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Polymorphism in DNA repair genes and oral squamous cell carcinoma in Thailand

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Abstract

DNA repair capacity is essential in maintaining cellular functions and homeostasis. However, the repair capacity can be altered based on DNA sequence variations in DNA repair genes and thus may cause cancer susceptibility. We investigated associations between polymorphisms in DNA repair genes and oral squamous cell carcinoma (OSCC) in a Thai population. Nine known single nucleotide polymorphisms (SNPs) in five common DNA repair genes were investigated: *XRCC1* (Arg194Trp and Arg399Gln); *XRCC3* (Thr241Met); *XPC* (PAT and Lys939Gln); *XPD (*exon 6, and Lys751Gln); and *MGMT (*Trp65Cys and Leu84Phe). We studied 106 cases and 164 healthy controls that were frequency-matched by age (± 5 years), gender, and cigarette smoking and alcohol drinking habits. The genotype assays were performed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The R version 2.0.1 statistical software was applied for statistical analysis of association. Based on multivariate analyses, we found that the variant genotypes with *XRCC3* 241Met exhibited a >3-fold elevated risk (OR = 3.3, 95% CI = 1.31−8.36, $p = 0.01$) for OSCC. There was a marginally significant risk observed in variants with *XRCC1* 194Trp (OR = 1.81, 95% CI = 0.91−3.63, $p = 0.09$) and *XPD* exon 6 (OR = 1.71, 95% CI = 0.93−3.16, $p = 0.09$). Combination of the variant genotypes of these three susceptibility genes was associated with a highly significant risk for OSCC (OR = 9.43, 95% CI = 1.98−44.9, $p<0.01$). From further multivariate analyses, the variants with *XRCC1* 194Trp and possibly *XRCC3* 241Met interacted with tobacco and alcohol to further increase the risk (OR = 3.37 95% CI = 1.41−8.02, $p<0.01$; OR = 2.92, 95% CI = 0.94−9.04, $p = 0.06$). On the other hand, increased risk was detected in non-betel chewers (OR = 2.88, 95% CI = 1.31−6.31, $p<0.01$; OR = 2.61, 95% CI = 0.97−7.11, $p = 0.06$) who carry the two variant genotypes, respectively. Males with the variants *XRCC1* 194Trp or X*RCC3* 241Met had a higher risk of developing OSCC than males with the corresponding wild-type genotypes (OR = 2.72, 95% CI = 1.34−5.52, $p<0.01$; OR = 2.95, 95% CI = 1.12−7.75, $p<0.05$). Such association was not detected in females. Interestingly, the risk increased in female carriers of *XPD* exon 6 (OR = 3.93, 95% CI = 1.14 − 13.6, $p<0.05$). We could not demonstrate a significant interaction of these SNPs with age in this study. Our data indicate that the variant genotypes with *XRCC3* 241Met and possibly *XRCC1* 194Trp and *XPD* exon 6 contribute to OSCC

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development in a Thai population. In addition, these SNPs influence the repair of DNA damage that is caused by environmental risk factors for oral cancer.

Keywords: DNA repair; Gene polymorphisms; Oral squamous cell carcinoma; Oral cancer; Head and neck cancer; Genetic susceptibility; Smoking

Introduction

On a daily basis, various DNA repair mechanisms function continuously to correct damaged DNA that is caused by exposure to either endogenous or exogenous toxic substances. Recent reviews indicate that there are at least 130 functional DNA repair genes in humans, which are grouped into five major DNA repair pathways (Wood et al., 2001; Yu et al., 1999). (1) Direct repair pathway such as O^6-methylguanine DNA methyltransferase (*MGMT*). (2) Base-excision repair (BER) pathway including X-ray repair cross-complementing group 1 (*XRCC1*), apurinic/apyrimidinic endonucleases (*APE*), DNA glycosylases, DNA polymerase-β and DNA ligases (I-IV). (3) Nucleotide-excision repair (NER) pathway including many genes, such as xeroderma pigmentosum complementing groups: *XPA–XPG*. (4) Double-strand break (DSB) repair pathway such as *XRCC3*, *BRCA1*, *BRCA2* and *LIG4*. (5) Mismatched repair (MMR) pathway including 6 genes in human: h*MSH2*, h*MSH3,* h*MSH6*, h*MLH1*, h*PMS1,* and h*PMS2*. Recently, there has been considerable interest in understanding genetic variability in DNA repair genes and their influence on modifying an individual's susceptibility to cancer. This topic has been reviewed (e.g. Spitz et al., 2003). Polymorphisms in *XRCC1*, *XRCC3*, *XPC, XPD,* and *MGMT* have been identified and reported to be associated with cancers of lung, head and neck, upper aerodigestive tract, urinary bladder, nasopharynx, etc. (Benhamou et al., 2004; Cho et al., 2003; Olshan et al., 2002; Shen et al., 2001, 2002, 2003; Spitz et al., 2003; Sturgis et al., 1999, 2000, 2002; Tae et al., 2004). Unfortunately, many of these observations have not been consistent (Goode et al., 2002; Au et al., 2004). The discrepancy can be due to the small sample size and the difference in ethnicity of populations investigated. More molecular epidemiological studies need to be conducted, using more vigorous study protocols, to provide a better understanding of genetic susceptibility to environmental related cancers, such as oral cancer. A topic that has received insufficient attention is genetic susceptibility to oral cancer.

Genetic susceptibility publications on oral squamous cell carcinoma (OSCC) have frequently been included in either that of head and neck cancer or cancer of the upper aerodigestive tract (including oropharynx and larynx) (Benhamou et al., 2004; Olshan et al., 2002; Shen et al., 2001, 2002; Spitz et al., 2003; Sturgis et al., 1999, 2000, 2002; Tae et al., 2004). Although most of these investigations have studied Caucasian populations, two were for Asian populations (Hsieh et al., 2003; Tae et al., 2004). It is possible that such investigations using broadly defined cancer sites may contribute to the discrepant observations because of the potential differences in etiology. Therefore, focusing studies on more homogeneous cancer sites may reduce variations.

In Thailand, the estimated incidence rate of cancer of the oral cavity (ICD-10 codes; C00-C06), including lip, buccal mucosa, gum, tongue, floor of mouth, and palate is 6.8 and 4.8 per 100,000 population in males and in females, respectively, becoming the 4th and 7th leading cancers for the two genders (Fritz et al., 2000; Sriplung, 2003). The major risk factors are tobacco, alcohol and betel consumption habits (Kerdpon et al., 2001). Information on genetic susceptibility to OSCC in Thailand is limited although we have reported previously that the *GSTM1* null genotype increased OSCC risk in this ethnic group (Kietthubthew et al., 2001). Here, we report our investigation on associations of nine SNPs in five DNA repair genes and OSCC risk in a Thai population.

Materials and methods

Study population

The population included in this case-control study was ethnically Thai. A total of 112 cases and 192 controls were recruited. The recruitment criteria were described previously (Kietthubthew et al., 2001). They were matched as described below (see Statistical analysis). In brief, patients with histologically confirmed squamous cell carcinoma in the oral cavity (tongue, buccal, palate, floor of mouth, and lip) were sequentially recruited from the Department of Radiology, Songkhlanagarind Hospital, Hatyai, Songkhla, Thailand, before they had chemo- and/or radiotherapy. The controls were recruited simultaneously from residents living in the similar geographic area (Songkhla province and its vicinity). All individuals voluntarily participated in the study after they had provided informed consent. Each participant was personally interviewed with a questionnaire that had