Reviewer's report

Title: Hepatitis viruses infection and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis

Version: 1 Date: 17 May 2012

Reviewer: Suneet Sood

Reviewer's report:

To complete your checklist:
1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes, acceptable. They may be marginally improved by including publications in non-English journals, but the message will not change.
3. Are the data sound? Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes, to a large extent, although I personally would question one of their conclusions
6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Not directly, although references 2 and 9 in their paper are to papers by the same team.
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Yes, of high quality

Minor Essential Revisions:
The authors should revise the sentence on page 6: “Carcinogenesis of such HPCs may cause cancer regarding the potential targets cells of chronic inflammation that induce similar carcinogenic processes for ICC and HCC in chronic viral hepatitis.” I think I know what the authors are trying to say, but I don’t think they meant to say it in exactly that way.

Major Compulsory Revisions: none

Duplicate publication: I do not think this paper has been published elsewhere, though the authors do have publications on similar themes.

Further Comments:
I think this is a well written paper, discussing an important theme. I like the methods and the presentation, and think that all the submitted illustrations are relevant. I also find the discussion well written.
However, I would suggest to the authors to reconsider one of their conclusions. The authors state in their discussion that ICC is characterized by wide variability in incidence and risk factors. They suggest that this variability is due to “different endemic hepatitis virus types”.

I think that this variability is more likely due to the fact that studies showing negative association between infection and cancer have low power. For example:

1. Shin et al. Zhou et al state that Shin et al (ref 7) “found neither HBV nor HCV infection was associated with the risk of ICC. However, that study showed clear trends towards increased risk from HBV or HCV infection, even if the numbers sometimes did not reach statistical significance. Looking at that paper, it is obvious that the relationship between hepatitis and hepatocellular cancer is much stronger. Perhaps the few cases of cholangiocarcinoma (41) were insufficient to confirm the association?

2. Zhou et al. Zhou et al (authors of the paper under review) quote a paper by Zhou et al (probably the same lead author) (reference 9). A study from China showed a positive association of ICC with HBV but not with HCV. Again, looking at reference 9, the prevalence of anti HCV positivity among cases was more than double the positivity among controls. With the number of cases so small (nine cases who were anti-HCV+, obviously because HCV is rare in this region), statistical significance could not be shown.

I have not looked very closely at all the papers reviewed by the authors in their discussion, but I suspect that the reason for the discrepancy among published studies is the power of the studies, rather than a variation in the strains of viruses. I would suggest to the authors to take a closer look at the papers they have quoted.

Sincerely

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Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests