iJRASET

International Journal For Research in
Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 9 Issue: V Month of publication: May 2021

DOI: <https://doi.org/10.22214/ijraset.2021.34570>

www.ijraset.com

Call: 08813907089

E-mail ID: ijraset@gmail.com

Genetic Polymorphism and Susceptibility to Oral Cancer

Ayushi Chaudhary¹, Divya Sethi², Aekansh Chaudhary³, Bankey Bihari⁴, Runjhun Mathur⁵, Abhimanyu Kumar Jha⁶

^{1, 2, 3, 5, 6}Department of Biotechnology, Faculty of Life Sciences, Institutes of Applied Medicines and Research, Ghaziabad (U.P.), India.

⁵Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

Abstract: Oral cancer, a disease which is linked to severe illness and death, illustrate a serious global health concern. It has been proved that the tobacco and alcohol exposure are main causative factors for oral cancer. Oral cancer is caused by a number of variables, including the alcohol, human papillomavirus (HPV), tobacco, cigarettes, areca nut, and genetic factors such as DNA alterations, infection, and poor dental hygiene. Tobacco smoke contains more carcinogenic precursors than other tobacco products, carcinogenic precursors in tobacco smoke namely as benzopyrene and nitrosamine, that are activated by metabolic enzymes, phase I and phase II and for these enzyme genes there are a few polymorphisms present, and these types of polymorphisms alter their function. It has been demonstrated that oral susceptibility has been linked to metabolic activity. However, there are some genes apart from these enzyme genes linked with cancer development. The genetic variants are also commonly addressed as single nucleotide polymorphisms (SNPs) and there are approx. ten million SNPs in the human genome. The SNPs were found on genes involved in a different biological functions including cell proliferation, signal transduction, DNA repair, apoptosis, immune function and metabolic activity. In this review, we confer about the connection between polymorphisms linked to oral cancer. Even though there are many research reports on the polymorphisms associates with oral cancer, but the result of these reports are doubtful. Later more researches are needed to determine how carcinogens interacts with the genetic polymorphism or genetic variations. For accurate assessments of the relationship between genetic polymorphism and oral malignant risk, many evidences highly suggested that age, sex, identity, diet, environmental exposure, and gene-gene interactions should be considered.

Keywords: oral cancer, genetic polymorphism, SNPs oral cancer risk, risk factors, genetic association.

I. INTRODUCTION

Oral cancer, a disease which is linked to severe illness and death, illustrate a serious global health concern. It is thirteenth most common cancer in the world. According to worldwide disease categorization guidelines, the tongue, alveolus and gingiva, floor of mouth, palate, and buccal mucosa are the most common sites in oral cancer. Every year around 657,000 new cases of oral cancer are diagnosed in Asia linked with high death rate. Oral cancer is commonly high among men. In spite of easy access and advancement in diagnosis, for example, surgery, radiotherapy, chemotherapy and targeted biological therapy, oral cancer is poorly prognosis at 40% for 5 years of survival [4]. Oral cancer is caused by a number of variables, including the alcohol, human papillomavirus (HPV), tobacco, cigarettes, areca nut, and genetic factors such as DNA alteration [1],[2], infection, and poor dental hygiene [3]. Tobacco and areca nut chewing is a major cause of oral cancer, especially in Asian Countries [5]. Tobacco smoke contains more carcinogenic precursors than other tobacco products, carcinogenic precursors in tobacco smoke namely as benzopyrene and nitrosamine, that are activated by metabolic enzymes, phase I and phase II and for these enzyme genes there are a few polymorphisms present, and these types of polymorphisms alter their function. It has been demonstrated that oral susceptibility has been linked to metabolic activity. However, there are some genes apart from these enzyme genes linked with cancer development. The genetic variants are also commonly addressed as single nucleotide polymorphisms (SNPs) and there are approx. ten million SNPs in the human genome. It has been defined that 34 SNPs in 30 genes represents a major association with oral cancer, and while 59 SNPs in 25 genes represents no association. The SNPs were found on genes involved in a different biological functions including cell proliferation, signal transduction, DNA repair, apoptosis, immune function and metabolic activity. With a view to better understand the significance of genomic variations in oral cancer. The PubMed and HUGE guide search engines were used to find data or research study using the terms 'oral cancer,' 'risk,' 'SNP,' and 'polymorphism, that identified the role of SNPs in oral cancer from the past date to update.

