Author’s response to reviews

Title: Risk Prediction for Breast Cancer in Han Chinese Women Based on a Cause-Specific Hazard Model

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Author’s response to reviews:

Dear Editor,

We sincerely appreciate your effort in reviewing our manuscript. We have viewed the reports via the online peer review system and modified our manuscript according to reviewer’s suggestions. For English language improvements, we asked native speaker to help revising the manuscript. We are glad to further revise the manuscript if language corrections are still needed. The point-by-point responses to reviewer’s comments are as follows.
Technical Comments:

1. We have noted that the corresponding author identified on the title page is different to the author on file in the editorial manager system. Please ensure that the corresponding author provided on the title page matches in the manuscript file and in the editorial manager system.

Response: Thanks for the attention. The corresponding author of this paper goes to Fuzhong Xue, E-mail: xuefzh@sdu.edu.cn Tel: +86 0531 8838 0280 Fax: +86 0531 8838 0280 and Zhigang Yu, E-mail: yzg@medmail.com.cn Tel: +86 138 6418 2636 Fax: +86 0531 8896 0949.

2. Please represent authors' names using their full initials, not their full name, in the Authors’ Contributions section.

Response: Thanks for the reminder. We corrected authors’ names in the contributions section. See “ZY and FX conceptualized the study, LW and LL analyzed the data and wrote the draft of the manuscript. ZL, LD, HG, FW, LY, YX and FZ substantially contributed to the line of argumentation and revision of the manuscript. All authors read and approved the final manuscript” in page 18 line 10-12.

3. Please remove the funding information from the Acknowledgements and include it in the Funding section instead. If you have no further acknowledgements please put “Not Applicable” in the Acknowledgements section.

Response: Thanks for the attention. We have removed the funding information to the Funding section. The corresponding content was modified as

“Funding

This research was primarily granted funding from the Science and technology plan projects of Jiangsu province (No:BL2014055) and the project of National Natural Science Foundation of China (No:81602912)” in page 19 line 2-4.

4. We encourage authors to upload clean copies of the questionnaire used as part of the study design. Please upload an English language version of the questionnaire used in your study as a supplementary file.

Response: Thanks for the comments. We have uploaded an English language version of the questionnaire used in this study as a supplementary file. See supplementary material 4.
Reviewer reports:

Reviewer #1: The authors have developed a risk prediction model to define high-risk population of breast cancer among Han Chinese women. However, the following revisions should be considered to improve their work.

1. In the part of "Study population" at page 5, the authors should give detailed information on the sources of breast cancer patients in the Shandong Case-Control Study, for example, from one hospital, several hospitals, or from local cancer registries. Additionally, the authors should also address whether these cases are only newly diagnosed breast cancers patients, or included patients diagnosed as the second cancer after primary cancer.

Response: Thanks for pointing this out. In Shandong Case-Control Study, all breast cancer patients were collected from the department of breast surgery, Second Hospital of Shandong University. These cases are newly diagnosed breast cancer patients. Following your instructions, we added “Breast cancer patients were from the department of breast surgery, Second Hospital of Shandong University. All cases are newly diagnosed breast cancer patients.” in page 5 line 12-14.

2. In the part of "Study population" at page 5, the authors should also give detailed information on Taixing Prospective Cohort Study. First, as described in the paper, 18831 participants completed questionnaire, and 18564 participants who have not been diagnosed as breast cancer at baseline were selected in the study. Namely, 267 (18831-18564) participants had been diagnosed as breast cancer at baseline, which led to a prevalence of breast cancer as 1.4%. This prevalence of breast cancer in China is so high. How were these baseline breast cancer patients found? Self-reported, or screening by several modalities? Second, 23 participants were excluded due to missing information of risk factors. However, the authors did not give a clear list of these risk factors. Third, 5365 subjects from 18541 eligible subjects were further excluded due to lost to follow-up. The author should clearly mark the rate of lost to follow-up as 28.9%, since the rate of lost to follow-up is also so high in a 7-year cohort. Fourth, after excluding baseline breast cancer patients, how were the newly incidence cancers were identified during the follow-up, from local cancer registries, or from active follow-up with telephone, face-to-face interview, or reviews from case report forms in hospitals.

