Reviewer’s report

Title: BRCA1/2 mutation screening in high-risk breast/ovarian cancer families and sporadic cancer patient surveilling for hidden high-risk families

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Reviewer: mads thomassen

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The manuscript describes clinical testing of 50 patients with HBOC for BRCA1/2 mutations from Latvia. The authors first analyze two known founder mutations that are also well known in other populations, one is a founder mutation in the Ashkenazi Jewish population. Subsequently, they screen BRCA1/2 in the remaining families and identify 4 additional mutations. Third they tests for the identified BRCA2 mutations in a cohort of 777 consecutive breast cancer cases and 278 ovarian cancer cases resulting in 7 more families with BRCA2 mutations. The identified families with BRCA2 mutations are not all obvious high risk families.

It is of clinical interest to identify more families with mutations in BRCA1/2 by screening certain high risk group. The most obvious groups are consecutive ovarian cancer patients or triple negative breast cancers, however, the concept might be extended to all new diagnosed breast cancer patients. If, in certain populations, a panel of few founder mutations account for majority of observed mutations, it may be a good strategy to limit the screening to. However, some information is missing in the manuscript to conclude on this. Furthermore, the manuscript needs substantial language edition.

The description of the consecutive patients is not satisfactory. Have the patients been tested for the two indicated well-known founder mutations or other mutations? It is highly unlikely, not to find any mutations in 278 ovarian cancer patients. Seven of out of 777 breast cancer is probably also a low fraction. Why is testing only performed for the BRCA2 mutations and not the BRCA1 mutation? Why did they test 301 healthy controls for the mutations that are predicted to be deleterious? Do they expect to find more hidden families or do they want to test if the mutations are deleterious? If so they should give a p-value for association.

Why do they provide the Latvia birth rate in the introduction?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.