Author's response to reviews

Title: Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking mate in healthy subjects from Rio Grande do Sul, Brazil

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Version: 2  Date: 24 January 2006

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BMC Cancer Editors

Re: MS: 2934494848544042 - Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking mate in healthy subjects from Rio Grande do Sul, Brazil

Hello,

We thank the reviewers and the editors for their comments on our manuscript. We have provided a detailed response to each of the queries below.

Referee 1:
1. Please correct reference No 9 and extend the discussion on mate temperature.

We have corrected the reference and added additional discussion of mate temperature on page 8.

Referee 2:
1. ...it could be helpful in the statistical analyses to consider other potential confounding factors, such as BMI or professional exposure.

Unfortunately, we did not collect information on height and weight so we cannot assess the potential role of BMI in urine 1-OHPG concentrations in this study.

We did collect information on occupation. We had twenty different occupations reported and the most common responses were homemaker, farmer, construction, clerk, nurse, and seller. These six professions accounted for about 75% of the subjects and none of these has an a priori likelihood of having high PAH exposures. We did plot 1-OHPG by job and found no suggestions of interesting results. Therefore, we had little potential to uncover occupations that were associated with 1-OHPG and we thought it better not to present an underpowered analysis.

2. ... add "oesophageal cancer" into the sentence "between mate consumption and risk of..."
3. ... might replace the first reference (Parkin 1999) with another more recent (for example, Parkin et al., CA Cancer J Clin 2005)
4. ... to correct in the title "Linxina" into Linxian

Each of these minor corrections was completed.

Referee 3:
1. The authors should expand on subject selection.
We added additional details on subject selection on page 4.

2. The method for analysis of cotinine should be included in the methods section and results presented.
   We stated the method cotinine analysis in the methods section (page 5) and the results are given in table 1.

3. The authors should explain the lack of adjustment of 1-OHPG and cotinine towards creatinine which is recommended procedure.
   Creatinine adjustment is particularly useful when comparing 1-OHPG distributions between populations which might systematic differences in hydration. A systematic difference is unlikely by any of the categories we examined. For example, it seems unlikely that we had substantial differences in hydration linearly associated with the quantity of mate typically consumed. If there are random errors, they should make the study null rather than positive.

4. The statistical methods used dividing some data into quartiles is not explained and should be justified in relation to data shown in table 1.
   Age and mate were divided into empirical quartiles. A sentence stating this has been added to the methods section.

5. Also the statistics used in table 2 should be further explained and the authors are recommended to make use of the GENMOD procedure available in SAS statistical package.
   We gave a detailed description of the statistical methods used and how the final model was built in the methods section. It is unclear to us why changing from PROC REG to PROC GENMOD in SAS would alter the analysis if the link function is linear. Since our data was normal outside the mode at the limit of detection, linear models are adequate. As stated in the results, we found similar results when using categorized 1-OHPG concentrations.
   Importantly, the multivariate model results differed little from the univariate, un-modeled results. This is confirmed by looking at the plots in figure 1 and 2 and the modeled results presented in table 2. Therefore, we see no strong rationale for changing the models.

6. In table 1 and 2 the number of study persons in each group plotted should be given.
   We think the referee means figures 1 and 2. The numbers of subjects plotted have been added to the figure legends.

7. The discussion is initiated in the results section and the authors are recommended to stick to the IMRD concept presenting results only in the results section.
   We are unsure of the referee's concern. We gave the interpretation of the cachaca result from the multivariate model and we gave a detailed explanation of how to examine the interaction data to aid reader's understanding of the interaction result - we do not believe that this constitutes discussion as such, but rather a textual reiteration of the results for the less statistically savvy reader.

8. There is an apparent lack of discussion and reference to the work on the ESCC causation by the authors available by search in the PubMed database. The hypothesis underlying the study should be further discussed.
   We are unsure of the referee's intent with this comment. Most of the discussion section covers the potential association between mate and ESCC and whether PAH exposure or high temperature is likely to be the underlying cause, because this is the more controversial association and the one that this current study has impact on. In response to Referee 1 we added additional discussion of high mate temperature. The only other etiologic exposure for ESCC that is relevant to PAH exposure is tobacco smoking. This topic has been covered in many papers, is not novel, and seems to us to be a poor use of space for this manuscript. The hypothesis that PAH exposure increases the risk of ESCC is covered in detail in the introduction.

9. In case this study includes other biomarkers or exposure or effect (e.g. p53) reference to these analyses should be made.
   No other biomarkers of exposure or effect have been measured

10. The quality of the written English is not suitable for publication unless extensively edited.
    The paper was co-written, revised, and edited by native English speakers. We don't understand the reviewers concerns on the quality of the written English.