Author's response to reviews

Title: Oxidative stress and counteracting mechanisms in triple-negative and basal-like breast carcinomas

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Author's response to reviews: see over
Dear Editor,

We thank you for additional comments regarding our manuscript “Oxidative stress and counteracting mechanisms in triple-negative and basal-like breast carcinomas”.

We have now made the changes that Reviewer 2 requested. We have also incorporated the requested changes and additions to the manuscript with “tracked change”. Hopefully the manuscript now fulfills your requirements is ready to be published in BMC Cancer.

We would be pleased to answer any questions related to this manuscript.

Sincerely,

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Reviewer’s (2) report:

1) It seems that the authors misunderstood the Nielsen immunohistochemical surrogate panel for BLBCs. According to Nielsen et al. (Clin Cancer Res 2004) and Cheang et al. (Clin Cancer Res 2008), BLBCs are defined as triple negative tumours expressing EGFR and/or CK5/6. Therefore, to classify BLBCs as “the triple negative tumours that also expressed both EGFR and CK5/6” may be incorrect and is certainly not very sensitive, considering that the panel as described by Nielsen et al. has a sensitivity of 76%. Moreover, requiring expression of both EGFR and CK5/6 would not increase the specificity, which is 100% when considering EGFR and/or CK5/6. This should be amended in the study and all analysis comparing the BLBCs re-done.

Reply: We have now modified the criteria of BLBC as the Referee suggests and re-analyzed the results. The proportion of basal-like subtype showing cancers in our material is now 83%, which is more in line with previous reports (reviewed in e.g. Foulkes et al. NEJM 2010). According to the new definition of BLBC, there is no association with PRDX IV, but instead we found larger T-class in BLBC group compared to non-BLBC triple-negative cancers (p=0.005).

RE-reply: OK, however the word “simultaneous” from the abstract should be deleted.

Authors’ re-reply: The word simultaneous has been removed from the abstract as the referee suggests.
3) In 2010, the ASCO/CAP guidelines for evaluation of ER and PR were published (Hammond et al J Clin Oncol 2010). According to those guidelines, a cut-off of more than 1% (and not 10% as used in the present study) of positive cells should be used for considering a tumour ER/PR positive. Therefore, the study has not been “updated to match the latest criteria concerning ER- and PR negative tumors”. This should be updated in the manuscript.

Reply: We are aware that several guidelines have recently suggested that any amount of positive ER staining should be considered as ER-positive cancer and ER-negative breast cancers as those without any ER-staining. As mentioned in the Materials and Methods section, the TNBC group did not show any ER- or PR-positivity, but tumors exhibiting more than 10% of invasive tumor cells were considered as steroid receptor-positive. The latter decision was made since 1-10% of positive cells may be “grey zone”, where estrogen responsiveness is uncertain. We have now modified the mentioned sentence in the Discussion: “Here we reassessed the steroid receptor status and HER2 status of tumors and updated them to match the latest criteria concerning ER- and PR-negative tumors [14], tumors exhibiting more than 10% of invasive tumor cells were considered as steroid receptor-positive.”

Re-reply: As it is, it is not clear if any tumour included in the study expressed low levels of ER/PR (between 1-10%). If there was (probably not), was this case excluded from the analysis? Finally, if the authors want to use a cut-off of 10%, they cannot mention in the text that they have “updated to match the latest criteria” as this is misleading for the readers of BMC Cancer.

Authors’ re-reply: We excluded tumors expressing 1-10% ER or PR from the analysis. The mentioned sentence in the first paragraph of discussion reads now “Here we reassessed the steroid receptor status and HER2 status of tumors; those tumors without any ER and PR immunostaining were considered as receptor negative and tumors exhibiting more than 10% of invasive tumor cells were considered as steroid receptor-positive.” Reference 14 [Goldhirsch et al.] is deleted.