Reviewer's report

Title: Hepatitis B and C coinfection and HCV genotype variation on hepatocellular carcinoma development: a population-based cohort study

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Reviewer: Sheng-Nan Lu

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The community-based cohort study from Korea followed 6694 tumor-free residents, age 30 years or old, to elucidate the risk factors of newly developed hepatocellular carcinoma (HCC). Besides of same results of published studies, they emphasized their finding of synergic effect dual infection of HBV and HCV and important role of HCV genotype 1. My comments were as follows:

General Comments:
1. Since this manuscript was submitted to this international Journal, you should not narrow your discussion in your country only. REVEAL study from Taiwan, a community-based study, published some papers on same issues. Please cite their publications and comparing your with them.
2. For the almost all Western and some Eastern studies reports the positive roles of DM and obesity in HCC development. In your study, the two factors were negative. You should emphasize the findings, enhance discussion of this part and add it in conclusion section.
3. Discussion was too long. It included well-known and unrelated issues. Some original findings and methods were not mentioned. Please see below comments

Minor comments:
1. [Title] Population-based study means that whole, not a sample or partial, of population was included. This study was not a population-based study. It may be a community-based study.
2. [Methods] There were two groups of study subjects were enrolled. One were during 1993~2004, and the other was during 2001 to 2010. There were a 17-year interval between 1st and the last of cases. During these 17 years, there were a lot of improvements of hepatology, including screening and diagnostic techniques of hepatocellular carcinoma (HCC) and treatment of hepatitis of B and C. Please describe these impacts in the study subjects, such as day of HB vaccine launching, status of reimburse of anti-viral treatment.
3. [Methods] What is the different between determinant HCV genotype by Okamoto methods and Inno-Lipa? Did the viral load take into consideration? If not, it should be discussed as a limitation of study.
4. [Results] The end of follow was 2008. Some subjects were observed as long as 15 years but some others were followed for only 4 years. Although the
person-year used in this study, but the biological effects of each person-year should be different between these two populations. Please draw Kaplan-Meier curves by age of entry and by date (or group) of recruitment.

5. [Table 1] In method section, the drinking was graded as 4 categories. In the results, percent of drinking was showed. Which grade and above were counted as drinker?

6. [Results and Tables] What is “relative risk (RR)” in tables 2~4? If you analyzed your data by Cox model, it should be hazard ratio (HR).

7. [Results and Table 2] You put an unknown group in each variable to prevent cases deleted in the multivariate analysis. The smart method should be mentioned in discussion. However, two points on unknown group should be described and explain. One was variable (FBS in this study) with a high missing rate and the other was variable (ASL in this study) with significant results.

8. [Results] History of acupuncture and transfusion should be deleted for this HCC study. Based-on your analysis, the drinking might be re-analyzed by cutoff as 24 g/day. It might become significant.

9. [Results] How did you adjust age in the analyses of tables 2 and 3, as an ordinal or a continuous variable?

10. [Table 4] HCV genotype 1+2 had much high OR than genotype 1 alone, but their 95% CIs were overlapping. It should be interpreted carefully.

11. [Discussion] Please shorten the part on association between chronic hepatitis B & C and HCC.

12. [Discussion] The key of the study was associated factor of HCC development. Please delete contents which were nothing to do with this study, such as pages 10~11, prevalence change of HBV and HCV, page 11 paragraph 2 HCC screening; page 11 follow-up study.

13. [Discussion] Carefully discuss on HBV vaccine and HCC development. The vaccinee should be too young to be included in your study.

14. [Discussion] Carefully discuss on occult HBV infection. If you checked anti-HBc, the discussion would become results. If not, please use more conservative words.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests