

1st December, 2014
The Editor
World Journal of Gastroenterology
Baishideng Publishing Group Inc
8226 Regency Drive
Pleasanton,
CA 94588
USA

My ID 02504712

Dear Editor

Thank you for inviting me to re-submit this review to the World Journal of Gastroenterology. Please find the manuscript of the systematic review: Cholecystectomy and the risk of alimentary tract cancers: A systematic review. This review focuses on a topical issue on the association between a history of cholecystectomy and cancers of the gastro-intestinal tract. The review is comprehensive and is the first systematic review to consider all cancers of the gastro-intestinal tract. This review has been revised to address all the reviewers' comments. The revisions on the manuscript have been highlighted. A response to all reviewers' comments is attached.

The final manuscript has been read and approved by all authors. Both persons listed as authors have contributed to preparing and revising the manuscript in accordance with the authorship criteria of The International Committee of Medical Journal Editors (ICMJE). No person or persons other than the authors listed have contributed to its preparation. All authors, had full access to all of the data (including statistical reports and tables) in the review and can take responsibility for the integrity of the data and the accuracy of the data analysis. The contents of this manuscript are original work and have not been presented, published or submitted, in whole or in part, prior to or simultaneous with our submission of the manuscript to The World Journal of Gastroenterology.

All authors have observed the "Unified Competing Interest" and declare no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work. This study was not funded from any source.

We look forward to approval of this article for publication in the World Journal of Gastroenterology.

Your Sincerely



Sami M Shimi,
Department of Surgery, Ninewells Hospital, Dundee, Scotland.
E mail: s.m.shimi@dundee.ac.uk

Response to reviewers

Reviewer 02540514

The authors present a very comprehensive review about a very interesting though quite controversial topic. I agree in most estimations with the authors and this is one reason why I am irritated by the abstract of the manuscript. The authors should here make quite clear that there is NO clear association and of course no causal relation between cholecystectomy and GI tract cancers. Based on the studies the authors analyzed this seems the only possible conclusion to me. Please rephrase the related sentences in the results and conclusions sections of the abstract.

We thank the reviewer for his comments. The relevant sentences in the results and conclusion of the abstract as well as the rest of the manuscript have been revised to address the reviewer's comments.

Reviewer 02527484

The authors performed a literature review in a manuscript entitled "Cholecystectomy and the Risk of Alimentary Tract Cancers, A Systematic Review." This is a comprehensive review of the world's literature highlighting the relationship between prior cholecystectomy and GI malignancies by site as well as proposed mechanism/pathogenesis. Given the dearth of literature on this topic, I commend the authors for tackling this topic. Identifying previously published longitudinal and observational studies, their review of pertinent studies on cholecystectomies and GI cancers is thorough and complete. I have several questions and concerns: 1) Please ask another colleague proofread the manuscript. There are gross syntax errors. Some paragraphs could be better phrased. Abbreviations are used sporadically throughout the manuscript. Be consistent. 2) The abstract should include a summary of relevant results of the literature review. Don't simply state "apparent association" of all GI sites. It should summarize pertinent findings in a succinct way. 3) For each GI site, can the authors provide additional concrete findings from studies reviewed? Besides noting the presence or absence of any association between prior cholecystectomy and each GI site, try to report (if available) median or mean intervals from cholecystectomy to diagnosis of malignancy. If available, report age, weight, sex, frequency of modifiable risk factors, etc.. Do not only report risk or odds ratios for cholecystectomy. Were there other important risk factors noted in these studies? If so, include in the result section. 4) Report age in the table or results section. This was a major point of the discussion, but the authors did not report age in the result resection. 5) Please include study period for each study. Increasing incidence of GI cancers could be temporal effect rather than cholecystectomy. I suspect improvements in imaging modalities and advancements in other diagnostic tools have resulted in the detection of more GI malignancies than in prior decades. 6) Good job summarizing proposed mechanisms. 7) I do not understand what the authors meant when they state that bile salts are "cancer promoters" but not "carcinogens/carcinogenic." 8) Rather than stating that there is "contradictory evidence" for the association between prior cholecystectomy and the development of GIT cancers, why not state there is no strong evidence supporting such association? Overall, what I

gleaned from this paper is that there is no clear association but given the variability in quality of prior studies, further investigation is warranted.

