Author’s response to reviews

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

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We thank the reviewer 1 and reviewer 2 for the comments.

Answers for reviewer 2 suggestions:

Reviewer #2: 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.

We agree that RRSO is not an only widely accepted risk reductive procedure for BRCA1/2 carriers. The term “gold standard” was used in a context that this operation is much more often accepted by carriers than prophylactic mastectomy, and is the major factor improving survival rate in carriers. Suggested improvements were introduced into the manuscript. According to the recommendation, the term “prophylactic surgery” was changed into RRSO.

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.

The sentence was improved into an unambiguous manner.

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?

According to the pathology report, these two cases demonstrated primary peritoneal 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.

The statement about “relatively late age” was used with the context of mean age of cancer (breast, peritoneum) diagnosis in BRCA1 carries, however, we agree that it was not precise and the statement was improved.

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.

The definitions and calculations for breast cancer events were changed according to the reviewer’s suggestion.
Appropriate improvements were introduced into Result chapter, Tables, Conclusions chapter.

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.

Breast cancer recurrence was not ipsilateral breast cancer but recurrence found in the scar.

An appropriate explanation has been entered into the manuscript.

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.

We do not have detailed data. We estimate that at the time when these operations were performed around 85% were mastectomies. It should be noted that the patients carry the BRCA1 mutation.

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.

We agree that cancer event could take place also in an unaffected carrier after RRSO. The conclusion was modified.

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.

We agree that conclusion bases on 2 cases in context of surveillance program. The conclusion was modified.

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.

The manuscript was read by a native speaker. Language errors were improved.
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.

We agree that new design would possibly allow answering additional questions, however, we are not ready at the moment for more extensive studies.

We hope that introduced improvements are satisfactory and allow publication of our paper in the Journal.