LETTER TO THE EDITOR

MDM2 SNP309 and risk of endometrial cancer

Stian Knappskog[1,2], Per Eystein Lønning[1,2]

[1]Section of Oncology, Institute of Medicine, University of Bergen, Norway
[2]Department of Oncology, Haukeland University Hospital, Bergen, Norway

Dear Editor,

We read with interest the paper "Association between *MDM2* SNP309 polymorphism and endometrial cancer risk in Polish women" by Zajac *et al*. in the „Polish Journal of Pathology" [1].

This paper assesses the impact of the *MDM2* promoter SNP309 (rs2279744) on risk of endometrial cancer in Polish women. The data presented by the authors indicate that the SNP309G allele is associated with a severely increased risk of endometrial cancer. While their data are interesting, we need to express some concerns regarding their conclusions.

As for their results, Zajac *et al*. found the OR associated with the SNP309GG genotype to be 2.28 (CI: 2.02-2.54). This is a very narrow confidence interval given the limited number of observations in the study. Based on the genotype data listed in their Table II, we found SNP309G to be associated with endometrial cancer with an OR of 1.68 (95% CI: 0.89-3.17; dominant model; GG + TG vs. TT) and OR 4.67 (95% CI: 2.70-8.08; recessive model; GG vs. TG+TT).

Secondly, a potential confounding factor relates to a second *MDM2* promoter SNP, SNP285G>C (rs117039649). SNP285 is located only 24 bps upstream of SNP309, and the C allele of SNP285 has been shown to counteract the effect of SNP309G: while the SNP309G allele elongates a binding site for the transcription factor Sp1, the SNP285C allele has the opposite effect, significantly reducing Sp1 binding [2]. Further, the combined SNP285C/SNP309G haplotype actually displays a weaker Sp1-transcription factor binding than the "wild-type" SNP285G/SNP309T haplotype. The SNP285C/309G haplotype accounts for about 12% of all SNP309G alleles in ~3500 North Western Europeans (Norway, the Netherlands and the UK) [3], and a similar frequency (15%) was recently reported in a cohort of 550 healthy Polish individuals [4]. Importantly, the SNP285C variant has been shown to reduce risks of breast, ovarian and endometrial cancer in large case control studies [2, 5]. Thus, to make a precise assessment of *MDM2* SNP309's impact on cancer risk, any study of this SNP in Caucasian populations should be corrected for SNP285 status in each individual.

Third, we are aware of a total of 7 previous studies reporting potential effects of the SNP309G allele on risk for endometrial cancer. In line with Zajac *et al*., 5 out of 7 studies report a positive association with risk for endometrial cancer while 2 showed no association. Notably, the 2 negative studies (and 3 out of the 5 positive ones) were performed in Europeans and would be subject to the confounding effect of SNP285C. However, most of these studies, similarly to the study by Zajac *et al*., contained a limited number of individuals (5 out of 7 studies enrolled < 200 patients each). Taking into account the potential of publication bias, with unpublished negative studies, we are not sure whether the combined data from these small studies provide a correct OR. In the largest sample sets reported so far, we compared 910 endometrial cancer patients to 3140 healthy controls [5] and calculated ORs for SNP309G in endometrial cancer risk both with and without correction for SNP285C. Here, we found SNP309G (dominant model; GG + TG vs. TT) to be associated with an increased risk of endometrial cancer corresponding to an OR of 1.17 (95% CI: 1.00-1.37), or 1.20 (95% CI: 1.02-1.41), when corrected for SNP285 status. In contrast, presence of SNP285C reduced the risk for endometrial cancer among heterozygous carriers of the SNP309G allele (OR 0.61; 95% CI: 0.41-0.90). Based on the similar frequencies of SNP309 and SNP285 between Poland and Norway, we may postulate that the OR for endometrial cancer related to these SNPs are not much different between individuals of Polish and Norwegian ethnicity.

Taken together, both contemporary in vitro results and case control data indicate SNP309G to increase the risk of endometrial cancer. However, the data so far may seem too limited for a precise assessment of the OR associated with the SNP309G allele. What seems clear, though, is that conclusive assessment of this question requires corrections for confounding factors, such as SNP285C, and analyses of large data sets.

References

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DOI: 10.5114/pjp.2013.34608 Pol J Pathol 2013; 1: 70

LETTER TO THE EDITOR REPLY

Agnieszka Zając[1], Grzegorz Stachowiak[1], Tomasz Pertyński[2], Hanna Romanowicz[3], Jacek Wilczyński[1], Beata Smolarz[3]

[1]Department of Gynecological Surgery, Institute of Polish Mother's Memorial Hospital, Lodz, Poland
[2]Department of Menopausal Diseases, Institute of Polish Mother's Memorial Hospital, Lodz, Poland
[3]Laboratory of Molecular Genetics, Department of Pathology, Institute of Polish Mother's Memorial Hospital, Lodz, Poland

Dear Sirs,

We would like to thank the authors for their remarks on our paper "Association between MDM2 SNP309 polymorphism and endometrial cancer risk in Polish women" in which the association between MDM2 SNP309 polymorphism and endometrial cancer (EC) risk in the Polish population was investigated. In this paper we reported a significant positive association between the MDM2 SNP309GG genotype and endometrial carcinoma. This is the first study linking single nucleotide polymorphisms of the *MDM2* gene with EC incidence in the population of Polish women.

Our study contained a limited number of individuals. In the paper we suggested that further studies conducted on a larger group are needed to clarify that MDM2 SNP309 polymorphism may be a predictive factor for endometrial cancer in Poland. The observed differences in statistical results may be associated with the use of various statistical methods.

We agree that a second *MDM2* promoter SNP285 polymorphism is very important. Its location in the promoter region indicated its possible role in the regulation of transcription of the *MDM2* gene. We investigated MDM2 SNP309 polymorphism because literature data suggested that this polymorphism may be very significant in EC development. Moreover, among the variants of the *MDM2* gene SNP309 was most frequently studied and its role is still unknown. The literature data are inconsistent. In conclusion, further research, conducted on a larger population, is needed to clarify the significance of MDM2 polymorphisms not only in EC but also in other cancers.