Author's response to reviews

Title: FGFR4 Gly388Arg polymorphism contributes to prostate cancer development and progression: A meta-analysis of 2618 cases and 2305 controls

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Author's response to reviews: see over
Dear Editor-in-Chief,

Thank you for your decision email on Oct.28, 2010, in which you encouraged us to revise our manuscript (MS: 5404498735274970) entitled “FGFR4 Gly^{388} Arg polymorphism contributes to prostate cancer risk: A meta-analysis of 2618 cases and 2305 controls”.

Here we submit the revision of our manuscript with highlighted changes and our response, point by point, to reviewers’ comments and suggestions.

We would like to thank the editors and the reviewers for their invaluable comments and recommendations that have greatly improved the quality of this manuscript. We hope our responses are satisfactory.

Sincerely,

Ming Chen

Enclosed
Response to the reviewers’ comments and suggestions on MS: 5404498735274970 submitted to BMC cancer by Xu et al.

Reviewer 1
These authors sought to further explore the relationship between a specific polymorphism in the FGFR4 gene and the incidence of prostate cancer by performing a meta-analysis using six previously published case-controlled studies. They found that overall the likelihood of prostate cancer increased by 17% if the Arg388 allele was present. This relationship between a specific gene polymorphism and prostate cancer was present among Caucasian and Asian populations but not among the African-American population.

Response: Thanks for the reviewer’s encouraging and positive comments.

1. Major Revisions - The authors include limited demographic and tumor-specific characteristics of the cases and controls included in their meta-analysis other than stating “all the studies used frequency-matched controls to the cases by the age, sex or ethnicity, and the distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium in all studies.” This additional information is important in order to determine if the increased likelihood of prostate cancer conferred by this gene polymorphism is in fact clinically relevant and to avoid the introduction of unnecessary bias. Although the authors state that this gene polymorphism has been associated with aggressiveness of prostate cancer, this conclusion is not supported by the data in this meta-analysis. A review of the studies included in this meta-analysis reveals that additional clinical and pathologic parameters are available for inclusion.

Response: Thanks for the reviewer’s advice. Among the four articles, three[8, 10, 11] mentioned the association between FGFR4 Gly388Arg polymorphism and progression of prostate cancer. The stratifications for pathological parameters of the cases in the three articles were also shown in Table 1. The cases of the three articles were all stratified by Gleason score and tumor stage. However, the classification standard of Gleason score was not uniform, thus, we only focused on the association between FGFR4 Gly388Arg polymorphism and tumor stage (advanced vs. localized). Advanced stage corresponded to T3 stage in the study of Wang et al.[11], regional/distant stage in the study of FitzGerald et al.[8], and stage C+D in the study of Ma et al.[10], respectively. And localized stage meant T2 stage in the study of Wang et al., local stage in the study of FitzGerald et al., and stage A+B in the study of Ma et al., respectively. Interestingly, we found that patients with prostate cancer with Arg/Arg genotype had a 1.34-fold increased risk of advanced or metastatic prostate cancer (95% CI: 1.03-1.74, \( P = 0.613 \) for heterogeneity) compared with the Gly/Gly+Gly/Arg genotype (seen Fig.2).

2. Major revisions - In addition, more information about the length of follow-up in
theses studies as well as how and why these patients were diagnosed with prostate cancer (and ruled out for prostate cancer) is needed in order to make conclusion about this polymorphism and the incidence of prostate cancer. As the authors correctly point out, it is unclear how many patients in the control arms of these studies either have occult prostate cancer or will ultimately develop prostate cancer. In this meta-analysis, this is particularly important since a review of table 2 suggests that statistical significance is somewhat tenuous. I do believe, however, that the findings of this meta-analysis are worthy of publication and as the authors suggest that they should stimulate a larger more in depth analysis of FGFR4 Gly388Arg as a significant risk factor for prostate cancer among certain ethnic groups.

Response: Thanks for the reviewer’s encouraging and positive comments. As the reviewer pointed out, the information of the controls in some studies were not clear, however, it was hard for us to rule them out for prostate cancer. And it was one of the limitations of present study.

Reviewer2
Xu and colleagues present a meta-analysis of four studies investigating the association between the FGFR4 Gly388Arg polymorphism and prostate cancer risk. This is a well described study using sound statistical methodology. The authors cover the previous literature well and make just conclusions from their findings.

Response: Thanks for the reviewer’s encouraging and positive comments.

