Reviewer's report

Title: Spectrum and prevalence of BRCA1/2 germline mutations in Pakistani breast cancer patients: results from a large comprehensive study

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Reviewer: Anna Jakubowska

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This is a very valuable and interesting study performed to summarize knowledge about prevalence and spectrum of BRCA1/2 mutation among HBC/HBOC patients from Pakistani population. The manuscript is very well written, however the description of methods seems to be inadequate. In my understanding, screening for BRCA1/2 mutation was performed and described in earlier published studies (ref. 11 and 22). In this study Authors analysed the available data, so in fact this study is a meta-analysis of previously published and as such should be described.

Specific comments:

Description of methods should be adapted to that which is appropriate for meta-analysis.

Minor comments:

1. Figure 1 presents not only description of the participants, it is more like a flow diagram of study selection, including number of participant, used screening methods and detected mutations

2. In fig. 2A and 2B is presented distribution and frequency of mutations along BRCA1/2 genes, with indicated functional domains and OCCR. It would be useful to mark which are 18 and 3 recurrent mutations, and also discuss the presented distribution. Otherwise, Fig. 2 is useless, because distribution and frequency of detected mutations can be obtained from table 2.

3. It is interesting if the distribution of BRCA1/2 mutation was the same in different ethnic groups, and in all are the same recurrent mutations. I am aware the in this study is overrepresentation of Punjabi and Pathan ethnic groups, but such analysis would have significant implications in clinical screening.

4. Discussion, page 11, line 6: how the 152.6% increased occurrence of BRCA1 mutation in BC families was calculated?
5. Page 11, last paragraph: in this study the number of patients was smaller than in previously published (ref. 11 and 22), so its size is not really the main strength. In my opinion, the main advantage of this study is comprehensive analysis mutations which allowed to identify the recurrent BRCA1/2 mutations in Pakistani population and define the frequencies among high-risk families.

6. In conclusion should be added possible clinical implication of these results in preventive strategies and treatment.

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