Response: Thanks for your insightful comments. We rechecked our data and found several mistakes in our original manuscript.

First, the total number of participants with completed questionnaire should be 18681, for 150 individuals were deleted due to duplicated id number. In addition, there are 116 rather than 23 participants excluded for missing risk factor values. There were 24 breast cancer cases at
baseline and led to a prevalence of breast cancer as 128/100,000. This included self-reported breast cancer patients and newly diagnosed cases. In this study, newly diagnosed breast cancer cases were diagnosed by ultrasound/mammogram/biopsies test. The following part was revised “In Taixing Prospective Cohort Study, 18681 participants who completed questionnaire in 2008 were involved as baseline population and outcomes were collected after 7 years follow-up. Participants who have not been diagnosed as breast cancer at baseline were selected in the study (n=18657), while of which with missing risk factors were excluded (n=116)” in page 5 line 18-21.

Second, the list of risk factors were the 6 risk factors we used to develop our HCBCP model. They were number of abortions, age at first live birth, benign breast disease history, BMI, breast cancer family history and life satisfaction scores. Individuals with any one of these missing risk factors were excluded. The complete questionnaire was provided as a supplementary file for interest. Third, as you mentioned, the rate of lost to follow-up if high. This was due to the adjustment of administrative jurisdiction, one township was excluded from Taixing City when follow-up information was collected. Thus, the follow-up information of this town was unavailable for us. This result in a total number of 2090 of participants lost to follow-up. We had added the lost to follow-up rate in this section as “Among 18541 eligible subjects, 5365 subjects were lost to follow-up. The rate of lost to follow-up was 28.9% (Due to the adjustment of administrative jurisdiction, one township was excluded from Taixing City when collecting follow-up information)” in page 5 line 21-23.

Fourth, the newly incidence cancers were identified from local cancer registries, from active follow-up with telephone and face-to-face interview. We have added this information and rewritten this part as “Newly incidence breast cancers were identified from local cancer registries, from active follow-up with telephone and face-to-face interview.” in page 6 line 1-2.

3. In the part of "Measurements and definition of risk factors" at page 6, the author mentioned only two reproductive factors (such as Number of abortions and age at first live birth) were collected in the standardized questionnaire, several other important reproductive factors, such as number of living births and months of breast feeding, were not collected. Moreover, several other risk factors, including age at menarche, age at postmenopause, oral contraceptive, and hormone replacement therapy, were also not collected in the questionnaire. The author should address these limitations in the end of discussion. Additionally, BMI should been given complete spelling when it first appeared at page 6. The author should also address how weight and height were collected, self-reported or measured. Lastly, how was life satisfaction scores scale developed or revised from previous similar scales, and the author should address why 13 were selected as the cut-off values of satisfaction or unsatisfaction.
Response: Thanks for pointing these out.

First, we are sorry for the ambiguous description in this part. The risk factors here refer to the significant factors in our study. Other reproductive factors were also collected in the questionnaire but did not pass the univariate analysis. Hence, we did not put these factors as risk predictors in our model and were not described in this section. A detailed questionnaire was attached as supplementary file. The following content was modified as “A self-designed structured questionnaire included demographic characteristics, female physiological and reproductive factors, medical and family history, dietary habits, lifestyle habits and breast-cancer-related knowledge gathered was used to obtain data [2]” in page 6 line 7-9.

Thank you for your reminder, we added the complete spelling of BMI (body mass index) at page 6. See “Body mass index (BMI) was calculated as weight in kilograms divided by square height in square meter and divided into three levels <24, 24 -27.9, ≥28 corresponded to normal, overweight and obesity” in page 6 line 9-10.

Second, the weight and height were measured values. The height was measured by meter ruler, the weight was measured by weight scale. The height measurement used a height of 2.0 meters and a precision of 0.1cm. The weight was measured using an electronic weight of 150 kg and an accuracy of 0.1kg. We added this information in page 6 line 11-14.