II. HIGH RISK FACTORS OF CARCINOGENIC COMPOUND LINKED WITH ORAL

A. Tobacco

Tobacco consumption remains the leading cause of cancer death, accounting for millions of deaths every year. Epidemiological studies have firmly identified the connection between smoking and oral cancer [6]. The most common carcinogens in tobacco smoke are the aromatic hydrocarbon benz-pyrene, as well as the tobacco-specific nitrosamines (TSNs) 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosornicotine (NNN). In animal studies, NNK and NNN in tobacco products have been shown to induce tumors of the oral cavity, lungs, oesophagus, and pancreas. When NNK, NNN, and their metabolites form DNA adducts when they bind covalently to the deoxyribonucleic acid (DNA) of keratinocyte stem cells [7]. Indispensable DNA replication mutations are caused by these adducts. Oxidation by P450 enzymes in cytochromes and conjugation by glutathione S-transferase are involved in the synthesis of these carcinogens (GST). [7] Genetic polymorphisms in these enzyme-coding genes are believed to play a role in the genetic predisposition to tobacco-induced head and neck cancers [8].

B. Betel Quid

In Southeast Asia, mainly in the Indian subcontinent, betel quid chewing with various ingredients is a common practice. Betel quid (also known as pan or paan) the most popular ingredients are betel leaf (leaf of the Piper betel vine), areca nut, slaked lime, and tobacco. These products have been linked to the development of oral cancer. Tobacco chewing has been linked to oral cancer and precancers including leukoplakia, erythroplakia, and oral submucous fibrosis [9]. Recent studies have focused on the carcinogenic, mutagenic, and genotoxic potential of betel quid ingredients, particularly tobacco and areca nut [10].

C. Alcohol

The consumption of alcohol has been linked to the development of oral cancer. Alcoholic beverages are thought to be carcinogenic to humans, causing tumors of the oral cavity, pharynx, larynx, oesophagus, and liver. Alcohol consumption has been shown to act synergistically with tobacco in increasing the risk of developing oral cancer. Few studies have been conducted on patients who drink alcohol but do not smoke, as well as patients who smoke but do not drink [11]. Alcohol was discovered to be an independent risk factor for oral leukoplakia in an Indian population [12]. Alcoholic beverages have been found to contain substances that are assumed to be carcinogenic to humans, examples such as N-nitroso compounds, mycotoxins, urethane, inorganic arsenic, and others. Acetaldehyde is the most important metabolite of alcohol, and it is primarily transformed by the enzyme alcohol dehydrogenase (ADH). Aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate. In cultured mammalian cells, acetaldehyde causes DNA damage. It disrupts the DNA synthesis and repair of DNA. Genetic polymorphisms in these two enzymes, ADH and ALDH, have been linked to an increased risk of alcohol-related cancers [13].

D. Virus Infection

Viruses have been strongly connected to the development of malignant squamous epithelial tumors, including the oral squamous epithelium. Human herpes virus, human papillomavirus (HPV), and herpes simplex virus are the prototypic viruses implicated in the development of oral cancer [14]. HPV is the most common virus investigated in oral carcinogenesis. HPV are DNA viruses that are epitheliotropic, particularly in squamous epithelia. They cause papillomas, condyloma acuminatum, verruca vulgaris, and focal epithelial hyperplasia (Heck's disease). Certain HPV types like HPVs 16, 18, 31, 33, 35, and 39 are involved and known as 'high-risk' types, have been linked to OSCC and oral premalignant lesions. The evidence of HPV's role in cancer development is due to the ability of HPV genes and gene products to disrupt the cell cycle machinery. The E6 and E7 are two main HPV-encoded oncoproteins. The E6 and E7 proteins have been shown to bind it and severely damage the tumor suppressor genes p53 and Rb, respectively, disrupting the cell cycle and causing a loss of control over DNA replication, repair, and apoptosis. Various techniques have been used to detect HPV in OSCC. HPV has been found in normal oral mucosa in some studies, raising the possibility about its own role in oral carcinogenesis [15].

