Author’s response to reviews

Title: Clinicopathological characteristics and health care for Tibetan women with breast cancer: a cross-sectional survey

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Shan Zheng

Prof., Department of Pathology
Dear Prof. Linda Gummlich:

Thank you for your letter of “Your submission to BMC Cancer - BCAN-D-18-00625” and for the reviewers’ comments concerning our manuscript titled “Clinicopathologic characteristics and health care for Tibetan women with breast cancer: a cross-sectional survey”. We have studied their comments carefully and the paper has been appropriately altered according to the reviewers' comments. In the revision, there are three colored highlights. The yellow ones represent the words we’ve adjusted this time. The grey ones with double strikethrough represent the words which we’ve deleted. The red ones represent the content of which we’ve added this time.

We answered the questions to the referees’ comments as follows:

Reviewer 1 (Benjamin Calhoun)

1. Background, line 23: change et al. to etc.

We have revised it following the suggestion (page 5, line 13).

2. Methods, Study Design and Quality Control, 2nd paragraph, line 48: separate medical oncology into two words (medical oncology)

We have revised it following the suggestion (page 7, line 13).

3. Methods, Statistical Analysis, 1st paragraph: Instead of making new categories called LNM +/- or invasion +/- why not just use the AJCC designations? One grouping could be N0 vs N1-3 and the other could be T1-T3 versus T4. And, later in Results, it looks like N2 was the most common 'LNM' group - why not just say N2?

We have revised all those following the suggestion in methods, statistical analysis (page 8, line 15, line 20-21) and results (page 10, line 14-16, 19-20). And we have also revised our Table 2...
4. Methods, Statistical Analysis, lines 1-4: Was the Nottingham combined histology grade used? Please clarify.

We have used the Nottingham combined histology grade in pathologic grade and we have added this information in methods, statistical analysis (page 8, line 19). We thanked the kind reminder from the reviewer.

5. Results, Clinicopathologic characters of 273 Tibetan female with BC, line 48-50: List the AJCC stage here For example, list the stage group (e.g., Stage IIIA) or list the TNM (e.g., T3 N1 M0).

We have revised it following the suggestion (page 10, line 21). And we also revised it in the method (page 9, line 2-3).

6. Results, The relationship between clinicopathological characters of 273 Tibetan females with BC and different HCSs, lines 20-31: Include the stage groups here - were Stages I-III compared to Stage IV?

We have compared stage I+II with stage III, and stage IV with stage III. And we have added this information in this paragraph (page 11, line 11-16). We thanked the kind reminder from the reviewer.

7. Results, The relationship between clinicopathological characters of 273 Tibetan females with BC and different HCSs, lines 28-31: The increase in advanced disease in the rural and urban HCS seems counterintuitive. Could this be attributed to increased access (i.e., patients who ordinarily would have stayed home went to the clinic or hospital)? Did these patients have other diseases that prevented them from seeking care earlier for breast cancer?

This could be attributed to increased access, and also the improvement of cancer awareness. We have revised our description of this view and discussed them in the discussion (page 15, line 21-page 16, line 14). We have also discussed the altitude sickness, the most common diseases which may prevent patients with BC from seeking care in Tibet (page 18, line 1-8). We thanked the kind reminder from the reviewer.
Reviewer 2 (Eva Kantelhardt):

I) the authors mention they want to assess influence of health care system HCS on "the clinicopathologic characteristics " or whether BC is "more aggressive" in restricted HCS. This assumes a causative effect of the health care system on the biology (aggressiveness) or probably the presentation of BC. The cited literature for this assumption is about differences in OUTCOME of BC among different ethnic groups in the US. The only association mentioned in the cited literature is between HCS and mammography which of course indeed my lead to differences in presentation. The authors discuss access to health care (this cannot be assessed since there is no information about proportion of women reaching the hospital and those who do not), screening (18% prevalence) probably mammography screening? and lack of impact of investment in HCS on lymph node metastasis (it is not clear how this can be derived from the results). There is no discussion about lack or availability of mammography in the manuscript and little discussion about reasons for early or late presentation which may influence the main outcome measures such as tumor size, stage and . We have admitted more aggressive characters at the presentation of BC and revised that in our manuscript (page 4, line 8 in abstract and page 6, line 6 in background, and page 18, line 22 in conclusion). The screening was clinical breast exam, and we added this information in our manuscript (page 5, line 21-page 6, line 1 in background, and page 13, line 14-17 in discussion). We have added the analysis about the reasons of the aggressive characters of Tibetan females with breast cancer (page 13, line 17-20 in discussion) and given the suggestion about the improvement of the prognosis of BC and screening model in Tibet (page 13, line 22- page 14, line 10; page 16, line 15-page 17, line 1). We thanked the kind reminder from the reviewer.

