Author's response to reviews

Title: Association between HIF-1alpha C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 41 case-control studies

Authors:

Qing Yan (yq3880752@hotmail.com)
Pin Chen (chenpin1987@126.com)
Ailin Lu (luailin.eric@163.com)
Peng Zhao (zhaopeng@njmu.edu.cn)
Aihua Gu (aihuagu@njmu.edu.cn)

Version: 2 Date: 7 October 2013

Author's response to reviews: see over
Dear Editors and Reviewers,

Thank you very much for your letter and detailed valuable suggestion on our manuscript of ’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:

1. The authors should be consistent and careful in their word choice to reduce confusion. They state that they reviewed 28 articles including 30 studies, but then state that the 28 studies included x cases and x controls in the abstract but 30 studies is stated in the title, making it unclear whether there are 28 or 30 studies were included. Plus, the figure shows 26 studies for 1 snp and 22 studies for the other snp, which makes it more confusing. Also, the authors often use the term pooled analysis, which usually is limited to studies where the raw data is used, instead of the aggregate results, which are used in a meta-analysis.

Thanks for the good advice. We have corrected this mistake in our revised manuscript.

2. The results section should be condensed. The pheterogeneity values could be provided in the table, instead of the listing them all in the results.

Thanks for the reviewer’s wonderful suggestion! We have replaced the pheterogeneity values in results, and providing them in the revised tables.

3. The authors should be clear about the genetic model, T vs. C. This appears to be the allelic model (e.g., having T allele vs. having C allele), but the authors refer to it...
as an additive model, which should refer to the model, where homozygote wildtype is coded a 0, heterozygotes as 1, and homozygote variant as 2 and the term is included as a continuous term in the model. The authors should clarify what they mean by this model.

Many thanks for the reviewer’s comments. It is really true as reviewer suggested that we have made an error about genetic model, we are so sorry for this. We have corrected it in our revised manuscript accordingly.

4. Tables 2 and 3. The authors should include the number of cases and controls for each genotype in the table. It is hard to evaluate the results without knowing the number of cases and controls with each genotype. Also, only two decimal places are needed for the ORs.

Thanks for the reviewer’s careful insights! We have included the number of cases and controls for each genotype in the revised tables, and corrected the ORs in our revised manuscript and tables according to the reviewer’s advice.

5. The pairwise LD (e.g., r2) information should be provided for the two SNPs.

Thanks for the reviewer’s comments! However, due to the lack of detailed original data, so we can’t calculate the pairwise LD for the two SNPs in our meta-analysis.

6. The authors need to provide the precise p-value and not write P=0.000.

Many thanks for the reviewer’s comments. We have provided the precise p-value in the revised manuscript.

7. Figure 4 should be a supplementary figure.

Thanks for the reviewer’s comments! Figure 4 has been removed to Additional file 1.

Replies to Reviewer #2:

1. Considering the last search was performed on 12 October, 2012 in this meta-analysis, it is necessary for the authors to update the search results and summarize the retrieval process clearly.

Thanks for the reviewer’s careful insights! We have updated the search results and summarized the retrieval process in our revised manuscript.

2. Generally speaking, any study that deviated from Hardy-Weinberg equilibrium could be removed. In this manuscript, the authors excluded five studies that were
deviated from HWE (please cited in the text and listed in the references). However, given that the numbers of participants in several studies were very large (e.g. Jacobs et al. Polymorphisms in angiogenesis-related genes and prostate cancer. Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):972-7.), and the mixed ethnicities might contribute to the disagreement with HWE, it should be remained in the meta-analysis. And the sensitivity analyses could be carried out to assess the stability of the final results by conducting subgroup meta-analysis of studies with controls in HWE.

Thanks for the reviewer’s professional recommendation, we have remained the studies that deviated from Hardy-Weinberg equilibrium, cited in the text and listed in the references in our revised manuscript. And we also have performed the sensitivity analyses in the subgroup meta-analysis.

3. In this meta-analysis, the significance of the association between the HIF-1 alleles and cancer risk was identified in the Asian population, lung cancer and other cancers. However, the results for the Asian population or lung cancer might dominate the overall results for each polymorphism. So the conclusions for the whole population should be made carefully, and this issue should be considered and deeply discussed. Furthermore, the stratified analysis by cancer type for these two polymorphisms should be provided in the results.

Given the ethnic variation in the distribution of genotypes in these two polymorphisms, sub-analysis based on cancer type in different ethnicities might be conducted if the subgroup for certain cancer had enough studies.

Many thanks for the reviewer’s comments. We have discussed the association between HIF-1 polymorphisms and cancer risk in Asian population and lung cancer in our revised manuscript. And the stratified analyses by cancer type for these two polymorphisms have been provided in the results of revised manuscript. We also have performed the sub-analysis of breast cancer in Asian population in our revised manuscript.

4. As shown in Table 1, “other cancers” group includes three studies of renal cell carcinoma (ref. 17, 38, 48). Therefore, please explain how do you define “other cancers” in this meta-analysis. In addition, three studies used the same control group (ref. 29), so they were grouped as one in the meta-analyses of all subjects with exception of those stratified by cancer type.

Thanks for the reviewer’s professional recommendation, It is really true as reviewer suggested that we have made an error in sub-group analysis by renal cancer. We are so sorry for this. We have corrected it in our revised manuscript accordingly. In the revised manuscript, we conducted the sub-group analysis by “other cancers” with any cancer types with less than two separate publications. And the three studies used the same control group (Konac et al.), we have grouped them as one in the meta-analyses of all subjects with exception when stratified by cancer type.
5. The authors should address the differences between the conclusions of this meta-analysis and those of individual published study in the discussion section. Many thanks for the reviewer’s comments. We have discussed this issue in the discussion section of our revised manuscript.

6. As mentioned in the “Statistical methods” section, the authors used 0.1 as a significant p value of heterogeneity Q test. Actually, the fixed-effect model (the Mantel-Haenszel method) was used when the p-value of the Q-test > 0.05. Also, the I² heterogeneity index from the meta-analysis are not shown in Table 2, nor do the authors mention the number of sample size for each comparison which I think it is very useful for indicating the power of the results. Please clarify. Thanks for the reviewer’s professional recommendation, which is undoubtedly helpful to our manuscript. It is really true as reviewer suggested that we have made an error in the “Statistical methods” section, we are so sorry for this. We have corrected it in our revised manuscript accordingly. The results of I² statistic has been added to Table 2 and Table 3 according to the reviewer’s advice.

7. Table 1: “first author” for the included studies was not uniformly used the last name of the first author. The results of Hardy–Weinberg equilibrium (HWE) test should be listed. Many thanks for the reviewer’s comments, We have corrected the last name of first author in our revised manuscript accordingly. And the results of HWE test have been added to Table 1.

8. The results of Egger’s test for either polymorphism should be performed in each genetic model. Many thanks for the reviewer’s comments, we have performed the Egger’s test for each polymorphism in our revised manuscript.

9. We recommend that you copyedit the paper to improve the style of written English. Thanks for the reviewer’s professional recommendation. We have gone over the English with the help of a native English speaker and then improved the style of writer English in revised manuscript.