Reviewer's report

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

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Reviewer: Nancy Hamel

Reviewer's report:

The study’s purpose was to examine the combined effects of three p53 polymorphisms and one p73 polymorphism and their interaction with lifestyle habits on the risk of head and neck cancer development. The question is well-defined and the methods adequate to answer the question posed. The work is well referenced and the results are placed in context with current knowledge in the immediate field.

The small size of the study limits the detection power (this weakness is acknowledged by the authors) and prevents analysis of some interactions where subcategories have numbers too small for analysis. In spite of this, significant associations between SCCHN risk and some genetic loci are reported by the authors, some for the first time, which may be of interest to others in this field.

Major Compulsory Revisions

1. There is no mention in the manuscript of correction for multiple testing effects. The authors are looking at many different interactions among many factors in this study. As a result, a large number of statistical tests are performed, and the possibility that the few significant interactions to emerge from such extensive analysis might be false positives should be addressed, as this could change some conclusions.

2. HPV infection is a known independent risk factor for SCCHN, as stated by the authors in their introduction. This potential confounder was not measured – and therefore not controlled for – in this study, and could contribute to some of the observed effects. I am aware that several of the previous genetic association studies published on SCCHN also lack HPV data; however, this lack cannot be as easily ignored in a study where significant associations are observed as it can in a negative study. The impact of this potential confounder needs to be considered by the authors when drawing conclusions.

3. On page 8 of the results, the last sentence of the middle paragraph states that “a more than additive effect was found for those carrying both p53 intron 3 and p73 unfavourable variants”, yet in Table 5, where the data is presented, a P value for interaction of p = 0.30 (non-significant) is presented for this analysis. The intended meaning of the statement needs to be clarified.

Minor Essential Revisions
4. A short figure legend or different figure labels would be helpful with the figure. The “p53int6carmt” designation was not previously used in the manuscript and was initially confusing to me. It was not immediately evident from looking only at the figure that “p53int6carmt = 1” refers to genotypes with at least one mutant allele, while “p53int6carmt = 0” is wild-type. Although this eventually becomes clear when reading the discussion, it should be clear when looking at the figure alone without the text.

5. The first 2 lines of the abstract’s Results section state that there was “a significant increased risk of SCCHN among individuals with combined p73 exon 2 G4A and p53 intron 6 mutant alleles”. Based on the text and figures, I believe this last should read p53 intron 3.

6. The last sentence of the abstract’s Results section states that a “poorer survival rate was observed among carriers of p53 intron 6 variant allele”, whereas the discussion (and the figure, but see point 4) state that the poor survival was in fact observed in non-carriers of the variant allele (i.e. in wild-type individuals) while carriers of the variant had improved survival. Please clarify the wording of this section.

Discretionary Revisions

7. Significant associations could be highlighted in the data tables (e.g. in bold face) to facilitate data perusal and rapid identification of points of interest when looking at the data.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.