Response to Reviewers Comments:

1. *The syntax errors in the manuscript have been amended.*
2. *The abstract has been amended to reflect the results of the literature review.*
3. *Like the reviewer, we acknowledge the importance of the additional information such as age, weight, sex etc. Unfortunately, this information is only reported by a small minority of the studies. We tried to be selective on the amount of information provided in the review so we did not distract from the main message of the review. Information reported by a minority of the articles was deselected as it would have provided an incomplete picture.*
4. *Unfortunately, the age of the patients in each of the studies is not reported since these studies have included relatively large cohorts of patients with varying age.*
We agree that the period of the study is an important factor. We have added the period of study for each article in the tables.
5. *We thank the reviewer for commending the section on mechanisms of carcinogenesis.*
6. *The sentences on cancer promoters (promoting tumorigenesis by other known carcinogens) as opposed to direct carcinogenesis has been expanded to convey the meaning.*
7. *The phrase “contradictory evidence” has been substituted with “There were inconsistent reports and no strong evidence”.*
8. *The reviewer suggested adding the phrase “ additional investigations are warranted”. We agree with the reviewer and have added this phrase at the main conclusion of the review.*

Additional Authors comments:

Under ABSTRACT

Comment 1: “apparent” is weak term and shouldn’t be used in scientific manuscripts. The association, if any, should be clearly stated in your abstract.

The word apparent has been removed and the structure of the sentence altered.

Comment 2: Under the abstract section, the reviewer has asked for an example of the mechanisms of carcinogenesis.

Examples of the mechanism of carcinogenesis have been added.

Under Core tip

Comment 3: At the Core Tip section, the reviewer has suggested to just simply state that there is no clear association between cholecystectomy and GIT cancers.

The Core tip section has been revised in accord with the reviewers suggestion.

Under INTRODUCTION

Comment 4: In the introduction, the reviewer has suggested adding examples of gallstone problems such as cholecystitis or choledocholithiasis.

The examples have been added in accord with the reviewer's suggestions.

Comment 5: "Variances" that reported here is based on a 1977 paper in your references. For this systematic review of the literature, I would recommend reporting patterns in modern practice rather than referring an archaic paper. Laparoscopic cholecystectomy is standard practice for benign gallbladder disease.

In accordance with the reviewers suggestion, the sentence has been altered and the historic reference has been removed.

Comment 6: The reviewer suggested using abbreviations.

Abbreviations for Gastro-intestinal Tract (GIT) have been used throughout the manuscript.

Comment 7: This entire paragraph is confusing. Need to rephrase to convey your message effectively.

The paragraph has been altered to make it easier to understand.

Comment 8: Strong assumption stating that both diagnosis of GIT and cholecystectomy are common. Please include reference.

Three references have been added to support the statement.

Comment 9: This probably would apply to all operations, not just cholecystectomies

We agree with the reviewer that the risks should be explained to all patients having an operation. However, we have focuses this sentence on the risk of GIT cancers after cholecystectomy.

Under METHODS

Search Strategy

Comment 10: What was your criteria for "poor study design." What were data were necessary. Incomplete data is unfortunately inherent in many studies, including population registries. Need to clearly state your inclusion/exclusion criteria.

The phrase of "poor study design" has been clarified. The phrase "incomplete data" has been removed. The inclusion and exclusion criteria have been clarified in the manuscript.

Data Extraction

Comment 11: I would try to include study time period for each of these studies in your tables. For example, a study conducted from 1977 to 1988 would interpreted much more differently compared to a study of a population from 2000-2010.

The study period for each article has been added to the tables in the manuscript.

Assessment of study quality

Comment 12: Please cite this in your references/bibliography. Also, spell out what STROBE stands for (not everyone knows it stands for strengthening the reporting of observational studies in epidemiology)

A reference has been cited for STROBE and the abbreviation expanded.

