Author's response to reviews

Title: No role for glutathione S-transferase genotypes in Caucasian esophageal squamous cell or adenocarcinoma etiology: an European case-control study

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

Thank you very much for the comments on our manuscript no. 20155345649220772 entitled: “No Role for Glutathione S-Transferase Genotypes in Caucasian Esophageal Squamous Cell or Adenocarcinoma Etiology: an European Case-Control Study”, by Polat Dura et al. We are pleased to get the opportunity to submit a revised version of this manuscript.

Enclosed is a point by point response to the comments of editors and reviewers:

Editorial Board Comments.
Some additional minor comments
In Table 2, by "Size" I presume you mean "n"? It would be clearer to use "n". We fully agree and we replaced the word “size” by “number”

In Table 3, the "*" used to indicate the footnote can be confused with the "*" in the genotypes. I suggest using another symbol (e.g. #) to indicate the footnote. Again we fully agree and now used the symbol # instead of * in the heading of Table 3.

Editorial Requirement:
Authors' contributions - Please include an 'Authors' contributions' section before the Acknowledgements and Reference list.
We included the following author contribution section before the acknowledgement: "PD, JPHD and WHMP designed the study. PD, JS, RHMtM, HMJR, JOK, TW, BJMW, ACITLT and WHMP were involved in acquisition, analysis and interpretation of data. PD and WHMP drafted the manuscript, which was critically revised by JS, RHMtM, HMJR, JOK, TW, BJMW, ACITLT and JPHD. All authors read and approved the final manuscript."

Please also ensure that your revised manuscript conforms to the journal style.
We carefully checked and corrected the title page, the abstract and the references; which are now all in accordance with the journal’s style. We also removed unnecessary capitalization in
the title and (sub)headings. The section competing interests is added before the authors contribution section.

Our remarks on the comments of the reviewers.

Reviewer 1

Comment 1. This is an interesting and well written paper which builds on previous studies that have examined the role of genetic variants of Glutathione S-transferases (GSTs) with respect to the aetiology of esophageal cancer. Most work in this field has examined the aetiology of squamous cell carcinoma rather than oesophageal adenocarcinoma and has primarily been from Asian studies so this paper is a welcome addition to the literature in the field.

We thank the reviewer for this positive comments.

Comment 2. In general, the methods used are well described and appropriate. Inclusion of response rates for cases and controls would have been a useful addition to enable the reader to guage how representative these groups are of the patient and reference populations (Discretionary revision).

Cases were asked to participate at the moment they were diagnosed in the hospital (see page 6), but we did not register how many patients refused to participate. As described in our paper (page 6), controls were recruited from the same geographical area as the cases, after advertisement in local papers, so here we also do not have a response rate.

Comment 3. The examination of interactions between genes is interesting and potentially informative analysis, however it would be useful if the authors could comment on whether this was an a priori objective and point to other examples in the literature where similar approaches have been used. (Minor Essential Revision).

As stated at the end of the introduction on page 5, “This study was set out to examine whether (combined) GST genotypes with altered predicted enzyme activities, modified EAC and ESCC risk in Caucasians”. So examination of interactions between genes clearly was an objective of our study. To the best of our knowledge, a similar approach has not been used before.

Comment 4. The results presented are interpreted as indicating no association between the polymorphisms examined and aetiology of cancer of either histological type. However in general the estimates for the low activity genotypes for squamous cell carcinoma are consistently below unity. The confidence intervals are very wide because of low number of these cancers included in the study. The authors should discuss more fully the lack of power of their study, especially with respect to the findings for squamous cell carcinoma. Low power is additionally an issue for the interaction analyses. (Minor Essential Revision).

We agree with reviewer that one of the reasons why we do not find associations between GST polymorphisms and aetiology of EC is the low number of cases involved (lack of power). We already mentioned this in the discussion section at pages 11 and 12 (as a limitation). On page 12 of the discussion section we now even more fully discussed the lack of power, especially for ESCC.

Reviewer 2
Discretionary Revisions
The authors can consider to explain more clear the tests for gene-gene interactions.
We fully agree with the reviewer that the gene-gene interaction testing was not clearly described. We now critically re-edited the text on this subject in the Methods section at page 8 and in the Results section at pages 9 and 10.

Results from stratified analyses by smoking status and biosample resource (tissue vs blood) can be added in text.
We do not have data on smoking status of cases and controls, which is now more clearly indicated at page 13 under limitations.
For some cases no blood was available as source of DNA and in these cases DNA was isolated from normal esophageal or gastric tissue, obtained after surgery, which was now more clearly described in the Methods section.

We feel that our paper is now improved considerably and sincerely hope that it is now acceptable for publication in BMC Gastroenterology.

Sincerely yours, also on behalf of Dr Dura,

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