There have been a number of genotoxic and carcinogenic metabolites found in tobacco and areca nut, including tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, aldehydes and hydroquinones [10]. The nicotine obtain nitrosamines- N'-nitrosornicotine (NNN) and 4 (methyl nitrosoamino)-1-(3pyridyl)-1butanone (NNK), and areca nut alkaloids-arecoline and arecaine, may cause oral submucosal fibrosis (OSF), precancerous oral lesions and oral cancer [16]. Besides, alcohol and a high risk oncogenic virus HPV types 16/18 comprise important risk factors to oral cancer [17],[18] as indicated in table. There are two types metabolic activation genes and enzymes (phase I and phase II) for chemical agents like benzopyrene and nitrosamine.

HIGH RISK FACTORS RELATED WITH ORAL CANCER			
High risk factors	Carcinogenic compounds	% Attributable risk	Reference
Alcohol	N-nitroso compounds (beer), mycotoxins (wine and maize beer), urethan (fruit brandies), tannins (wine), inorganic arsenic and other pesticide residues, and asbestos filtration products	7-19 %	[17],[19],[22]
HPV 16/18	E6 and E7 oncogenic proteins	5-10%	[18],[20],[21]
Tobacco-Smoking and smokeless	N'nitrosomnicotine (NNN), 4 (methylnitrosoamino)-1-(3 pyridyl)-1 butanone (NNK)	75-80%	[10],[16],[22]
Areca-nut (with/without betel nut)	arecoline and arecaidine	50%	[10],[22]
Diet (Probable Risk)	Micronutrient deficiency	10-15%	[22]

Fig.1: High risk factors linked with oral cancer

III. SNP-ORAL CANCER ASSOCIATION

Oral carcinogenesis is facilitated by epigenetic control of several genes [24]-[26], and genomic variations representing inherent individual differences are important risk factors for the turn of events and progression of normal cells to malignant phenotype [27]. Single nucleotide polymorphisms (SNPs) are also commonly addressed to describe genomic variations, and there are approx. ten million SNPs in the human genome [28], with 3,000,000 SNPs identified in the SNP information base dbSNP with a specific reference ID number [29]. SNPs (single nucleotide polymorphisms) are single base variations in the genome that are observed in more than 1% of the population [30]. It was determined that 34 SNPs in 30 genes had a relation with cancer, while 59 SNPs in 25 genes had no association. When the SNP is present in one or both alleles, heterozygous or homozygous genotypes are identified, and the ancestral allele is referred to as the wild type (WT).

The SNPs investigated were found on genes involved in a different biological functions including cell proliferation, signal transduction, DNA repair, apoptosis, immune function and metabolic activity.

Fig.1: Basic functions of SNP containing genes in oral carcinogenesis. The basic natural elements of DNA damage, cell proliferation, invasion, angiogenesis and apoptosis of genes containing the significant SNPs in oral carcinogenesis are shown. The genes holding the SNPs (light blue circles) and related functions (sky blue boxes) and the interactions are illustrated [23].

A. SNP in Genes Involved in Cell Proliferation

As studied, Oral cancer cases and controls had significant differences in 9 SNPs in variety of genes involved in cell cycle and proliferation, including the transforming growth factor TGF-1, p21, ATM, p27, Rb, and cyclin D1/D2/E/H. In oral cancer cases, homozygous SNP genotypes in ATM [31], p27 [32], and Rb [32] were found to be extensively increased frequency with OR ranging from 1.44 to 3.46. Furthermore, the SNP allele in p21 was shown with an increased risk, with an OR (1.0–2.0) [34], while the WT homozygous genotype in TGF- β 1 [33] and heterozygous and homozygous SNP genotypes in cyclin D1/D2/E/H [32] were found to be more prevalent in controls, suggesting a reduced risk and therefore safety from oral cancer.

B. SNP in Immune Function Associated Genes

The SNP homozygous WT genotype in interleukin-6 (IL-6) [35], heterozygous genotype in SDF-1 [41], IL-18 [39], and RAGE [40], and homozygous SNP genotype in IL- β 1/17A/7F/23R [36]–[38] and RAGE all showed an increased risk of oral cancer, with Odd ratios ranges from 1.75 to 3.05. Moreover, the SNP allele in IL-4/17A/7F/23R has been linked to a higher risk of oral cancer, with OR ranging from 1.4 to 1.74, whereas in controls, the homozygous WT genotype in IL-4 and the SNP allele in IL-6 showed increased frequency, suggesting a connection with a lower risk of oral cancer [35].

