Author's response to reviews

Title: Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China

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Author's response to reviews:

Dr. Alexander J Pemberton, PhD
Senior Assistant Editor
BMC Cancer
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Dear Dr. Pemberton,

Thank you for your informing us the re-review comments from three reviewers for our revised manuscript entitled "Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China" (Manuscript ID# 2141159512106379). We are submitting a re-revised version of the manuscript which addresses the reviewers' comments for your further consideration. Our point-by-point response to the reviewers' concerns is listed as follows:

For Reviewer 1

After carefully reading the modifications made by the authors, I consider that the paper is fully acceptable for publication in BMC Cancer.

We greatly appreciate the reviewer for the encouraging comments.

For Reviewer 2

A significant improve in presentation of the article submitted this time compared with the previous one, however, here is a few notes should be considered summarized on the following points:

1. How to get 107 diagnosed cases, from hospital or population screening? More information about the 5 township should be helpful to understand.
The 107 cases were diagnosed as ESCC at local hospitals within one year (between 2002 and 2003) and reported to the malignant tumor registry of Huaian CDC. All cases and controls were residents from 5 townships of Chuzhou area in Huaian city which were located at the north side of the General Irrigation Canal. These townships have been reported as a historically high risk area of ESCC in Huaian City. These changes have been made in the manuscript at Study Subjects, Page 5-6, accordingly.

2. Maybe, some ESCCs was not excluded in "health control" with esophageal lesion, especially in Taihang Mountain area, because these lesion didn't confirmed by endoscopy

Although our study site is not in the Taihang Mountain area, we agree with the reviewer's comment that individuals with esophageal lesion are at high risk for developing esophageal cancer. As demonstrated in others and our studies, esophageal lesion is one of the defined risk factors for development of esophageal cancer. It was possible that "health control" with esophageal lesion was included in our study, and as a matter of fact, a total of 5% (11/214) subjects were found with esophageal lesion in our study, including 2 in controls and 9 in cases. Physical examination and clinical and biochemical analyses showed that 2 subjects in controls did not have malignant transformation or any evidence of having esophageal cancer. Therefore, our conclusion that esophageal lesion was significantly associated with ESCC will not be changed.

For Reviewer 3

The statistical methods used are valid (on the whole, see my comment in Minor Essential Revisions though) and the results are presented with clarity and are correctly interpreted. The authors' comment in the discussion regarding sample size is sufficient. 1:m matching could have been used (m>1), but the gain in power would be relatively small.

We are very appreciative of the statistician's review of the manuscript, and fully agree with the points raised in the review.

It seems likely that the stratified analyses that included interactions in the multivariable models were overfitted (the total number of terms is not stated). I would suggest that the relevant sections be omitted.

We agree with the reviewer's comment. Indeed, multivariable models which include interactions are likely to suffer from overfitting, especially when stratified. This is one reason we did not include such analyses in our original version of the manuscript (they were added at the request of initial reviews). We attempted to compensate for this fact by only examining for an effect of genotype when the data were stratified by one environmental factor. (Thus, we did not really use multivariable models when stratified). Nevertheless, we agree with the statistician's recommendation to remove the relevant sections and agree that they only distract from the main message of the manuscript. Thus, we have removed the paragraph on the bottom of page 10 and modified text accordingly.

We believe that we have fully addressed the reviewers' comments and look forward to our manuscript being accepted and published in BMC Cancer.

I will be happy to provide you with any further information. Please feel free to contact me at: Tel: (806)885-0320; Fax: (806)885-2132; E-mail: js.wang@ttu.edu

Sincerely,

Jia-Sheng Wang, M.D., Ph.D