Author's response to reviews

Title: Association between polymorphisms in XRCC1 gene and clinical outcomes of patients with lung cancer: a meta-analysis

Authors:

Zhihua Yin Dr (zhyin@mail.cmu.edu.cn)  
Zhigang Cui (zgcui@mail.cmu.edu.cn)  
Xuelian Li (zimu0124@yahoo.com.cn)  
Wei Wu (wuwei@mail.cmu.edu.cn)  
Peng Guan (pguan@mail.cmu.edu.cn)  
Baosen Zhou (bszhou@mail.cmu.edu.cn)

Version: 2 Date: 9 January 2012

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

Thank you for your kindly considering our manuscript entitled *Association between polymorphisms in XRCC1 gene and clinical outcomes of patients with lung cancer: a meta-analysis*.

The manuscript has been revised according to the suggestions of two reviewers. We also have checked the manuscript thoroughly to find more mistakes and corrected them. Next are the point-by-point responses to the concerns of two reviewers:

Reviewer 1:

1. It is important that the positive findings should be tested for false positive reporting probability.

**Response:**

We have tested our positive results for false positive reporting probability and most results were not false positive, excepting overall survival of XRCC1 399 AA vs. GA and interaction results. We specified the false positive report probability (FPRP) cutoff value to be 0.5 and assigned a relatively high prior probability range (i.e., 0.01– 0.1). For each genetic variant, the FPRP value was calculated using the estimated prior probability range, the statistical power to detect an odds ratio of 1.5 (or its reciprocal, 0.67), and reported results (using estimated odds ratios and P values). Calculate FPRP from the observed P value, statistical power, and prior probability by using the FPRP calculation spreadsheet. Determine whether the estimated FPRP value is below the prespecified FPRP value (0.5). The estimated FPRP values of our positive results for objective response were all lower than 0.5 (0.000 to 0.500), however the FPRP value for overall survival of XRCC1 399 AA vs. GG was 0.866 (>0.5), FPRP values for interaction positive results were 0.726 and 0.765 (>0.5), suggesting the possible false positive results. We have
discussed about it in the discussion of manuscript.

2. The conclusion should be confined to Chinese or Asian populations.

Response:
We have confined the conclusion to Asian population in abstract and the manuscript.

3. Minor comments:

1) The gene name should be italicized throughout the text.

Response:
The gene name has been changed as italicized throughout the text.

2) Please provide the rs# for the SNPs included in the analysis in the abstract.

Response:
The rs# for the SNPs included in the present study have been added in the abstract.

3) The column label of Table 1 “Biomarker” should be “Outcome”.

Response:
The column label of Table 1 “Biomarker” has been changed as “Outcome”.

4) Table 2 is unnecessary, and the contents can be put into the footnotes of Table 3 and Figure legends instead.

Response:
The contents in Table 2 have been put into the footnotes of Table 3 and Figure legends instead.

5) Figures 2-4: It is not clear what genetic model was used for each of the 2A, 2B, and 2C figures, such as dominant, recessive, additive or other genetic models? Please state this in the figure legends.

Response:
The dominant genetic model was used for analysis and this was stated
in the figure legends and the results of manuscript.

6) Figure 4: The genotype comparisons were not labeled in each of the figures, nor the events out of the total number of the subjects were given.

Response: The genotype comparisons were stated in the figure legends. For the events out of the total number of the subjects in Figure 4, because most of the studies only provided MSTs instead of the specific number of the events, we could not add this in the Figure 4.

7) Some of the forest plots showed one study to be an outlier. In this case, a sensitivity test should be performed by excluding such an outlier to see any improvement in the estimates.

Response:
A sensitivity test is important in meta-analysis and we have performed it in our initial analysis. Because the result after excluding an outlier was similar with the outlier, so we have not put the results in the manuscript.

8) Figure 5 should be eliminated because the numbers were too small to test for an interaction.

Response:
Interaction analysis was an interesting result so we would not eliminate it. We have read the included studies again and found another paper containing the combination of these two SNPs with objective response, but the combinations were different from our previous result. So we changed the previous 9 combinations to now 4 combinations for further analysis. Now there are four studies for an interaction analysis, although the number was still not large, but this interesting result gave rise the idea that analyzing multiple genes with large sample size to find more reliable prognostic or predictive biomarkers should be made, because it is hard to predict complex clinical outcomes of lung cancer patients by using only single gene.

9) There are numerous typos or grammatical errors throughout the text that need to be corrected. For example, just in the Abstract, a) “genotype”
should be “genotype”. b) “significantly statistically” should be “statistically significantly”. c) “%95CI” should be “95% CI”.

**Response:**
The typos or grammatical errors throughout the text have been corrected.

Reviewer 2:

1. Any informations on codon 280 are missing and have additinally to be adressed.

**Response:**
There are only two studies analyzing XRCC1 codon 280 polymorphism with overall survival of lung cancer. As the number of relevant studies was not enough for meta-analysis, these two studies were excluded from our analysis and XRCC1 280 polymorphism could not be analyzed.

2. We propose, that the studies were also radiation might be of influence have to be marked separately.

**Response:**
Most of the studies have not stated clearly whether the patients have been treated by radiotherapy, so this information could not be marked. We know this may be a confounding factor and future studies with detailed information of treatment, including chemotherapy, radiotherapy and et al, would be helpful.

The present work has not been published or is currently under consideration for publication elsewhere. We declare that we have no conflict of interest.
Address correspondence to: Baosen Zhou, Department of Epidemiology, China Medical University. No 92 North Second Road, Shenyang 110001, PR China. Phone: 86-24-23258982; Fax: 86-24-23258982; E-mail: bszhou@mail.cmu.edu.cn.

Thank you very much.

Sincerely yours,

Corresponding author on behalf of all authors

2012-1-8