Title: Association between HIF-1alpha C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 40 case-control studies

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Author’s response to reviews: see over
Revise response

Dear Editors and Reviewers,

Thank you very much for your letter and detailed valuable suggestion on our manuscript entitled “Association between HIF-1α C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 40 case-control studies” (Manuscript number: 2003748191956639). The suggestions are quite helpful for us. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed below this letter.

The major changes are highlighted in the revised manuscript. We hope that the revised version of the manuscript is now acceptable for publication in your journal.

Thanks and Best regards!

Yours sincerely,

Peng Zhao
Responses to the quests:

Replies to Reviewer #1:

Major Compulsory Revisions

1. As I previously mentioned that a new systematic review and meta-analysis with the same topic was published in Tumor Biology (Hu et al. The association between HIF-1# polymorphism and cancer risk: a systematic review and meta-analysis. Tumor Biol. 2013 Sep 18.). And Hu et al. conducted an estimation of the relationship between four polymorphisms in this gene (C1772T, G1790A, C111A and rs2057482) and cancer risk, and obtained the similar conclusion with this study. Therefore, it lost its characteristic of novelty from this point of view. However, in the revised manuscript, the author neglected this important paper, why? I think the authors should discuss the difference and show the advantage or importance of their study in detail when compared with the meta-analysis by Hu et al.

Response: Many thanks for the reviewer’s comments! It is true that Hu et al. conducted a wonderful meta-analysis on HIF-1a gene polymorphism and cancer risk, however, our meta-analysis also has many advantages. First, in the subgroup analyses of cancer types, sensitivity analyses were carried out to assess the stability of the results by conducting analyses of studies with controls in HWE, and after sensitivity analyses were performed, our results did not vary substantially, which strongly indicating that the results of our meta-analysis are robust and reliable. Second, no publication bias was detected in our meta-analysis. Finally, all of the data were
extracted from well-selected studies, providing stronger statistical power for our study.

2. In Supplemental File 1 author shown the influence of individual studies on the summary odds ratio (OR) for the HIF-1#C1772T polymorphism. Actually, i found that overall significance of the pooled ORs was altered by certain studies (eg. Kuo.2012, Alves. 2012, Naidu. 2009). Please provide the data for the Corresponding results of OR and 95% CI.

Response: Thanks for the reviewer’s professional recommendation. The OR and 95%CI of these studies are provided as follow, Kuo.2012: OR=1.73, 95%CI=1.04-2.86; Alves.2012: OR=1.83, 95%CI=1.12-3.01; Naidu. 2009: OR=1.77, 95%CI=1.06-2.95.

3. The quality of the written English was not improved greatly, so please copyedit the paper to improve it indeed.

Response: Many thanks for the reviewer’s comments! We have gone over the English with the help of a native English speaker and improved the style of writer English in our revised manuscript as your suggestion.

4. Please explain why the author “Ailin Lu” was deleted and the author “Ning Liu” was added in the revised manuscript arbitrarily?

Response: Thanks for the reviewer’s careful insights. This is due to the personnel changes in our laboratory, and both of the author “Ailin Lu” and “Ning Liu” are agree
with this. In addition, Songtao Wang participated in the revision, so we added him as joint first authors.

Replies to Reviewer #2:

1. The results could be streamlined a bit better. Instead of listing every significant result, the authors could focus on one genetic model that fits their data well and then just refer the reader to the tables for the other genetic models.

Response: Thanks for the reviewer’s professional recommendation! It is true that focus on one genetic model that fits our data well is streamlined better, and we think that list all genetic models can provide more comprehensive data, the reader can select the appropriate models according to their own needs.

2. The authors added the case-control counts to the tables. It would be helpful if the case-control counts were given for each genotype in these tables.

Response: Many thanks for the reviewer’s comments! We have included the case-control counts for each genotype in the revised tables according to the reviewer’s advice.

3. There are some grammatical errors in the manuscript (e.g., wrong verb tense, etc.). The manuscript would benefit from a close read by a native English speaker.

Response: Thanks for the reviewer’s comments! We apologize for this negligence. We
have corrected the error in our revised manuscript. And we have gone over the English with the help of a native English speaker and improved the style of writer English in our revised manuscript as your suggestion.

4. There are also some typos, such as on page 9 under quantitative data synthesis, the authors provide results for CT+TT vs. CC and TT+CT vs. CC, but these are the same model. I suspect that they meant to write TT vs. CT+CC.

Response: Thanks for the reviewer’s careful insights. We apologize for this mistake. We have corrected the error and scrutinized the rest of the manuscript.