td>
<td>Location/sex sub team</td>
</tr>
<tr>
<td>Chen 2003</td>
<td>Guangdong</td>
<td>CHE</td>
<td>4</td>
<td>Group</td>
<td>Negative colonoscopy</td>
<td>Age, sex</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Chen 1998</td>
<td>Beijing</td>
<td>CHO &amp; CHE</td>
<td>5</td>
<td>1/2 age sex paired</td>
<td>Negative colonoscopy or negative occult blood</td>
<td>Age, sex</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Li 2003</td>
<td>Jiangxi</td>
<td>CHO &amp; CHE</td>
<td>5</td>
<td>Group</td>
<td>Other tumor</td>
<td>Age, sex, weight</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Li 2007</td>
<td>Inner Mongolia</td>
<td>CHO &amp; CHE</td>
<td>1</td>
<td>Group</td>
<td>Other tumor</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Li 2005</td>
<td>Zhejiang</td>
<td>CHO &amp; CHE</td>
<td>2</td>
<td>Group</td>
<td>Other tumor</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Li 2001</td>
<td>Guangxi</td>
<td>CHO</td>
<td>6</td>
<td>1/2 age sex paired</td>
<td>Negative colonoscopy</td>
<td>Age, sex</td>
<td>Location/sex sub team</td>
</tr>
<tr>
<td>Liu 2000</td>
<td>Tianjin</td>
<td>CHO &amp; CHE</td>
<td>3</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Age</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Hu 1994</td>
<td>Jiangsu</td>
<td>CHE</td>
<td>1</td>
<td>Group</td>
<td>Appendicitis</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Lan 2007</td>
<td>Zhejiang</td>
<td>CHO &amp; CHE</td>
<td>4</td>
<td>Group</td>
<td>Negative colonoscopy</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Shen 2007</td>
<td>Zhejiang</td>
<td>#</td>
<td>*</td>
<td>Group</td>
<td>Other tumor</td>
<td>Not mentioned</td>
<td>Conference abstracts only</td>
</tr>
<tr>
<td>Shi 1994</td>
<td>Shanghai</td>
<td>CHE</td>
<td>1</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Su 2008</td>
<td>Shandong</td>
<td>CHO</td>
<td>3</td>
<td>Group</td>
<td>Other digestive tumor</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Sun 2007</td>
<td>Anhui</td>
<td>CHO &amp; CHE</td>
<td>4</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Age, sex</td>
<td>Location/sex sub team</td>
</tr>
<tr>
<td>Sun 2007</td>
<td>Zhejiang</td>
<td>CHO &amp; CHE</td>
<td>4</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Not mentioned</td>
<td>Master’s thesis</td>
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<tr>
<td>Tian 1994</td>
<td>Fujian</td>
<td>CHE</td>
<td>2</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Wang 1997</td>
<td>Shanghai</td>
<td>CHO &amp; CHE</td>
<td>5</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Age</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Wu 2005</td>
<td>Yunnan</td>
<td>CHO &amp; CHE</td>
<td>3</td>
<td>Group</td>
<td>Other digestive tumor</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Xi 2002</td>
<td>Hebei</td>
<td>CHO &amp; CHE</td>
<td>1</td>
<td>Group</td>
<td>Other tumor</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Yang 1996</td>
<td>Shanghai</td>
<td>CHO</td>
<td>5</td>
<td>1/1 age paired</td>
<td>Community e</td>
<td>Age</td>
<td>Location/sex sub team</td>
</tr>
<tr>
<td>Yang 2004</td>
<td>Fujian</td>
<td>CHE</td>
<td>4</td>
<td>1/2 age paired</td>
<td>Physical exam</td>
<td>Age</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Yue 2001</td>
<td>Shanghai</td>
<td>CHE</td>
<td>5</td>
<td>Group</td>
<td>Gastric cancer</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
<tr>
<td>Zeng 1993</td>
<td>Nanjing</td>
<td>CHE</td>
<td>*</td>
<td>Group</td>
<td>Physical exam</td>
<td>Not mentioned</td>
<td>Location sub team</td>
</tr>
</tbody>
</table>

| Province | Disease (CHO/CHE) | NOS | Design (group/paired) | Selection of control | Compatibility | Notes | Notes |
|----------|------------------|-----|-----------------------|---------------------|--------------|-------|
| Hangzhou | CHO | 5 | Group | Gastric cancer | Not mentioned | Location sub team |
| Zhang 2009 | Beijing | CHO & CHE | 2 | Group | Other tumor | Not mentioned | Location sub team |
| Zhao 2006 | Zhejiang | CHO & CHE | 5 | Group | Gastric cancer | Age, sex | Location/sex sub team |
| Zhu 2005 | Shandong | CHO & CHE | 4 | Group | Negative colonoscopy | Not mentioned | Location sub team |

CHO, cholecystectomy; CHE, cholecystolithiasis.