C. SNPs in Genes Involved in Cell Growth

The homozygous SNP genotype in CRYAB [45] and heterozygous genotype in neuropilin-1 [46], and also SNP alleles in WNT-11 [48], GSK-3B [48] were all linked to a higher risk of oral cancer, with Odd ratios ranging from 1.4 to 1.96.

The heterozygous MMP-14 genotype was associated with a reduced risk of oral cancer, with an Odds ratio (0.4–0.8) [47].

D. SNPs Involved in Apoptosis and DNA Repair Genes

Five SNPs in two apoptosis-related genes, survivin [44] and AKT1 [43], were linked to an increased risk of oral cancer, with odd ratios ranging from 1.5 to 3.0. Just one SNP in the DNA repair gene hMLH1 had a homozygous SNP genotype with an OR of (3.9–11.5). The SNP allele was also linked to a higher risk of oral cancer with odd ratios ranging from (2.3–4.0) in Indian population [42].

E. SNPs Involved in Cell Metabolism in Genes

Three SNPs in two genes active in cell metabolism, SULT [50] and SOD [49], showed that heterozygous genotypes were linked to a higher risk of oral cancer, with ORs ranging from 1.48 to 5.8.

Interleukins, NAT-1, SOD, CYCLINS, CD44, ICAM, X-ray repair cross-complementing protein 3 (XRCC3), and X-ray repair cross-complementing protein 1 (XRCC1) were among the genes with SNPs that had a p value >0.05 , suggesting that genotypes and alleles had no association with oral cancer.

F. SNPs in Signal Transduction Genes

The homozygous SNP genotypes in *RASGRP3*, *PREX2* and *GRIK2* showed a relationship with a higher risk of oral malignancy, with OR going from 1.34 to 2.77, and the homozygous WT genotype in *PREX2* was higher in cases, demonstrating a relationship with high risk [53]. On the other hand, the heterozygous genotypes in *GRIK2* and *PREX2* showed increased recurrence in controls, suggesting a correlation with a lower risk of oral disease, with OR going from 0.49 to 0.68. Furthermore, two SNPs in genes related with cell interaction including *ICAM-1* [52] and *CD44* [51] illustrated a relationship with an altogether increased risk of oral malignant growth within the sight of heterozygous or homozygous SNP genotype, with OR going from 1.28 to 2.88.

Table I Genes and Associated SNPs Indicating Risk to Oral Cancer

Gene(SNP)	Genotype	p-value	Reference	Gene(SNP)	Genotype	P-value	Reference
TGF- β 1 (rs1982073)	TT	0.0004	[33]	PREX2(rs451236)	CC	0.008	[53]
	CC	0.0004			CT	0.004	
ATM(rs189037)	AA	3.71*10	[31]		TT	<0.000	
p27(rs 34329)	GG	<0.0001	[32]	GRIK2(rs133502)	CT	0.029	[53]
Rb(rs 3092904)	AA	0.006	[32]		TT	0.008	

