Author's response to reviews

Title: Association between TGFBR1*6A and susceptibility to osteosarcoma in a Chinese population in the case-control study

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Author's response to reviews: see over
Dear Professor Ciudad:

First of all, we wish to thank the reviewers for the constructive, encouraging comments. According to the comments, we revised the manuscript and hope the present form can clarify our meaning well. We have the informed consent from the subjects involved in the study, and a statement about the informed consent is indicated in the Methods. The manuscript was formatted according to a template from BMC cancer. The revisions were marked in red in the manuscript.

The point to point responses to reviewers are as following:

Reviewer: Adela Castillejo
1. We acknowledge that this study is underpowered as it is a case-control study. The retrospective, non-randomized nature of case-control studies limits the conclusion drawn from them. However, considering that the subjects were from different regions in China and that the subjects were selected during a long period from 2001 to 2009, we think the results were informative although this study is underpowered. We indicated the limitation of the study in Discussion (Page 4, line 41-43).
2. The controls were selected from blood donors who did a health checkup and were found no diseases. There should be no interference from other diseases in the study. It is indicated in Methods (Page 3, line 37).
3. We analyzed the data in the additive model and calculated the p value using Amitage’s tread test. We corrected the p value in Table 1. We are grateful for pointing out the error. (Page 10, Table 1)
4. We understand the reason for the suggestion to remake Table 2, but we did not do the stratification analysis to determine the extent of osteosarcoma for relevant factors. The association between TGFBR1*6A and osteosarcoma was shown in Table 1. The aim of Table 2 is to do association analysis for the identification of clinicopathological characteristics associated with the cases of osteosarcoma. It is an association analysis, and Table 2 in the present form should be suitable to express the aim. We hope for your understanding.
5. As suggested, we eliminated the sentence: “The ORs of TGFBR1*6A genotypes in dominant model and in recessive model were 3.48 [95% CI, 1.92-6.17] and 4.03 [95% CI, 1.99-6.87], respectively.”. Because we did not do the stratification analysis, the OR and CI for the association of TGFBR1*6A with metastasis was not calculated.
6. We revised the title by adding in “in a Chinese population”. It makes the title more accurate and informative. Thanks for the good suggestion.
7. We corrected the mistake in the introduction (Page 3, line 14-16). Thanks for pointing out the mistake.
8. We checked the recorded case history of the cases, and it was found that cases did not show the hereditary in their case history reports. We indicated it in Methods in the revised manuscript (Page 3, line 35-36).
9. The association of TGFBR1*6A with metastasis was rewritten in Discussion (Page 6, line 15-25). Some new references including that mentioned in the comments about TGFBR1*6A were cited to make the discussion comprehensive.

Reviewer: Boris Pasche

1. It is a writing mistake in the Discussion. “The increased risk of distant metastasis……” should be “The decreased risk distant metastasis……”. We corrected the mistake in the revised manuscript (Page 6, line 10). We are grateful for pointing out the mistake.

2. We agree with the reviewer that it is worthwhile to check for loss of homozygosity of TGFBR1 in the tumor samples. The check can further clarify the reasons for the decreased metastasis in patients with TGFBR1*6A. We finally obtained 10 tumor samples of osteosarcoma with distant metastasis (7 of 9A/9A genotype and 3 of TGFBR1*6A genotype) and observed the TGFBR1*6A genotype in the DNA specimens from the 10 tumor samples. It was found that the TGFBR1*6A genotypes in the tumor samples were same to that observed with blood samples. There was not loss of homozygosity of TGFBR1 in the tumor samples. Although there is differences between our results and the in vitro results obtained in breast cancer cells, site specificity and tumor specificity for the role of TGFBR1*6A may be the reason for the difference since TGF-beta signaling is different in different tissues. We cited some new references and discussed it in Discussion (page 6, line 15-25).

We hope the revised manuscript can be accepted by BMC cancer.

With best wishes,

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