Reviewer’s report

Title: Selected features of breast and peritoneal cancers diagnosed in BRCA1 carriers after risk-reducing salpingo-oophorectomy

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Reviewer: Arvids Irmejs

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Review HCCP-D-19-00004

Topic and material is interesting; however, design and message of the study is not clear. I have following comments:

1) First statement Risk-reducing salpingo-oophorectomy is considered the gold standard for prophylaxis in carriers of the BRCA1/2 gene mutation should be improved - RRSO is gold standard for ovarian cancer prophylaxis, but this is not an only widely accepted risk reductive procedure for BRCA1/2 carriers. Risk reductive mastectomy has an important role to reduce contralateral primary breast cancer events. Role of RRSO influence on breast cancer reduction is controversial and this should be at least mentioned. For the same purpose I recommend further in text in all places to use only term RRSO instead of prophylactic surgery

2) At the time of observation 16 out of 195 patients were diagnosed with primary breast cancer - 9 (4.61%) cases, relapse of breast cancer - 5 (2.56%) cases, or peritoneal cancer - is not clear formulated, somebody could understand that there are 16 primary breast cancers

3) Is it possible to rule out that in 2 cases peritoneal cancer is pure peritoneal cancer, but not a metastasis/dissemination form previous breast cancer?

4) The patients were diagnosed with cancer at a relatively late age - the median of 51. This statement is not clear as there is no group for comparison provided. In addition for 10/16 patients this is their second cancer and first one was at younger age

5) Please, consider to change the definitions for breast cancer events both in text and tables - true primary breast cancers (PBC) should be differentiated from contralateral primary breast cancers (CPBC). According to Table1 there are only 6 true PBC and 3 are CPBC. It is not correct to put both events in one group and to calculate/to make conclusions about age at event as for both groups age at event differs.

6) Please, consider to rename breast recurrence as ipsilateral breast cancer event as it is impossible to differentiate between true recurrence and new primary ipsilateral breast cancer, in particular in BRCA1 carriers.
7) In order to talk about ipsilateral breast cancer events it would be also good to know what type of surgery 85 breast cancer patients have underwent before RRSO - mastectomy or breast conserving surgery.

8) Patients that had been treated for breast cancer before risk-reducing surgery should be closely monitored due to an elevated risk of cancer development in the postoperative period. This conclusion is not clear as new cancer event could take place also in an unaffected carrier after RRSO.

9) Possibly the carriers of c.181T > G BRCA1 mutation should be the subject of special care in surveillance program of BRCA1/2 carriers who performed prophylactic salpingo-oophorectomy. This conclusion has been made on a basis of 2 cases and I am not aware of special surveillance program for peritoneal cancer.

10) English should be improved. For example, several times dependence is used instead of difference. The peritoneal cancer was diagnosed almost 9 months earlier than primary breast cancer (46 months vs. 54.78 months), but this dependence was not statistically significant. Breast cancer recurrence was diagnosed almost twice as fast as primary breast cancer and peritoneal cancer (25.4 vs. 52.5 months), but this dependence was also not statistically significant.

Finally, I would recommend seriously to consider to change the design of the study as cohort of RRSO is rather large and interesting. It would be nice to have a control group of BRCA1 carriers without RRSO matched for mutation type, status on previous breast cancer and age at onset of PBC and then to compare the differences of cancer event frequency and other features, including survival in both groups. This design would give important info about the role of RRSO on new breast cancer events, their features and survival.

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