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Short Communication Open Access

Single Nucleotide Polymorphisms and Risk of Oral Cancer: Indian Case-Control Study

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Short Communication

Oral cancer is ranked as the thirteenth most common cancer in the world with an annual incidence of 300,373, mortality rate of 145,238 and five year prevalence of 702,149 [1]. In India, it is a major health concern with an annual incidence of 77,003 constituting 26% of the global burden [1]. The common sites in oral cancer primarily include tongue (C01, 2), alveolus and gingival (C03), floor of mouth (C04), palate (C05) and buccal mucosa (C06) as per International Classification of Diseases (ICD-10) guidelines. Despite the easy accessibility and advances in treatment including surgery, radiotherapy, chemotherapy and targeted biological therapy, the prognosis of oral cancer is poor with a 5-year survival rate of 40% [2]. Tobacco and areca nut chewing are high risk factors of oral cancer, particularly in Asian countries [3]. Tobacco and areca nut contain several genotoxic and carcinogenic metabolites including tobacco-specific nitrosamines, polycylic aromatic hydrocarbons, volatile aldehydes and hydroquinones [4]. The nicotine derived nitrosamines-N'nitrosonornicotine (NNN) and 4 (methylnitrosoamino)-1-(3 pyridyl)-1butanone (NNK), and areca nut alkaloids- arecoline and arecaidine, may cause oral submucosal fibrosis (OSF), precancerous oral lesions and oral cancer [5]. A dose response association has been observed between frequency and duration of tobacco chewing and oral lesions/malignancies [3]. Besides, alcohol and high risk oncogenic virus HPV types 16/18 comprise important contributory risk factors to oral cancer [6,7] as indicated in Table 1, with carcinogenicity often dose-dependent.

Despite the lifestyle habits of exposure to high risk factors for oral cancer with 80% attributable risk of tobacco per se, a small proportion of the tobacco habitués develop persistent premalignant lesions, and 3-8% transform to the malignant phenotype [8]. Genomic variants, somatic mutations and epigenetic regulation play a critical role in oral cancer. The focus of the current communication is to highlight the role of genomic variants commonly represented as Single Nucleotide Polymorphisms (SNPs) in oral cancer. The SNPs are single base changes present in >1% of an ethnic population, present in the exonic coding region of the gene or in the non-coding intronic regions, directly or indirectly affecting gene expression and function [9]. In the intronic regions, SNPs may alter the three dimensional structure of DNA resulting in changes in characteristics of the molecule such as Gibbs free energy affecting stability of the molecule, and may impact DNA polymerase activity and transcription factor binding [10]. SNPs may be present in a single allele or both alleles resulting in heterozygous or homozygous genotypes. The ancestral allele is the wild-type (WT) allele and the altered allele is the SNP allele. The differential frequency of the allelotypes and genotypes in a cancer case-control cohort indicates association of the SNPs with the cancer.

High Risk factors	Carcinogenic compounds	% Attributable risk	Reference
Tobacco – Smoking and smokeless	N'nitrosonornicotine (NNN), 4 (methylnitrosoamino)-1-(3 pyridyl)-1butanone (NNK)	75-80	[4,5,29]
Areca nut (with/without betel nut)	arecoline and arecaidine	50	[4,29]
Alcohol	N-nitroso compounds (beers), mycotoxins (wines and maize beer), urethan (fruit brandies), tannins (wines), inorganic arsenic and other pesticide residues, and asbestos filtration products	7-19	[6,26,29]
HPV 16/18	E6 and E7 oncogenic proteins	5-10	[7,27,28]
Diet (Probable Risk)	Micronutrient deficiency	10-15	[29]

Table 1: High risk factors associated with oral cancer.

DNA methylation is an epigenetic regulation resulting in transcriptional silencing of genes and plays an important role in early and advanced stages of oral cancer [11]. The relationship between SNPs and DNA methylation have been studied in several non-communicable diseases including obesity [12], bipolar disorder [13], alcohol dependence [14], as well as cancers of breast, colon, lung, liver, kidney, prostate, etc [15]. Methylation quantitative trait loci (meQTL), demonstrates a direct relationship between SNPs and DNA methylation, with SNPs in non-coding sequences regulating methylation with functional roles in cancer [15]. SNPs and DNA methylation have been independently investigated in oral cancer; and thus a link between the two regulatory functions is not established.

