Author’s response to reviews

Title: Prognostic effect of preoperative Serum estradiol level in postmenopausal breast cancer

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Author’s response to reviews: see over
Dear Ms. Cherry Battad

Thank you very much for your e-mail of Aug 16, 2013. We are pleased to hear that our manuscript “Prognostic effect of preoperative serum estradiol level in postmenopausal breast cancer” will be accepted for publication if appropriately revised. We are resubmitting the revised manuscript, on which we indicated where we made changes in response to the suggestions of you and two reviewers.

I guarantee that this or similar material has not been and will not be submitted by me or my colleagues to any other publication prior to its appearance in the BMC Cancer, and that all of my co-authors have made a substantive and specific intellectual contribution to the article.

We wish to thank you and the reviewers for the valuable comments and helpful suggestions which contributed significantly to the revision of our manuscript.

With regards,
Wonshik Han

Reviewer: Barbara J Fuhrman
Compulsory edits:
1. Please provide the number of outcomes in the abstract. This is important context for the finding. You could write, for example: “After a median follow-up of 52 months (IQR: X to XX months), 21 women were found to have metastatic disease.”
   Response: We made the revision accordingly. We add that sentence in Methods.
2. Also in abstract, please remove “After a median follow-up of 52 months” from the Results section—this information is more appropriate in the methods section and placed where it is, it seems to suggest that estrogen levels were measured after, rather than prior to, clinical recognition of metastatic disease.
   Response: We removed it from Results section.
1. Table 1: Please include column percentages for all variables including histologic grade, etc.
2. Also please show how unknowns are distributed (which are ER+, which are ER-?).
   Response: About 1 and 2, We made the revision accordingly in Table 1.
3. Please define “Switch” under Adjuvant hormonal therapy.
   Response: We added the definition of Switch under the table.
4. Table 3: Please add a footnote to your last table explaining how variables were selected for inclusion in multivariate models.
   Response: In response to this comment, we added “A multivariate analysis was set by using all of the predictors with p values under 0.05 in univariate analysis.” under the table 3.

Minor but essential changes
5. (paragraph 2, 2nd sentence) Circulating estrogens are sometimes found to be associated with mammographic density, but just as often are NOT seen to be correlated with this variable or in fact are seen to have inverse correlations. You might want to remove mention of mammographic density or consider qualifying your statement.
   Response: We removed that sentence.
6. Your reasons for studying postmenopausal women and not premenopausal women may seem obvious to you, but it is not clear to me whether it is only because of greater variation and therefore more difficulty in measuring estrogen exposure in premenopausal women, or if it is, in part, because premenopausal women with breast cancer receive different therapies (for example, do they all get aromatase inhibitors/tamoxifen?) Please clarify this here and also in the discussion.
   Response: We added this comment in Background as “.. And postmenopausal women have been consistent in E2 levels without variation according to menstrual cycle..”. And we also added in Discussion (paragraph 5) as..” Therefore, to analysis the difference of prognosis according to serum E2 level in premenopausal women, constant measure of E2 in time is important..”
7. If the entry criteria for the trial(s) that led physicians to order the estrogen measure were substantially different from the entry criteria to the present study, please provide this as context. If not, please ignore this comment.
   Response: No, our study was retrospective study, so we didn’t have entry criteria.
8. Mention how you assessed whether assumptions of proportional hazards were met.
Response: At first, we didn’t perform LLS plot by using SAS program. However, we identified the p value of Goodness of fit in Cox model of SPSS.

9. It is not clear to me how you handled missing / unknown categories – were they included when you tested for differences in distribution in table 1, for example? What about in tables 2 and 3? What about when you adjusted for these variables as covariates in your Cox models? Please clarify this in the methods and/or in a footnote to each table.

Response: We excluded the missing or unknown data when we performed statistical analysis such as student’s t-test, Pearson’s correlation test or survival analysis. This sentence added in Method section.

Discretionary Revisions:

RESULTS

10. In the results, you might consider including a description of the findings that include locoregional recurrences and contralateral cancers – while they do not achieve statistical significance, they do provide context for the other findings.

Response: In response to this comment, we added the number of locoregional recurrences and contralateral cancer. Also in the end of result, we added the results of Disease-free survival according to ER status.

DISCUSSION

2. In the discussion (4th paragraph, starting “It is unclear why …” you might consider mentioning that there were fewer outcomes and thus limited power in the ER+ subgroup.

Response: Yes we added this comment to Discussion.

3. Discussion, paragraph 5, starting “premenopausal women experience changed in their serum estrogen levels throughout their menstrual cycles,” I think you mean “changes” and you should use a period after “cycles” and before “In contrast” to begin a new sentence.

Response: We made the revision accordingly.

4. Discussion, paragraph 6, starting “This study had several limitations.” I believe you should use the present tense when talking about your study here—the limitations apply to your study findings forever – not just at the time that you carried out the study.

Response: We made the revision accordingly.

Reviewer: Louk V Beex

Concrete remarks:
1. Abstract: fore-last sentence: add in the investigated …… Postmenopausal women…
Response: We made the revision accordingly.

2. Introduction: The referred study of James et al does not give information about ER levels and prognosis, but mainly discusses the relationship between hormone levels and development of breast cancer, which is a completely different subject.
Response: In response to this comment, we delete that sentence and reference.

3. Results: in the text 195 patients with HR positive disease are mentioned, in table 1 it is 190 patients. Furthermore, the percentage of women with HR positive disease and 1-3 nodes is not correct (table 1)
Response: We corrected the number and percentage of Table.
   In the text 195 patients with HR positive are ER positive or PR positive. 5 Patients are PR positive but ER negative.

4. Results: As already said, BMI is not included in the multivariate analysis for ER negative women, although there is overall a nearly significant correlation between BMI and ER levels.
Response: In response to this comment, we added the BMI in univariate analysis in ER negative group.
   However the p value was >0.05, so it excluded in multivariate analysis.

5. Discussion: To avoid clinical misinterpretation of the results, a more to the point discussion about the possible influence or lack of effect on prognosis of estrogen (lowering measures), as far as available, is welcome. The present discussion suggests more influence of estradiol levels on prognosis, than given in the mentioned literature. This paper deals with prognosis of established ER positive or negative breast cancer, not with the role of estrogens as etiologic factors for those diseases. From a clinical point of view, a possible role of higher estrogen levels in the prognosis of ER negative breast cancer is expectedly and obviously not counteracted by adjuvant tamoxifen therapy. But some data about the, for this paper important role of estrogen lowering treatments like aromatase inhibitors, also suggest that the effect for recurrence is neglectible.
Response: In response to this comment, we added the reference 24(Viale et al, BIG-1-98, J Clin Oncol 2007) and more comment as “… However it is unclear where the estrogen lowering treatments like aromatase inhibitors were effective in ER negative tumors. According to the study of Jones et. al which was central review of pathological specimens from patients entered in BIG 1-98 trials, aromatase inhibitors might have advantage in only patients whose tumor express ER. However, they didn’t measure the preoperative estradiol level, so it was impossible to compare the difference of effect according to estradiol level in patients with ER negative or positive tumor.”