

RESPONSE TO REVIEWERS

October 4, 2013

Dear Editor:



Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript No. 5084-Review.doc).

Title: Smoking, alcohol consumption, and the risk of extrahepatic cholangiocarcinoma: a meta-analysis

Authors: Xiao-Hua Ye, Jia-Ping Huai, Jin Ding, Yan-Ping Chen, Xue-Cheng Sun

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5084

The manuscript has been improved according to the comments made by the reviewers:

1. The format has been updated.

2. Revisions have been made according to the suggestions of the reviewers:

- (1) We thank the reviewer for the comments on the difference in the association between smoking and extrahepatic cholangiocarcinoma (ECC) in Asian and non-Asian studies and have discussed the possible reasons for this difference in the third paragraph of the Discussion.
- (2) The reviewer's comments on the inclusion and exclusion criteria are very important. The aim of our study was to investigate risk factors of ECC. ECC arises from cholangiocytes lining the biliary tree and is different from gallbladder cancer (Cardinale V, Semeraro R, Torrice A, Gatto M, Napoli C, Bragazzi MC, Gentile R, Alvaro D. Intra-hepatic and extra-hepatic cholangiocarcinoma: New insight into epidemiology and risk factors. *World journal of gastrointestinal oncology* 2010; **2**(11): 407-416 and Rustagi T, Dasanu CA. Risk factors for gallbladder cancer and cholangiocarcinoma: similarities, differences and updates. *Journal of gastrointestinal cancer* 2012; **43**(2): 137-147). We systematically searched the databases and excluded studies that did not meet our inclusion criteria. The studies suggested by the reviewer were considered and excluded from the meta-analysis because of unspecified cancer type (Bulajic 2002; Grainge 2009; Yi 2010; Murata 1996) or irrelevant cancer type (Zatonski 1997; Yagyu 2008), because they were based on the same population as other included studies (Zhang 2006), or because they reported non-relevant outcomes (Ishiguro 2008). We have specified these criteria in the 'study selection' subsection of the Material and Methods in the revised manuscript.
- (3) We strongly agree with the reviewer's comments that a sensitivity analysis should be performed to assess the impact of the two studies of lower quality on the final pooled RR. According to the reviewer's comment, a sensitivity analysis has been performed and the results have been added to the revised manuscript (Page 13 and Figure 5).
- (4) We have added discussion of the previously published meta-analyses to the first paragraph of the Discussion and have illustrated the difference between our study and these previous studies.
- (5) A brief description of the Q and I^2 statistics has been added to the 'statistical analysis' section of the Materials and Methods as suggested by the reviewer.
- (6) The duplicated references have been corrected as the reviewer suggested.
- (7) The labels inside Figures 2 and 3 have been changed according to the reviewer's suggestion.
- (8) We agree with the suggestion that we include information on other risk factors for ECC and have added discussion about other risk factors to the second paragraph of the Introduction. To date, there are no studies that have focused on whether the cessation of smoking or alcohol consumption would

reduce the risk of ECC development, and we intend to perform research on this topic in the future.

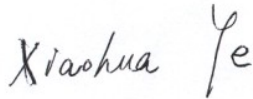
- (9) We have added a figure that illustrates the possible process of formation of ECC by cigarettes or cigars as suggested by the reviewer.
- (10) We concluded that smoking rather than alcohol consumption is associated with an increased risk of ECC. We also consider that alcohol consumption, particularly heavy alcohol consumption, may be a possible risk factor for ECC; however, stratified analysis could not be carried out because of a paucity of data. We intend to perform research on this topic in the future.

3. References and typesetting have been corrected.

4. We apologize for the language problems in our manuscript and thank the reviewer for carefully checking our manuscript. We have sent our manuscript to a professional English language editing company for improvement. All the language mistakes have now been corrected.

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading 'Xiaohua Ye'. The 'X' is large and stylized, and the 'Ye' is written in a cursive script.

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