Third, the life satisfaction scores was revised from the World Health Organisation Quality of Life assessment (the WHOQOL) scale. 13 was the population mean of this study and was regarded as the cut-off values of satisfaction or not. The corresponding part was revised as “A total point of 30 was divided into two levels by the mean value 13, people with score lower than 13 were defined as satisfied and others with score equal to or higher than 13 defined as unsatisfied” in page 6 line 15-17.

4. RRs and AR should been given complete spelling when it first appeared at page 6.

Response: Thanks for pointing these out. We have provided the complete spelling for RR (relative risks) and AR (attributable risk) at page 7. See “which included (1) estimating relative risks (RRs) and attributable risk (AR) in the Shandong Case-Control Study” in page 7 line 1.

5. In the part of "Statistical methods" at page 6, 13 age groups were defined. However, the incidence rates of breast cancer for Chinese females aged either younger than 30 years old or elder than 85 years are very low. Therefore, age-specific risk predictions among Chinese females aged either younger than 30 years old or elder than 85 years seem useless.
Response: Thanks for your insightful comments. In this study, age groups were defined based on the population age-specific breast cancer incidence rates and non-breast cancer mortality rates of Taixing province. Following your instruction, we redefined the age groups and excluded group under 25 or elder than 85 years old. We keep the age group with age from 25 to 29 because we want to project their absolute risk for 10 or longer years. Age groups were redefined as “12 age group were defined ranges 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84” in page 7 line 11-12. In table 3 initial age was modified from 20 to 25 years old correspondingly.

6. In the part of "Statistical methods" at page 7, the authors should address which packages of R software were used in their studies.

Response: Thanks for your attention. In this study, the HCBCP model was implemented by self-developed R code, and the corresponding code was also provided as supplementary material. See supplementary material 3.

7. At page 8, the author should list the P values for the comparisons between cancers and non-cancers in table 1.

Response: Thanks for your reminder. Following your instructions, we have revised Table 1. P values were added for the comparisons between cases and controls. Due to the small number of incident cases in Taixing prospective cohort study, there were cells equal to 0 and leads to biased P values. For benign breast disease history, P value was 1 because there was no case had positive benign breast disease history.

Reviewer #2: This paper outlines a new risk model for breast cancer developed on a Han Chinese population. There are few if any breast cancer models developed to show applicability to Chinese populations and the need is certainly there. There are several issues that I have identified, however, that need to be addressed by the authors before being suitable for publication.

Background

1. "...the mammographic screening participation rate is only 21.7% in China...". Does this apply for all ages? In what time-period?
Thanks for your insightful comments. In this reference, data collected from the 2010 China Chronic Disease and Risk Factor Surveillance System that included 53,513 women aged 18 years or older showed an overall of 21.7% of respondents reported previous breast cancer screening. The participation rates were highest among women aged 30 to 39 years (30.7%; 95% CI, 26.9%–34.4%) and lowest among women 70 years or older (6.3%; 95% CI, 5.1%–7.6%). Compared with women living in the western region, women in the eastern region were 1.5 times more likely to be screened (adjusted odds ratio [OR], 1.5; 95% CI, 1.2–2.0). Compared with women without insurance, women with urban insurance were more likely to be screened (prevalence ratio = 2.6; 95% CI, 2.3–3.0) and be screened within the last 2 years (OR = 1.3; 95% CI, 1.0–1.7; P = .04). [Wang B, He M, Wang L, Engelgau MM, Zhao W, Wang L. Breast cancer screening among adult women in China, 2010. Prev Chronic Dis. 2013;10:E183.]

2. Discussion about the Gail model "...showed poor effect when directly applied in Han Chinese women." Can the authors cite reference(s) to back this claim?

Response: Thanks for your attention. Gail model is well calibrated among Caucasian women who received annual screening [1-3]. However, due to the wide variation in international breast cancer, Gail model may not always perform well [4-7]. Kaur et al concluded that Gail model only applied to their subpopulation of women who had received screening mammograms and is not readily applicable to all American-Indian and Alaska-Native women [5]. Similar conclusions were found for women from the Czech Republic [6] and Italy [7]. The recalibrated Gail model performed good calibration in the study of Singapore Breast Cancer Study, but the discriminative power was limited with the AUC of about 0.60 [8].