Comment 13: What was the minimum score required to be included in this study?

This review was designed to be comprehensive. As such papers which met the inclusion and exclusion criteria were subsequently scored and the score provided. As such, no minimum score was required for inclusion in the review.

Statistical analysis

Comment 14: Save words—no need to spell out confidence interval every time.

This has been revised throughout the manuscript.

Under RESULTS

Oesophageal Squamous Cell Carcinoma

Comment 15: You used the same studies for adenocarcinoma of the esophagus. Consider merging these paragraphs

The two paragraphs on oesophageal carcinoma have been merged.

Pancreatic cancer

Comment 16: Interesting.

We thank the reviewer for his comment.

Liver Cancer

Comment 17: What other risk factors were identified?

Having examined the publications cited, the authors did not identify other risk factors for liver cancer

Intestinal (Small Bowel) Cancer

Comment 18: What was the annual risk reduction?

This has not been reported by the publication cited. The publication reported the risk ratio in 5-year bands.

Colorectal Cancer

Comment 19: Unless you decide to delve into the significance of geography, no need to state that these results were abstracted from studies from different locations.

The country of origin for the different articles have been removed from the tables.

Distal Colon Cancer

Comment 20: Again, not sufficient to merely report OR only.

Unfortunately, we are limited by the data reported in the publication. We did not have access to raw data to derive Risk Ratio.

Proposed mechanisms of carcinogenesis:

Comment 21: What is the difference between carcinogens and cancer promoters? Clinically, the same.

The sentences on cancer promoters (promoting tumorigenesis by other known carcinogens) as opposed to direct carcinogenesis has been expanded to convey the meaning.

Comment 22: Good job describing the mechanisms in relation to the development of GI malignancy (by site).

We thank the reviewer for this comment.

Under DISCUSSION

Comment 23: Please report age in your results. Include in your table.

The publications cited have reported on cohorts with populations of different ages. As such, this information was intermittently reported and would add little to the results. More importantly, it would not alter the conclusion.

Comment 24: This is based on a 1970s paper. Also, I do not understand why you are discerning “cancer promoters” and “carcinogens.”

The publication from 1974 has been replaced by a more up-to-date publication. It was felt important that the controversy in the literature on whether bile acids were promoters (promoting the effects of other known carcinogens) or as carcinogens acting independently is not ignored completely particularly for a substance that is so ubiquitous in the gastrointestinal tract.

Conclusion

Comment 25: I would say no association. “Casual” association seems to be a stretch based on your results.

The wording of the conclusion has been altered.

Reviewer 02822880

The authors are to be congratulated for an extensive literature review. It is very difficult to answer the question the authors have posed in the absence of large multiple homogenous well done institutional studies with a long term follow up. As pooled analysis could not be performed due to inhomogeneity of studies this is a descriptive review from which it appears that cholecystectomy may not be causal in GIT cancer development however I dont think any conclusions can be drawn.

We thank the reviewer for his comments. The final conclusion of the review is in line with the reviewer’s conclusion.

Reviewer 02948135

Dear authors, You are trying to assess the evidence of linkage between cholecystectomy and GI cancer. This proposed link can not be proved by studies other than randomised controlled trial. Therefore whatever evidence you present won't stand and won't be accepted from scientific point of view. 1. All studies you presented are suffering from heterogeneity, inconsistency and majority based on author assumption rather than robust scientific proof, 2. In this century, scientist can not accept that bile is carcinogenic, if that the case then we are going to develop GI cancer because our body is secreting bile! 3. Studies which are published in 1977 is out of date! and no impact on our current evidence is possible to be made. 4. If cholecystectomy is associated with GI cancer as a cause, then more aggressive procedure that involved removed hormone secreting organs like small bowel resection, clonic resection, gastrectomy should be associated with cancer!! 5. Your conclusions are suggestive of no association, but actually every scientist would know before start that there will be no association if you are trying to prove it with the type and quality of studies made on this issue. 6. The studies that support or suggest association are those which are suffer most from flaws in methodology, poor selection, bias and heterogeneity. 7. As such your article [although you put huge efforts to reference more than 90 papers] would add no thing to the current knowledge. 8. If this article to be published, it needs major revisions to address the following points: 1. Scientific, robust studies that have sound methodology should be selected. 2. Studies which are published more than 10 years have little impact and should be avoided. 3. The theories of association are posing concepts that contradict with basic scientific principles. These theories need no hard efforts to cancel them. 4. The study is very long and should be shortened to focus on 10-15 scientifically acceptable papers. 5. Even if you do above, it will still scientifically not possible to prove or disprove association!

