Author’s response to reviews

Title: Sexual Dimorphism in the Incidence of Human Cancers

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Author’s response to reviews:

Reply: We sincerely thank all great comments from both reviewers to help us to improve the quality of our manuscript and study. Please see below our reply point-by-point with all changes highlighted in yellow in the main text. In addition to responses to reviewers’ comments, we also updated all SEER data from 1975-2014 to 1975-2015 in the text, figures, and tables.

Reviewer 1:

The authors analyzed the sex differences of cancer incidence rates from four sets of cancer incidence data. While this report provide some useful information, some concerns needs to be addressed.
1. The authors stated "The incidence rates were normalized ... and age-adjusted to population 2000". Where population was refereed to? American or the World population?

Reply: we changed to “...population 2000 in the United States, Sweden, and the World, respectively”.

2. Usually we use the term "the standardized incidence rates", not the "normalized" rates.

Reply: changed “normalized” to “standardized”.

3. The authors used the ANOVA test and Student's t-test to compare standardized incidence rates. The appropriate methods should be Poisson test or based on the Gamma Distribution. (see Fay, M. P. and Feuer, E. J. (1997), "Confidence Intervals for Directly Standardized Rates: A Method Based on the Gamma Distribution," Statistics in Medicine, 16, 791-801)

Reply: We add the results of Poisson distribution test in the Table S1 and S2.

4. The authors stated "If the incidence ratio was less than 1, the negative reciprocal ratio was used as the sex-dimorphic ratio." Why a ratio less than 1, such as 0.5, is negative?

Reply: we changed this to “for distinguishing sex-dimorphic ratio between men- and women-prevalent cancers, if the incidence is male-prevalent, the sex-dimorphic ratio was calculated by men’s incidence divided by women’s incidence (men/women); if the incidence is female-prevalent, the sex-dimorphic ratio was calculated by the negative women’s incidence divided by men’s incidence (-women/man).”

5. On page 8, the authors compared sex-specific incidence rates between USA and Sweden, the incidence rates in USA and Sweden were plotted in two different figures. To visually compared incidence rates between USA and Sweden, they need to be plotted in the same figure.

Reply: we plot them together as suggested as the new Figure 2.

6. The last two sentence on page 9 (starting with "The interesting regional") are abrupt, and should be moved to the Discussion section.

Reply: we move this part to the end of the discussion.
7. Please delete the sentences "We collected 30 types ...' and "from 24 types ..." in the "Sources of cancer incidence data" section on page 5, because they were mentioned again in the next section (page 6).

Reply: deleted as suggested.

8. Please change "because of no female incidence" to "because of lack of female incidence" on page 10.

Reply: changed as suggested.

9. The sentence "and the incidence of stomach, no sexual dimorphism was observed" on page 10 is not clear.

Reply: we remove "and the incidence of stomach”.

10. The sentence "It would be interesting to investigate what historical factors affect sexual dimorphism or incidence of these cancers for better understanding of the underlying mechanisms" on page 11 could be deleted.

Reply: we deleted it as suggested and add “Therefore, historically there were many differences in cancer incidence and sexual dimorphism of incidence between USA and Sweden.”

11. The whole section "Sexual dimorphism between Mayo Clinic hospitalization and the USA populations" provided little useful information, and could be deleted.

Reply: we just want to provide additional evidence from Mayo Clinic hospitalization data to support the finding of sexual dimorphism of cancer incidence in the USA populations and provide data regarding clinical practice that may be involved in sex differences in human cancers.
12. The Discussion section only discussed sex hormones, as if sex hormones are the only major factor for the sex differences of cancer incidences. The discussion section needs to be strengthened. Many factors, such as life styles, behaviors, environmental exposures, play important roles in sex differences of cancer incidences. In addition, this report mainly compared USA and Sweden populations. the limitation in generalization of this report needs to be addressed.

