Author's response to reviews

Title: TGFB1 and TGFBR1 polymorphisms and breast cancer risk in the Nurses’ Health Study

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Author's response to reviews: see over
To the Editors,

On behalf of my co-authors, I would like to thank you and your reviewers for their careful consideration of our manuscript, “TGFB and TGFBR1 polymorphisms and breast cancer risk in the Nurses’ Health Study” (MS 1411665211401487). We have addressed their comments in the resubmission of the manuscript (attached, modifications underlined), and provided a summary of the reviewers’ comments, and our response to them (in italics) below.

Sincerely,

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Reviewer #1 (David Goldgar):

“Although most likely simply due to sampling variation, perhaps the authors could postulate additional reasons for this finding. Given that the case control studies are largely European-based (or at least not US-based), could population differences play a role? Also, if the BCAC cases are composed largely of prevalent cases, while the NHS ones by definition are incident cases, could this be a possible explanation.”

*We have included more discussion (pages 6-7) on possible explanations for heterogeneity between our results and those presented by the BCAC.*

Reviewer #2 (Wilfried Renner):

“The sub-group analysis in estrogen receptor positive patients was obviously a post-hoc analysis and not based upon an a-priori hypothesis stated before collection of data. Strictly speaking, this subgroup finding should therefore stated as hypothesis-generating and not hypothesis-testing – no matter how low the p-value may be.”

*We have added a phrase to the last paragraph of the discussion (page 7) stating that these analyses were not based on the original hypothesis, and therefore should be considered hypothesis generating and in need of further replication.*

Reviewer #3 (Ewa Grzybowska)
“I highly recommend to include more tables with statistical analysis in respect of ER status of breast cancer cases.”

*Table 4 with these results has been added.*

“The groups under study are not described at all and the authors did not provide the information about the approval of the study by Bioethical Commission.”

*Additional detail has been added to the methods section (page 5) further describing the study population, as well as affirming the approval of the protocol by the IRB.*

Reviewer #4 (Boris Pasche)

“It is incorrect to state that there is ‘no overall association between the L10P polymorphism and breast cancer’. A recent report by Cox et al Nat Gen 2007, 39:352-358, demonstrates a weak but significant association between TGFβ1 L10P and breast cancer. These findings are particularly important as they reconcile previous conflicting results. They also underscore the need to study very large populations to answer questions related to low penetrance susceptibility alleles. The authors genotyped 15,109 controls and 12,946 cases to reach their conclusion. This study now firmly established a small but significant association between TGFβ1 L10P and breast cancer risk.”

*We would like to respectfully note that in context, it is clear that we are stating that there is no overall association between the L10P polymorphism and breast cancer risk in our study alone. We discuss the association presented by Cox et al. as well as include an analysis of our results in combination with theirs, and show that if our subjects were included in the referenced analyses, no association with this polymorphism would be observed, and that there is significant heterogeneity in results. This would argue against “firmly established” association with this polymorphism. In response to reviewer #1 above, we also discuss in more detail the heterogeneity between our results and those of Cox et al.*

“With respect to TGFBR16A and breast cancer, a meta-analysis of 13,000 cases and controls published by Zhang et al, J Clin Onc 2005, 23:7743-7743 showed a significant association between this allele and overall cancer risk. The authors also genotyped 2,422 breast cancer cases and 2,998 controls and showed a significant association with breast cancer. Since then, two small studies have reported the lack of an association between TGFBR16A and breast cancer: Chen et al, Clin Cancer Res 2006, 12:392-397 and Spencer et al CEBP 2006, 15:1236 – 1237. Both studies were underpowered but the first study showed a trend towards an association between TGFBR16A and breast cancer and the other did not. Overall, the association between this allele and breast cancer is very likely to persist when a new meta-analysis is conducted.”

*We have performed an additional meta-analysis of the prior reports of genotyping of the TGFBR16A polymorphism in breast cancer cases and controls. The results of this meta-*
Reviewer #5 (Victor Moreno)

“This study includes the cases and matched controls identified prospectively within a cohort and this should be resistant to biases. However the authors give no detail about the studied population. They use a reference from 1998 when this cohort only had 156 women with breast cancer. A table 1 with characteristics of the cohort and the selected cases and controls would be helpful, or a more recent reference for these data that agrees with the 1267 cases and 1758 controls.”

“Reference 33 states that 2 controls per case were selected, but in this analysis the ratio control:case is 1.4. Some explanation about that and missing data should be given so that any reader can assess that selection bias cannot be a relevant issue in this study.”

*Reference 33 was intended to show overall study design of the Nurses’ Health Study. Additional text has been added to the Methods section to describe the study and selection criteria in response to both of these comments.*

“The interaction with estrogen receptor status is only reported as conditional OR and CI, but we don’t know the number of cases for each status and the number of missing data. This is important to give more or less relevance to this finding.”

*In response to reviewer 3 above and this reviewer, a Table 4 with the ER+ results has been added to the manuscript.*

“The authors report unconditional logistic regression estimates. This usually is more powerful when some matched set have missing values, but could lead to biased estimates towards the null hypothesis. The adjustment for matching criteria can avoid this, but the authors should also perform the conditional logistic regression analysis and state that the results are similar, if this is the case, or report the conditional estimates if the unconditional show bias.”

*Both conditional and unconditional analyses were carried out, with results similar between the two. We have included a phrase to this respect in the results section (page 5).*