***MDM2* SNP309 and risk of endometrial cancer**

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Dear Editor,

We read with interest the paper “Common variant on *MDM2* contributes to endometrial cancer susceptibility: evidence based on 7 studies” by Zhao et al. in Tumor Biology [1].

In this paper, the authors assess the impact of the *MDM2* promoter SNP309 (rs2279744) on risk of endometrial cancer by performing a meta-analysis of seven original articles (eight independent case-control designed studies). Based on their findings, the authors conclude that the SNP309G-allele is associated with an increased risk of endometrial cancer, both in an allele contrast model and in a recessive model. Further, the authors find this to be true both among Caucasians and Asians. Most original articles assessing the impact SNP309 on risk of endometrial cancer have so far been small, and it is therefore highly appropriate to perform meta-analyses in order to elucidate the potential role of this *MDM2* variant. While the data presented by Zhao et al. are interesting, we would like to make some additional comments.

In their meta-analysis, Zhao et al. included seven original articles, with a total number of 1,278 cases and 2,189 controls, omitting our study from 2012, which is the largest study on SNP309 in endometrial cancer to date [2]. In our study, we included 910 Caucasians diagnosed with endometrial cancer and 2,465 controls. If this data set had been included in the meta-analysis, it would weigh approximately 50 % and, therefore, would have had a major impact on the output, both in the

overall assessments and even more so in the subgroup of Caucasians. Notably, our data set, in addition to being published in our original article [2], was also included in a previous meta-analysis assessing the impact of SNP309 on endometrial cancer risk [3].

We would also like to point out that any study of *MDM2* SNP309 in Caucasians has a potential confounding factor that needs to be taken into account/discussed. This relates to a second *MDM2* promoter SNP, SNP285G>C (rs117039649). SNP285 is in complete linkage disequilibrium with SNP309. The variant C-allele of SNP285 is present on about 12 % of the SNP309G-alleles in North Western Caucasian populations but absent in East Asian and African populations [4–6]. Importantly, SNP285C has an antagonistic effect against SNP309G: in vitro studies have shown the SNP309G-allele to elongate a binding site for the transcription factor Sp1 and thereby increase *MDM2* transcription [4, 7], while the SNP285C-allele reduces Sp1 binding and transcription [4, 8]. In line with the in vitro findings, case-control studies have shown SNP285C to significantly reduce the risk of ovarian, breast, and endometrial cancer [2, 4]. Notably, censoring individuals harboring SNP285C from the analyses has been shown to increase the odds ratios related to SNP309G, for endometrial as well as for ovarian cancer [2, 4]. Thus, any study assessing the impact of SNP309 on cancer risk among Caucasians may probably benefit from correcting for SNP285-status in the cohorts.

Taken together, the data presented by Zhao et al. are interesting and gives insight into the effect of *MDM2* SNP309. However, the number of studies assessing the impact of SNP309 on risk of endometrial cancer is low, and larger studies and meta-analyses are required in order to elucidate the effect of SNP309 status, not only on endometrial cancer risk but also on the risk of any cancer form evaluated in this respect.

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