Cyclin D1(rs647451)	CT	<0.0001	[32]	hMLH1(rs1800734)	GG	0.006	[42]
	TT	<0.0001		AKT1(rs1130214)	GT+TT	0.006	[43]
CyclinD2(rs3217901)	AG	<0.0001		AKT1(rs3803300)	AG	0.03	
	GG	<0.0001			GG	0.003	
Cyclin E (rs1406)	GT	<0.0001		Survivin(rs9904341)	GG	<0.05	[44]
	TT	<0.0001		Survivin(rs2071214)	AA	<0.05	
Cyclin H(rs3093816)	TC	<0.0001		Survivin(rs1042489)	TT	<0.05	
	CC	<0.0001			CT+TT	<0.05	
CRYAB(rs14133)	GG	0.0002	[45]	TGF- β 1(rs1800471)	GG	<0.000	[33],[132]
Neuropilin-1	AG	0.036	[46]		GC	<0.000	
(rs1412115)	AG+GG	0.042		CYP1A1(rs1048943)	AA	0.009	[[66]-[78]
MP-14(rs2236307)	TC	<0.05	[47]		AG+GG	0.003	
	TC+CC	<0.05		GSTM1(Null)	WT	<0.000	[66]-[68],[70]-[75]
SOD(rs4880)	TC	0.037	[49]		Null	<0.000	[77],[82]-[84]
SULT(507C/T)	CT	<0.01	[50]	MTHFR(rs1801133)	CT	0.007	[136]-[139]
CD44(rs187115)	AG	<0.05	[51]		TT	0.001	
	GG	<0.05		IL-10(rs1800870)	AA	<0.000	[132],[134],[135]
	AG+GG	<0.05			AG	<0.000	
ICAM-1(rs5498)	CG	<0.05	[52]		GG	<0.000	
	GG	<0.05		IL-10(rs1800871)	TT	<0.000	
	CG+GG	<0.05			AG+GG	0.043	
IL-4(rs2070874)	TT	0.006	[35]	IL-7F(rs 9382084)	GG	0.03	[36]
IL-6(rs1800795)	GG	0.008	[35]	IL-23R(rs10889677)	AC+CC	0.012	[37]
IL-17A(rs2275913)	GG	0.018	[36]		CT	0.044	
IL-1 β (rs16944)	TT	0.017	[38]	COX-2(rs20417)	GC+CC	<0.000	[141],[142]
	CT+TT	0.02			GG	<0.000	[144],[145]
IL-18(rs187238)	GC	0.003		HIF(rs11549467)	GG	0.007	[146],[147]
RAGE(rs1800625)	TC	<0.05	[40]		GA	0.011	
	TC+CC	<0.05		XRCC3(rs861539)	CC	0.021	[90]-[93]
SDF-1(rs1801157)	GA	<0.05	[41]		CT	0.034	
RASGRP3(rs2124437)	AA	<0.000	[53]	WNT11(rs1533767)	GA	0.03	[48]

IV. ASSOCIATION BETWEEN POLYMORPHISM OF METABOLIC ACTIVATION GENES AND SUSCEPTIBILITY TO ORAL CANCER

A. Cyclin D1

The regular control of the cell cycle assures that there is a period of resting during the cell cycle, allowing the repair of DNA damage, before cell growth, mitosis, and division begins [54]. Cyclin-dependent kinases (CDKs) regulate the cell-cycle transition from the G1 to the S phase [54]. The main cyclins linked to cyclin-dependent kinases are CyclinD-1(CCND1) [55]. In this process, CCND1 represents a major metabolic protein, which plays a key role in the cell cycle transition from G1 to S phase. During the G1 phase, CCND1 movement is maximum and CDK4 and CDK6 are associated with mid to late G1 phase. CCND1 shows a common A/G polymorphism(G870A). The A/A genotype of the CCND1 polymorphism increased susceptibility to squamous cell carcinoma of the head and neck [56]. There were only two reported cases of oral malignancy. A study discovered a correlation between allele A and premalignant oral lesions (OPL) [57]. The CCND1 GG genotype is related to an increased risk of oral squamous cell carcinoma in German patients [58].

B. Cytochrome P450

Cytochrome P450s (CYP) are the phase I catalysts in the stimulation pathway. More than 30 families of CYPs have been discovered in humans yet, and basic CYP families (CYP1A1, CYP1A2, CYP2A6, CYP2C19, CYP2D6) being the most studied. The one of the most studied CYP is CYP1A1, considered to perform a key role in the formation of poly aromatic hydrocarbon compounds (PAH) such as benzo(a)pyrene [30]. CYP1A1 metabolizes benzo(a)pyrene in tobacco smoke to a significant cancer-causing agent, 7 β ,8 α -dihydroxy-9 α ,10 α -oxy-7,8,9,10-tetrahydrobenzo(a)pyrene. CYP1A1 contains two polymorphisms. The CYP1A1 Ile462Val polymorphism is a result of A (CYP1A1*1A) to G (CYP1A1*2C) exchange in exon7, causing a change in an amino acid heme-binding region [31]. The other CYP1A1 polymorphism (MspI polymorphism) is a T (CYP1A1*1A) to C (CYP1A1*2A) transition 1197bp downstream of exon 7 [33]. The MspI polymorphism of the CYP1A1 gene has a risk factor [36]. A meta-investigation showed a critical relationship with a nearly two fold increased risk among oral and pharyngeal malignancy and the CYP1A1 MspI homozygous variation [37]. As of late, another polymorphism of CYP1A1 gene, the isoleucine-valine(Ile-Val) polymorphism, has been accounted for as a threat factor for tobacco related diseases such as oral cancers [38],[39]. However, a report in Japan revealed an interrelation between Val-Val genotype and increased risk of OSCC of the head and neck [41]. The CYP1A1 SNP rs1048943 (AG) causes isoleucine (ATT) to valine (GTT) substitution, and 13 studies have been published, including five Indian [66-70], four Japanese [71]-[74], one Indonesian [75], one Taiwanese [76], and two Brazilian [77],[78] populations. A meta-analysis of oral cancer cases and controls found that the AG+GG SNP genotype was associated with a high risk of oral cancer [$p = 0.003$], whereas the WT AA genotype was associated with a reduced risk of oral cancer [$p = 0.009$]. Several studies have discovered a link between CYP1A1 SNPs and oral cancer, and a combination of risk-associated SNPs may define SNP cancer risk. Regarding other polymorphisms of CYP, it was that the CYP2E1 *Ras/PstI* *cl/cl* and *c2/c2* genotypes were related with a possibly increased risk of oral cancer [79], but there are limited reports about CYP2E1. Further studies will be required for meta-evaluation.

