Author’s response to reviews

Title: A meta-analysis and The Cancer Genome Atlas data of prostate cancer risk and prognosis using epithelial cell adhesion molecule (EpCAM) expression

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections in accordance with approval. We have made all the required changes suggested by the editor and the reviewers. Please find our point by point response to all the inquiries as follows:

Reviewer reports:

Jay Ciezki (Reviewer 1): I had difficulty following this manuscript. It may be my ignorance, but I don't understand the difference between "normal prostatic tissues" and "benign prostatic tissue samples". There are several other terminology issues that confuse me. For example, should this sentence from the conclusion "EpCAM overexpression may be correlated with the development, bone metastasis, and worse biochemical recurrence free-survival of PCa" be written as "EpCAM overexpression may be correlated with the development of bone metastasis and worse biochemical recurrence free-survival of PCa" or is there another factor to which "development" is referring?

I would be happy to review the manuscript if the language issues are addressed. As it is, I cannot review the authors' work in a manner that it deserves.
Response: Thank you for your kind suggestions. For example, ‘the difference between "normal prostatic tissues" and "benign prostatic tissue samples’ has been stated in Introduction section (Highlighting, Introduction section, Page 5, line 3-5). The sentence from the conclusion "EpCAM overexpression may be correlated with the development, bone metastasis, and worse biochemical recurrence free-survival of PCa" be written as "EpCAM overexpression may be correlated with the development of bone metastasis and worse biochemical recurrence free-survival of PCa" (Highlighting, Abstract section, Page 2, line 23). Additionally, we are very sorry for our imperfect writing. According to your comments, we read and revised the manuscript again.

Kasonde Bowa (Reviewer 2):

The study summary: This is metanalysis, which uses the PRISMA guidelines to assess the value of Epithelial Cell Adhesion Molecule (EPCAM) a glycoprotein cell membrane in determining the risk and progression of Prostate Cancer. The study collected 847 article and analysed 7 articles. The study found that EPCAM expression was high in Ca P. However EPCAM overexpression was not linked with clinicopathological stage. It was linked only to the Gleason score. Only one study linked EPCAM to recurrence and long term prognosis.

The comments

Title: the abbreviations should be written in full. The study method should proceed, and the disease should proceed the study technique i.e a metanalysis of Ca P risk and prognosis using EPCAM expression. The current title is more difficult to understand.

Response: Thank you for your good suggestion. The title has been revised (Highlighting, Title section, Page 1, line 1-2).

Abstract. The abstract is well written and clear.

Response: Thank you for your kind support.

Introduction: This provides a good context and well as the scientific basis for EPCAM as a potential measure of Ca P risk and Prognosis. The abbreviation EPCAM should be used consistently the same in the title and the text. Otherwise it distracts the reader from the content.

Response: Thank you for your kind support and nice suggestion. We carefully check this word throughout the manuscript, ‘EPCAM’ in the previous title has been revised as ‘EpCAM’.
Study objective: The main objectives appears to be one of using EpCAM to determine Ca P risk. The prognosis and clinicopathology objective is presented as an after thought, or a subsidiary objectives, this should be rephrased to avoid that conclusion.

Response: Thank you for your kind suggestion. The study objectives in Introduction section have been revised (Highlighting, Introduction section, Page 5, line 9-12).

Method. The study appears to have used PRISMA guidelines in the study methods however this is not specifically mentioned in the study methods. The study should include the standard metanalysis guidelines and the standard guideline flow chart such as the PRIMSA guidelines. Without this the metanalysis appears to be subjective.

Response: Thank you for your good comment. Our study was performed based on the PRIMSA guidelines. We have added the statement in this paper (Highlighting, Methods section, Page 5, line 16-17). Additionally, Figure 1 has been re-revised based on the guideline.

Data Analysis: the impression is created that the secondary data obtained was overanalysed and insufficient mention is made of the completeness of the secondary data obtained. This study would be more convincing if this data was primary data obtained by the researchers themselves. The TCGA substudy should probably be done as a separate paper from the rest of the metanalysis, to make the paper easier to understand for the reader.

Response: Thank you for your nice suggestion. We have added the content on the secondary data obtained (Highlighting, Methods section, Page 7, line 6-8). Additionally, TCGA data was used to validate the results of meta-analysis, to make the paper easier to understand on meta-analysis and TCGA data for the reader. For example, we have added the statement in Methods and Results sections (Highlighting, Methods section, Page 5, line 15, Page 6, line 3 and 16; Results section: Page 8, line 11 and 22, Page 9, line 13, Page 10, line 3).

Results: These need to be presented in a progressive manner with the descriptive data first eg metanalysis flow charts first and the analytical data last. This would make it easier to understand.

