Reviewer’s report

Title: Chronic Hepatitis Infection Is Associated with Extrahepatic Cancer Development: A Nationwide Population-Based Study in Taiwan

Version: 0 Date: 11 Aug 2016

Reviewer: Silvia Franceschi

Reviewer's report:

The present article includes the findings of an extraordinary record linkage study in a population that is unique in terms of high burden of HBV and/or HCV infection. Unfortunately, statistical analyses are not adequate and are inconsistent across tables. Some findings, I suspect, are distorted by insufficient adjustment or standardization by age, sex, and, possibly, region of living. By the way, some tables are wrongly embedded in the text.

Major issues

Page 7, lines 15-20: authors state that "The index date for patients with chronic HBV or HCV infection was the first instance the chronic HCV or HBV". In which way were individuals with dual infection dealt with? You should mention, if possible, how often the two infections were detected at the same time and comment on whether of either HBV or HCV had been diagnosed the earlier, possibly before the availability of record linkage, of subsequently to the other infection.

Figure 1: individual matching was made but I understand that the three groups of CHI were eventually all compared with the pool of controls. Is it so? Then the substantial unbalance in sex and age, and, possibly, region, across the three group of CHI and the controls should be always adjusted for in order to compare like with like.

Table 1: findings are widely discussed and many different comparisons across the four columns are described in the Results. However the only statistic is a p-value for chi-square that does not even indicate degrees of freedom. P-values are obviously highly significant on account of the large study population but the direction of the associations is not given and, most important, comparisons should be adjusted at least for sex and age group that vary substantially between HBV-positive and HCV-negative individuals.

Table 2: IRR should be standardized for a standard population (like in cancer incidence studies). The standard should be the sex and age distribution of the control group if the three CHI group are all compared with the same pool of controls.
Table 3: I do not see any reason to adjust for urbanization, hypertension, and hyperlipidemia in Table 3 and also 4. I actually think that this is actually a dangerous complication. In addition, sex- and age- adjustment is adequate to compute HRs in each of the three groups of CHI but it does not allow to compare HRs across the three groups of CHI as they are too different. Notably HCV-positive are older than HBV-positive and less often male. Age and sex are, obviously, important modifiers of cancer risk as it clearly shown by the differences in HR between individuals < and >= 60 year-old (Table 4).

Last but not least, it is wrong to state that certain extrahepatic cancer are uniquely associated with one of the two infections when HR ratios are of similar size but only one is statistically significant, e.g., for thyroid cancer in Table 3 the Hrs are similar (1.67 and 1.51) and the 95% confidence intervals are overlap. To state a difference you should test for heterogeneity in the association (Wald chi-square).

Other issues

Abstract, line 8: add "hepatic" before "extrahepatic"

Page 7 and Figure 1: the sentence "Insurants without hepatitis or missing information on age and sex" is ambiguous. Please change into "Insurants without hepatitis and with information on age and sex"

Page 8, line 12: please find a "label" to identify dual infection, e.g., HBV/HCV, and use it all over the text

Page 12, line 27: correct 192 into 1.92


Discussion: authors make enormous efforts to provide biological explanations of the associations of HBV or HCV and some extrahepatic cancers. They neglect, however, the high probability of surveillance bias especially for cancers like thyroid, colorectal, kidney, skin, or ovary that can be very easily be over-diagnosed if HBV- or HCV positive people receive special medical attention, e.g., ultrasonography.

Page 14, lines 49-51: interferon-alpha is mentioned in relation to HBV as a possible disruptor of the thyroid but then: 1) information on the frequency of use of antiviral treatment in HBV-positive patients should be reported; and 2) till recently interferon was also used to treat HCV infection.

Table 1: indicate "lowest" and "highest" at the side of 1st and 4th category of urbanization
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal