MDM2 SNP309 and risk of cervical cancer

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Dear Editor,

We read with interest the paper “MDM2 SNP309 variation increases cervical cancer risk among Asians” by Zhuo et al. in *Tumor Biology* [1].

This paper assesses the impact of the *MDM2* promoter SNP309 (rs2279744) on risk of cervical cancer through a meta-analysis of four original articles (five independent case-control designed studies). The overall data presented by the authors indicate that the SNP309G-allele is not associated with an increased risk of cervical cancer. However, when restricting their analysis to Asian cohorts, the authors find a significantly increased risk of cervical cancer among individuals harbouring the SNP309GG genotype versus individuals with the SNP309TG or TT genotypes. The remaining cohorts (one Caucasian and one cohort of mixed ethnicity) yielded nonsignificant results. Notably, such a difference with respect to ethnicity is similar to what others have observed previously in other cancer forms [2, 3]. In their discussion, Zhuo et al. state that their observations indicate interactions between the *MDM2* polymorphism and ethnic variations. Further, they point to factors such as age, smoking and HPV-status as nonassessed potential confounding factors. While the data presented and the authors’ discussion are interesting, we would like to make some additional comments.

A clear confounding factor relates to a second *MDM2* promoter SNP, SNP285G>C (rs117039649), located only 24 bps upstream of SNP309. The C-allele of SNP285 has been shown to have an antagonistic effect versus SNP309G: while in vitro studies have shown the SNP309G-allele to elongate a binding site for the transcription factor Sp1 and thereby increase *MDM2* transcription [4, 5], the SNP285C-allele has the opposite effect, significantly reducing Sp1 binding [5]. The SNP285C/309G haplotype accounts for about 12 % of all SNP309G alleles in ~3,500 North Western Europeans (Norway, the Netherlands and the UK) [6], and a similar frequency is reported in the Caucasian cohorts of the 1000 genomes project (www.1000genomes.org). Notably, the SNP285C-allele has been found to be absent in Asian (Chinese and Japanese) populations both in our studies [5] and in the Chinese and Japanese cohorts of the 1000 genomes project.

While no study so far has addressed odds ratio for cervical cancer with respect to SNP285 status, notably, this variant has been associated with a significantly reduced risk of cancer of the breast, ovaries and endometrium [5, 7]. Further, the odds ratios for these cancers, related to SNP309G, increased when individuals harbouring the SNP285C variant were censored from the analyses [5, 7]. If the SNP285C-allele has a protective effect against cervical cancer resembling what has been recorded for the three malignancies mentioned above, this may explain the discrepancy with respect to SNP309 status and risk of cervical cancer between Asian and non-Asian cohorts, as recorded by Zhuo et al.

Taken together, the interesting data presented by Zhuo et al. underlines the importance of determining SNP285 status and correcting for this variant whenever addressing Odds Ratios for cancer related to SNP309 status across different ethnic cohorts.

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