Author’s response to reviews

Title: Association between polymorphisms in ERCC2 gene and oral cancer risk: evidence from a meta-analysis

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Version: 2
Date: 31 October 2013

Author’s response to reviews: see over
Dear Editors and reviewers:

Thank you for your kindly considering our manuscript entitled *Association between polymorphisms in ERCC2 gene and oral cancer risk: evidence from a meta-analysis*.

The manuscript has been revised according to the suggestions of three reviewers. Next are the point-by-point responses to the concerns of three reviewers:

**Reviewer 1:**

1. Minor comments: Please add in table 1 age and gender of study participants, when available.
   
   **Response:** Age and gender of study subjects, which are available, have been added in table 1.

**Reviewer 2:**

Major Compulsory Revisions:

1. The authors must better disclose the data sets used for their combined analysis.
   
   For example, the authors state that 9 datasets (only 6 studies) were used for the evaluation of the rs13181 SNP in the ERCC2 gene for their work. It appears that these 9 datasets were not necessarily independent of one another. This would seem to be an inherent flaw in their meta-analysis. Parsing the same subjects under a single study into separate groups and using them all as representative (independent) of cases and controls for risks of developing oral cancer (as opposed to the risk of leukoplakia) seems improper.
   
   **Response:** This is a very important problem in this meta-analysis. Thanks very much for your question. We have adjusted the datasets and now they are more reasonable, also we have recalculated the results so the results part and tables and figures in the revised manuscript have been changed. Fortunately, the results and conclusion did not have changed a lot. All of the revisions have been stated in different color.

Minor Essential Revisions:

1. Italicize ERCC2 following proper gene symbol nomenclature (throughout).
   
   **Response:** The words “ERCC2” following proper gene symbol nomenclature were all italicized throughout the manuscript.

2. The gene name is excision repair cross-complementing ... not complimentary
Response: The gene name has been corrected and italicized.

3. Six most prevalent cancers are lung, breast, prostate, colorectal, liver, and stomach. Oral is not sixth (background).

Response: The first sentence of background was indexed from previous published papers. It is our mistake not to check it carefully and now this statement has been corrected.

4. Reactive oxygen species are not DNA damage in and of themselves. They can cause DNA damage (background).

Response: This is our mistake and we have corrected it.

5. ERCC2 is not the most important gene or protein in the TFI/H/ner complex. It is an important component (background and discussion).

Response: Thank you for your carefulness and these have been revised. “The most important gene” has been changed as “an important gene”.

6. NER is not the most important DNA repair pathway. They are all important and there are essential genes and proteins in all repair pathways. ICR also repairs crosslinks. Many oxidized or alkylated bases are repaired by BER. Should read thymidine dimer not dimmer. In addition, simply repeating what was written almost verbatim in the discussion what was written in the background is unnecessary (discussion pages 12-13).

Response: Thank you for your advice and I am so sorry for our error. Wrong and inaccurate statements in the discussion have been corrected. Spelling error has been revised too. And the duplicate contents in the dissection have been deleted. Remainder statements now may be somewhat similar to that in the background, but we think these are essential for presenting the whole context of the discussion. We hope you could understand.

7. The rs13181 SNP (aka 751) is not located in the active helicase domain. It is adjacent to this domain. The reference used to support this is miscited. Those authors, Coin et al. did not examine the 751 site in their study of ERCC2 helicase activity and further Taylor et al. (1992) PNAS which was cited in that manuscript as impetus for examining the carboxy terminus for active site domains describes mutations in sites 675-730 (XPD disease) and sites 713-730 (TTD disease).

Response: Thank you for your kind and professional interpretation. We have revised the contents and deleted the miscited reference after reading the
manuscript that you mentioned. The specialties of our authors are molecular epidemiology and oral medicine so we do not clearly know the details of the gene. This aspect is our shortcoming and we will strengthen it in later research.

**Reviewer 3:**

1. They first assessed HWE in control groups. So did they group all the data from the different studies?

   **Response:** We have assessed HWE of the combining control from the different studies and found the total is not in Hardy-Weinberg equilibrium. In previous published meta-analyses, they did not report the HWE in combined subjects, so we are not sure whether this result should be added in the manuscript. If you think this is necessary, we could add it.

2. Major Revision: They calculated ORs for different types of genetic models but could be useful to make a likelihood ratio test to verify the departure from the additive model and to establish, if possible, the correct genetic model.

   **Response:** As your suggestion, we have checked and studied the likelihood ratio test. We found a methodology paper about the application of the likelihood test to SNP model comparison, which is published on *International Journal of Epidemiology* by Minelli et al in the year 2005. Similarly, we have compared these models by calculating their AIC values. But the SNP model is not the nested model and it seems not likely to use likelihood ratio. A likelihood ratio test is a statistical test used to compare the fit of two models, one of which (the null model) is a special case of the other (the alternative model). The test is based on the likelihood ratio, which expresses how many times more likely the data are under one model than the other. This likelihood ratio can then be used to compute a p-value, or compared to a critical value to decide whether to reject the null model in favor of the alternative model. To establish the correct genetic model is a difficult problem and needs strong statistical or mathematical knowledge, we are so sorry that we are unable to accomplish it.

3. In the paragraph "Study selection and data extraction" they described the inclusion criteria. Give more details on point "c) there was sufficient published data for the computation of OR". Specify the word "sufficient".

   **Response:** We have specified the word “sufficient” in the end of the paragraph.

4. Minor essential revision: There are some errors throughout the manuscript as
"Rs" instead of "rs" or "r rs".

Response: One error "r rs" in the manuscript and all “rs” at the beginning of the sentence have been changed to “Rs”.

We have filled the PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram according to Systematic Reviews http://www.prisma-statement.org/.

The present work has not been published or is currently under consideration for publication elsewhere. We declare that we have no conflict of interest.

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Thank you very much.

Sincerely yours,

Corresponding author on behalf of all authors

2013-10-28