The original sentence was not precise and we have modified this sentence to “However, the model is first developed in Caucasian ethnic population and the effect maybe uncertain when directly applied in Han Chinese women” in page 4 line 15-17.

Reference:


3. Also with the Gail model "...the use of number of previous breast biopsies as a predictor also make it difficult for application." I don't agree with this statement as this does not disqualify its ability to be used as it is can simply be marked "unknown".

Response: Thanks for your suggestions. We have changed this sentence to “Besides, since the biopsies tests are not widely used in China (especially in rural areas), the information of number of previous breast biopsies is not easily available to the majority of Chinese women” in page 4 line 17-19.

4. The IBIS model has not (yet) incorporated genetic variants explicitly, though some of the effects will likely be captured in the unknown dominant gene component.

Response: Thanks for your suggestions. We have changed the sentence to “Although some other prediction models are genetic risk prediction models, e.g. IBIS model” in page 4 line 19-20. Because their model contains genetic part. Jonathan et al stated that the genetic part of the model is that there are two autosomal loci which contain genes predisposing to breast cancer. The first locus contains information about the BRCA genes and may either contain the normal allele, a BRCA1 allele or a BRCA2 allele. The second locus contains a hypothetical susceptibility gene

5. The sentence about adding 7 SNPs is very much out of date as there are now over 200 SNPs associated with breast cancer. Anyhow, a 0.02 gain can make substantial difference to discrimination.

Response: Thanks for your pointing this out. The reference we cited compared prediction models with and without SNPs as predictors, and they considered 7 highest correlated. Since there are over 200 SNPs associated with breast cancer, we think the difference between models with and without genetic variants would have much more difference. In addition, a 0.02 gain would help a lot to improve the discriminative ability. We think our model is aimed to provide a more applicable predictive tool for breast cancer risk since the cost of testing all these variants maybe large. Following your instruction, we have modified the corresponding part as “the increased cost may lead to a limited application considering the large risk population in China” in page 4 line 20-21.

6. In discussing ref 9, the mutation rates of BRCA1/2 genes are lower in Chinese populations, but the authors of that publication state they are still the most important genetic indicators of risk.

Response: Thanks for your attention. In ref 9, they do state that the most important genetic factors in hereditary breast cancer in Han Chinese population are BRCA1/2. However, due to the lower mutation rates in Han Chinese population, the overall genetic testing may cost larger than in other ethnic groups. We believe adding genetic effect in prediction model would improve the predictive ability, our model is focus on providing convenience model to apply on general breast cancer risk population in China. This was one of our study limitations that we do not incorporate gene effect in breast cancer prediction model. We also revised corresponding content as “In addition, as the most important genetic factors of breast cancer, BRCA genes’ mutation rates are lower in Chinese population than in western countries” in page 4 line 21-22.

Methods

7. In the case-control study, when were the breast cancer patients selected? Was it at diagnosis or sometime after? If it's sometime after, then there may be the possibility that some would have been missed due to dying before being recruited. Also, does the case group include in situ breast cancer cases?
Response: Thanks for your insightful comments. Basic questionnaire information was collected at baseline for all subjects, and cases were selected when diagnosed at hospital. The case group included in situ breast cancer cases.

8. What was the response rate for recruitment of cases and controls?

Response: Thanks for your attention. The response rate for case group was almost 100%, control group was 84.56%. Our previous paper has detailed information about data collection and quality control. [Yu ZG, Jia CX, Liu LY, Geng CZ, Tang JH, Zhang J, et al. The prevalence and correlates of breast cancer among women in Eastern China. PLoS One. 2012;7:e37784.]

9. 5365/18541 women were lost to follow-up is a large proportion, and it greatly affects the validity of the results. How many were known to have died? Those who are known to have died should not be excluded from the validation dataset. There should also be a comparison of baseline characteristics of those who were lost to follow-up with the rest of the cohort. Preferably, women lost to follow-up (but not known to have died) should be censored at last known date of contact.