* Only abstract was available, no score was calculated.
# Unable to distinguish CHO from CHE.
NOS scores of literatures included were from 1 to 6. The one that only had abstracts didn’t participate in scoring. In the remaining 24, 1 scored 6, 6 scored 5, 7 scored 4, 3 scored 3, 3 scored 2, 1 scored 1.

**Statistical analysis.** We merged the results of 26 articles. Heterogeneity was statistical significant (p<0.05), the pooled OR was 3.00, 95% confidence interval was 2.30-3.91. 18 in them discussed the correlation of cholecystolithiasis and colorectal cancer, heterogeneity was also statistical significant (p<0.05), OR was 2.85, 95% CI was 2.13-3.81. 21 discussed the correlation of cholecystectomy and colorectal cancer, heterogeneity was still statistical significant (p<0.05), OR was 2.6895% CI was 1.93-3.72. (Fig. 1)

In these literatures, subgroup analysis was done in five to discuss the correlation according to sex. In mens group, heterogeneity between the groups reduced (p=0.05), when using random effects model, OR was 1.13, 95% CI was 0.65-1.95. In womens group, heterogeneity between the groups also reduced, when using fixed effects model, OR was 2.95, 95% CI was 2.15-4.03 (Fig.2)

Subgroup analysis was done in 10 literatures according to position of tumors. For tumors in the right-side colon, heterogeneity after mergence was statistical significant, (p<0.05), using the random effects model, the pooled OR was 4.68, 95% CI was 2.68-8.17. For tumors in the left-side colon, heterogeneity was statistical significant, (p<0.05), using the random effects model, OR was 2.1595% CI was 1.10-4.18 (Fig. 3). Subgroup analysis about 14 literatures that

![Figure 1](image-url)  
**Figure 1** Forest plot of the association among cholecystectomy, cholecystolithiasis or the combination of the two with colorectal cancer.
the NOS score was more than 4, heterogeneity was statistical significant (P<0.05), using the random effects model, OR was 2.32, 95% CI was 1.69-3.19. Checking the sensitivity, when changing random effects model to fixed effects model, the nature of researches did not change.

**Discussion**

**Similar previous researches.** In 1993, Giovannucci et al.\(^\text{34}\) merged the results in 33 articles about retrospective case-control studies, found that the proportion of a history of cholecystectomy in colorectal cancer patients group was higher than control group (OR = 1.34, 95% CI = 1.14-1.57), in the subgroup analysis of proximal colon cancer, the difference was obvious (OR = 1.88, 95% CI = 1.54-2.30). But in six prospective cohort study articles, after merging the results, no difference revealed (RR = 0.97, 95% CI = 0.82-1.14). In the same year, Bollschweiler et al.\(^\text{35}\) did meta-analysis about related problems, considered that neither prospective and retrospective studies, nor gender
and position subgroup analysis, could prove the correlation of cholecystectomy to colorectal cancer. As evidences accumulated, in 1996, Reid et al.\textsuperscript{9} chose 35 literatures adjusted by gender and age confounding factors in 95 literatures, did meta-analysis. They found that there was a slight relevance between cholecystectomy and colorectal cancer (OR =1.11, 95% CI= 1.02-1.21), it was more obvious in female and proximal colon cancer. Chinese scholars Chou et al.\textsuperscript{97} merged 5 literatures based on Chinese people, found that cholecystectomy increased the risk of colorectal cancer (OR =3.36, 95% CI= .31-8.63).

From these four meta-analysis mentioned above, we could see that they explored the correlation of cholecystectomy or cholecystolithiasis to colorectal cancer, while neglected that most cholecystomys were for curing cholecystolithiasis, and the types of most cholecystolithiasis patients were gallbladder full of stones, gallbladder neck embedded with stones or gallbladder atrophy which would lead to self-sectional gallbladder, then lose the function of storing bile. The pathogenesis was similar to cholecystectomy. So we considered both cholecystolithiasis and cholecystectomy to be different stages of the same disease, merged them together to analyze, then separated them for subgroup analysis.

