Author's response to reviews

Title: Association between TP53 codon 72 polymorphism and risk of oral squamous cell carcinoma in Asians: A meta-analysis

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Version: 2
Date: 9 May 2014

Author's response to reviews: see over
Response to Reviewers’ Comments

Dear Ms Roselyn Remoto and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Association between p53 codon 72 polymorphism and risk of oral squamous cell carcinoma in Asians: A meta-analysis” (MS: 68944491811187531).

Thank you for spending your valuable time to review our manuscript! Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. According to the reviewers’ comments, we have revised the manuscript carefully and made a point-by-point response. Revised portion are highlighted in red. Details of the revision and the responses to the comments were described as flowing:

Reviewer #1 (Carolina Gomes)

In the manuscript entitled “Association between p53 codon 72 polymorphism and risk of oral squamous cell carcinoma in Asians: A meta-analysis”, Zeng and colleagues assess the association between the p53 codon 72 SNP and the development of OSCC. Although the study was well conducted, there are some issues that need to be addressed.

Major compulsory revisions:

Comment 1 Abstract:
1) “Only the cases in the studies with immunohistochemical staining of OSCC were considered.”

It is not clear what immunohistochemical staining the authors are mentioning. Please, clarify this information.

Response: Thank you for your comment. We mean that the patients were considered included if the he/her was clearly diagnosed as OSCC using pathological methods. For the abstract limits the number of words, we revised the sentence as “Only the cases in the studies were diagnosed with OSCC by pathological methods were considered” and also added the specific method of each included studies in Table 1.

2) In conclusion, current result suggest that p53 codon 72 polymorphism is not associated with OSCC in Asians who without HPV infection but associated with HPV-related OSCC patients.”

As only 2 studies included in this meta-analysis reported HPV-status information (about 200 OSCC patients), the authors should consider not to include such information in the abstract and conclusions. I feel that the authors overestimated this finding in their manuscript, just because there was a positive association.

Response: Thank you for your good comment. We agree with you that “the authors overestimated this finding in their manuscript, just because there was a positive association” and sincerely apologize for our words. However, considered abstract should provided “take home message” for readers, although “only 2 studies included in this meta-analysis reported HPV-status information (about 200 OSCC patients)” we remain think it’s necessary to “include such information in the abstract and conclusions”.

According to your comments, we used subjunctive mood and revised the conclusions as “In conclusion, current result suggest that p53 codon 72 polymorphism is not associated with OSCC in Asians who without HPV infection but might be associated with HPV-related OSCC patients”.

Comment 2 Introduction:
3) The authors state that “Oral squamous cell carcinoma (OSCC) derived from the flat cells (squamous cells) that cover the surface of the mouth”, however, despite the squamous phenotype, there is no evidence that such cancer is derived from the flat cells. This “flat cells” origin information is found in sites for “patients”.

**Response:** Thank you for your comments and precise attitudes. We have revised the sentence as “Oral squamous cell carcinoma (OSCC) was considered derived from the squamous cells that cover the surface of the mouth”.

**Comment 3 Discussion:**

4) “In 2011, Heah et al., indicated that p53 expression is a marker of microinvasion in OSCC which contradicts the results of our meta-analysis.”

The authors did not assess p53 expression nor OSCC microinvasion. They need to revise this sentence.

**Response:** Thank you for your comments and precise attitudes. We re-read this cited article again. This article aimed “to determine the usefulness of immunohistochemical techniques and fluorescent in situ hybridization (FISH) of the tumour suppressor TP 53 gene to identify microinvasion in marginal tissue sections and to relate the possible correlation between protein expression and genetic aberrations in OSCC cases in Malaysia”, as you said, “The authors did not assess p53 expression nor OSCC microinvasion”. We think there was a misunderstanding between us due to our language expression and we apologize for this. From the Results section of this article (page 1019), the results showed that p53 expression and TP53 gene aberration is associated with microinvasion in OSCC. Hence, although the aim of this article does not assess p53 expression or OSCC microinvasion, the relevant information can be concluded from the article and we concluded that “p53 expression is a marker of microinvasion in OSCC”. Besides, there conclusions also indicated that “There is a correlation between p53 protein expression and aberrations of the TP 53 gene OSCC cases in Malaysia”.

According to your comments combined with the text of this cited article, we revised this sentence as “In 2011, Heah et al., indicated that p53 expression and TP53 gene aberration was associated with microinvasion in OSCC”.

**Comment 4 Minor essential revisions:**

1) As non-native English speakers, the authors should consider a professional English language revision.

**Response:** It is really true as you suggested that we are all non-native English speakers and our manuscript is poorly written, we are very sorry for this making you feel confused. We have attached great importance to this problem. After revision, we have revised grammar issue by using an academic editing service provided by Essaystar Group (http://essaystar.com/). The “Review Certificate” is also uploaded. Besides, we also asked the associate professor Joey S.W. Kwong, who is the Copy Editor of Cochrane Database of Systematic Reviews to help revise our manuscript. Her email is j.s.w.kwong@gmail.com.

2) In additional, several typing errors are found throughout the text, as follows: “HPV-nonrelated OSCC cases it is not clear whether the p53 codon 73 OSCC susceptibility n Asians; the subgroup”.

**Response:** Thank you for your kindly suggestion. We carefully reviewed our manuscript and revised relevant errors.
Reviewer #2 (Saima Saleem)

This is with reference to manuscript 'Association between p53 codon 72 polymorphism and risk of oral squamous cell carcinoma in Asians: A meta-analysis' submitted for publication in “BMC Cancer”. I have reviewed the manuscript and submitting my comments and suggestions about the manuscript.

The above mentioned manuscript is well written and provides sufficient contribution in the association studies of p53 codon 72 polymorphism in different types of cancers.