Response: Thanks for your reminder. Due to the adjustment of administrative jurisdiction, one township was excluded from Taixing City when collecting follow-up information. This result in a total number of 2090 of individuals lost to follow-up. This was one of our study limitations that we were not able to collect the death information of people who lost to follow-up.

Following your instructions, we compared the baseline characteristics of those who were lost to follow-up with the rest of the cohort. Population lost to follow-up were younger (45.07±12.19) than the others (46.78±11.45, P-value <0.0001). There was no evidence for significant difference between age at first live birth, benign breast disease history, BMI, breast cancer family history and life satisfaction scores (P-value >0.05). However, number of abortions showed a P-value of 0.01.

Women lost to follow-up have been given a following time of 4 years and marked as censored.

10. The authors need to define "family history of breast cancer". Is it confined to first-degree relatives or does it include distant relatives?

Response: Thanks for your insightful comments. In the questionnaire, we collected family history of first-degree relatives, second-degree relatives and third-degree relatives separately. In our prediction model, we consider any one of these positive options as a positive family history of breast cancer.
“A positive breast cancer family history was defined as anyone breast cancer patient from their first-degree relatives, second-degree relatives and third-degree relatives” was added in page 6 line 17-19.

11. How was the cut point of 13 chosen for the life satisfaction score?
Response: Thanks for your attention. 13 was the mean of this study population and therefore was regarded as the cut point of life satisfaction score. We adjusted the following part as “A total point of 30 was divided into two levels by the mean value 13, people with score lower than 13 were defined as satisfied and others with score equal to or higher than 13 defined as unsatisfied” in page 6 line15-17.

12. Age range groups go from <20 years up to 85+ years, but they limited the case-control study to 25-70 years. Is it valid to apply the model to all ages when it was developed on a narrower range?
Response: Thanks for pointing this out. Considering the low incidence rate of people younger than 30 years old and elder than 85 years old in China, we changed the study age range from 25 to 84. The prediction accuracy for women over 70 years old might be affected due to the age limit of our case-control study. This was our limitation that we did not collect breast cancer cases over 70 years old. For our model incorporate baseline hazards (which were derived from age-specific breast cancer incident rate and non-breast cancer mortality in Taixing) and relative risks, case-control study was mainly used to estimate relative risks and the bias may be acceptable.

See “12 age group were defined ranges 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84” in page 7 line 11-12. In table 3 initial age was modified from 20 to 25 years old correspondingly.

Results

13. The number of incident cases in the Taixing study is small (n=34), which will give low precision to the validation estimates. Cell counts in certain combinations equal zero. This needs to be mentioned as a limitation of the study.
Response: Thanks for your suggestions. Following your instructions, we have revised the following part as “Thirdly, the incident cases in the Taixing study was small (n=34), therefore, the precision to the validation estimates maybe affected” in discussion page 17 line 20-21.
14. It would help if the authors could state explicitly in the results section that diabetes drops from the multivariable model (it is later mentioned in the discussion).

Response: Thanks for pointing this out. We changed the following part as “Diabetes was a risk factor in univariate logistic regression but did not show significance after multivariate-adjusted and was not included in the final risk model” in Results page 10 line3-5.

15. Likewise with the attributable risk, should state (maybe better in the methods) that it applies only to the Taixing province.

Response: Thanks for pointing this out. “The AR was estimated from Taixing cohort and applied only to Taixing city” was added in the method part, see Method page 7 line 6-7.

16. A 95% CI should be reported for the E/O ratio. Given the small number of incident cases, though, the CI will include 1.

Response: Thanks for pointing this out. The 95% CI of E/O ratio was 1.03 (0.74, 1.49), we have added the CI in the result part. As you mentioned, the 95% CI included 1 because the incident cases number was small. The following part is revised as “The E/O ratio and 95% CI was 1.03 (0.74, 1.49)” in page 14 line 5-6.

Discussion

17. I have several issues about the following statement: "Compared with other breast cancer prediction model, our model showed better E/O ratio and AUC". Firstly, it depends on the population one is assessing the model on. Secondly, as long as a E/O ratio from a model includes 1 and that there is reasonable precision around the estimate (which based on 34 incident cases this study does not really have), then one cannot truly say one model is "better" than the other, except perhaps for certain subgroups within the population. Thirdly, comparing AUCs between different studies is fraught with numerous hazards. The underlying structure of the validation population (such as age, stronger family history, etc) can have a huge impact on the AUCs. Basically, comparing model AUCs can only really be done within the same study population.

