Author's response to reviews

Title: The PstI/RsaI and DraI polymorphisms of CYP2E1 and head and neck cancer risk: a meta-analysis based on 21 case-control studies

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Author's response to reviews: see over
Dear Miss. Gabriella Anderson
Thank you very much for your most quick edition on our manuscript “The PstI/RsaI and DraI polymorphisms of CYP2E1 and head and neck cancer risk: a meta-analysis based on 21 case-control studies” (MS: 2052541857316477). According to your suggestions, we have responded to the comments of reviewers on the one to one basis as follows.

**For Reviewer Comments:**

**Reviewer: Varghese George**

Comments to the Author

*For the RsaI analysis, the authors have consistently shown that there is no difference between the models “Homozygous vs wild” and “Recessive”, indicating that if at all there is a statistical significance, it is simply for the case of “recessive vs. rest”, and the other finding is redundant. Same thing applies for the DraI analysis also (“AA vs TT” and “Recessive”). Thus, eliminating redundancies will reduce the size of tables 2 by half and make them more comprehensible.*

**Answer:** Yes, we agree with the reviewer. So, we have deleted the redundant information (Recessive model) from table 2 and 3 to save space. In addition, the abstract, method, result and discussion part of the manuscript are revised accordingly.

*The authors found significance only in the Asian sub-population. However, it is not clear how “Asian” is defined. I infer from the manuscript that the Indian subpopulation is not included among Asians. If so, it should be clarified.*

**Answer:** Yes, we agree with the reviewer. Indeed, the Indian population is not included among Asians since the genotype distribution and allele frequency of controls of CYP2E1 among Indian population seems more similar as Caucasians, as shown in the table I. To increase statistics power, so we pooled the Indian into Caucasians. In addition, we have performed a subgroup analysis in which Caucasian and Indian populations were analyzed separately. However, no positive results were detected. According to your suggestion, we have added the definition of Asian behind it.
It is somewhat strange to conclude that the significance found among Asians is potentially due to chance. Both RsaI and DraI analyses have consistent positive results, and majority of the studies were included in the RsaI analysis. Investigation of ethnic differences may need further exploration.

**Answer:** There are only two studies using Asian population to investigate the relationship between the DraI polymorphism and the risk of head and neck cancer. Thus, the statistics power may not big enough. Besides, there is no evidence that the RsaI and DraI polymorphism are in strong LD (linkage disequilibrium) block in Asian population. Based on these reasons, we can not exclude the possibility of finding positive results by chance.

The quality assessment (high vs low) is so vague and poorly defined, and therefore stratification based on that is ill advised.

**Answer:** Yes, we agree with Dr. Varghese George and that is why we discussed this problem in discussion of the manuscript. It is known that a validated quality assessment system does not currently exist [1], but making quality assessment to the paper included in meta-analysis is very important and it would help us to minimize the potential for selection bias and thus help us to get a more reliable result. Main points included in our quality assessment system are listed as follows:

1. Diagnostic criteria
2. Ethnicity (subjects were composed of the same ethnicity or different populations were analysis separately)
3. Hardy-Weinberg equilibrium (genotype distribution in controls)
4. Sex (matching between cases and controls)
5. Age (matching between cases and controls)
6. Experimental method
7. Bias in data processing (raw data rechecked or use “blind” during experimental and statistical periods)

Because these points are relatively objective and have been used by another published paper [2], thus we adopt the quality assessment system.

The DraI analysis indicates significance for low-quality study, which is counter-intuitive.

**Answer:** We have rechecked the raw data, and there is no problem with the result. There are some explanations to the phenomenon. Using unmatched cases and controls, ethnicity even vague diagnostic criteria, low-quality studies would be more susceptible to random influence and hence get some counter-intuitive results. And that is why we still perform subgroup meta-analysis according to quality of included studies, because positive result gain from low-quality studies should be explained with caution. We just try to make all these meta-analysis result as robust as possible.

It is not clear if any adjustments for multiple comparisons are incorporated in the analysis.

**Answer:** The information about sex, age and tumor type is very limited, which makes
adjustment for multiple comparisons almost impossible. So, all the results are based on unadjusted estimates as mentioned in the discussion part of the manuscript.

*To test possible heterogeneity among studies, the authors performed both Q-test and I-square test. In the result section, the authors should clarify from which test the P-values for heterogeneity come from.*

**Answer:** In fact, the P-value for heterogeneity is come from Q-test. In the revised manuscript, we have added subscript to the P value to clarify this problem.

The authors presented forest plot for random-effects model in Fig 1 and Fig 2. In The Statistical Analysis section, the authors stated that "If heterogeneity existed, the random effects model, ..., was adopted to calculated the overall OR value. Otherwise, the fixed effects mode (the Mantel-Haenszel method) was used". Given that no heterogeneity was found, why bother presenting these figures? They could easily be eliminated without losing any meaningful information.

**Answer:** Yes, we agree with the reviewer. Since there is no significant heterogeneity between studies in most of the comparison, so we have deleted these figures according to you suggestion.

The legends of both Fig 1 and Fig 2 states, "... its area is proportional to the weight of the study". If figures 1 and 2 are included, then these weights should be defined in the main text.

**Answer:** Those figures and legends have been deleted in the revised manuscript.

Thanks a lot for your attention to our paper. We look forward to hearing from you soon.

Yours sincerely,

Kefu Tang

**Reference**