We thank the reviewer for his comments.

- 1. We agree with the reviewer that the reported studies suffer from heterogeneity and inconsistency. There are no reported randomized clinical trials nor is it feasible that such trials will ever be carried out. We have included comments on the limitations of this review which encompass the reviewer's views.*
- 2. We agree with the reviewer that bile in normal concentrations is not carcinogenic. However we would respectfully point out the bile has been shown in experimental studies to be carcinogenic. The references for this work are included in the manuscript. The contention in here is that after cholecystectomy, there is continuous secretion of bile without storage in the gallbladder. This continuous bile secretion varies with different food intake and can reach high physiological concentrations which can induce mutagenic events.*
- 3. This review was intended to be comprehensive and has included all studies to avoid selection bias. If we had omitted some studies, we would have been criticized for such omissions. We have now included the year of the study against each article in the table to enable the reader to select which studies are more credible to them. The difficulty we have encountered is that the more comprehensive studies have spanned a longer period of time. This undoubtedly has caused some bias. For example, some of the patients in these long-term studies will not have benefited from advances in diagnostic*

imaging that occurred during the long time period. Consequently, the diagnostic error at the time of presentation with gallbladder symptoms are larger!

- 4. This review has focused on cholecystectomy and not on other major GI operative procedures. In this review, we have reported on the published mechanisms of carcinogenesis. The aim of the review was to explore this association. In this exploration we have discussed causality and ruled it out.*
- 5. As clinicians, this review has enabled us to be reasonably comfortable that there is no clear association between cholecystectomy and GI cancers. As such, we can recommend cholecystectomy (when necessary) to our patients without fear or anxiety that we are predisposing them to cancer. We can also reassure them of these facts based on such a comprehensive review. Through the World Wide Web, our patients are well informed of the literature nowadays. They ask pertinent questions and demand answers. Clinicians need to be armed with a comprehensive review in order to answer these questions.*
- 6. We agree with the reviewer that studies which suggest an association are probably flawed in methodology, poor selection bias and heterogeneity. This is already stated in the review. This review has attempted to counterbalance the flawed studies with less flawed ones in order to produce a balanced argument that no clear association exists. This further emphasizes the importance of this review. By not publishing this review will not make the other publications which are flawed suddenly disappear.*
- 7. We would respectfully point the reviewer to the above responses under 5 and 6. Some articles have suggested that there is an association between cholecystectomy and GIT cancers and other articles have ruled out such an association. The importance of this review was to clarify the issue on the association between cholecystectomy and all GIT cancers rather than to add new knowledge. We believe that we have been successful in clarifying that there is no clear association. This is important to the clinical community.*
- 8. We partially agree with the final contention of this reviewer that by focusing the search and selecting studies, we will be unable to scientifically prove or disprove an association. 1. A review per se will never be able to prove or disprove any association. 2. All the cited articles which have reported on the association are retrospective epidemiological studies with inherent flaws. This has been emphasized in the limitations of the study. There are no randomized controlled trials to base evidence on. However, having collected all the published studies and put them side by side, segregated into different parts of the digestive tract, we believe that we have produced a cogent discussion to conclude that there is no clear association. As part of the methodology, it was essential to formulate inclusion and exclusion criteria and to report these in accordance with the PRISMA methodology. In formulating the criteria we have intended not to be selective but rather to be comprehensive. The main reason for this comprehensive approach is the relative dirth of studies on this subject. While doing so, we have rated the quality of the studies according to the STROBE checklist. We believe that this strategy constitutes a major strength to this review.*