LETTER TO THE EDITORS

Reply to the contribution of Hainaut, Olivier and Pfeifer (TP53 mutation spectrum in lung cancers and mutagenic signature of components of tobacco smoke: lessons from the IARC TP53 mutation database)

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The topic of my contribution published recently in a ‘Discussion Forum’ in Mutagenesis was the comparison of different versions of the IARC p53 database with respect to data on lung cancer of smokers and non-smokers. Most importantly, this comparison revealed a number of discrepancies in the classification of smoking status of identical lung cancer entries in different versions (R1, R2 and R3) of the database. Additionally, no statistically significant differences in G→T transversion mutation frequencies or in mutational hotspots at codons 157, 248 and 273 were found in the R3 version of the database comparing lung cancer in smokers and non-smokers. Finally, a possible influence of confounding factors on p53 mutation spectra was demonstrated. In the present Letter Hainaut et al. refer to my paper and conclude that ‘indiscriminate inclusion of mutations in his dataset may partially explain what he sees as discrepancies’. I appreciate the editors of Mutagenesis giving me the opportunity to reply to some critical comments made by Hainaut et al.

On the basis of the R4 version of the IARC p53 database, Hainaut and Pfeifer (2001) performed an additional comparison of G→T transversion mutation frequencies in lung cancer of smokers and non-smokers. They found frequencies of 29 and 10% for G→T transversions in lung cancer of smokers and non-smokers, respectively. This result was statistically significant (P < 0.0001, χ² test). Since the R4 version of the p53 database was not available at the EBI-server (ftp://ftp.ebi.ac.uk/pub/databases/p53/) until mid July 2000, it was not possible to include this version in my analysis, which was submitted to Mutagenesis in May 2000.

As already reported (Paschke, 2000), 179 lung cancer entries classified as smokers and 34 classified as non-smokers in R1 (January 1998) were no longer classified for smoking status data in comparison with both versions (R4) also shows considerable discrepancies with respect to the smoking status data of these entries. The changes concerning all five non-smoker entries listed in R3 with mutated guanine bases at ‘hotspots’ 157, 248 and 273 are shown in Table I.

Taking these findings as the reason for a preliminary examination of the smoking status data of lung cancer entries in different papers (Huang et al., 1998a; Miyake et al., 1999; Konishi et al., 2000) concerning 114 mutations in tumours which had already been published in two more papers of the IARC p53 database. Another attempt by Hainaut et al. (2001) to explain the findings of my study on different versions of the IARC p53 database was the redundancy of identical tumours in different publications which were repeatedly included in successive versions of the database. In this connection they cited three publications (Huang et al., 1998a; Miyake et al., 1999; Konishi et al., 2000) concerning 114 mutations in tumours which had already been published in a previous paper by the same group of authors (Huang et al., 1998b). Although this information can be helpful for users of the current version of the IARC p53 database (R4), the authors overlooked the fact that only mutations in tumours reported in one paper by these authors (Huang et al., 1998b) had been included in the R3 version of the database, which was released in January 1999.

In conclusion, the reasons for systematic changes in smoking status data of identical entries listed in different versions of the IARC p53 database remains unclear. Since the current version (R4) also shows considerable discrepancies in the classification of smoking status data in comparison with both the earlier R3 version and the original literature, the results of analyses of this version should also be interpreted with caution. Careful control of the underlying original publications seems...
Table I. Mutations at guanine bases at the codons 157, 248 and 273 in non-smoker entries with mutations at guanine bases at the 'hotspots' codons 157, 248 and 273.  

<table>
<thead>
<tr>
<th>Literature reference</th>
<th>Codon in R3 and R4</th>
<th>Codon in original literature</th>
<th>Smoking status in original literature</th>
<th>Smoking status in R3</th>
<th>Smoking status in R4</th>
</tr>
</thead>
</table>

The information listed in the R3 and R4 versions of the IARC p53 database was compared with the original literature.

to be absolutely necessary for future studies analysing p53 mutational spectra on the basis of the IARC p53 database to prevent the creation of a novel kind of publication bias.

Finally, it is worth mentioning that the study published recently by Rodin and Rodin (2000), which was also based on the R3 version of the IARC p53 database, confirmed major parts of my analysis (Paschke, 2000) in not finding significant differences between smokers and non-smokers with respect to both the frequency of different types of mutations and the frequency of their occurrence along the p53 gene.

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References


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