**Author's response to reviews**

**Title:** Ten-years breast cancer overall survival as an indicator of BRCA mutation in a caucasian population with high probability to be hereditary

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**Author's response to reviews:**

Dear Editor,

as requested by the reviewers we have extensively revised the manuscript MS:1116127491266873 entitled "Ten-years breast cancer overall survival as an indicator of BRCA mutation in a caucasian population with high probability to be hereditary".

Furthermore we have addressed the editorial points concerning:

1) A statement in the Method section has been added on the approval by the Ethics Commitee of Modena (reference number 45/00)regarding the identification, counselling, genetic testing, and clinical data of individuals at risk of developing breast cancer.

2) All the Manuscript sections, including a Conclusions section at the end of the Discussion, have been reedited.

3) A competing interests section has been added writing:"The authors declare that they have no competing interests"

4) Authors’ contributions section has been reported

5) Acknowledgements have been included

**Reviewer 1:**

1) As suggested we have limited the analysis to 80 patients carrying a BRCA1 mutation, counting out 35 BRCA2 carriers.

2) As suggested by the editor and the reviewer 2, an extensive revision and copyediting has been performed by a native English speaking person

3) The abbreviations H and IS have been explained also in the Introduction
4) The logistic regression analysis for BRCA mutation has been eliminated both in the text and as Table 3.

Reviewer 2:

1) The primary aim of the study was changed and further two secondary aims were added. The primary aim of our study was to calculate disease free survival (DFS) and overall survival (OS) of breast cancer patients at high risk (H) or intermediate slightly (IS) increased risk based on family history and those without a family history of breast cancer using the population registered with the Breast Cancer Registry in Modena. Since a statistically significant differences in OS between the three groups was seen, a secondary aim was to determine whether patients with a better prognosis were BRCA1 mutation carriers and whether chemotherapy could play a role in the prognosis of BRCA1 carriers.

2) We demonstrate that a long-term survival in a family at high risk to have a genetic predisposition for breast cancer could help to select patients carrying a BRCA1 mutation. This result is important when, as happens in a family cancer centre like in ours, we are faced with a patient who reports a family history of breast cancer; by collecting all the information about individuals affected by breast cancer, very long-term survivors can be identified by predicting a predisposition for being a BRCA1-mutation carrier in the descendants.

Further we have added in the Table 1 the histotype characteristics showing a difference for the Medullary carcinoma which more frequently arises in High Risk patients and which is a well known favourable tumor.

3) The title has been changed as suggested by reviewer in "Favourable Ten-Year Overall Survival in a Caucasian Population with High Probability of Hereditary Breast Cancer"

4) As already explained for the Reviewer 1 we have separated BRCA1 and BRCA2 carriers in the survival analysis, showing that the better prognosis is related to BRCA1 carriers. The number of patients carrying BRCA1 mutation is detailed in the "Mutational Analysis" paragraph, inside the "Result" section

5) As mentioned in the "Statistical Analysis" a database with a total of 4912 cases of sporadic breast cancer was used to find four matched controls for each case. Matching was based on age at diagnosis (within 1 year) and stage (I, II, and III). The study group of 80 BRCA1 cases was compared with 320 matched sporadic cases from the Modena cancer registry. No statistically significant differences in OS were seen for BRCA1 patients with any stage of breast cancer since only three deaths occurred in stage I (one caused by ovarian cancer), five deaths occurred in stage II (three from ovarian cancer and one from sarcoma), and no deaths occurred in patients with stage III disease. So in conclusion the total deaths caused by breast cancer in the BRCA1 group of patients were only three, since five were caused by second tumors, which is a frequent event in the BRCA1 carriers.

6) We have rephrased the sentence relative to the Results section in the Abstract
7) The differences between OS and DFS shown in our study are justified by the higher number of local recurrences in the BRCA1 (41%) than in the sporadic BC group (25%) which reduce the DFS but don't impact on the OS. The difference in OS could be explained by the use of alkylating agents, such as platinum-derived drugs, in metastatic disease that are well known to be more effective in BRCA-related tumours.

8) A detailed assessment for ER/PgR was provided in the Results section.

9) In the Results section the chemotherapy regimens used in different lines of treatment were explained.

11) We have plotted the OS curves between BRCA1 carriers patients treated vs. no treated in the Fig.4. No difference was seen in terms of OS (see Fig. 4), even if all the death events in the treated group of patients were derived from second tumours (4 cases).

We have provided all the point-by-point responses and we hope that in this revised form the paper would be accepted for publication in BMC Cancer.

Best Regards

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