II) The authors describe 3 different levels of HCS: "free HCS", "new rural cooperative HSC" and "rural and urban integration HCS"

There are three problems: 1) it is a historical comparison since the first was implemented 1973-2001; the second 2002-2012 and the third 2013-15. There is no detailed description about what are the differences except graphic No. 1 where e.g. subsidies by government and health expenditures are given in local currency. These items are highly dependant on spending power, inflation, number of people served, age-distribution of population served, competing priorities etc. The other items mentioned beds per person and medical personal do not differ between the time-periods. The reader will not understand about these differences. 2) Seeing only 14 women in the "free HCS" seems extremely low compared to the other two groups (especially when used as reference category). The reader may wonder why there were so few - were the others excluded due to incomplete data (consort diagram does not mention these issues) or did the rest of expected breast cancer patients never reach the hospital? Tibet had between 1 and 3 Mio
inhabitants in the given time-period. China has an estimated 22.1 cases per 100,000 women in 2012. This means 220 cases per year, the study only reflects a very minor proportion of the expected patients especially for the early years. All comparisons between the 3 HCS become problematic reflected by the large confidence intervals having such a very small comparison group.

3) there are various other factors which changed during those time-periods of HCS influencing the presentation of BC patients. These are: reproductive factors: use of contraceptives/hormone replacement therapy, number of births, duration of breast feeding etc. Co-morbidities and competing morbidities have greatly changed over the years and also highly influence the women’s choice for or against early presentation at the hospital.

We have added the description of the differences among three HCSs (page 14, line 12 and page 15, line 3) to answer the problem 1). Tibet was a low-incidence area, where the incidence of BC was 5.2/100000, based on the data of 2012. Selection bias might be ascribed to the underestimation of the cases in the early years. We have also added the explanation (page 17, line 10-13) to answer the problem 2). Since the anoxic plateau was not suitable for most of the nationalities except for Tibetan, the population features in this nationality showed relative stability. We have described some population features of Tibetan in background (page 5, line 18-20) and also these feature and the possible co-morbidities and competing morbidities in discussion (page 17, line 17- page 18, line 9) to answer question 3). We thanked the kind reminder from the reviewer.

General comments:

* The English grammar and spelling needs some review, terms should be defined and used precisely (aggressive BC is not clear, seeing more cases >2cm or advanced stage does not mean aggressiveness but later presentation during the course of the disease).

We have improved the English language by professional experts and corrected our description and made it more concise in our manuscript. We thanked this kind reminder.

CONSORT diagram must be enhanced.

We have revised the CONSORT diagram of Figure 2. We thanked this kind reminder.
Literature from low and middle income countries needs to be included especially about other factors influencing BC presentation such as genetics, social factors, screening/early detection etc.,

We have added another nine literatures in this revision which was highlight. We thanked this kind reminder.

If interest is about tumor biology then hormone receptor status must be included and HER2 is available.

In this manuscript, we only focused on the clinicopathological characters of Tibetan females with BC. We will continue our research in the future research about tumor biology. We thanked this kind reminder.

Results of other papers or own results are not clearly identified (e.g. first passage of discussion - are Han women another population in the same study or are they cited from other papers?)

Some results were from our previous research focused on Han women. However, it was not related with this research. We’ve given the explanation in our manuscript (page 12, line 10-12). We thanked this kind reminder.

Figures and tables need more precise wording.

We have revised our Figure and tables. We thanked this kind reminder.

One organization of our authors (Zheng, Li and Guo) was update according our organization document. And we had revised our organization’s name in this revision (highlight in yellow).

We thank the reviewers and are confident that this adequately addresses the issues raised. We look forward to hearing from you again in due course.

Yours sincerely,

Yong-ge Ze and Shan Zheng