Reviewer's report

Title: Distinct distribution and prognostic significance of molecular subtypes of breast cancer in Chinese women: a population-based cohort study

Version: 1 Date: 22 March 2011

Reviewer: Gary Tse

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Major comments

1. It would be of interest to the readers to know the case selection from the SBCSS: now many institutions, any potential selection biases?

2. The impression given was that all cases had HER2 immunostaining, but only 200+ cases were done for ER and PR. Most of the results of ER and PR appeared to be obtained from the medical charts. Were the diagnostic criterion uniform among all the participating centers? More detailed information on ER and PR staining need to be provided for those patients with data obtained from medical charts in M&M. For those patients whose ER and PR status could not be obtained, double staining for PR/HER2 and ER#/ER# were conducted. Are different protocols used for these two groups? If yes, it is not clear how comparable are the data generated with the different protocols. The authors mentioned ER staining in the manuscript but they did not illustrate what is the role of this staining in the evaluation of breast cancer subtype.

3. The author used a 10% cut-off for ER positivity while a 1% cut-off for PR positivity. ER, PR staining is now generally accepted to use 1% cut off. It is not clear how these differences in cut-off affecting the prevalence of the different molecular subtypes.

4. In the materials and methods, the authors mentioned that ‘demographic characteristics, reproductive history, disease history, medication use, selected lifestyle factors, diet, use of complementary and alternative medicine, and quality of life.’ were evaluated. Please explain in greater details as to what exactly were evaluated? And also what anthropometric measurements were taken?

5. There was no mention of the results of the histologic (WHO) typings of the tumors in this study cohort. It would be of interest to the readers, and also to assess the relationship of the histologic and molecular typing results.

6. Although the author adopted the ASCO guideline, they used IHC staining 3+ only to identify HER2+ subtype. The HER2 borderline group which comprised of 8% of the total breast cancer could not be readily classified into a recognized subtype. A minor proportion of these cancers having HER2 amplification would belong to HER2+ group as suggested by the authors while those remaining could be either luminal A or triple negative subtypes. It was hard to properly interpret the present data with the unclassified HER2 borderline group and compare the results with the published data. The unclassified population could affect the
prevalence in particular the rare subtypes. What were the PR and ER status of the HER2 borderline cases?

7. The authors stated that ‘Women with triple negative breast cancer also more frequently reported a family history of breast cancer than did women with other subtypes. This suggests that genetic factors may play a more important role in this molecular subtype of breast cancer.’ This statement has to be discussed in light of the known association of triple negative cancers with BRCA1 mutations.

8. What were the significance levels of different subtypes in comparison to the reference group for cox regression analysis for the survival data?

9. In the discussion, the author suggested that triple negative, HER2+ and luminal B subtypes were associated with patients of younger age. Although it was in concordance with published data, the mean age at diagnosis from the present study were not very different. One possible reason was the presence of a small subgroup of patient either very young or old could skew the mean. How was the distribution of patients in different cancer subtypes stratified by age groups?

10. The distribution of molecular subtypes could be affected by environmental factors as well as ethnicity. More discussion on the comparison of breast cancer subtypes with other Asian populations and other Chinese populations could be of interest to the readers.

11. Some patients were subjected to immunotherapy. What kind of immunotherapy did they receive? Were there any differences in treatment with patients belonging to different subtypes? It would be interesting to briefly discuss the cancer prognosis of different subtypes in relation to the treatments.

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

'I declare that I have no competing interests'