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Oral Cancer and Gene Polymorphisms: International Status with Special Reference to India

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ABSTRACT

Oral cancer is the sixth most common cancer in the world and most common neoplasm in the India. The exposure to environmental agents and byproducts of cellular metabolism results in damage of DNA, which if left unrepaired, could lead to the process of carcinogenesis. Individual specific difference in the susceptibility to chemical carcinogens is one of the most important factors in the estimate of risk of cancers along with an ability to repair DNA damage. Molecular epidemiological studies have shown that an individual's susceptibility to oral cancer is modulated by both genetic and environmental factors. Therefore, genetic polymorphisms of phase-1 and phase-2 xenobiotic metabolizing enzymes as well as DNA repair genes can modify an individual's response to carcinogens and hence, the carcinogenic potential of such exposures. In the present study, we have reviewed the literature about association of polymorphisms of phase 1 enzymes (CYPs), phase 2 enzymes (GSTM1, GSTP1, GSTM3) and DNA repair genes (XRCC1, XRCC3, XPC, HOGG1) with risk of oral cancer, with special emphasis on Indian studies. It can be concluded that the effect of these polymorphisms on oral cancer risk was inconclusive and showed variation in different populations and even within same population. Thus future studies should involve more number of patients as well as more SNP's of specific gene for better evaluation of significance of genetic markers in oral cancer assessment.

Key words: Carcinogens, oral cancer, polymorphism, xenobiotic, susceptibility

INTRODUCTION

Oral cancer is reported to be the sixth most common cancer in the world and third most common cancer in developing nations (Blot *et al.*, 1996; Jhavar *et al.*, 2004; Gatoo, 2008). It accounts for approximately 4% of all cancers and 2% of all cancer deaths worldwide (Boring *et al.*, 1993). In India, it is the most common malignant neoplasm accounting for 20-30% of various types of cancers (Kuruvilla, 2008; Nair *et al.*, 1999). Oral cancer has one of the poorest five year survival rates and only 52% survive after five years of diagnosis (Sidransky, 1995; Vokes *et al.*, 1993; Silverman, 1988). Areas of high risk for oral cancer in world include South East Asia, Central and Eastern Europe and South America. Because of their epithelial origin, they are classified as squamous cell carcinoma (Silverman and Gorsky, 1990; Zarbo and Crissman, 1988).

Globally, tobacco consumption in its various forms (smoking, chewing and snuff dipping etc.) is the commonest aetiological factor for the subsequent development of oral cancer (Blot *et al.*, 1988; Elwood *et al.*, 1984). Tobacco smoke comprises nearly 60 carcinogenic compounds while its unburnt form contains 16 identified carcinogens. The concomitant use of betel quid increases concentration of carcinogenic tobacco specific nitrosamines and reactive oxygen species in the mouth. Alcohol is an independent risk for oral cancer and also acts synergistically with tobacco in an additive or multiplicative fashion (Elwood *et al.*, 1984). The risk level for the oral cancer has been shown to increase with increasing meat and animal fat consumption and to decrease with fruit and cabbage consumption (Hebert *et al.*, 1993). Although lifestyle factors play an important role in etiology, some patients appear susceptible because of inherited trait(s) in their ability or inability to metabolize carcinogens or pro-carcinogens, possibly along with an impaired ability to repair DNA damage.

