Reviewer's report

Title: BRCA1 Mutations in Women with Familial or Early-Onset Breast Cancer in Estonia

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Reviewer: THANAGARAJAN RAJKUMAR

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The study describes the BRCA1 mutation and polymorphisms in Estonian population. They have analyzed 95 early onset breast cancer patients and 28 pedigrees (49 individuals) from Estonia for BRCA1 mutations, using PCR-SSCP-HD followed by direct sequencing. There was no data available on BRCA1 mutation in the Estonian population.

Major compulsory revision

1. Table 2 is confusing. While the text mentions that 28 pedigrees (49 individuals) were included in the study, the Table has only 44 patients included. While the Table mentions that it provides information on mutation results in patients with family history, there are 16 patients in whom there is no family history at all of cancer. In addition, 11 patients have a family history of cancers other than breast and ovary.

Further, 4 subjects had no evidence of cancer but had BRCA1 mutation analysis done since family history of breast or ovarian cancers was present in their first or second degree relatives. Among these 4, only one has a pathogenic mutation (c.5385dupC) while the rest are all polymorphisms of no or unknown significance. Normally Predictive testing (testing an unaffected member in a family which has another member/members affected by cancer and carrying a deleterious mutation) is usually limited to the pathogenic mutation only. It does not seem clinically relevant to check for polymorphisms when they are of no or unknown clinical significance.

Additionally, a new mutation c.5385dupC is mentioned in the Table for the first time. This mutation is not described in the BIC database as well. I am not sure whether this refers to c.5382insC.

I would suggest a Table which lists only the clinically significant mutations along with other information such as family history, clinico-pathologic features of relevance. All the polymorphisms as mentioned earlier can be given separately excluding the family history, providing the frequency of detection only.

The low rate of mutation detection in families is likely to be due to poor selection/eligibility criteria.
Minor Essential Revisions
1. The mutation/polymorphisms are not consistently named using the HUGO recommendation. This needs to be done both in the Text and in the Table.

2. The discussion can focus more on the pathogenic mutations, including clinico-pathological information on these patients.

Discretionary Revisions
1. Literature has several definitions for early breast cancer – ranging from <36 to <50. It would be better if the Authors limited their early onset cases to either less than 41 years of age or <36 years. In addition, the discussion section compares different age cut-off used by other investigators (Latvia - <48 years, Russia <40 years, France <46 years and Sweden <41). It would be better to compare their data with a more related cohort of patients.

Level of interest: An article of limited interest

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