Author's response to reviews

Title: The INSIG2 rs7566605 polymorphism is not associated with body mass index and breast cancer risk

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

Please find here enclosed the revised version of the article entitled: The **INSIG2 rs7566605 polymorphism is not associated with body mass index and breast cancer risk**. We provide here a point-by-point response to the reviewer questions.

I hope that our manuscript, in the present form, will be suitable for publication in BMC Cancer and I am looking forward to hearing from you.

Best regards.

Federico Canzian
Reviewer: Niloufar (Neely) Kazerouni

Reviewer’s comments:
The study by Campa et al. attempts to explore the association between the single nucleotide polymorphism rs7566605 and BMI and BC risk, respectively. The study design is a nested case-control study within the very large EPIC cohort. The majority of women and BC cases included in the study are post-menopausal women, which needs to be highlighted in the article.

A paragraph has been added in the Discussion section to address this point

The BC analysis was also conducted by menopausal status. Did the sample size among pre-menopausal women yield an adequate power to explore any associations between BC risk and the polymorphism? The power among pre-menopausal women was of 0.81 to detect an OR of 1.3 in a log additive model (considering MAF= 0.33, which we observed in the controls used for the pre-menopausal analysis).

Was a stratified analysis by menopausal status also done for the BMI association?
We have also stratified for menopausal status at baseline and we did not find any difference in the genotype distribution.

There is no mention of the family history of BC in the study. I am wondering whether the inclusion of such variable in the BC risk logistic regression model would make any differences in the estimate of associations.
In the Epic cohort the information on family history is very sparse and incomplete so we have not taken into account this variable.

In the calculation of OR for the association of BC risk and the polymorphism in Table 2 is the CC genotype the common allele and the referent group? If so, this should be mentioned in the footnote of the Table. Also, it should be clarified that the OR in the table is the OR for BC risk. As for the BMI analysis in Table 2, it seems that you have reported the results from the unconditional regression analysis and not from the logistic regression. This needs to be clarified in the Table. It would be more informative to report the results from the logistic regression analysis for the BMI in the same table or in a separate table as well with clarifications regarding the comparison groups (different BMI categories) and the referent allele group.
Table 2 has been modified according to the reviewer’s suggestions and results on BMI have been added as well as clarification on the reference allele.
In the text for results and discussion section, 3rd paragraph, by dominant, codominant, and recessive models do you mean GG genotype for dominant, GC genotype for codominant, and CC for the recessive model? If so, I would add these genotypes in parentheses. The text has been modified. In order to avoid confusion we left only the codominant model.

Also, I would separate the results and discussion sections according to the instructions to authors: http://www.biomedcentral.com/bmccancer/ifora/. The discussion could start from the second page of this section starting with the paragraph “in this report we explored....” Also, under this section, 5th paragraph, the reference for Walley, 2009 needs to be mentioned under the references section.

This has been done.

In Table 1, with the use of an asterisk, it should be noted in the footnote that the 2,194 controls include 52 duplicate controls. This has been done

Also, under the “selection of case and control subjects” section, it is mentioned that the 123 cases and 125 controls had genotyping failure, while in Table 1 and in the text under statistical analysis, these incomplete matched sets are included in the counts for subjects with genotypes. This needs to be clarified.
A more complete description has been added in the text (in the selection of case and control subjects paragraph) to avoid confusion.

Under the key words, insuline should be spelled as insulin.
This has been done
Reviewer Tanya Agurs-Collins

Reviewer’s comments:
The authors adhered to the relevant standards for reporting and data deposition. However, study limitations were not discussed. Also not discussed is a possible alternative for the lack of an association and how the finding contrast or are in agreement with previous research. One such possibility for a lack of association could be the role of gene-environment interactions. The overall writing is clear and the data is sound.

A paragraph has been added in the Discussion section to address the study limitations. We have remarked in the introduction that previously published results on the association between this SNP and BMI are conflicting. Our results add to the weight of evidence against an association.