Author's response to reviews

Title: A case-control study on the combined effects of p53 and p73 polymorphisms on head and neck cancer risk in an Italian population

Authors:

Paola Gallì (paola.galli@edu.rm.unicatt.it)
Gabriella Cadoni (gabriella.cadoni@rm.unicatt.it)
Mariangela Volante (mariangela.v@libero.it)
Emma De Feo (emmadefeo@yahoo.it)
Rosarita Amore (rosarita.amore@rm.unicatt.it)
Arianna Giorgio (ariannagiorgio@yahoo.it)
Dario Arzani (dario.arzani@rm.unicatt.it)
Gaetano Paludetti (gaetano.paludetti@rm.unicatt.it)
Gualtiero Ricciardi (wricciardi@rm.unicatt.it)
Stefania Boccia (sboccia@rm.unicatt.it)

Version: 3 Date: 9 March 2009

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

Please find enclosed the manuscript after a second revision stage. I hope that the major and minor revisions implemented fully address the comments and criticism received in order to warrant its publication.

The criticisms of the three reviewers have been addressed across the manuscript and marked with the blue colour, while a point-by-point response to the concerns is provided below.

With many thanks for your assistance.

Best regards,

Stefania Boccia
1st reviewer: Jean-Gilles Charles AHOMADEGBE TOMETIN

Title: A case-control study on the combined effects of p53 and p73 polymorphisms on head and neck cancer risk in an Italian population

Reviewer's report:
After the major compulsory revision, I think that this manuscript is suitable for publication in BMC cancer

We thank the reviewer for the favourable report on our revised manuscript.
**2nd reviewer: Nancy Hamel**

**Title:** A case-control study on the combined effects of p53 and p73 polymorphisms on head and neck cancer risk in an Italian population

**Reviewer’s report:**
As stated in my first review of the manuscript, the study design and execution are good, and the results are of interest to others in this field provided the associations observed are genuine and not false positive results.

*We thank the reviewer for the favourable report on our revised manuscript.*

**Minor Essential Revisions**

1. There is one instance where FDR correction for multiple testing rendered a formerly significant association non-significant, as clearly pointed out by the authors in the text (association between the p73 polymorphism and risk of oral cavity cancer, Table 2). It would be useful for the authors to also indicate this in the table itself, as an additional footnote, so it can be immediately clear when browsing the Tables that this positive result is not statistically significant in spite of the suggestive odds ratio.

*As you suggested, an additional footnote has been added on Table 2 to clearly show that the formerly significant association between the p73 polymorphism and risk of oral cavity cancer didn’t remain noteworthy after the FDR test correction.*

2. I would like to see a specific comment/statement for every significant association reported in the manuscript regarding the fact that the association remains significant even after correction for multiple testing (which I assume it does given that they are still presented as significant, as in the first version of the manuscript), and the appropriate corrected P-values presented so the strength of the corrected association is evident.

*As several authors suggest,\(^1\)\(^2\) the FDR correction was implemented when testing the association between each of the four polymorphisms and the different tumour locations. This has been clarified by adding a specific sentence in the methods section (page 7, line 9 from the top).*


**3rd reviewer: Sujata Patil**

**Title:** A case-control study on the combined effects of p53 and p73 polymorphisms on head and neck cancer risk in an Italian population

**Reviewer’s report:**
The revised manuscript is greatly improved, and clarifies many issues. However, some comments and questions remain.

**Major Revisions**
1) The authors have stated that the power calculation in the discussion (page 10) was not done a prior. Such calculations are difficult to interpret, though I do acknowledge that there is debate on this issue. In my view, power calculations are done to inform a study design before accrual and I would not include this. However, if the authors want to include this, state clearly that this power calculation was done after the completion of the study.

   *When the limitations of our study are acknowledged, a specific comment has been added to clearly state that the power calculation has been performed *a posteriori* (page 10 line 12 from the top)*

2) I am still not clear why a multinomial logistic regression rather than several multivariate logistic regressions were done. With multinomial logistic regression, the endpoint would be oral cavity oropharynx, larynx, controls as a single categorical outcome, and not split out into pairwise comparisons. Also, the goodness of fit statistics are stated in the text but never interpreted.

   *As you suggested we have performed in the revised manuscript a multinomial logistic regression analysis by using the healthy control subjects as reference group. So we added a specific sentence in the Methods section (page 7 line 4 from the top) and we presented the corrected results given by that approach in Results section (page 8 line 6 from the bottom) as well as in Table 2 (page 21).*

3) Since this is matched study design, does one need to use the appropriate matched analysis techniques (e.g. conditional logistic regression)? This should be clarified.

   *The original publication*3 *was based on an age and gender matched case-control study design (first paragraph Study Population section of Methods on page 4 of the revised manuscript). We are aware that the previous sentence could be misleading about the current study design, which is not matched any longer, therefore we added a*
specific sentence (Page 5, 3rd line from the top) to clarify this difference from the original publication. That’s why we use logistic regression instead of the conditional one.

**Minor Revisions**

1) For the Kaplan-Meier plots, does x-axis really go to 200 months? This means some patients had over 16 years of follow up. But, in the text, patients were recruited from 2002. Can this be clarified? Please label the y-axis.

Thanks a lot for your comment because it was a mistake. In fact, we checked the original database and the follow up time for some patients was recorded as 200 months instead of 20 months by mistake. So we performed again the survival analysis and the correct results have been reported in the Results section (last paragraph of page 9). In addition, the correct version of Kaplan-Meier curve was reported in the MS (page 25).