The manuscript can be accepted for publication after minor corrections mentioned below.

Comment 1: There are some typographical/grammatical errors that need to be addressed. I am listing some of these.

Response: It is really true as you suggested that our manuscript with some typographical/grammatical errors, we are very sorry for this making you feel confused. We have attached great importance to this problem. After revision, we have revised grammar issue by using an academic editing service provided by Essaystar Group (http://essaystar.com/). The “Review Certificate” is also uploaded. Besides, we also asked the associate professor Joey S.W. Kwong, who is the Copy Editor of Cochrane Database of Systematic Reviews to help revise our manuscript. Her email is j.s.w.kwong@gmail.com.

Comment 2: In abstract, first sentence is too long and is confusing. A better syntax could be “preparations of different combination” instead of “different other preparations of combination”.

Response: Thank you for your kindly suggestion. We have revised the sentence as you suggested.

Comment 3: Reference section should be carefully checked and brought in the format of the journal.

Response: Thank you for your kindly suggestion. We have revised the format of our manuscript using the style of EndNote X3 software for BMC Cancer.

Reviewer #3 (Lucyana C Farias)

Some questions about paper "Association between p53 codon 72 polymorphism and risk of oral squamous cell carcinoma in Asians: A meta-analysis" are shown below according to the paper topic:

Comment 1: - Background:

In Background was shown that “genetic predisposition is gaining increasing attention”. Indeed, the importance of genetic alterations in cancer pathogenesis is not new information. New studies are being conducted to better understand not only the influence of genetic alterations but also epigenetic changes. I think it is necessary to further enrich the first paragraph.

I suggest change p53 to TP53 gene.

Response: Thank you for your comments. We have changed “p53” to “TP53” from the title to conclusion, included tables and figures of our manuscript.

As you said, “Indeed, the importance of genetic alterations in cancer pathogenesis is not new information. New studies are being conducted to better understand not only the influence of genetic alterations but also epigenetic changes”. We think that the aim of our manuscript is to explore the relationship between TP53 codon 72 polymorphism and risk of oral squamous cell carcinoma using a meta-analytic method. Hence, it is also focused on “the genetic alterations in cancer pathogenesis”. The reason for performing this meta-analysis due to the results of relevant
studies was inconsistent. Therefore, we do not think the relevant information for “epigenetic changes” is necessary. Please consider our application and give further guidelines.

Comment 2: - Materials and Methods:
Inclusion Criteria:
What difference between OSCC diagnosed by “Histology or Pathology”? It is noteworthy that “Pathology” and “Histology” are areas of knowledge; is more appropriate to use histologic diagnosis. I suggest reviewing how to write the inclusion criteria in regard to diagnosis. Surgical biopsy followed by histopathology is considered the gold standard for diagnosing the oral lesions, including especially OSCC. Why it was included cases diagnosed by citologic diagnosis?

Considering the limitations of molecular methods for genotyping, I think that genotyping method should to be “inclusion criteria”. I suggest to perform analyzes using only a single method of genotyping. So, it will be possible to check if the results are independents of the molecular method.

I suggest to specify more clearly in this topic, that in all selected study the studied population was Asian origin.

Response: Thank you for your comments. We have revised the “histology, pathology, or cytology” as “histologic methods” and also added the specific method of each included studies in Table 1.

According to your suggestion, we added the molecular methods for genotyping in the “inclusion criteria”, which was described that “and (5) the molecular method for genotyping is polymerase chain reaction (PCR), including PRC-RFLP (polymerase chain reaction-restriction fragment length polymorphism) and PCR-SSCP (polymerase chain reaction- single strand conformation polymorphism)”. In fact, all included studies were used PCR, Table 1 showed the details.

Table 1 present the country origin, which can be provided that all selected study the studied population was Asian origin.

Comment 3: - Search strategy:
The study did not indicate the time interval, which the studies surveyed were published. Only was pointed out that those articles were performed up to December 2013. Why “codon 72” was not included as key word in search strategy, since this codon is one focus of the meta-analysis?

Response: Thank you for your comments.

As you said, we described “The PubMed and Embase databases were searched up to December 10, 2013”. Hence, this means that time interval of all the included studies were published before December 10, 2013. Besides, Table 1 showed the details of publication year for each included studies.

The reason for why we did not use “codon 72” as a key word in search strategy is that when we used this keyword, many eligible studies were missed. On the other hand, the key words “p53 OR TP53” can identify the “codon 72”. Moreover, the number of all identified items is not large enough which need to set further restrictions on retrieval.

Comment 4: - Data extraction:
It was not shown if there are criteria to guide discussion in situation of disagreements.
Response: In fact, we described the relevant information, which was “The studies were selected and two authors independently extracted the data of included studies; disagreements were resolved by discussion”.

**Comment 5: - Results:**
Meta-analysis: in second line, change codon 73 to codon 72.

**Response:** Thank you for your comments and precise attitudes. We have revised it.

**Comment 6: - Discussion:**
It was very favorable the authors have acknowledged the limitations of the study.
I did not identify that this meta-analysis aimed to investigate TP53 gene as marker of invasion in OSCC. Why the results of this study were compared with Heah et al. (2011), given that the latter did not evaluate the TP53 codon72 polymorphism?

**Response:** Thank you for your comments and affirmation.

As you said, this cited article did not evaluate the TP53 codon-72 polymorphism. Just as its conclusion described “There is a correlation between p53 protein expression and aberrations of the TP53 gene OSCC cases in Malaysia”. We cited this article in order to provide evidence that the TP53 gene is associated with OSCC and to analysis why it is not consistent with our results, did not mean this article was eligible for inclusion of our manuscript. The details of included studies were showed in Table 1.

We tried our best to improve the manuscript and made some changes. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for editors/reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.