Reviewer’s report

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

Version: 1 Date: 8 August 2013

Reviewer: Barbara J Fuhrman

Reviewer’s report:

I remain convinced that this manuscript describes interesting findings from a well-conducted study. Also the description of the methods and results have been greatly improved in response to the last round of comments. Tables still need some cleaning up (or is it a problem with my pdf reader?) and the manuscript would still benefit from some text editing for clarity. I recommend this article for publication pending a few additional changes:

Compulsory edits:

ABSTRACT

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.”

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.

TABLES

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-?).

3. Please define “Switch” under Adjuvant hormonal therapy.

4. Table 3: Please add a footnote to your last table explaining how variables were selected for inclusion in multivariate models.

Minor but essential changes:

INTRODUCTION

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.
6. (paragraph 4) You have added a sentence stating that premenopausal women have higher estrogen levels than their postmenopausal counterparts. This does not in itself address the question of why you have not included premenopausal women in your study – presumably if higher circulating estrogens impact risk, then this should also be true in premenopausal women. 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.

METHODS

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.

8. Mention how you assessed whether assumptions of proportional hazards were met.

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.

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.

DISCUSSION

1. When you mention the previous findings from the WHEL study in the discussion, it suggests an analysis that you do not present, in which ER+ and ER- subgroups are lumped together. You might run this analysis and mention it in your results section if you don’t want to provide another table. Or you could explain here why it is not appropriate to do so (differences in underlying hazards ... )

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.

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.
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.

**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.

**Declaration of competing interests:**

I declare that I have no competing interests in relation to this paper.