Minor Essential Revisions:
I have only two comments that can be addressed at the editor’s discretion. Firstly, whilst the manuscript is generally very well written, there are a few sentences and sections where the English needs to be corrected. In particular, the conclusion paragraph of the abstract, the second paragraph under the Quantitative Synthesis section of the results, and the final concluding paragraph. Also, in the first sentence of the second paragraph of the Discussion, there is a “not” missing from “but not in African Americans (OR=1.15, …etc)”.

Response: Thanks for the reviewer’s advice. We have carefully revised our manuscript and made several changes in the sections the reviewers had mentioned above.

Secondly, there is a preprint publication by Xu and colleagues in the European Journal of Cancer that has just been released. This group has done a meta-analysis on the Arg388Gly polymorphism in relation to a number of cancers, including prostate cancer. As you state in the discussion that this is the only meta-analysis done to your knowledge, but this manuscript has only been released, it is up to the editor as to whether you should acknowledge this publication.

Response: Thanks for the reviewer’s advice. However, as the editor said, we have
submitted our manuscript to the journal before this paper was published. He left us to make the decision. Thus, we decided that we would not include it in our study.

Reviewer3
First off, the language needs a bit of work. For example, numbers of worldwide participants are expected to examine associations to make a comprehensive and true conclusion? and ?There were seven papers relevant to the searching words. Through the step of screening the title, three of these articles were excluded?. Or take ?Our results suggested that Arg388 was a risk effect on prostate cancer risk in Caucasians (OR = 1.24, 95% CI: 1.02-1.51) and Asians (OR = 1.21, 95% CI: 1.00-1.47), but in African-Americans (OR = 1.15, 95% CI: 0.73-1.82).? Or even the use of the term ?dominatw I strongly recommend that the authors have the paper edited by a native English speaker with experience of scientific writing.
Response: Thanks for the reviewer’s advice. We have carefully revised our manuscript and corrected the puzzled sentences. “larger numbers of worldwide participants are expected to examine associations to make a comprehensive and true conclusion” was corrected to “Based on the limitations of present study list above, further prospective researches using standardized unbiased methods, and larger numbers of worldwide participants are expected to examine the association to confirm our results”; “There were seven papers relevant to the searching words. Through the step of screening the title, three of these articles were excluded “was corrected to “Using the searching terms, seven papers were reviewed in the two online databases.”;
“Our results suggested that Arg388 was a risk effect on prostate cancer risk in Caucasians (OR = 1.24, 95% CI: 1.02-1.51) and Asians (OR = 1.21, 95% CI: 1.00-1.47), but in African-Americans (OR = 1.15, 95% CI: 0.73-1.82).” was corrected to “Our results suggested that Arg388 represented a risk effect on prostate cancer in Caucasians (OR = 1.24, 95% CI: 1.02-1.51) and Asians (OR = 1.21, 95% CI: 1.00-1.47), but not in African-Americans (OR = 1.15, 95% CI: 0.73-1.82).”

As regards the meta-analysis, there is a very small number of papers, so the heterogeneity and funnel plot analyses are very underpowered. Indeed, I would remove reference to funnel plots entirely.
Response: Thanks for the reviewer’s advice. Although the heterogeneity and funnel plot analyses are very underpowered in present study, they are indispensable in meta-analysis according to the meta-analyses of observational studies (MOOSE) guidelines as the editor mentioned.

A couple of other points:
1. Don’t report p values to 3 significant figures.
Response: Thanks for the reviewer’s advice. We have changed it into two significant figures.

2. Don’t accept the null hypothesis; a high p values means insufficient evidence of an effect, not evidence of no effect. So you can’t say “no effect in African Americans?”, indeed, the effect in African Americans appears to be very similar to that in other racial groups.
Response: Thanks for the reviewer’s advice. All the p values in Table 1 represent p values for heterogeneity test. And significantly increased risk was found among Caucasian populations (Arg\(^{388}\) and Gly\(^{388}\) comparison: OR = 1.21, 95% CI: 1.00-1.47; \(P = 0.090\) for heterogeneity; dominant genetic model: OR = 1.23, 95% CI: 1.08-1.40; \(P = 0.390\) for heterogeneity) and Asian population (Arg\(^{388}\) and Gly\(^{388}\) comparison: OR = 1.24, 95% CI: 1.02-1.51; homozygote comparison: OR = 1.52, 95% CI: 1.05-2.22; dominant genetic model: OR = 1.53, 95% CI: 1.10-2.14). However, we did not find and significant association in African-American population in any genetic models. Thus, we concluded that this polymorphism might have no effect in African-American population.

3. Shouldn’t the authors say somewhere that the effect is trivial? The odds ratio for an elevated PSA in early middle age is something like 30; here we have an odds ratio of 1.2
Response: Thanks for the reviewer’s advice. We have added this statement in the limitations section in the discussion.