Response: Thanks for your insightful comments. Following your instruction, we compared the results of the Gail model using our Taixing prospective cohort study population. Predictors of the number of biopsies and biopsy atypical hyperplasia were marked as unknown. The E/O ratios and 95% CI was 2.39 (1.71,3.46). AUC was 0.54 (95% CI: 0.44-0.63). Although the race group was defined as Chinese-American, the incidence rate may still higher than in Taixing province.
The results showed that the Gail model tends to overestimate the absolute risks in Taixing cohort population. Considering the lack of risk predictors, the prediction accuracy may be biased. Above analysis was performed using R package “BCRA”.

In discussion part, we modified the following content as “In western countries, Gail’s model was widely used in clinic decision-making [38]. However, the application of Gail’s model in China was limited because biopsy tests were not popularized. Besides, several validation studies were conducted in Asian population and found the performance was not well [39]. We compared Gail model in Taixing prospective cohort study. Due to the lack of information of the number of biopsies and biopsy atypical hyperplasia, those predictors were marked as unknown. The E/O ratios and 95% CI was 2.39 (1.71, 3.46). AUC was 0.54 (95% CI: 0.44-0.63). Although the race group was defined as Chinese-American, the incidence rate may still higher than in Taixing. The results showed that the Gail model tends to overestimate the absolute risks in Taixing cohort population. Considering the lack of risk predictors and lower incidence rate in Taixing, the prediction accuracy may be biased.” in page 16 line 18-23 to page 17 line 1-3.

18. Further to the previous point, it would be better to compare the results of the Gail model (probably should use Asian American reference rates) using the same validation cohort. Just because biopsy tests were not collected doesn't preclude one from using the model. Sure, the AUC might not be as good, and this can be mentioned as a limitation. Could also compare with Yuan et al model as well, but again, not all variables might not be available. The point I'm making is unless they can show there is a clear improvement over the existing models, then what benefit is there in developing yet another model?

Response: Thanks for your insightful comments. For Yuan et al model (HRA model), their certification was performed in the database obtained from merely the first round of screening of a breast cancer project without any further follow-up. Therefore, it may not be an appropriate way to test the reliability of the model in predicting the 5-year risk of breast cancer. Following your instruction, we also performed the HRA model in Taixing cohort study, the E/O ratio was 1.88 (95%CI: 1.33-2.75) and the AUC was 0.52 (95%CI: 0.43-0.61). Without taking competing risks into the prediction model, the HRA model seems to overestimate the probability of developing breast cancer in Taixing cohort study.

The following part was rewritten as “Although their model’s AUC was 0.64 (95 % CI: 0.50–0.78), their certification was performed in the database obtained from merely the first round of screening of a breast cancer project without any further follow-up. Therefore, it may not be an appropriate way to test the reliability of the model[37]. We also performed the HRA model in Taixing cohort study, the E/O ratio was 1.88 (95%CI: 1.33-2.75) and the AUC was 0.52 (95%CI: 0.43-0.61). Without taking competing risks into the prediction model, the HRA model seems to
overestimate the probability of developing breast cancer in Taixing cohort study. In our validation cohort, E/O ratio was near 1 and showed good projection”. See page 17 line 4-11.

19. Notwithstanding the difficulties of comparing AUCs, stating that their "model showed narrower confidence interval" is totally meaningless.

Response: Thanks for your suggestions. Following your instruction, the sentence was deleted in the manuscript.

20. The sentence comparing E/O ratios of your model with the Gail model is also totally meaningless. The authors only need to be concerned about whether their model calibrates with the external population they're testing the model on.

Response: Thanks for pointing this out. Following your instruction, we modified the discussion part as “The E/O ratio was 1.03, which was very close to 1. AUC was 0.64 showed HCBCP model performed well in validation study” in page 17 line 13-14.

Sincerely yours,

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