Response: Thank you for your kind suggestion. According to your good comment, we have revised the content in Results section, for example, (Highlighting, Methods section, Page 9, line 1-2, line 14-15, line 18 and 20).

Discussion: this is fair and interesting

Response: Thank you for your kind support.
Conclusion: This should be moderated, it seem to exceed the conclusion which can be reasonably be drawn from a metanalysis.

Response: Thank you for your good suggestion. The previous conclusion has been removed and re-revised (Highlighting, Conclusion section, Page 14, line 1-9).

Alcides Chaux (Reviewer 3): In this study, authors present the results of a meta-analysis of EpCAM expression and outcome in patients with prostate cancer. Authors included 7 studies which met their selection criteria. They found that EpCAM was associated with tumor progression, recurrence and dissemination. A few recommendations for the manuscript are provided below.

1. The manuscript needs some language corrections before being ready for publication. Please conduct a grammar check with a native English speaker or consider using an editing service.

Response: Thank you for your kind suggestions. We are very sorry for our imperfect writing. According to your comments, we have read and revised the manuscript again.

2. Systematic review: Please specify if the search included unpublished results from repositories and studies presented at conferences and meetings. If not, please conduct a new search to avoid publication bias.

Response: Thank you for your good suggestion. The unpublished papers, or conference abstracts were excluded based on incomplete information such as the detailed the information of IHC method. We have added the relevant statement in this paper (Discussion section, Highlighting, Page 13, line 5-13).

3. Selection criteria: Please check if the immunohistochemistry protocols used in the included studies are similar or equivalent, as this can be a significant source of heterogeneity.

Response: Thank you for your good suggestion. We carefully check them, although the immunohistochemistry protocols used anti-EpCAM antibody for EpCAM expression among all studies. However, as shown in Table 1, for example, the cut-off values were different among some studies, which may be unavoidable. We have added the relevant statement (Discussion section, Highlighting, Page 13, line 18-22).

4. Avoid the term multivariate analysis throughout the manuscript. This term is utterly unspecific and can be confusing (v.g., multivariate regression is a specific type of regression that should not be confused with other types of regression).
Response: Thank you for your good suggestion. We have carefully read this manuscript and have revised the term multivariate analysis (Highlighting, Abstract section, Page 2, line 20, Methods section, Page 6, line 11, Page 7, line 12; Results section, Page 8, line 19).

5. Justify the rationale of using two statistical packages (STATA and R), considering that a proper meta-analysis can be conducted using any of them. If in doubt, prefer R and publish the code to make the analysis reproducible. Also, please correct the data from the R publishers.

Response: Thank you for your kind suggestion. Generally, a meta-analysis was commonly and mainly analyzed using STATA, genome sequencing data were primarily analyzed using R. Data of our meta-analysis and genome sequencing data was not needed for giving the code. For example, the pooled OR was calculated using the simple code (metan a b c d, label(namevar=study) random or). Our data analyses were correct and reliable. Many publications using STATA and R software are published such as [1-4]. Additionally, we correct the information from the R publishers (Highlighting, Methods section, Page 8, line 7-8).

6. RoB: report the results from Egger's test and include funnel plots to assess publication bias.

Response: Thank you for your kind suggestion. Because the included studies were small (<10 studies), thus, we did not analyze the results of publication bias (Red, Page 7, line 19). Moreover, we also added the statement on the publication bias (Highlighting, Discussion section, Page 13, line 5-13).

7. Reported OR are excessively large, please check standard errors. If the standard errors are large, then the ORs are not valid.

Response: Thank you for your kind suggestion. As shown in Table 2, we check and add standard errors.

Standard error between EpCAM overexpression and lymph node metastasis was 4.48, other values were small. Regarding the result about EpCAM overexpression with lymph node metastasis, we also added the discussion (Discussion section, Highlighting, Page 12, line 19-21).

8. Please include the results of the sensitivity analyses that were carried out (i.e., the change in the I-squared statistic)

Response: Thank you for your good suggestion. The results of the sensitivity analyses had been described in Methods section. When we the study of Ni 2013 et al., the change of heterogeneity p values varied from P = 0.043 to P = 0.242. (Red, Results section, Page 9, line 6-11).

9. Please review the forest plots that include P = 0.000. Report the exact P value.
Response: Thank you for your good suggestion. P = 0.000 in Figure 3 has revised as P <0.001.

10. Figure 4 is of low quality and mainly uninformative, as it does not add any significant information that is not included in the text. Please consider removing it.

Response: Thank you for your good suggestion. The previous Figure 4 has been removed.

11. Did the authors conduct a fixed-effects model analysis or they went straight to the random-effects models? Please justify the choice.

Response: Thank you for your good suggestion. The random-effects model was used in the present meta-analysis (Red, Methods section, Page 7, line 15-16).

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

Best wishes,

Yours sincerely,

References

