Author's response to reviews

Title: Tamoxifen Use Reduces the Risk of Osteoporotic Fractures in Women with Breast Cancer in Asia: A Nationwide Population-based Cohort Study

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Author's response to reviews: see over
Reviewer's report Title: Tamoxifen Use reduces Osteoporotic Fracture Risk in Asia Breast cancer woman: A nationwide population-based cohort study

Reviewer: Lisa Lix

Major Compulsory Revisions:

1. The authors report that they recruited subjects between 2000 and 2011. It is unclear how the duration of follow-up times might have differed for the Tamoxifen and non-Tamoxifen user groups. The authors must provide information on the mean and median follow-up times. Also, given that the recruitment period extended to 2011, and the follow-up time ended in 2011, it seems possible that some individuals had no observation time for fracture. Please provide additional detail to address this point.

Reply: Thank you for this and all of your comments and suggestions. Both the Tamoxifen and non-Tamoxifen user groups were followed from 2000 to 2011. The mean and median follow-up times of observing fracture cases were 5.32 and 4.82 years, respectively, for the Tamoxifen users, and 4.44 and 3.64 years, respectively, for the non-Tamoxifen users. The longer follow-up time showed a better outcome for the users. Further investigations of the mechanism responsible for this are certainly worthwhile, and we may perform further related studies.

Yes, some individuals recruited in 2010 had a short observation time for fractures. We have further analyzed the data and found that the shortest observation time was within 1 month in both the Tamoxifen users and non-users. We observed 16 and 15 cases of fractures in the Tamoxifen and non-Tamoxifen groups, respectively, in 2010.

2. It is not clear how the exposure (i.e., Tamoxifen use) was measured as a time-dependent covariate, and at what intervals these measurements were taken. Also, the authors should provide the list of the Anatomical Therapeutic Chemical (ATC) codes used to indicate Tamoxifen use. Please provide clear information in the Methods section about the unit of measurement for Tamoxifen use.
Reply: We have added sentences to explain the detailed exposure of Tamoxifen in the Methods as follows (Please see p.6, line 13-18)

The exposure was defined the breast cancer women received Tamoxifen during the study period. According to the World Health Organization defined the assumed average maintenance dose per day for a drug used for its main indication in adults, defined daily doses (DDD) is a statistical measure of drug consumption. (WHO Collaborating Centre for Drug Statics Methodology. Available from: http://wwwhoccno/atcddd/2010). The accumulated Tamoxifen DDDs during the study period was calculated for each user.

3. Using administrative health data to identify individuals with breast cancer requires the use of a validated algorithm for case ascertainment. Please provide information about the sensitivity and specificity of the algorithm. High specificity is required to decrease the chances of misclassification of cases. As well, six comorbidities were included in this analysis as confounding covariates. Please provide a justification for their inclusion and address the potential for misclassification bias in the diagnoses used to ascertain these comorbidities. It is unlikely that the diagnoses will have equivalent sensitivity and specificity for case ascertainment.

Finally, the manuscript lacks important details about the sensitivity and specificity of the diagnosis codes for osteoporosis-related fracture. As well, if they authors are interested in capturing major osteoporosis-related fractures, they should have included diagnosis codes for fractures of the humerus.

Reply: There are many papers on osteoporotic fractures according to previous Taiwan
nationwide population-based studies. [1-21] These literatures most choose hip, wrist and spine fractures as an indicator of osteoporotic fractures in Taiwan. Therefore, we feel that coding of hip, wrist and spine fractures is well qualified to represent osteoporosis-related fractures in Taiwan.

Ref.


9. Lin TC, Yang CY, Yang YH, Lin SJ: Comparative effectiveness of osteoporosis


population-based cohort study. Medicine (Baltimore) 2014, 93(26):e188.


4. Why did the authors not use a propensity-score model to adjust for confounding? Also, potentially important variables such as cancer stage, socioeconomic status, and rural/urban residence, which could all affect fracture occurrence and Tamoxifen exposure, are absent from the model. There is the potential for confounding bias in the hazard ratio estimates that were obtained.

Reply: We used a Cox proportional model with time-dependent covariates to estimate the association between fractures and Tamoxifen treatment in this study. All study subjects were followed from the date of breast cancer diagnosis until the date the fracture occurred, withdrew from the program, or the end of 2011. During the study period, each subject could switch between the exposure and non-exposure groups based on the Tamoxifen treatment in each follow-up year. Therefore, we could not use propensity-score matching to adjust for confounders.

According to your suggestion, we have added the adjustment for urbanization level and monthly income level in the model. Please see the new tables and manuscript. Because the LHID-CIP does not contain information of cancer stage, we have added this as a limitation.

