

Peer Review File

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Reviewer A

Many compliments to the authors for this topic, very interesting and unexplored. I think it deserves to be investigated with further studies for the great implications on the possibility of prevention.

The regional sub-analysis is very interesting, but the authors do not mention them as secondary endpoints. So, I advise them to describe the regional sub-analysis and the reasons why they perform it among the endpoints of the study.

**Reply: Thank you for your comments. We have made the necessary modifications.
Changes in the text: Paragraph 2 /Introduction**

Reviewer B

1) First, I suggest the authors to clearly indicate what the term “impact” is, i.e., the relationship between viral hepatitis and the risk of CCA.

**Reply: Thank you for your comments. We have revised the title.
Changes in the text: Paragraph 1 /Title**

2) Second, the abstract needs some revisions. The background did not describe the controversies regarding the relationship between viral hepatitis and the risk of CCA and did not explain why a meta-analysis is needed. The methods did not describe the literature search, inclusion criteria according to the PICOS principles, data extracted, and risk of bias assessment of included studies. The results need to summarize the characteristics of the included studies such as the total sample size and research methodology, as well as the risk of bias of included studies. The conclusion needs more detailed comments for the clinical and public health implications of the findings.

Reply: Thank you for your comments. We have added the background section. Due to limited space, we did not list the inclusion criteria for PICOS principles in the methodology section of the abstract. We have already listed it specifically in the methods section of the main text. We have added the results and conclusion section.

Changes in the text: Paragraph 1,2,3,4 / Abstract

3) Third, the introduction of the main text is poor, which did not describe the controversy regarding the relationship between viral hepatitis and the risk of CCA, analyze the potential reasons for the controversy, and explain why a meta-analysis is suitable to address this controversy. Please also directly indicate the potential public health significance of this research focus.

Reply: Thank you for your comments. We have added these contents in Introduction.

Changes in the text: Paragraph 2 /Introduction

4) Fourth, in the methodology of the main text, the literature search within these databases is not adequate, please consider EmBase and SinoMed. In the inclusion criteria, it is wrong to include RCTs, since RCTs cannot answer the question of risk factors. The authors need to explain why they considered case-control studies, because strictly speaking case-control studies cannot answer the question of risk factors. One inclusion criterion is also not feasible such as “the original literature provides specific case and control data”. The authors must clearly describe the data extracted for the pooling analyses such as the adjusted RR, HR or OR values. It seems that the authors extracted data from univariate analyses, which were wrong. The authors need to describe the details of NOS and the criteria for studies of low risk of bias. The current cut-off scores were not convincing. In statistics, please describe the subgroup analysis for the sources of heterogeneity, as well as the influence of levels of risk of bias on the pooled effect sizes. The authors need to explain why the OR values from cohort and case-control studies can be pooled together. Please ensure $P < 0.05$ is two-sided.

Reply: Thank you for your comments. We strongly agree with your viewpoint. We have added searches for EmBase and SinoMed databases. We have corrected the errors in the statistics section.

Changes in the text: Paragraph 1,2,4,5 /Methods

Reviewer C

1. Table 1

The year is different between table and reference list, please check and revise.


12	Tanaka (31)	2009	Japan	HBV/HCV
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31. Tanaka M, Tanaka H, Tsukuma H, et al. Risk factors for intrahepatic cholangiocarcinoma: a possible role of hepatitis B virus. *J Viral Hepatol* 2010;17:742-

Reply: Thank you for your comment. We have modified it.

2. Figure 4, 7-8

The year is different between figure and reference list, please check and revise.

 Tanaka, 2009

31. Tanaka M, Tanaka H, Tsukuma H, et al. Risk factors for intrahepatic cholangiocarcinoma: a possible role of hepatitis B virus. *J Viral Hepat* 2010;17:742-

Reply: Thank you for your comment. We have modified them.