ORAL CANCER AND SUSCEPTIBILITY

Molecular epidemiological studies have now provided evidence that an individual's susceptibility to oral cancer is modulated by both genetic and environmental factors. The environment-gene interaction on carcinogenesis has been well documented by phase-1 and phase-2 enzymes that are involved in the metabolism of carcinogens. Individual specific difference in the susceptibility to chemical carcinogens is one of the most important factors in the estimate of risk of cancers. Most chemical carcinogens require metabolic activation by phase-1 enzymes (cytochrome P450s) and detoxification by phase-2 enzymes (epoxide hydrolyase, N-acetyl transferase and gluathione transferases etc.). Thus, the coordinate expression and regulation of phase-1 and phase-2 xenobiotic metabolizing enzymes and their metabolic balance may be an important factor in determining whether exposure to carcinogen results in cancer or not. Therefore, genetic polymorphisms of these enzymes can modify an individual's response to carcinogens and hence, the carcinogenic potential of such exposures. The exposure to environmental agents and byproducts of cellular metabolism results in damage of DNA, which if left unrepaired, could lead to the process of carcinogenesis. The major pathways of DNA repair mainly include base/nucleotide excision repair and double strand break repair. Base excision repair pathway involves repairing of minor base alterations such as oxidized or reduced bases or methylated bases and covers XRCC1, hOGG1 and APEX genes etc. while nucleotide excision repair pathway repairs bulky lesions such as pyrimidine dimers, large chemical adducts and involves ERCC1, XPD, XPC and XPF genes etc. Double strand break repair (DSB) is achieved by homologous/non homologous pathway and involves BRCCA1, BRCCA2 and XRCC3 genes etc. Because of the importance of maintaining genomic integrity in the general and specialized functions of cell as well as in prevention of carcinogenesis, genes coding for DNA repair molecules have been proposed as candidate cancer susceptibility genes. Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA, which may eventually lead to genetic instability and carcinogenesis. Assessment of effect of modifications may be particularly beneficial in studies of DNA repair polymorphisms because it would be conspicuous only in the presence of DNA damaging agents such as tobacco smoke or ionizing radiation. Besides as cancer treatment regimens are often based on the induction of DNA damage, DNA repair polymorphisms may prove relevant in pharmacogenetics by modifying the repair capacity in response to cytotoxic or radiation therapy. Table 1 shows the gene(s) whose polymorphism plays important role in cancer susceptibility particularly in India.

Table 1: List of genes studied whose polymorphism affects oral cancer risk with special reference to India

Effective roles	Genes
Xenobiotic metabolizing Phase-1 enzymes	CYP1A1, CYP2E1
Xenobiotic metabolizing Phase-2 enzymes	GSTT1, GSTP1, GSTM1, GSTM3, NAT-2
DNA repair genes	XRCC1, XRCC3, XPC, XPD, HOGG1

PHASE-1 and PHASE-2 ENZYMES

Phase-1 xenobiotic metabolizing enzymes include members of cytochrome P450 (CYPs).The CYP1A1 encodes an aryl hydrocarbon hydoxylase enzyme that catalyzes the oxidation of polycyclic aromatic hydrocarbons (PAH's) to their phenolic metabolite or diol epoxide. A transistion from T to C in the $3'$ non coding region results in the introduction of an Msp1 restriction site. The ile/val polymorphism occurs because of an A-G transistion at exon 7 in this gene. CYP2E1 is involved in the metabolic activation of N-nitroso-compounds and other low molecular weight carcinogens. Rsa1 and Pst1 restriction fragment length polymorphism (RFLP) are located in the transcription regions of this gene while CYP2E1 Dra1 is located on intron 6. There are conflicting reports on the association of CYP1A1 polymorphisms and oral cancer. Most of studies have reported that CYP1A1 Msp polymorphism is associated with risk of oral cancer (Tanimoto *et al.*, 1999; Sato *et al.*, 1999; Cha *et al.*, 2007). However there is certain degree of ambiguity as other workers have not found any link between Msp polymorphism and oral cancer (Gattas *et al.*, 2006). Similarly, studies by various researchers have observed that CYP1A1 exon 7 (ile/val) polymorphism is risk factor for oral cancer (Park *et al.*, 1997; Lazarus *et al.*, 1998; Sato *et al.*, 2000) but this has also been contradicted by other workers (Hahn *et al.*, 2002; Xie *et al.*, 2004; Leichsenring *et al.*, 2006). Studies have also reported association of CYP2E1 Rsa1 and Pst1 polymorphisms with oral cancer (Gattas *et al.*, 2006; Hung *et al.*, 1997).

In India, various studies have been done to assess the association of phase-1 enzymes (CYPs) with risk of oral cancer (Sreelekha *et al.*, 2001; Sikdar *et al.*, 2003; Anantharaman *et al.*, 2007). CYP1A1 (Ileu/Val) genotype has been reported to be associated with increased risk of oral cancer in Kerala state, Southern India (Sreelekha *et al.*, 2001) but not with oral leukoplakia in Kolkota, Eastern part of the country (Sikdar *et al.*, 2003). Further it was observed that CYP1A1 Msp1 polymorphism does not independently confer risk to Oral Squamous Cell Carcinoma (OSCC) in Indian population but confers risk only in presence of tobacco as an environmental exposure factor (Anantharaman *et al.*, 2007). It was reported that rare C allele at the Dra1 polymorphic site in CYP2E1 gene enhances susceptibility to leukoplakia among tobacco users in Eastern India (Kolkata) while CYP2E1 Pst1 and Rsa1 polymorphisms were not associated with risk of leukoplakia in this population (Sikdar *et al.*, 2003).