SNP studies in various populations emphasize association of SNPs with risk predisposition or susceptibility to oral cancer. Our group has recently reviewed SNPs in oral cancer in a meta-analysis study and defined 34 SNPs in 30 genes significantly associated with oral cancer [16]. The SNPs associated with oral cancer in multiple studies and varied populations included SNP rs1800471 in TGF-β gene with GC genotype associated with increased risk and GG genotype with decreased risk; SNP rs1048943 in CYP1A1 gene resulting in increased risk with AG+GG genotypes and decreased risk with WT AA genotype. GSTM1 null genotype showed association with increased

risk and the WT with decreased risk. Similarly heterozygous genotypes of SNP rs1800870-AG in *IL-10* gene, rs11549467-GA in *HIF* gene and rs861539-CT in *XRCC3* genes, indicated increased risk of oral cancer; whereas the corresponding WT genotypes were associated with decreased risk. On the other hand, the WT genotype rs1801133-CC in *MTHFR*, and rs20417-GG in *COX-2* demonstrated an increased risk, with the corresponding SNP homozygous genotypes TT and CC respectively, associated with decreased risk [16] as indicated in Table 2. The meta-analysis studies provide cumulative data on a number of SNPs in various ethnic populations.

SNP (Gene)	Genotype p-value	Reference	SNP (Gene)	Genotype p-value	Reference
rs1982073 (*TGF-β1*)	TT p=0.0004; CC p=0.0004	[30]	rs16944 (*IL - 1β*)	TT p=0.017; CT+TT p=0.02	[43]
rs189037 (*ATM*)	AA p=3.71*10-6	[31]	rs187238 (*IL-18*)	GC p=0.003	[44]
rs34329 (*p27*)	GG p<0.0001	[32]	rs1800625 (*RAGE*)	TC p<0.05; TC+CC p<0.05	[45]
rs3092904 (*Rb*)	AA p=0.006		rs1801157 (*SDF-1*)	GA p<0.05	[46]
rs647451 (*Cyclin D1*)	CT p<0.0001; TT p<0.0001		rs2124437 (*RASGRP3*)	AA p<0.000	[19]
rs3217901 (*Cyclin D2*)	AG <0.0001; GG p<0.0001		rs4512367 (*PREX2*)	CC p=0.008; CT p=0.004; TT p<0.000	[19]
rs1406 (*Cyclin E*)	GT p<0.0001; TT p<0.0001		rs1335022 (*GRIK2*)	CT p=0.029; TT p=0.008	[19]
rs3093816 (*Cyclin H*)	TC p<0.0001; CC p<0.0001		rs1800734 (*hMLH1*)	GG p=0.006	[47]
rs14133 (*CRYAB*)	GG p=0.0002	[33]	rs1130214 (*AKT1*)	GT+TT p=0.006	[48]
rs1412115 (*Neuropilin-1*)	AG p=0.036; AG+GG p=0.042	[34]	rs3803300 (*AKT1*)	AG p=0.03; GG p=0.003	
rs2236307 (*MMP-14*)	TC p<0.05; TC+CC p<0.05	[35]	rs9904341 (*Survivin*)	GG p<0.05	[49]
rs4880 (*SOD*)	TC p=0.037	[36]	rs2071214 (*Survivin*)	AA p<0.05	
445C/T (*SULT*)	CT p<0.01	[37]	rs1042489 (*Survivin*)	TT p<0.05; CT+TT p<0.05	
507C/T (*SULT*)	CT p<0.01		rs1800471 (*TGF-β1*)	GG p<0.000; GC p<0.000	[16]
rs187115 (*CD44*)	AG p<0.05; GG p<0.05; AG+GG p<0.05	[38]	rs1048943 (*CYP1A1*)	AA p=0.009; AG+GG p=0.003	[16]
rs5498 (*ICAM-1*)	CG p<0.05; GG p<0.05; CG+GG p<0.05	[39]	Null (*GSTM1*)	WT p<0.000; Null p<0.000	[16]
rs2070874 (*IL-4*)	TT p=0.006	[40]	rs1801133 (*MTHFR*)	CT p=0.007; TT p=0.001	[16]
rs1800795 (*IL-6*)	GG p=0.008	[40]	rs1800870 (*IL-10*)	AA p<0.000; AG p<0.000; GG p<0.000	[16]
rs2275913 (*IL-17A*)	GG p=0.018;	[41]	rs1800871 (*IL-10*)	TT p<0.000;	[16]

