Reviewer's report:

Title: Hereditary Breast and Ovarian Cancer: Assessment of point mutations and genomic rearrangements in Brazilian Patients

Version: 1  Date: 8 March 2014

Reviewer: Pierre Hainaut

This manuscript reports on the prevalence and types of mutations in breast cancer susceptibility genes in a single-center clinical series of 120 Brazilian women fulfilling the criteria for HBOC. Capillary sequencing and MLPA has been used to investigate mutations and rearrangements in BRCA1 and BRCA2. Additionally, the CHEK2del100 variant has been investigated. A further group of 14 genes has been investigated for LOH using array-CHG.

The main interest of this work is to provide information on the prevalence and distribution of BRCA1 and BRCA2 mutations in a Brazilian HBOC series. In this respect, the study is well executed and informative. The study also reports on the presence of CHEKdel100 in 1 case, suggesting that this form of predisposition is present in the population analyzed, although at low prevalence.

Major compulsory revisions:

(1) The selection criteria for the series of 120 patients are not given. It seems to be a consecutive series of patients recruited in one major center, but the recruitment period is not given and it is unclear whether the series includes all patients matching HBOC criteria during a given period – or whether the series is an ad-hoc subgroup. One concern is that, based on previous publications from that center, there is in Southern Brazil a high prevalence of subjects with a rare germline TP53 mutations who develop a variant form of Li-Fraumeni Syndrome, a familial syndrome characterized by several cancers including Breast cancer. At least some of these patients and families are expected to meet HBOC criteria. If the group of 120 patients is unselected, it is recommended to test them for the rare germline TP53 mutation. If the series of 120 patients excludes patients with this rare TP53 mutation, this should be explained, together with details on how the series has been assembled.

(2) Another concern regarding the selection of patients is that recruitment in one center in Sao Paulo does not capture the very broad ethnic and socio-economic diversity of the Brazilian population. Although defining ethnicity in this context is very complex and beyond the scope of the present study, it is expected that this group of patients may be biased in being mostly Caucasians of European descent, and of higher-than-average socio-economic status. These considerations should be taken into account when discussing whether the prevalence and mutation types reported here are representative of “Brazilian” population.
Minor essential revision:

(1) The screening of LOH in 14 genes does not capture the whole range of molecular alterations that may predispose to breast cancer. Again, it is expected that a proportion of patients who are negative for BRCA1/BRCA2/CHEK2del100 may carry germline TP53 mutations. In series from other parts of the world, the prevalence of TP53 mutations in HBOC subjects varies between 2 and 7%, making it the third most frequently mutated gene in this pathology. It should be made clear that scoring LOH does not amount to a comprehensive screening of the 14 genes.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests