Author’s response to reviews

Title: Sexual Dimorphism in the Incidence of Human Cancers

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Author’s response to reviews:

Dear Editor,

I apologize for delayed revision of our manuscript because we re-analyzed and re-generated all figures and tables upon the request from the reviewer 1 who suggested us to use the world population data to normalize the SEER and Swedish data for sound comparison. And our original first-author is leaving the lab, so my another postdoc Dr. Justyna Trynda completed all these analyses and revision, so I listed her as the co-first-author for this revised manuscript. In addition to responses to reviewers’ comments, we also updated the text, figures, and tables by separating data between non-small cell lung cancer and small cell lung cancer in the Swedish data as the data became available.
We sincerely thank all great comments from the editor and both reviewers to help us to improve the quality of our manuscript and study. Please see below our replies to these comments point-by-point.

Best regards,

Zhaoyu Li

Editor Comments:

1. Consent for publication refers to consent for the publication of identifying images or other personal or clinical details of participants that compromise anonymity. Seeing as this is not applicable to your manuscript please state “Not Applicable” in this section.

[Reply]: changed to “Not Applicable”.

2. Please specify where or from whom the data is available from in the Availability of data and materials section, please include specific names or links to the data.

[Reply]: Yes, we add the following in the “Availability of data and materials” section, “The incidence data for all types of cancers were collected from four sources, the SEER Program (NCI/NIH), the cancer incidence data of Sweden (Swedish Cancer Registry), the Cancer Registry data from Mayo Clinic, and the World Cancer Report data in 2012 (IARC).”

3. Please note, the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared in the Funding section.

[Reply]:
4. Please clarify if the initials CM in the Authors' Contributions refer to author Cecilia Williams, if so, please amend to CW.

[Reply]: changed to CW.

5. Please consider the list of authors as it currently stands with reference to our guidelines regarding qualification for authorship (http://www.biomedcentral.com/submissions/editorial-policies#authorship).

Currently, the contributions of the authors do not automatically qualify them for authorship. In the section “Authors’ contributions”, please provide further clarifications on their contributions, and see our guidelines for authorship below.

[Reply]: we revised the “Author’s contributions” section as “Z.L. designed and wrote the manuscript. D.Z., J.T., and C.M. analyzed all data and wrote and revised the manuscript. J.A.V. provided the Mayo Clinic Cancer Registry data and analyzed the data. J.H.N., D.M.H, S.P.B, and S.A.M. wrote a part of manuscript and revised the entire manuscript.”

An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. Authors are expected to fulfil the criteria below (adapted from McNutt et al., Proceedings of the National Academy of Sciences, Feb 2018, 201715374; DOI: 10.1073/pnas.1715374115; licensed under CC BY 4.0):

Each author is expected to have made substantial contributions to the conception OR design of the work; OR the acquisition, analysis, OR interpretation of data; OR the creation of new software used in the work; OR have drafted the work or substantively revised it

AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study);

AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acquisition of funding, collection of data or general supervision of the research group, alone, does not usually justify authorship.
If these guidelines are not met, we would request the following change of authorship form be filled out and sent to our editorial office - https://resource-cms.springernature.com/springer-cms/rest/v1/content/7454878/data/v5

[Reply]: All authors met the criteria. Please refer to the revised “Author’s contributions”.

Anyone who contributed towards the article who does not meet the criteria for authorship can be acknowledged in the ‘Acknowledgements’ section.

[Reply]: Not applicable.

6. Please include a statement in the Authors' contributions section to the effect that all authors have read and approved the manuscript, and ensure that this is the case.

[Reply]: Added as suggested.

7. Please add a section "Additional files" (after the References/Figure legends) where you list the following information for each additional/supplementary file in the file inventory:

- File name (e.g. Additional file 1)
- Title of data
- Description of data

[Reply]: added.

8. Please put your responses to the reviewers'/editors’ comments in the Response to Reviewers box in Editorial Manager, please do not upload a separate letter.

[Reply]: yes.
9. At this stage, please upload your manuscript as a single, final, clean version that does not contain any tracked changes, comments, highlights, strikethroughs or text in different colours. All relevant tables/figures/additional files should also be clean versions. Figures (and additional files) should remain uploaded as separate files.

[Reply]: yes.

BMC Cancer operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Wanqing Wen (Reviewer 1):

The authors have improved the manuscript and adequately addressed the reviewers' concerns for the most part except for the incidence rate standardization. The authors standardized the cancer incidence rates for the SEER/Mayo data, Sweden data, and the World Cancer Report data using three different standard populations (i.e., US population, Sweden population, and the world population, respectively). It may be appropriate for the comparisons of yearly incidence ratios of men to women (or women to men) across populations by using different standard populations as plotted in Fig 1, since the incidence sex ratios was independent to age effect within a population. However, it is not appropriate for the comparisons of yearly incidence rates across sexes and populations by using different standard populations as plotted in Fig 2, since different populations have difference age distributions. The simple solution is to use the same standard population, e.g., the World population, for all the SEER/Mayo data, Sweden data, and the World Cancer Report data. The standardized rates can only be compared based on the same standard population.
[Reply]: we re-analyzed all data using the World standard population data from WHO and re-generated all figures, tables, and the method section using age-adjusted standardized rates (ASR) for comparison. And we did not observe clear differences in the ratios between these newly standardized data and our previous data and only observed minor changes in the incidence data. The following is for the method section “We collected the crude incidence rate for 30 types or subtypes of human cancers from the SEER data and Mayo Clinic, 29 types or subtypes of human cancers from Sweden data, and 24 types from the World Cancer Report in 2012. All these incidence rates were standardized to the population of 100,000 and were age-adjusted to the World standard population (WHO 2000-2025) as the age-adjusted standardized rate (ASR).”

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study
INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The revised manuscript does improve a lot particularly on the arbitrary definition of sexual dimorphism of the cancer incidence.

The authors have done well on the aspect of discussing the plausible underlying mechanisms for the dimorphisms.

However, the conclusions statements in the Abstract are still not acceptable.

[Reply]: we revised the conclusion statement in the Abstract as the following “Sexual dimorphism is a clear but mostly neglected phenotype for most human cancers regarding the clinical practice of cancer. We expect that our study will facilitate the mechanistic studies of sexual dimorphism in human cancers. We believe that fully addressing the mechanisms of sexual dimorphism in human cancers will greatly benefit current development of individualized precision medicine beginning from the sex-specific diagnosis, prognosis, and treatment.”

ADDITIONAL REQUESTS/SUGGESTIONS:

I believe the revised manuscript does not contain research findings on the investigation of the underlying mechanisms of the sexual dimorphism. Thus, the conclusions stating about the mechanisms of sexual dimorphism and its relationship with the development of precision medicine are premature statements.

[Reply]: Revised as above.