	AG+GG $^{p=0.043}$			CT $^{p=0.044}$	
rs9382084 (*IL-7F*)	GG $^{p=0.03}$		rs20417 (*COX-2*)	GC+CC $^{p<0.000}$; GG $^{p<0.000}$	[16]
rs10889677 (*IL-23 R*)	AC+CC $^{p=0.012}$	[42]	rs11549467 (*HIF*)	GG $^{p=0.007}$; GA $^{p=0.011}$	[16]
			rs861539 (*XRCC3*)	CC $^{p=0.021}$; CT $^{p=0.034}$	[16]

Table 2: SNPs and associated Genes indicating risk to oral cancer.

Analysis of SNPs via high throughput genomic analysis as reported in genome-wide association studies (GWAS) and next generation sequencing have emerged as a powerful approach to identify susceptibility loci enabling information on thousands of SNPs simultaneously. These platforms generally use smaller samples and are rather expensive and need to be validated in larger samples using alternative technology including nucleotide sequencing and Real-time PCR [17]. A highthroughput microarray study by Saranath et al. in 55 oral cancer patients and 92 healthy controls identified 93 SNPs in 70 genes with association to oral cancer. A majority of the genes (33.6%) containing SNPs were associated with cell signal transduction [18]. Hence, representative SNPs in genes critical in biological functions were examined in 500 oral cancer patients and 500 healthy long term tobacco habitués as controls [19]. The 500 oral cancer patients were histopathologically confirmed and were obtained from Prince Aly Khan hospital, Mumbai, India. The controls were tobacco users with an average duration of 18.1 years (median 15 years) of tobacco habit, obtained from cancer screening camps conducted by Cancer Patients aids association, Mumbai, India. The age, gender, tobacco habits and clinicopathological data was recorded. DNA was extracted from peripheral blood samples using PureLink DNA extraction kit as per manufacturer's instructions (Invitrogen, CA, USA) and checked using Nanodrop Spectrophotometer 2000 (Thermoscientific, Walthman, USA).

We examined a panel of SNPs constituting rs2124437 in *RASGRP3*, rs1335022 in *GRIK2*, rs4512367 in *PREX2*, rs4748011 in *CCDC3* and rs1435218 in *LNX1* genes. Allelic discrimination Real-time PCR assay with SYBR green dye and melt-curve analysis was used to determine the frequency distribution of the various alleles and consequent genotypes in the oral cancer patients and controls. The melt curves of the SNPs were analyzed using StepOne software v2.3. The genotyping and sequencing primers were designed using AlleleID software and are listed in Multani et al. along with the detailed protocol [19]. The amplimers for genotyping ranged 89 to 148 bp and for nucleotide sequencing, 430 to 544 bp, sequenced on automated genetic analyzer ABI 3730xl (Foster City, CA, USA) at SciGenom Adyar, Chennai, India. The results demonstrated that rs1335022 (*GRIK2*) WT C allele was associated with decreased risk to oral cancer [OR 0.73 (0.6-0.88)]. Further, heterozygous genotypes in rs1335022 (CT) [OR 0.68 (0.53-0.870] and rs4512367 (*PREX2*) (CT) [OR 0.49 (0.37-0.64)] demonstrated decreased risk. Whereas, the homozygous SNP genotypes in rs2124437 (*RASGRP3*) (AA) [OR 1.34 (1.01-1.76)], rs1335022 (TT) [OR 1.58 (1.23-2.03)], rs4512367 (TT) [OR 2.77 (1.68-4.570] and WT genotype in rs4512367 (CC) [1.56 (1.15-2.10)] showed significantly higher frequencies in oral cancer patients indicating an increased risk with oral cancer. On the other hand, SNPs rs4748011 (*CCDC3*) and rs1435218 (*LNX1*) genotypes and alleles showed equidistribution in oral cancer and control groups, thus indicating absence of association with oral cancer (Table 3). SNP based variants are primarily low penetrant alleles, and a panel of SNPs with differential frequency distribution may better reflect increased or decreased risk with higher susceptibility or protection to oral cancer. Hence, coinheritance of a panel of high-risk SNPs exhibiting increased risk individually in the Indian cohorts including rs2124437 (*RASGRP3*), rs1335022 (*GRIK2*) and rs4512367 (*PREX2*) were examined. We observed that simultaneous presence of the three high risk genotypes further increased risk of oral cancer [OR 4.99 (1.89-13.19)] indicating that SNP-SNP interactions may be involved in increasing the risk to oral cancer [19].

