Author’s response to reviews

Title: Metabolomic Profiles of Hepatocellular Carcinoma in a European Prospective Cohort

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Author's response to reviews: see over
Dear Dr. Lin Lee,

In reply to your message of August 13th, please find associated with this letter a revised version of the manuscript entitled "Metabolomic Profiles of Hepatocellular Carcinoma in a European Prospective Cohort" by A. Fages et al.

We have received comments from 2 expert reviewers (Referee 1 and 3). Referee 1 is satisfied with the answers and revisions already provided. Please find below our answer to the point raised by Referee #3.

Reviewer 3 states that: « It is appreciated that funding availability can limit the possibility of follow up studies but without them it is challenging to understand if these biomarkers are reflective of HCC or lifestyle or some other latent metabolic condition. I think it is necessary that the authors include discussion as to the specificity of the biomarkers for HCC. They have nicely identified associations of the identified biomarkers but a more thorough discussion as to what else they might indicate would be helpful to the reader.»

As developed in the discussion, HCC largely arises from a background of increasingly severe liver damage, and the process ending with HCC is largely considered as gradual. Some individual exogenous biomarkers are clearly reflective of an environmental risk exposure/lifestyle (e.g. ethanol), while other biomarkers may rather reflect changes in the liver metabolism. Due to the above-mentioned gradual process, longer follow-up time would be required in order to thoroughly assess, prior to any liver damage, the specificity of the identified HCC risk associations. In the revised manuscript, we have added a sentence p.20 to emphasize this point. Meanwhile, we have in parallel to this work conducted an analogous prospective case-control study on EPIC subjects for extrahepatic/intrahepatic bile duct carcinomas that did not provide any significant associations. We have added a sentence at the beginning of the discussion p.17 to mention this result, which supports the idea that the obtained associations are not generic to all types of liver cancer.

A couple of editorial concerns, regarding ethics statement and acknowledgments, were also raised in your message. We have amended these two sections accordingly and hope they now provide sufficient details for publication. All changes made to the document have been highlighted with Word track change in the submitted revised manuscript.
In conclusion, we believe that we have addressed all comments raised by the Reviewers as well as editorial concerns, and I hope you will find the revised version suitable for publication in BMC Medicine. I look forward to hearing from you at your earliest convenience.

Yours sincerely,

Dr. Bénédicte Elena-Herrmann
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