Author's response to reviews

Title: Risk of breast cancer and family history of other cancers in first-degree relatives in Chinese women: a case control study

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Author's response to reviews: see over
Dear editor:

Thank you very much for your letter dated on June 13, 2014 in which you sent us the Referees' Reports on our manuscript. We would also like to thank the referees and editor for their valuable comments and suggestions.

The concerns raised by the referees are responded as follows.

I hope the manuscript has been improved satisfactorily and that it will be accepted for publication in your journal.

With best wishes.

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Reviewer: GEMA LLORT
Reviewer's report:
- Major Compulsory Revisions

1- In the conclusion I think is possible to explain the same in other words less confusing in the sentence: “An increased breast cancer risk ...and younger, is not clear, and I counsel specify better”... It is not clear: that subjects have more risk? limited to first-degree relatives? Who must be under 50 years?
Response: Thank you for your work on our manuscript. The changes in our revised manuscript were marked in red. Sorry for not describing it clearly. We have revised the manuscript. (Line 8-9, Page 16)

2- In the conclusion: Risk-reduction options should be considered for these women with high risk of breast cancer. I think is important to be cautious at this point because the definition of women at HIGH RISK for breast cancer is more complex. Perhaps this women are at moderate risk of breast cancer?? I think that the important is to remark that we need future cohort studies with a larger sample and that also consider other risk factors for breast cancer.
Response: Sorry for no correct description. We have deleted the sentence and revised the manuscript according to your suggestions. (Line 9-10, Page 16)

3- In discussion: In the second paragraph: is it not correct when the authors said: for women with family history of above cancer, risk-reductions options, including increased screening, chemoprevention and even prophylactic surgery, should be considered. I suggest to modify this sentence, because at this moment the prophylactic surgery only has to be considered and offered after genetic risk assessment to women who are carriers of a genetic mutation of a breast cancer gene of a high penetrance.
Response: We are appreciated for your valuable comments. We have deleted this sentence (Page 13) and revised the conclusion. Thanks.

4- In the discussion, I will recommend to include include and compare the results with those of the Turati et al case control- study (F Turati et al, Annals of Oncology, 00:1-6,2013), and those from contrast different results. I recommend include and compare the results with those of the case control study Turati, and also with the findings of the Swedish database (Hemminki K, Eur J Cancer 2012). In the study of Turati, they provide a case-control study a Picture of the associations between family history of cancer and cancer risk, and confirmed and quantified known associations with family history of cancer at discordant sites. Turati et al found a significant association between breast cancer and family history of colorectal cancer and of hemolymphopoeitic cancers, with a OR of 1.5 and 1.7, respectively.
Response: Thank you very much for your valuable comments. We have revised our manuscript according to your comments. (Page 12-13)

5- In the discussion: IN the fourth paragraph, before reference 31: When the authors said: The presence of BRCA1/2 mutations are associated with hormone receptor
negative breast cancer (31). It would be important to correct and to say: The presence of mutations in the BRCA1 gene are associated with hormone receptor negative breast cancer, because BRCA2 has a higher prevalence of breast cancer with hormone receptors positives.

Response: Thank you very much for pointing this out. We have corrected it in the manuscript. (Line 4-6, Page 14)

- Minor Essential Revisions
6-Before and after reference 26-28, and also other times in the article: there is the same expression that the authors repeated some times: “AND SON ON”, that I would recommend to the authors than they consider to vary for another expression.
Response: We have revised this manuscript according to your comments. (Line 3 and 5, Page 13)

- Discretionary Revisions
7-In the Brackground, after Ref 8: I would recommend changing the phrase: “the incidence, clinical and mortality of breast cancer are different in different populations and countries”, because it does not fit the context of the paragraph. And assess and replace this with a sentence that includes the following concept: “The magnitude of the association with family history varies between studies, cancer sites, countries, and State of sex and age, being generally stronger for younger probands.
Response: Thanks for your suggestion. We have replaced that with a new sentence according to your comment. (Line 15-17, Page 5)

8- at the end of the discussion when referring to the point: “third, due to the nature of the design of this study, our findings should be confirmed by future cohort studies. In this point, is very important to consider adding: ” cohort studies that also considering other risk factors for breast cancer in patients
Response: Done. (Last line but two, Page 15)

9-Please consider that in any point of the discussion to consider to explain the concept that family history reflects the consequences of genetic susceptibilities, Shared environment, and common behaviors. Most of the increased risk found for family history are supported by existing evidence pointing to genetic aspects of cancer. Although most of the cancer susceptibility genes confer a high risk of developing the disease and are highly penetrant, they are to rare so they not account for a large proportion of common cancers, and probably They would be explained by predisposing genes of lower penetrance, as is the case of common polymorphisms in genes involved in the production of sex hormones or their analogues or genes involved in the metabolism of exogenous or endogenous mutagens.

10- In the limitations consider that the number of incident cases from some neoplasms is relatively small, and this limits the precision of the risks estimates, especially for subgroup analyses. Some associations may be chance findings or others based on a
limited number of exposed cases and controls and need independent confirmation.
Response: We have added this limitation in the manuscript. (Last three lines Page 15, and line 1-2, Page 16)

Reviewer: Catherine Schairer
Reviewer's report:
Review of “Risk of breast cancer and family history of other cancers in first-degree relatives in Chinese women: a case control study.”
1. Is the question posed by the authors well-defined? – Yes, but the study does not appear to be optimally designed to answer the question – no information on age at cancer diagnosis among first degree relatives, no information on number of siblings and number of children.
Response: Thank you very much for your comments and work on our manuscript. We have revised our manuscript according to reviewer’s suggestions point by point. The changes in our revised manuscript were marked in blue. We have added the limitations in our manuscript according to your comments. (Line 13, 15, and 16, Page 15)