C. Glutathione S-Transferases

Glutathione S-transferases (GSTs) are a very important family of enzymes/catalysts that catalyze the detoxification of a wide types of active metabolites of tobacco cancer-causing agents, for example, benzo(a)pyrene and other polycyclic aromatic hydrocarbons and mono halo-methanes. Therefore, variations in the expression of GSTs because of genetic polymorphism most likely regulate the processing of tobacco-determined cancer-causing agents. Common polymorphisms of GSTs are GSTM1, GSTT1, GSTP1 and GSTM3. GSTM1, GSTT1 and GSTP1 have been assessed frequently. The null genotype of GSTM1 and GSTT1 was related with an increased threat of oral cancer [80], and the GSTM1 null genotype was one of the main factor that comes with the high risk of oral tumor at low levels of cigarette revelation [81]. GSTM1 SNP association studies have been published in six Indian populations [66]-[68], [70], [82], [83], four Japanese populations [71]-[74], and one each from Pakistani [84], Indonesian [75], and Brazilian [77]. A meta-analysis of approx. 2542 cases and 3259 controls revealed that the null genotype is associated with an increased risk of oral cancer ($p = 0.00$; OR 1.8), whereas the WT genotype is associated with a lower risk ($p = 0.00$; OR 0.65). An end hasn't been reached yet. The GSTP1 has variation alleles containing a point mutation at codon 105 and at codon 114. There were a couple of reports on oral malignant growth and GSTP1. The GSTP1 genotypes of codon 105 and 114 could be a risk factor for oral malignant growth, particularly among light smokers [85]. The researchers also revealed that the GSTP1 polymorphism at nucleotide 313 may be connected with vulnerability to oral squamous cell carcinoma in the Japanese population [86].

D. DNA Repair Genes

DNA repair genes are considered to play an effective role in the development of wide range of tumors. DNA repair genes play a role in repairing damaged DNA, and three pathways work on different form of DNA damage are: 1. Base excision repair (BER), 2. Nucleotide excision repair (NER), and 3. Mismatch repair (MMR). X-ray repair cross complementing Protein 1 (XRCC1) is one of the enzymes found in the BER [87]. In terms of oral disease, a lack of XRCC1 (codon194 T allele) was a significant risk factor for oral cavity and pharyngeal cancer, and a lack of XRCC1 (codon399Arg allele) was also a threat factor for oral and pharyngeal malignant growth in smokers or drinkers [88],[89]. Betel quid chewers with the variation allele of (*codon399Arg allele*) additionally showed increased risk of oral tumor. The X-ray repair cross complementing protein 3 (XRCC3) gene is responsible in homologous recombination DNA repair via an interaction with Rad51[80]. The SNP rs861539 has been found in Taiwanese [90],[91], Thai [92], and Brazilian [93] populations. A meta-analysis revealed an association between the heterozygous SNP CT genotype and a higher risk of oral cancer ($p = 0.034$) and the WT CC genotype and a lower risk ($p = 0.021$).

The outcomes about the polymorphism of XRCC1 and oral disease are disputable. The connection between other repair genes (XRCC3 XPC XPD) polymorphisms or oral cancers risk are additionally questionable, yet there were no reports on oral malignancy.

E. *Tp53 Tumor Suppressor Gene*

The tumor protein 53 (Tp53) gene is a tumor suppressor gene. The Tp53 gene mutation can change its DNA-binding properties and transcription function, as well as disrupt cell cycle control and cellular proliferation [94]. It has been discovered that the Codon 72 polymorphism on the 4th exon of the TP53 genes results in variant proteins containing either arginine or proline. But found no link between the TP53 codon 72 polymorphism and the risk of oral cancer in a Brazilian and Southern Thai population [95]. However, these studies no longer used smoking to sub classify patients in order to investigate the relationship between the TP53 polymorphism and cancer risk. They looked at the relationship between Tp53 genotypes and the risk of oral cancer in combination with smoking status. It was discovered that the incidence of oral cancer was significantly higher in nonsmokers with the arginine/proline genotype and the aggregate of arginine/proline and proline/proline genotypes [96]. The study revealed that any proline allele was linked to a higher risk of oral cancer in non-smokers.

F. *Aldehyde Dehydrogenase*

Heavy alcohol drinkers have a higher incidence of various types of oral cancer (floor of mouth, tongue, and lower gingival). It has been proposed that the direct carcinogenic effects of alcohol are capable of progressing these types of oral malignant growth [97]. In terms of the cancer-causing mechanism of alcohol-related malignant growth. The major metabolic chemical of acetaldehyde that is derived from alcohol in the body is aldehyde dehydrogenase (ALDH). At residue 487, a single nucleotide polymorphism in the ALDH2 gene codes for lysine (ALDH2*2) rather than glutamine (ALDH2*1). ALDH2, which is encoded by the gene ALDH2*1/*2, as a risk factor for esophageal and oropharyngolaryngeal cancer [98]. Another study reported that people with ALDH2*1/*2 had a significantly high risk of squamous cell carcinoma w.r.t. head and neck [99], but research on the role of ALDH2 in oral malignant growth is limited. Surprisingly, Nomura [100] discovered that ALDH2 polymorphism was a risk factor for oral cancer. Alcohol dehydrogenase (ADH) also intervenes in the metabolic responses in alcohol utilization. There are at least seven alcohol dehydrogenases (ADH1–ADH7) present in humans. However, ADH1C*1 has been suggested as a risk factor in alcohol-related malignant growths. An investigation of oral malignant growth in Puerto Rico revealed that the ADH1C*1/*1 genotype was a possible cause for oral cancer [101], but it was found that the ADH1C*2 genotype was a risk factor for oral cancer [102],[103].

G. *N-Acetyltransferases*

Polycyclic fragrant hydrocarbons, Aryl- and heterocyclic amines, and nitroso-compounds are the most common carcinogens found in tobacco smoke. N-acetyltransferases (NAT) are a phase II catalyst. NAT1 and NAT2 help facilitate the NO-acetylation of aromatic amines. NAT1 is found in all tissues, while NAT2 is found primarily in the liver and the bladder. Polymorphisms in the NAT1 and NAT2 genes result from precise point mutations that cause phenotypic variation. In humans, at least 15 NAT1 alleles have been identified. There has been conflicting information on head and neck cancer. According to a study [104], the NAT1 polymorphism (NAT1*10/NAT1*4 and NAT1*10/NAT1*10) is associated with a nearly 5-fold increased risk of head and neck cancer in smokers. There haven't been many reports of oral cancers. The NAT1*10 polymorphism was correlated with the presence of oral squamous cell carcinoma in a Japanese population that was unrelated to smoking behavior [105].

H. *Cytokines*

Cytokines are small secreted or membrane-bound proteins that control immune function, inflammation, and hematopoiesis [106]-[109]. Interleukins (ILs), tumor necrosis factors (TNFs), growth factors (GFs), and interferons (IFNs) are structurally and functionally classified as pro-inflammatory cytokines (IFN-, IL-1 group, IL-6, IL-8, IL-18, TNF- α , TNF- β , and FASL) and anti-inflammatory cytokines (IL-4, IL-10, TGF- β , and VEGF) [109]-[110]. Different polymorphisms in the IL-6, IL-8, IL-10, IL-4, TNF- α , and VEGF genes were found to have a strong association with oral oncogenesis [112]-[119]. A progression of dataset calculated relapse models in relation to all considered cytokine polymorphisms, along with changing age and sexual orientation, show that the main commitment in the event of oral disease was that of IL-6 and TNF- α cytokines [120]. Furthermore, IL-6 and TNF- α dominant genotypes were found to be independent predictors of overall, early, and advanced oral squamous cell cancer [120]. The mechanism by which cytokines contribute to the occurrence of oral cancer may be based on a significant increase in serum or saliva levels of the pro-inflammatory cytokines TNF- α , IL-6, and the anti-inflammatory cytokine IL-10 following an inflammatory stimulus [121]. TNF- α has been shown to promote angiogenesis by activating IL-6, IL-8, and VEGF [122],[123].

