We thank Drs. Rajiv Kumar and Kari Hemminki for their letter (1) in reference to our article (2) on haplotype analysis of p16 variants and risk of head and neck cancer. In essence, they pointed out two misquotations: one being line 4 of paragraph 3 of the “Introduction” on p. 640, “C580T” should be “C540G”, and another being our incorrect citation of their work. Specifically Ref. “17” in paragraph 2 of “Materials and Methods” on p. 641 should be Ref. “18” (3). We sincerely apologize for these two misquotations.

The 540C→G was first identified and reported by Xu et al. (4) in 1994 and Ueki et al. (5), and the 580C→T was first identified and described by Holland et al. (6) in 1995. The Ref. 18 published in 2001 was the most recent and relevant publication by Kumar and Hemminki and their co-workers at the time the manuscript was being prepared. They have had another three publications since as mentioned in the letter, which are not relevant in this context. We did indeed want to confirm the molecular work done in their 1998 publication (7) by using the sequence provided. However, the GenBank accession number for the primer sequences was not provided in the methods of their 1998 publication (7). In the later publication in 2001 (8), the accession number was provided not in the methods but in a table footnote that we overlooked. Because we were not able to identify sense primer in L27211, we decided to perform sequence analysis on the PCR products and confirmed the two polymorphisms (540C→G and 580C→T) according to the accession number L27211. In our paper, we wanted to point out our uncertainty by stating “… (antisense; confirmed by the reported sequences: accession number L27211).” Indeed, we recently found that the sense primer sequence was consistent with that described in accession number U12820 as Kumar and Hemminki have correctly pointed out.

It is clear we have successfully replicated the molecular work described in Ref. 18, based upon which we described a new haplotyping method that we applied to our molecular epidemiological study of head and neck cancer. Unfortunately, because of our incorrect reference citation, the method of Kumar and Hemminki was not appropriately acknowledged.

However, we believe the two major important findings in our paper are not affected in any way by these misquotations. One is the haplotyping by linking the gel patterns of the PCR products with the related sequencing results so that one can identify haplotype by reading the gel results correctly. This was not described in their earlier papers (7) they mentioned in the letter or even in their three later publications. Another finding is that association between these two polymorphisms and related haplotype and risk of head and neck cancer was observed.

As for the significance of these two polymorphisms, it is always difficult to compare studies with different sample sizes and target populations. Although Kumar and Hemminki agreed that the biological functionality of these two polymorphisms remains unknown, they reported that these two polymorphisms were important as demonstrated in their earlier work in familial and metastatic melanomas and, in particular, in a recently published study of 229 patients with primary melanoma and 235 healthy controls (8). They have shown that the T allele of the 580C→T polymorphism, but not the G allele of the 540C→G polymorphism, was significantly associated with increased risk of melanoma. However, no age and sex information was provided, and tumor DNA from the cases and blood from the controls were used for genotyping (8), a less than ideal epidemiological study design to address the role of these two variants in the etiology of melanoma.

Studies of the potential roles of these two 540C→G and 580C→T polymorphisms and their haplotype in the etiology of melanoma and other cancers are under way in our laboratory.

References

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