**Features of this study.** Meta-analysis in this study found that gallbladder diseases (including cholecystolithiasis and cholecystectomy) were closely associated with colorectal cancer (OR=3.00, 95% CI= 2.30-3.91), separate subgroup analysis found that cholecystectomy and cholecystolithiasis were associated with colorectal cancer closely, too (cholecystolithiasis: OR =2.85, 95% CI= 2.13-3.81; cholecystectomy: OR =2.68, 95% CI= 1.93-3.72).

Many basic researches also gave pathophysiological evidences for the correlation of gallbladder diseases to colorectal cancer. After excision, gallbladder can not store bile any more, liver constantly excretes bile into intestinal canal directly, increases cycles between intestinal canal and liver. Subprime bile acid in bile acid was considered to be very strong carcinogenic substance. Besides, high protein, high adipose and low fiber food was known as important factors for the occurring of colorectal cancer, while also closely be related to cholecystolithiasis and cholecystitis. These dietary factors may be one of the causes of the correlation of cholecystolithiasis and cholecystectomy to colorectal cancer.

Subgroup analysis displayed that in womens group, the correlation between gallbladder diseases and colorectal cancer was obvious (OR =2.95, 95% CI= 2.15-4.03), while in mens group, there was no statistical significance (OR =1.13, 95% CI= 0.65-1.95). It might be interpreted by few individuals and small sample. It is also interpreted by other reasons, firstly, publication bias, only five in 26 literatures provided data on sex to be extracted. Secondly, hormones are different in men and women. Basic researches proved that estrogen could promote the metabolism of blood cholesterol in liver, increased bile acid and cholesterol excreted by liver into intestinal canal. Estrogen receptor in Induced colorectal cancer tissue was detected. Estrogen and similar agent could stimulate and accelerate the growth of colorectal cancer cell lines in vitro. These may be the reasons for the more susceptibility in women than men.

**Limitations of this research.** Though we indicated the close correlation of gallbladder diseases to colorectal by our research and sufficient biological evidences, the correlation wont be absolutely true owing to method, quality and so on in including literatures.

Firstly, our meta-analysis, as one part of the research of etiology, was about the risk of gallbladder disease to colorectal cancer. Sakeet et al.\textsuperscript{98} thought that the best evidence was from meta-analysis based on homogeneous randomized control trial (RCT), the second was from prospective cohort study and relevant meta-analysis, the third was retrospective case-control study and meta-analysis. Because of limitations of design types of the original literatures, literatures included were all case-control studies.

Secondly, in original literatures, diagnosis of cholecystectomy was from medical history, intervals between cholecystectomy and colorectal
cancer were not described. Diagnosis of cholecystolithiasis was from type B ultrasound before operation, types of cholecystectomy were not described, too. Some researches indicated that, in exploring risk factors in some chronic non-communicable diseases, there was a need of long time to observe results because of the long latency. Short observation period will lead to negative results easily.

Thirdly, in literatures included, most cases in contrast groups were from hospitals. Many were other gastrointestinal tumors (such as gastric). Whether diagnostic method was the same in contrast groups and cases groups, only one or two literatures had mentioned. It was said in some researches that the authenticity of the correlation was exaggerated when case-control study was based on hospital.

Fourthly, we retrieval literatures as comprehensively as we can to reduce publication bias in literatures, took in more literatures, extracted useful data. Disposition of two grey literatures and two abstracts could prove this. But 26 literatures included were from 15 provinces or municipalities in China, most of which were developed regions. So it needs more supports from more regions to support the representative of the results.

Lastly, we must control the known confounding factors strictly in exploring the correlation of gallbladder diseases to colorectal cancer because of the possible common causes of gallbladder diseases and colorectal cancer. Group design was used in most literatures included, matched design was used only in four literatures, while matched design was a better method to control confounding factors. So bias was inevitable.

Form the above, a history of CHE or CHO may be associated with higher incidence of colorectal cancer in Chinese population closely, sub-group analysis in sex and position of tumors revealed obvious correlation of CHE or CHO to colorectal cancer except for the mens subgroup. But the possibility of bias can not be neglected. Case-control study from community people, matched design to control confounding factors in cases and controls, or population-based prospective cohort study based on large sample were suggested in the future researches.

References:


[14] Li YZ. Research on relationship between cholecystolithiasis