Reviewer’s report

Title: Association between HIF-1alpha C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 30 case-control studies

Version: 1 Date: 2 July 2013

Reviewer: Jue-Yu Zhou

Reviewer’s report:

In this manuscript, Qing Yan and collaborators investigate the role of HIF-1α polymorphisms (C1772T/G1790A) in cancer susceptibility by performing a meta-analysis of previously published association studies. I find that the study design and the methods are mainly appropriate. Although the relationship between HIF-1α polymorphisms and cancer risk had been reported by Zhao et al. in 2009, this meta-analysis conducted a more comprehensive literature search and obtained a more powerful estimation of the interesting relationship. But, the following issues should be considered.

Major Compulsory Revisions

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. The following references should be included or discussed accordingly.


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.

3. In this meta-analysis, the significance of the association between the HIF-1# polymorphisms 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.

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.

5. The authors should address the differences between the conclusions of this meta-analysis and those of individual published study in the discussion section.

Minor Essential Revisions
1. 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.

2. 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.

3. The results of Egger’s test for either polymorphism should be performed in each genetic model.

4. We recommend that you copyedit the paper to improve the style of written English.

**Level of interest:** An article whose findings are important to those with closely related research interests
**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests