Reviewer's report

Title: BRCA1 mutations in women with familial or early-onset breast cancer and BRCA2 mutations in familial cancer in Estonia.

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Reviewer: THANAGARAJAN RAJKUMAR

Reviewer's report:

Comments on the revised manuscript
MS: 1064152417300593
BRCA1 mutations in women with familial or early-onset breast cancer and BRCA2 mutations in familial cancer in Estonia.
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The Authors have made substantial changes and have added the BRCA2 mutation data. However, some major concerns remain.

MAJOR COMPULSORY CORRECTIONS
1. The Authors talk about Early onset cancer cases (<45 years) and the Familial cancer cases. Some of the early onset cases have a family history as well. It seems illogical to club them under early onset. It is well known that Hereditary cancers can affect women at an earlier age. They have done this for the BRCA2 case wherein a deleterious mutation was detected (c. 6190C>T) in a lady aged 36 years with breast cancer with 2 first degree and 1 second degree relative with breast cancer.

Hence, it would be essential to re-analyse the data, including the patients whose onset of disease was <45 years but with a family history as Familial cancers. This results in 6 deleterious mutations being seen in the familial cases (5 with family history of breast / ovarian cancers and <45 years of age; and 1 with family history of breast / ovarian cancers and >45 years of age). One individual had not developed any cancer but only had strong family history and was found to have a deleterious mutation. This is more of predictive testing and can be mentioned separately.

Additionally, I am not still clear about their inclusion of 49 cases under the “Familial cases”. Do all the 49 individuals included have had breast or ovarian cancer? The Result section mentions that from the 28 pedigrees, 49 individuals were tested but only 17 had cancer and that the rest were high risk relatives. Are these high risk relatives, ones whose family member had been detected to have deleterious mutation or are they merely a member of a family which had several members affected? Either way, it is necessary to remove this group from the analysis, and only take patients who had developed cancer. The Predictive
testing carried out on unaffected members whose family member carried a deleterious mutation can be mentioned separately.

The authors will need to re-look at the 95 early onset cases and identify those with family history of breast and/or ovarian cancer. These patients will need to be removed from the early onset group and brought under the familial cancer group. Just as an example, if there are only 17 breast or ovarian cancer patients with a family history of breast or ovarian cancer, the number of deleterious mutation then would be 6 of 17 (35%). However, this is only an example and I think the denominator will increase from 17, since there are likely to be a significant number of patients who will be under 45 years of age and with a family history of breast and ovarian cancer. The same will also apply to BRCA2.

The Authors will need to redo the analysis and hence modify the contents as well.

MINOR ESSENTIAL CORRECTIONS

1. The terminologies used for relatives can be corrected – for e.g. instead of Mother’s Mother – Maternal Grandmother and so on.

2. There are several grammatical errors in the manuscript which will need to be corrected.

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 have no competing interests to declare