Phase-2 enzymes include members of various transferases such as N-acetyl transferase, sulfo transferase, glucorynyl transferase and glutathione transferase. Glutathione S-transferases (GST's) are a superfamily of ubiquitous, multifunctional enzymes that facilitate detoxification thus protecting cell from oxidative stress. GSTM1 catalyzes the conjugation of tripeptide GSH to PAH diol epoxides where as GSTT1 participates in detoxification of monohalomethanes and reactive diol epoxides. GSTP1 plays an important role in detoxification of carcinogenic compounds such as benzo(a) pyrene diol epoxide. The Val 105 form of GSTP1 enzyme has been reported to be 2-3 times less stable than canonical ile 105 form. GSTM1 null genotype has been considered as a risk factor for OSCC (oral squamous cell carcinoma) development (Sato *et al.*, 1999; Gattas *et al.*, 2006; Sato *et al.*, 2000; Hung *et al.*, 1997; Katoh *et al.*, 1999; Nomura *et al.*, 2000; Kietthubthew *et al.*,

2001; Drummond *et al.*, 2004; Peters *et al.*, 2006), although, studies from some other groups have negated such association (Tanimoto *et al.*, 1999; Cha *et al.*, 2007; Park *et al.*, 1997; Hahn *et al.*, 2002; Deakin *et al.*, 1996; Hatagima *et al.*, 2008). Furthermore, one study has observed that GSTM1 null genotype is associated with decrease in oral cancer risk (Xie *et al.*, 2004). Similarly, most of studies have reported that there is no association of GSTT1 null genotype with oral cancer (Gattas *et al.*, 2006; Xie *et al.*, 2004; Katoh *et al.*, 1999; Kietthubthew *et al.*, 2001; Hatagima *et al.*, 2008; Suzen *et al.*, 2007) but other studies have reported that GSTT1 null genotype is risk factor for oral cancer development (Hung *et al.*, 1997; Olshan *et al.*, 2000; Drummond *et al.*, 2005). However, one study (Peters *et al.*, 2006) has reported that GSTT1 null genotype is associated with decrease in oral cancer risk. There are conflicting reports in literature on the association of GSTP1 polymorphisms and oral cancer. Most of the studies have observed no association between polymorphisms at GSTP1 and susceptibility to oral squamous cell carcinoma (Leichsenring *et al.*, 2006; Peters *et al.*, 2006; Hatagima *et al.*, 2008) but some studies have observed positive association between GSTP1 polymorphisms and oral cancer risk (Matthias *et al.*, 1998).

In India, various studies have been done to assess the association of phase-2 enzymes with risk of oral cancer (Sreelekha *et al.*, 2001; Anantharaman *et al.*, 2007; Buch *et al.*, 2002). Most of the studies have observed that GSTM1 null genotype is a risk factor for development of oral cancer among Indian tobacco habituals (Lazarus *et al.*, 1998; Sreelekha *et al.*, 2001; Anantharaman *et al.*, 2007). Besides, GSTM3 (A/A) genotype has been reported to be associated with the risk of both oral cancer and leukoplakia in smokers in Kolkota, Eastern India (Sikdar *et al.*, 2004) but not in Mumbai, Western India (Buch *et al.*, 2002). Further one study (Majumder *et al.*, 2005) has reported that simultaneous presence of two risk genotypes in smokers, one on each of the two loci, GSTM3 and XRCCI (codon 280), increased the risk of oral cancer. Most of studies (Sreelekha *et al.*, 2001; Sikdar *et al.*, 2004; Sharma *et al.*, 2006, Gatoo, 2008) have reported that GSTT1 null genotype is significantly associated with increased risk of oral cancer in Indian tobacco habituals while one study has found no such association (Buch *et al.*, 2002) and other study (Anantharaman *et al.*, 2007) has reported that GSTT1 null genotype acts as a protective factor in OSCC development in Indian tobacco habituals and reduces risk of oral cancer. There are conflicting reports about association of GSTP1 polymorphisms with oral cancer in India. While one study (Sikdar *et al.*, 2004) has found significant association between GSTP1 codon105 polymorphism and oral cancer, other study (Soya *et al.*, 2007) reported that although there was no significant association between GSTP1 codon 105 polymorphism and UADT cancer risk, but in presence of potential hazardous environmental factors and genotypes, a significant gene-environment as well as gene-gene interaction was observed among the carriers of the GSTP1 polymorphisms.