Major Compulsory Revisions (#s 2-6)
2. Are the methods appropriate and well-described? The methods are not well-described. Therefore, it is not possible to ascertain whether they are adequate. The reader should not have to reference another article (ref 25) in order to understand this article. Very basic information typically required in reporting of such studies is missing. More specifically,
   a) the types of benign breast disease in the control group are not adequately described – e.g., the number of each type, whether the types are related to increased breast cancer risk; b) the response rate for cases and controls is not described; c) it is not clear whether the information on family history and the risk factors was obtained from medical record review or in person interviews; d) it is not clear how complete the data on family history and risk factors are – was there any missing data?; e) was hormone receptor status missing for any of the cancers (it typically is)?; f) how many cancers were hormone receptor positive and hormone receptor negative?; g) how was positive hormone receptor status determined at the study hospital? h) how were the covariates defined and adjusted for (e.g. childbearing – is this ever/never gave birth to a live born child?)? i) why was age used rather than menopausal status to define subgroups – missing data on menopause status?; j) table 3 would benefit from number of cases/controls with family history of each type of cancer; k) family history of breast cancer should also be addressed – can help clarify the usefulness of the control group; l) statistical methods are not rigorously described.
Response: Thank you very much for so many valuable comments on our manuscript. We have revised our manuscript according to your comments point to point. Your comments made our results more reasonable and reliable. Thanks again.
a) the types of benign breast disease in the control group are not adequately described—e.g., the number of each type, whether the types are related to increased breast cancer risk;
   We have added the detailed information about benign controls in the manuscript. (Line 2-6, Page 7)
b) the response rate for cases and controls is not described
   The clinical data and risk factors were extracted from medical record review. Not all data were complete in this study, and we have added the information in the manuscript. (Lines 14, 16-20, Page 7)
c) it is not clear whether the information on family history and the risk factors was obtained from medical record review or in person interviews;
   Sorry for not describing it clearly. The information on family history and the risk factors was obtained from medical record review. We have added it in the manuscript. (Line 14, Page 7)
d) it is not clear how complete the data on family history and risk factors are—was there any missing data?
   We have added the information in Lines 16-20 Page 7.
e) was hormone receptor status missing for any of the cancers (it typically is)?
   Hormone receptor status was missing in 95 cases. We have added the detailed information about hormone receptor status in the manuscript in Lines 4-6 Page 8.
f) how many cancers were hormone receptor positive and hormone receptor negative?
   We have added the detailed information about hormone receptor status in the manuscript in Lines 4-6 Page 8.
g) how was positive hormone receptor status determined at the study hospital?
   We have added the definition of positive hormone receptor status in Lines 1-2 Page 8.
h) how were the covariates defined and adjusted for (e.g. childbearing—is this ever/never gave birth to a live born child)?
   We are appreciated for your valuable comments. Sorry for not describing it clearly. We have added the detailed subgroups of each covariate (Lines 17-19, Page 8).
i) why was age used rather than menopausal status to define subgroups—missing data on menopause status?
   In our country, about 40% of breast cancer patients are younger than 50 years old. Therefore, it is important to determine the relationship between family history of other cancers and breast cancer risk among women younger than 50 years old. Moreover, menopausal status was not available in 105 cases and 41 controls, while age was available in all cases and controls. Moreover, most women become postmenopausal around 50 years old. Subgroup analyses, defined with age, were more reliable, and more information could be given.
j) table 3 would benefit from number of cases/controls with family history of each type of cancer;
   The number of cases/controls with family history of each type of cancer has been added in table 3.
k) family history of breast cancer should also be addressed—can help clarify the usefulness of the control group;
Family history of breast cancer has been added in this study. (Table 2 and 3)

1) statistical methods are not rigorously described.

Sorry for not rigorously describing the statistical methods. We have revised the methods section according to your comments. (Last six lines Page 8)

3. Are the data sound? Not sure given the above deficiencies in the description of the methods. Number of children/siblings was not adjusted for. The results are at odds with the Negri study – could be due to chance, and definitely need replication.
Response: Thank you very much for your comments. In our study, number of children (childbearing) was adjusted for the multivariate analyses. As you said, number of siblings was not adjusted in this study, and we have added this limitation in the manuscript. (Line 13, Page 15)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? No, as described in point 2 above.
Response: We have revised our manuscript according to your comments (point 2).

5. Are the discussion and conclusions well balanced and adequately supported by the data? The statement in the discussion that based on these data women with a family history of the above cancers should consider prophylactic surgery is inappropriate. The statement that “our findings..suggest that healthy lifestyles..should be kept in our country” seems irrelevant to the topic. More thoughtful discussion of the disparity of the results with the Negri study would be helpful in the discussion.
Response: Thanks. We have revised inappropriate descriptions, and have added discussion of the disparity of the results with the Negri study. (Lines 12-14, Page 12; Lines 5-8, 12-17, Page 13)

6. Are limitations of the work clearly stated? Some weaknesses are not cited, such as issues with accurate cancer reporting in even first degree relatives (e.g. Mai PL article, JNCI 2011) no adjustment for number of first degree relatives. The authors don’t adequately address points made in 2 above.
Response: We have added this limitation in the discussion. Number of first degree relatives was not adjusted in this study due to small number of cases ≥ 2 first degree relatives. (Lines 15-16, Page 15)

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.
8. Do the title and abstract accurately convey what has been found? Yes.

Minor Essential Revisions (#9)
9. Is the writing acceptable? The article needs editing for English proficiency. There are also too many instances of “and so on” and awkward phrases (e.g. old women and young women). The language is not scientifically rigorous.
Response: According to your comments, we have revised our manuscript.