Reply: we add the following in the discussion section “However, the mechanisms underlying sexual dimorphism for these cancers have been under-investigated and mostly neglected in clinical diagnosis and therapy. Both genetic and environmental factors contribute to the initiation and progression of cancer in the form of germline genetic variations and defects, somatic mutations, and the inflammatory responses resulting from exposure to toxic chemicals, excessive alcohol consumption, and/or viral infection [21-23]. In addition to environmental exposures, many other factors, such as life styles, and behaviors, could play important roles in sex differences of cancer incidences [27-38]. e.g., previous studies also showed that sex-dimorphic energy balance and homeostasis might lead to sex differences in gastrointestinal cancers [38]. miRNA expression were also sex-dimorphic in many types of cancers [39, 40], non-mining men still had higher incidence of mesothelioma than non-mining women [27-30], and male-dominant HIV infection did not show similar degrees of male-dominant incidence in Kaposi Sarcoma [32-37]. However, sex hormones are the natural differences between males and females, and most sex-dimorphic factors or observations could lead to the changes in the levels of sex hormones or be derived from the differences in sex hormones between sexes. Sex hormones, i.e., estrogens in women and androgens in men, are the drivers of sexual dimorphism in general.”

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (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 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?

No - there are major issues

Reply: we revise the discussion section by adding two parts “However, the mechanisms underlying sexual dimorphism for these cancers have been under-investigated and mostly neglected in clinical diagnosis and therapy. Both genetic and environmental factors contribute to the initiation and progression of cancer in the form of germline genetic variations and defects, somatic mutations, and the inflammatory responses resulting from exposure to toxic chemicals, excessive alcohol consumption, and/or viral infection [21-23] In addition to environmental exposures, many other factors, such as life styles, and behaviors, could play important roles in sex differences of cancer incidences [27-38], e.g., previous studies also showed that sex-dimorphic energy balance and homeostasis might lead to sex differences in gastrointestinal cancers [38], miRNA expression were also sex-dimorphic in many types of cancers [39, 40], non-mining men still had higher incidence of mesothelioma than non-mining women [27-30], and male-dominant HIV infection did not show similar degrees of male-dominant incidence in Kaposi Sarcoma [32-37]. However, sex hormones are the natural differences between males and females, and most sex-dimorphic factors could lead to the changes in the levels of sex hormones or most sex-dimorphic observations be derived from the differences in sex hormone signaling between sexes. Sex hormones, i.e., estrogens in women and androgens in men, are the drivers of sexual dimorphism.”
We also add three more paragraphs of discussions “Sex differences in the incidences of cancers become a critical issue in both cancer research and the development of precision medicine. Following the increasing understanding of sexual dimorphism in the incidence of these cancers, sex-specific diagnosis, prognosis, and treatment would become an important addition and an initial step towards personalized precision medicine.”, “The interesting regional differences in sexual dimorphism of cancers and cancer incidence between two countries provide novel model systems for us to reveal the mechanisms underlying sexual dimorphism of human cancers. It would also be worthwhile to investigate whether expression of sex hormone receptors or activity of sex hormone signaling could have geographic differences and how genetic, dietary, and environmental factors could contribute to sexual dimorphism of human cancers, which requires international collaborations on this topic.”, and “The origins of sexual dimorphism are the differences in sex chromosomes. The final answers to sexual dimorphism in human cancers could be fully revealed once we have better understanding of how X and Y chromosomes regulate sexual dimorphism?”. 

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Maybe - with major revisions

Reply: we made major revision as suggested below.

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This manuscript leveraged three population-based datasets to gain a different perspective on the so-called 'sexual dimorphism' phenomenon of cancer incidence. The yearly incidence ratios of men to women curves for different cancer types were well demonstrated in various figures. However, the significance and gold standard definition of 'sexual dimorphism' were not well defined. For example, how many fold difference in terms of the ratio will inevitably mean a dimorphism?