DNA REPAIR ENZYMES

DNA repair enzyme X-ray repair cross-complementing group (XRCC1) is thought to be involved in the base excision repair of oxidative DNA and single strand break repairs. XRCC1 protein is proposed to interact with poly (ADP-ribose) polymerase and DNA ligase 111 in recognition and rejoining of DNA strand breaks and with DNA polymerase β in base excision repair. The human 8-oxoguanine glycosylase 1 (hOGG1) encoded by the hOGG1 gene located on chromosome 3p 25/26 can directly remove 8-hydroxy- 2-deoxyguanine (8-OHdG) from damaged DNA as a part of BER pathway (Blot *et al.*, 1988; Elwood *et al.*, 1984). 8-OHdG is highly mutagenic because of its propensities to mispair with adenine during DNA replication and to cause ultimately GC to TA

transversion. XRCC3 gene is located in the 14q32.3 region and participates in DNA double strand break/recombinational repair and is a member of a family of Rad-51-related proteins that probably participate in homologous recombination to maintain chromosomal stability and repair DNA damage. The xeroderma pigmentosum group D (XPD) protein is an evolutionary conserved helicase, a subunit of transcription factor 11 F (TH11F) that is essential for transcription and nucleotide excision repair. Mutation in XPD prevents its protein product from interacting with p44, another subunit of THF11 and reduces its helicase activity, resulting in a defect in NER. The xeroderma pigmentosum group C (XPC) is involved in the recognition and initiation of nucleotide excision repair pathway and binds to HR23B to form the stable XPC-HR23B complex, which recognizes and binds to damaged DNA. The associations of various polymorphisms of DNA repair gene XRCC1 with oral cancer has been reported by various studies (Kietthubthew *et al.*, 2006; Ramachandran *et al.*, 2006) but some other studies (Yen *et al.*, 2008; Majumder *et al.*, 2007) have observed that none of XRCC1 polymorphisms is independent risk factor for OSCC but in combinations with other DNA repair genes, XRCC1 modulates the risk of oral cancer. The association of XRCC3 (241Met) polymorphism with oral cancer development was reported by one study (Kietthubthew *et al.*, 2006) while other study (Benhamou *et al.*, 2004) did not found such association in UADT cancers. hOGG1 Ser 326 Cys polymorphism was shown to modulate risk of oral cancer in some studies (Elahi *et al.*, 2002) but not by other studies (Zhang *et al.*, 2004). There are conflicting reports about association of XPD polymorphisms with oral cancer. While some studies have reported positive association between XPD polymorphisms and oral cancer (Kietthubthew *et al.*, 2006; Ramachandran *et al.*, 2006; Wang *et al.*, 2007), others have found no such association (Bau *et al.*, 2007).

There are only few studies that have studied association of polymorphisms of DNA repair genes with oral cancer in India. In southern India, it was observed that presence of polymorphic variants of XRCC1 codon 194 and 399 and XPD codon were independently associated with risk of oral cancer (Ramachandran *et al.*, 2006) but in Eastern India (Kolkota), it was reported that variant genotypes on three polymorphic sites of XRCC1 (codon 194, 280, 399) and one site on XRCC3 (codon 241) did not modulate risk of oral cancer independently but simultaneous presence of two risk genotypes in smokers, one on each of the two loci, GSTM3 and XRCC1 (codon 280), increased the risk of oral cancer (Majumder *et al.*, 2005). Further it was observed that in tobacco users carrying susceptible NAT2 (N-acetyl transferase-2) and DNA repair loci, none of the SNPs on NAT2, XRCCI and XPD loci could independently modify the risk of oral cancer in Eastern India (Kolkata) but two loci in combination, working in two different biochemical pathways, could modulate risk of oral cancer in this population (Majumder *et al.*, 2007).

CONCLUSION

It can be concluded that the effect of polymorphisms of phase-1 and phase-2 xenobiotic metabolizing enzymes and DNA repair genes on estimation of oral cancer risk shows variation in different populations and even within same population, conflicting results have been observed in different areas for the same gene polymorphism. The observed discrepancies among studies could be due to population specific differences as well as sample size and multiple subgroup analysis. Thus future studies should involve more number of subjects for the better evaluation of significance of genetic markers in cancer assessment as has been evaluated by Khan *et al.* (2007a, b) and Arif *et al.* (2009) for treatment of cancer related aspects. Besides in order to confirm gene involvement in the absence

of functional evidence, more SNP's of a specific gene should be studied to better define population specific tagging SNP's. As cancer is a multifactorial disease, more than one genetic parameters would influence cancer causation by environmental agents so role of combined effect of polymorphisms of various metabolic and DNA repair genes should be investigated to ascertain their role in oral cancer susceptibility.

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