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Reviewer Comments

Although cancer due to tar exposure is currently rare, it is interesting to know possible mutations in TP53 and how they are involved in human skin carcinogenesis. For this reason, I consider the approach of this manuscript interesting but I have several questions:

Reply: Thank you for constructive comments.

Subjects and methods section

1) When the authors indicate that PCR amplification of DNA in some of the samples was not possible, it is not clear to me if there are individuals that no sample is worth or are some of the samples of each individual those that not could be used. I think it is important that the authors indicate the number of individuals who have been studied. In the table when they indicate in the column of mutations "none" is that it has been analyzed several samples and there are no mutations?

Reply: Thank you these important questions. "none" in the table means the samples could be analyzed and no mutations of p53 was detected. I included all the individuals and some portions of FFPE were not possible amplify even in the same individuals. I did attached a supplementary figure (line 103) to show how we picked up the portions for DNA sequencing.

2) I can't find the supplementary figures.

Reply: Very sorry for forgetting to upload. The low magnified view of the sections and sampled portions are indicated in blue circles. See the supplementary figure.

3) They should point out in the text that the DO7 antibody identifies both the wild type and the mutated form of the p53 protein.

Reply: Thank you for your important comment. As you know DO7 identifies both the wild type and the mutated form of the p53 protein and mutant p53 has longer half-life in the cells. This notion is classical view and some type of mutations (null mutation) did not show up any immunohistochemical colorization. We added the explanation in the revised manuscript on page 4 in red. (line 113-117).

Results section

1) I find it difficult to understand the results. The figures indicated do not correspond in the text with what is indicated in them at the end of the manuscript.

We apologize the mixed up of the sentence, figure legends and figure numbers. We

corrected in the revised manuscript in red. (Line 122-129)

2) Although they have not been able to amplify the DNA by PCR, the IHC technique detected a positive signal in all the cases analyzed, both exposed to tar and ionizing radiation? This would indicate with a high probability that it could be a mutated protein even though the mutation had not been detected by PCR, since the mutated protein, in most cases, is kept longer in the tissue so it can be detected by the IHC technique. They should include results obtained by the IHC technique in all cases analyzed.

Thank you for your important suggestion. Actually, clonal type of immunoreactivity of TP53 was found only in the cases PCR amplification and successful sequencing was obtained.(Line 104)

Discussion section

1) There are data (lines 124-125) that should be indicated in the subject and methods section.

We moved them to Line 102-

2) I find data that are inconsistent or I do not interpret them well, as in line 128, in which 18 cases are mentioned and then in 129, it indicates that 15 of them were a type of cancer and in 131 they indicate than the remaining 5.

We corrected the numbers and updated the data source.

3) Line 136: the authors have to delete the letter “a”

Figures

1) Figure legends do not correspond to what is indicated in the text

2) I consider that figure a or b is unnecessary because I understand that both correspond to individuals exposed to tar. Figure h is not the same as figure a or b, it would be interesting if it were a serial section of one of them.

We corrected.