Reviewer's report

Title: Comparing the frequency of common genetic variants and haplotypes between carriers and non-carriers of BRCA1 and BRCA2 deleterious mutations in Australian women diagnosed with breast cancer before 40 years of age

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Reviewer: Patricia Tonin

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This study investigates the possibility that haplotypes revealed by the analysis of SNPs are associated with deleterious (or pathogenic) BRCA1 or BRCA2 mutations. These breast-ovarian cancer susceptibility genes are large and complex. Numerous pathogenic mutations have been identified that vary in their nature which confound mutation screening and thus screening remains costly and laborious. Identifying haplotypes associated with rare pathogenic mutations may facilitate the identification of carriers. As mentioned by the authors prior studies have shown that this approach has some merit.

The investigators used data from 680 participants for BRCA1 genetic analysis and 245 participants for BRCA2 genetic analyses. However the haplotype analyses was restricted to 392 (for BRCA1) and 179 (for BRCA2) which comprise the cohort diagnosed with breast cancer under 40 years of age. They identified tagSNPs using Haploview suitable for genetic analyses and assayed the frequency of these variants with respect to pathogenic mutation status. They observed differences in the frequency of the common genetic variants of BRCA1 and BRCA2 and their haplotypes inferring phase between early-onset breast cancer cases who did not carry pathogenic mutations in these genes. However the analysis was limited by sample size and thus evidence presented was suggestive (or weak) and would have to be substantiated using a larger pool of data.

The study appears sound, but could be improved by addressing the following points that should be considered as major compulsory revisions:

It is not clear why the study was restricted to investigating haplotypes from cases diagnosed under 40 years of age? The first paragraph of the Results section states that “some sequencing was performed for cases in the other groups but sample sizes were small and not sufficient to warrant a separate analysis.” Does this imply that only a portion of cases were sequenced and/or investigated for SNP analyses? This does not correspond to the information indicated in Table 1 referring to “total DNA sequenced”. Given that only a ‘weak’ association was observed have authors investigated the possibility of using all available data – particularly as BRCA1-positive cases also occur in the later-age-of –onset group? While it may not be possible to analyze each age group a combined analysis may improve outcome.
The population studied is from the Australian Breast Cancer Study from participants from metropolitan areas of Melbourne and Sydney. It is evident from the genotyping results presented in Tables 2 and 3 which contain the BRCA1 and BRCA2 pathogenic mutations that there is little evidence of recurrent (or founder) mutations at least within the population studied. Given the finding that study would have to be extended to include a larger sample size is it feasible to do so in the Australian population? A comment in the Discussion section addressing this issue could provide a useful discussion point for researchers investigating this avenue of research and the applicability of haplotype analyses for genetic testing of rare essentially monogenic disorders.

**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