Reply: we add our definition of sexual dimorphism for cancer incidence in the first paragraph as “Our definition of sexual dimorphism in each cancer was based on the calculation of the significance of cancer incidence between men and women during the past 40 years (p values < than 0.05).” We used three statistical methods, Poisson distribution test, ANNOVA test, and Student’s T-test to calculate the yearly differences in the cancer incidence between men and women during the past 40 years. Thus, even men only have only 26-39% more incidence than women for colon cancer (cancer type 24 in the Table 1) or even it may not show much sex difference in certain years, but histologically and statistically it is still significant (1.54E-09) to be considered as a sex-dimorphic cancer.
REQUESTED REVISIONS:

In the Abstract, the authors pointed out that sex differences are critical for the development of precision medicine. This part should be elaborated in the Discussion to complete the whole story.

Reply: we add the following in the discussion as suggested “Sex differences in the incidences of cancers become a critical issue in both cancer research and the development of precision medicine. Following the increasing understanding of sexual dimorphism in the incidence of these cancers, sex-specific diagnosis and treatment would become an important addition and an initial step towards personalized precision medicine.”

The definition of sex dimorphism should be clearly explained and well referenced in the first paragraph in the Background section.

Reply: we add our definition of sexual dimorphism for cancer incidence in the first paragraph as “Our definition of sexual dimorphism in each cancer was based on the calculation of the significance of cancer incidence between men and women during the past 40 years (p values < than 0.05).”

The discussion only sees efforts focusing on sex hormone receptors as the underlying mechanistic explanation for cancer susceptibility is dangerous.

Reply: we add more discussion for many other factors by adding “However, the mechanisms underlying sexual dimorphism for these cancers have been under-investigated and mostly neglected in clinical diagnosis and therapy. Both genetic and environmental factors contribute to the initiation and progression of cancer in the form of germline genetic variations and defects, somatic mutations, and the inflammatory responses resulting from exposure to toxic chemicals, excessive alcohol consumption, and/or viral infection [21-23] In addition to environmental exposures, many other factors, such as life styles, and behaviors, could play important roles in sex differences of cancer incidences [27-38], e.g., previous studies also showed that sex-dimorphic energy balance and homeostasis might lead to sex differences in gastrointestinal cancers [38], miRNA expression were also sex-dimorphic in many types of cancers [39, 40], non-mining men still had higher incidence of mesothelioma than non-mining women [27-30], and male-dominant HIV infection did not show similar degrees of male-dominant incidence in Kaposi Sarcoma [32-37]. However, sex hormones are the natural differences between males and females, and most sex-dimorphic factors could lead to the changes in the levels of sex hormones or most sex-dimorphic observations be derived from the differences in sex hormone signaling between sexes. Sex hormones, i.e., estrogens in women and androgens in men, are the drivers of sexual dimorphism.”
We also add three more paragraphs of discussions “Sex differences in the incidences of cancers become a critical issue in both cancer research and the development of precision medicine. Following the increasing understanding of sexual dimorphism in the incidence of these cancers, sex-specific diagnosis, prognosis, and treatment would become an important addition and an initial step towards personalized precision medicine.”, “The interesting regional differences in sexual dimorphism of cancers and cancer incidence between two countries provide novel model systems for us to reveal the mechanisms underlying sexual dimorphism of human cancers. It would also be worthwhile to investigate whether expression of sex hormone receptors or activity of sex hormone signaling could have geographic differences and how genetic, dietary, and environmental factors could contribute to sexual dimorphism of human cancers, which requires international collaborations on this topic.”, and “The origins of sexual dimorphism are the differences in sex chromosomes. The final answers to sexual dimorphism in human cancers could be fully revealed once we have better understanding of how X and Y chromosomes regulate sexual dimorphism?”.

Sexual dimorphism also exists in energy balance/homeostasis. Moreover, some studies also discover numerous cases of somatic sex-biased miRNA expression. A more extensive literature review is required for a good discussion.

Reply: we totally agree on this. We add more discussions on this part as described above.