MDM2 SNP309 does not confer an increased risk to oral squamous cell carcinoma but may modulate the age of disease onset

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The MDM2 SNP309 has been associated with increased expression of the protein which could suppress p53 function, and has been shown to modulate risk to cancer. We have previously shown that overexpression of MDM2 is a common event in oral cancers. In the present study, we determined the association between the MDM2 SNP309 polymorphism and oral cancer in 207 oral cancer patients and 116 normal subjects. We genotyped the MDM2 SNP309 by PCR-RFLP. Logistic regression was adapted to calculate odds ratios for MDM2 SNP309 polymorphism from univariate and multivariable adjusted models. Our results suggest that MDM2 SNP309 does not confer increased risk to oral cancer (OR = 1.55, 95% CI = 0.77–3.11). However, the GG/TT genotype was associated with later disease onset in women above 55 years of age. Collectively, our data suggests that MDM2 SNP309 may modulate the risk to oral cancer and is a modifier of the age at oral cancer onset in women above the age of 55 years.

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Introduction

The p53 pathway is central in controlling cellular proliferation and senescence by regulating the cellular response to DNA damage,1,2,3 and the p53 gene has been reported to be mutated in more than 50% of human cancers.4 However, this pathway can be inactivated by mechanisms other than p53 mutations, including the overexpression of MDM2.5 MDM2 acts as a negative regulator of the p53 tumour suppressor, by tagging p53 for ubiquitin-associated degradation, modulating the translocation of p53 in and out of the nucleus and directly binds to p53 to regulate its transcriptional activity. Therefore a change in MDM2 may affect the overall function of the p53 pathway and notably in vivo, alterations of MDM2 levels have been shown to affect p53-dependent tumour suppression6 and the upregulation of MDM2 results in the progression of tumours in mice.7,8 Moreover, MDM2 overexpression has been reported in many cancers, including sarcomas, breast, lung and oral squamous cell carcinomas.7,9,10

With the advent of high-throughput technologies to screen single nucleotide polymorphisms (SNPs), many SNPs have been associated with an increased risk to cancer development. This includes a recent discovery of a SNP in the promoter region of MDM2 (SNP309) demonstrating that the GG genotype may contribute to an increased risk to cancer.11 This SNP, increases the binding efficiency of the SP1 transcription factor resulting in an increase in MDM2 transcription and subsequently higher levels of the MDM2 protein.12,13 In turn, this alteration in MDM2 levels disrupts the p53/MDM2 ratio and affects the oscillating levels of p53 and MDM2 in response to DNA damaging agents.14 In addition, p53 activation and induction of its downstream target p21 in response to DNA damaging agents in cell lines with the SNP309 is delayed, again suggesting that this polymorphism may contribute to an increased risk to cancer onset. Indeed, MDM2 SNP309 has been shown to modulate the risk to cancer development both in Li Fraumeni patients as well as individuals who have no known predisposition factors.15

Given that we and others have demonstrated an up-regulation of MDM2 in oral squamous cell carcinomas (OSCC), we postulated that MDM2 may play a significant role in the development of OSCC. As oral cancer is closely linked to carcinogenic exposure through betel quid chewing and smoking, a compromised DNA damage surveillance in these patients through MDM2 overexpression and attenuation of p53 pathway may lead an increased risk to OSCC in individuals who practice these habits. Therefore, in the present...