Author's response to reviews

Title: Genotypic and phenotypic analysis of male breast cancer shows under representation of the HER2 and basal subtypes in BRCA-associated carcinomas.

Authors:

Siddhartha Deb (Siddhartha.Deb@petermac.org)
Nicholas Jene (Nicholas.Jene@petermac.org)
kConFab investigators . (heather.thorne@petermac.org)
Stephen B Fox (Stephen.Fox@petermac.org)

Version: 4 Date: 6 September 2012

Author's response to reviews: see over
Dear Editors.

Re: Manuscript revision.
MS: 9754374127390275
Title: Genotypic and phenotypic analysis of male breast cancer shows under representation of the HER2 and basal subtypes in BRCA-associated carcinomas.
Authors: Siddhartha Deb, Nicholas Jene, kConFab investigators and Stephen B Fox.

Thank you for consideration of this paper.

We have addressed the comments raised and made the revisions requested by the reviewers and editor. The changes are outlined below:

In regards to the following comments by Ottini and Korde respectively:

"Due to the small number of cases analyzed in this study, statistical associations may be underestimated and some associations may be missing. The authors should discuss this limitation of their study."

Although this is the only study of it's kind, I would be very careful about drawing general conclusions from these results, given the small number of cases. In particular, given that there were only 3 male breast cancer cases in BRCA1 carriers, I don't think it is valid to make any conclusions or generalizations about this group in the discussion section, aside from reporting the incidence.

We agree with the reviewers that the limited numbers of BRCA1 carriers precludes extensive description of this group. We feel however, that the absence of certain BRCA1 associated features seen in female breast cancer such as early onset and basal cell phenotype are relevant and requires comment. We also agree with the reviewers that some statistical associations may be underestimated or missing in general. We have accordingly added comments on the limitations as such in the discussion and conclusion.

In regards to the comments by Larissa Korde:

"In the Abstract, it is not clear what the HR's for clinicopathologic features and prognostic variables describe. Please clarify."

The HR was for disease specific survival. This has been revised to be more accurate in the abstract.

"Conclusion of Abstract states that MBC in BRCA1/2 carriers and BRCAx families is different to females. While this is well discussed in the paper, the abstract itself only describes results of comparison between BRCA1/2 and BRCAx MBC and comparison to results of other studies in sporadic MBC. The results section of the abstract should be revised to include summary of the
The abstract has been revised to include the comparison with female breast cancer within the kConFab cohort.

“Methods: Provide a bit more detail on the criteria for family enrollment in the kConFab registry.”

The details for patient enrollement have been included in supplementary figures as Supplementary Table 1.

“Last sentence of abstract: “Comparison with sporadic MBCs shows several some differences...” - please revise.”

This has been revised.

“Discretionary Revisions:
1) I am not sure that Figures 2-5, and Supplementary Figures 1-2 are all necessary - consider eliminating.
2) Figure 7 - consider including figures for only those variables that were statistically significant. “

Alongside providing comprehensive clinical data for our cases, as pathologist we have considerable interest in the histological and immunohistochemical features of these tumours. We wish to include figures 2-5 as they provide an example of the most common tumour subtypes as well as those of interest discussed in the paper.

Supplementary figures 1-2 are included as Ottini et al. has shown an association between BRCA2 mutation carrier status and PgR amplification which is not present in our cohort.

We also hope to include all variables in figure 7 as with some of the analysis, due to small numbers in some groups, the associations may be underestimated and some associations may be missing. We feel that a graphic representation of this is useful and demonstrated well in the Kaplan Meir curves.

In regards to the comments by Ottini:

“The authors should discuss their results taking into consideration the results reported by previous studies on larger series of MBC (i.e. Ottini et al Breast Cancer Res Treat. 2012).”

This study has been incorporated into table 6 and discussed in the paper where relevant.

“Attention should be made to typing errors (i.e. double () and %%) within the text, tables and references and to the discrepancy of the number of cases
reported in the text and in the tables (i.e. number of IDCs with micropapillary component; number of cases analyzed for HER2 status).”

The paper has been corrected for formatting errors and numbers of cases in the paper and tables checked for concordance.

“The quality of the figures should be improved (i.e. in the figure 5a the cell morphology cannot be distinguished) and in general a larger magnification is needed (i.e. fig 2a, b, d).”

These photos have been retaken in higher resolution and higher magnification for figures 2a and 2b. 2d and 2e are low and high power images on an invasive papillary carcinoma. For diagnosis of this lesion, a low power image of 2d is required to show features of this lesion and was thus included.

In regards to comments from the editor:

“Please move the mention of kConFab investigators to the acknowledgments section.”

The contribution of kConFab to this project has been considerable, in particular the genotyping of cases. The policy for kConFab authorship is from inclusion of their contribution as “kConFab investigators”.

“Copy Editing - After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.”

The manuscript has been reformatted with particular emphasis on the English quality. We feel that this is now at an acceptable standard.