5. The authors make the following statement in the Discussion section: “Our study
doesn’t compare the effect of other aromatase inhibitors with Tamoxifen. The current results revealed the protection effect was not related to the duration or dosage. It may then be due to the steady usage of Tamoxifen once a patient has prescribed this agent in Taiwan.” This statement is difficult to interpret without the authors providing clear explanations of how dosage and duration of Tamoxifen use were measured.

6. The Results section is missing important information about model fit.
Reply: Because each subject could switch between the exposure and non-exposure groups based on the Tamoxifen treatment during the study period, we thought this violated the Cox proportional hazard regression assumption. Therefore, we considered Tamoxifen treatment to be a time-dependent covariate, and the risk of fracture was assessed using Cox proportional hazard regression with time-dependent covariates.

Minor Essential Revisions:
1. The authors mentioned testing for gender differences in the Methods section (page 6). This seems to be an error, as the study was supposed to be conducted amongst women only.
Reply: Thank you for pointing this out. We have deleted the “gender” in this sentence.

2. Table 1: Please include column headings to distinguish frequencies and percentages. Also, provide a definition of the acronym PAD in the table note. Using both the chi-square test and Student’s t-test for age is redundant. It is preferable to treat age as either a continuous or categorical variable, but not both types of variables. Finally, given that the p-values were all less than 0.0001, it would be more efficient to report in the table note that all differences between exposure groups were statistically significant at alpha = .05.
Reply: We have inserted a column to present the distribution frequency and percentage in Table 1. We have also deleted the continuous age variable and the Student’s t-test. All variables in Table 1 were analyzed using the chi-square test.

3. Table 2: Please provide a note to define the acronym DDD. Also, include “HR” in bracket after “Hazard risk” in the table title as is done for the 95% confidence intervals. There is redundancy in reporting both 95% CIs and p-values in the same table to indicate statistical significance. The latter should be excluded.

4. Table 3: Please provide a note to define the acronym PAD. Similarly, include “HR” in brackets after “Hazard risk” in the table title as is done for the 95% confidence intervals. Again, there is redundancy in reporting statistical significance with 95% CIs and p-values.

5. Table 4: Please include column headings in the table to indicate hazard risk and 95% CIs. Again, there is redundancy in the reporting of statistical significance with 95% CIs and p-values.

6. Table 5: Same comments as for Table 4.

Reply: We have modified Table 2, 3, 4 and 5 according to your comments.
Reviewer: Andrew Cooke

Reviewer's report:

This article is of interest and I would recommend publication. The authors are to be commended for including comorbidities incl osteoporosis in model.

1. Minor: English grammar etc needs some minor edits

Reply: Thank you for this and all of your comments and suggestions. The manuscript has now been edited for language.

Discretionary revisions:

2. Methods: ER is not discussed. Is it not available from macro data? If not available then that limitation should be stated in methods. The absence of stage is mentioned in the discussion, but a line in methods would be helpful up front so that the limitation of macro data granularity is evident immediately.

Reply: Thanks for your suggestion. According to the regulation of Taiwan NHI, Tamoxifen only can be used in cases with ER positive breast cancer. The insurance system will not only pay for case without positive ER but also fine the institutions that violate regulations. Therefore all these cases are ER positive breast cancer. As your comment, we also mention about absence of stage in the methods. (Please see p.6, line 6)
3. Methods: prior HRT use? Is this available from the drug registry? If tam dose is available wouldn’t HRT be available also?

Reply: We have added prior HRT (included estrogen and progestin) use in the new analyses, which was defined as that used before the index date, in the Results.

Compulsory

4. (Major) Methods: Tamoxifen dose and duration are shown in the results but there is no mention in the methods how tamoxifen dose and duration is determined. Please provide a description

Reply: The accumulated Tamoxifen DDD during the study period (from the index date to the date the fracture occurred, withdrawal from the program, or the end of 2011) was calculated for each user.

5. (minor) Abstract: The age distribution of patients is required in the abstract to show this paper concerns both pre and postmenopausal subjects

Reply: Because the LHID-CIP does not contain information on menopause, we could not present the data. We have added this as a limitation.

6. (minor) If tam dose and duration can be determined, then cannot AI dose and
duration also be determined? Some further discussion of AI dose and its potential confounding should be added.

Reply: We have included AI treatment as a time-dependent covariate in the new analyses. In this study, we focused on the association between fractures and Tamoxifen. After including AI treatment in the new analyses, the results were similar to the original results. According to your suggestion about the association between fractures and AI, we will investigate this in future studies.

7. (minor) Please mention if cross over [tam to AI] at 2-3 years may have occurred and how it might affect results.

Reply: We will investigate the relationship between fractures and AI in future studies. However, we have added AI treatment as a time-dependent covariate in the new analyses.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.