

Molecular epidemiology of oral cancer susceptibility genes in Southern Thailand

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Oral squamous cell carcinoma (OSCC) is a global health concern because it is the 6th leading cancer in the world for both genders, especially in developing countries. In Thailand OSCC incidence is high among the Southeast Asian countries, and the cancer ranks the 4th in males. The highest incidence of the OSCC in Thailand is in the Southern region of the country. The age standardized incidence rates (ASR) are 12.9 and 3.5 for males and females, respectively. Risk factors for OSCC in this region are related to lifestyle habits, particularly the use of tobacco, alcohol and betel quids. However, relatively few persons among these who have been exposed to the risk factors actually develop cancer. Therefore host susceptibility may play an important role in modulating the risk.

A line of evidence suggests that development of OSCC depends on the ability of the host (i) to metabolize carcinogens or pro-carcinogens from tobacco smoke and other toxic substances, (ii) to repair induced DNA damage, and (iii) to control cell signaling in the cell cycle. Therefore, genetic variations in genes participating in these biological pathways should be responsible for OSCC susceptibility. Genetic polymorphisms of the xenobiotics metabolizing enzymes (XMEs) that are involved in the bioactivation (by phase I) and detoxification (by phase II) of carcinogens in tobacco and alcohol were described with alterations in enzymes expression. Many polymorphic XMEs genes have been addressed to modulate cancer susceptibility, including OSCC. Similarly, many DNA repair genes are polymorphic and their associations with cancer have been reported. Evidence from epidemiological studies however, produced inconsistent results. Possible factors for the inconsistency are ethnic variation of the studied populations and cancers investigated.

This study is a case-control study to determine association of OSCC susceptibility and genetic polymorphisms in Thai population. Subjects were OSCC patients (ICD-10: C00-C06) recruited from the Prince of Songkhlanagarind Hospital, Songkhla Province in Southern Thailand. A total of 106 cases and 164 controls were frequency-matched on gender, within 5-years of age, smoking and drinking status. The techniques of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were adopted for genotyping assays. Eight polymorphisms in seven XMEs genes: *CYP1A1* Ile462Val, *CYP2E1* 5'flanking, *Pst*



I, *MPO* -463 upstream in exon1 of phase I, and *GSTM1*, *GSTT1*, *GSTP1* Ile105Val, *EPHX1* Try113 His, *EPHX1* His139Arg of phase II; nine polymorphisms in five DNA repair genes: *XRCC1* (Arg194Trp, Arg399Gln), *XRCC3* Thr241Met, *XPD* (exon6, Lys751Gln), *XPC* (-PAT, exon15), *MGMT* (Trp65 Cys, Leu84Phe);

and one polymorphism in tumor suppressor gene: *p53* codon72 were explored.

On XMEs, polymorphisms and OSCC susceptibility, the data showed that there was no statistical difference between the genotype frequencies of the cases and controls. Regression analyses for odd ratios (ORs), exhibited no statistically significant difference ($p > 0.05$) between the XMEs polymorphisms investigated and OSCC risk. The risk habits practiced showed no interactive effect with the XMEs polymorphisms to modify the OSCC risk.

Results on polymorphisms in DNA repair gene and OSCC risk showed that the *XRCC3* 241Met exhibited a significantly higher risk (OR = 3.3, 95%CI = 1.31-8.36, $p = 0.01$). The triplet of the risk genotypes (*XRCC3* e41Met, *XRCC1* 194Trp and *XPD* exon6) was associated with highly significant increase in risk (OR = 9.43, 95%CI = 1.98-44.9, $p < 0.01$). Additionally, the variants *XRCC1* 194Trp interacted with the smoking and drinking habits to significantly elevate the risk (OR = 3.37, 95%CI = 1.41-8.02, $p < 0.01$), and positive interactions were detected in individuals with the non-betel chewing habit (OR = 2.88, 95%CI = 1.31-6.31, $p < 0.01$). The *XPD* exon6 variants exhibited a significantly elevated risk in non-smokers and non-drinkers (OR = 4.10, 95%CI = 1.20-14.0, $p = 0.03$). Males with variants *XRCC1* 194Trp and *XRCC3* 241Met had significantly higher risk (OR = 2.72, 95%CI = 1.34-5.52, $p < 0.01$; OR = 2.95, 95%CI = 1.12-7.75, $p < 0.05$, respectively), whereas variants *XPD* exon6 exerted a higher risk in females (OR = 3.93, 95%CI = 1.14-13.6, $p < 0.05$).

The study on *p53* codon 72 polymorphism and risk for oral cancer comprised 97 matched-pair of cases and controls. It showed no significant association between OSCC risk and *p53* codon72 polymorphism. There was also no link with respect to smoking or drinking habits.

In conclusion, the present study is the first epidemiological study on OSCC susceptibility in Thai population. It shows that three polymorphisms in DNA repair genes are involved in OSCC susceptibility in a Thai population: *XRCC1* 194Trp,

XRCC3 241Met and *XPB* exon6. The interesting point is that enzymes from each of the three genes are known to participate in different DNA repair pathways. This observation is consistent with the induction of multiple DNA lesions by tobacco smoke and by other environmental agents that require different pathways for the repair. Presumably in the OSCC susceptible patients, the squamous epithelium that covered the oral cavity mucosa were genetically damaged by the carcinogens in tobacco and failed to repair due the predisposition of the defective DNA repair genes. Therefore, this study represents an important addition to previously published work on polymorphism of genetic susceptibility of cancer. The overall observation from my investigation is consistent with the hypothesis around the world that genetic susceptibility contributes to human cancer. This study also provides useful genetic database information on allele frequencies of common candidate genes for gene-environment studies on cancer susceptibility as well as evolutionary genetics for Thai populations.