SNP ID WT → SNP (Gene)	**Genotypes**	**Indian Cohort (n=1000)**	**Oral Cancer (n= 500)**	**Control (n= 500)**	**P value**	**OR (95% CI)**
rs2124437 C → A (*RASGRP3*)	CC	0.072	0.064	0.080	0.413	0.79 (0.49-1.27)
	CA	0.647	0.626	0.668	0.409	0.83 (0.64-1.08)
	AA	0.281	0.31	0.252	**<0.000**	1.34 (1.01-1.76)
rs1335022 C → T (*GRIK2*)	CC	0.084	0.074	0.094	0.275	0.77 (0.49-1.21)
	CT	0.445	0.398	0.492	**0.029**	0.68 (0.53-0.87)
	TT	0.471	0.528	0.414	**0.008**	1.58 (1.23-2.03)

rs4512367 C → T (*PREX2*)	CC	0.229	0.268	0.190	**0.008**	1.56 (1.15-2.10)
	CT	0.689	0.614	0.764	**0.004**	0.49 (0.37-0.64)
	TT	0.082	0.118	0.046	**<0.000**	2.77 (1.68-4.57)
rs4748011 T → C (*CCDC3*)	TT	0.017	0.02	0.014	0.467	1.44 (0.54-3.81)
	TC	0.361	0.382	0.340	0.227	1.19 (0.93-1.55)
	CC	0.622	0.598	0.646	0.336	0.82 (0.63-1.05)
rs1435218 C → T (*LNX1*)	CC	0.879	0.886	0.872	0.762	1.14 (0.78-1.67)
	CT	0.113	0.106	0.120	0.510	0.87 (0.59-1.29)
	TT	0.008	0.008	0.008	1.000	1.0 (0.25-4.02)
OR: Odds Ratio; CI: Confidence Interval; Source: Multani et al. [19]						

Table 3: Association of SNP genotypes with oral cancer in Indian population.

SNPs in signal transduction genes have also been associated with various cancers. A recent study by Hyland et al. demonstrated association of ten SNPs in Fas signalling pathway with increased risk to gastric cancer [20]; Chen and colleagues demonstrated association of increased risk of four SNPs in the P13K-AKT pathway with bladder cancer [21]; rs1078985 in *TGFBR2* gene showed increased risk to breast cancer [22]; and SNP rs3087465 with decreased risk to esophageal cancer [23]. Additionally, exonic SNPs 8227G/A [24], 216G/T and 191C/A [25] in *EGFR* gene was associated increased risk to lung cancer.

Heterogeneity is a characteristic of cancers with genomic, transcriptional, proteomic and epigenomic microheterogeneity reflected at the cellular level as indicated by differential biomarker – *p53*, *EGFR*, expression in the cancer tissues. Besides, response to drugs due to CYP450 polymorphisms; *K.Ras*/*EGFR* mutations are used for stratification of cancer patients for appropriate targeted therapy. Identification of SNPs is mandatory in determination of optimal warfarin dose in several clotting disorders [50,51]. The SNP rs1801282 in Peroxisome Proliferator-Activated Receptor Gamma (*PPARγ*) gene indicates risk to Type 2 diabetes, and is associated with pathogenesis of the disease [52]. Our study identified SNPs and their association with increased/decreased risk in oral cancer, and hence indicate 'Predictive Biomarkers' to screen high-risk individuals in tobacco habitués. The SNPs may define binding sites for small drug like molecules. The information from next generation sequencing technology and *in silico* drug designing, will facilitate molecular classification and stratification of cancers, define cancer gene fingerprints, identify drug targets and prove useful in Precision/Personalized Medicine.

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