A research study determined any possible gene polymorphisms of TNF- α (-308), TGF- β 1 (codons 10 and 25), IL-10 (-1082, -819, and -592), IL-6 (-174), and IFN- γ (+874) that may influence any susceptibility to oral precancerous lesions [127].

SNPs in genes encoding risk factors may have an effect on gene expression, protein function, and disease functionality. SNPs in cytokine genes, such as TNF- α (308), TGF- β 1 (codons 10 and 25), IL-10 (1082, 819, and 592), IL-6 (174), and IFN- γ (+874), have been associated with a higher risk of developing oral malignancies [124],[126],[125]. However, studies of the relationship between cytokine polymorphism and oral precancerous lesion is restricted.

- 1) *Transforming Necros Factor- α* : TNF- α activated signaling pathways promote the expression of inflammatory genes via the transcription factor nuclear factor-kappa B. TNF- α has been linked to the development and progression of several cancers. TNF- α expression is increased in vitro and in vivo by a G-to-A transition in the promoter region (308) of the TNF- α gene [127]. TNF- α overexpression alleles are associated with an increased risk of oral cancer [127]. When compared to healthy controls, patients with oral leukoplakia had significantly higher levels of salivary TNF- α [128]. TNF- α and IFN- γ polymorphisms have been linked to oral lichen planus [129]. A high-producing G/A genotype of TNF- α at position -308 was more generally found among the oral precancerous lesion patients.
- 2) *Interleukin-6*: IL-6 is a type of anti-inflammatory cytokine. IL6 is a pro-inflammatory cytokine that activates the JAK1/STAT3 signaling pathway [130]. The expression of IL-6R and IL-6 mRNA transcripts was much higher in tumor samples than in non-tumor mucosa [131]. A G/C SNP in the IL-6 (-174) promoter region was found to affect transcription and alter plasma IL-6 levels. Patients with oral leukoplakia had higher levels of salivary IL-6 than healthy controls [128]. The researchers discovered a link between the variant C allele of the -174 G > C SNP in the IL-6 promoter region and an increased risk of oral precancerous lesions.
- 3) *Transforming Growth Factor- β* : TGF- β SNP rs1800471 (+915 G/C) has been studied in Taiwanese [132] and Indian [33] populations. A meta-analysis of the collected data showed a significantly increased risk of oral cancer associated with the GC genotype $p < 0.0001$; OR (1.9–4.2). as well as a lower risk of oral cancer with the GG genotype $p < 0.0001$; OR (0.2–0.5). The meta-evaluation results may be influenced due to the high frequency of GG genotype in the Taiwanese group, and perhaps even the diverse ethnic genomic background in which the Taiwanese study found a significant association but the Indian study has found no correlation with oral cancer.
- 4) *Interleukin-10*: The anti-inflammatory cytokine IL-10 prevents the activity of Th1 immune cells [133]. The two SNPs rs1800870 (-1082A/G) and rs1800871 (-819T/C) reported in Taiwanese [132],[134] and Chinese [135] populations have been implicated in the development of oral cancer. A meta-analysis of statistics demonstrated that in rs1800870 (-1082A/G), the AG and GG genotypes confirmed an association with accelerated $p < 0.000$, (1.3–1.9), and $p < 0.000$, (1.7–4.0) while the AA genotype confirmed an association with decreased vulnerability $p < 0.000$; (0.4–0.6). A meta-analysis of the SNP rs1800871 found an increased risk with the CT genotype [$p = 0.044$; (1.0–1.4)] and a lower risk with the TT genotype [$p < 0.00$; (0.5–0.8)]. The study by Hsu et al. provides evidence for an association between the IL-6, TNF- (308), and TGF-1 codon 10 genotypes and an overall increased OPL risk in the Taiwanese population.
- 5) *Methylene Tetrahydrofolate Reductase*: MTHFR, a critical compound in folate digestion, catalyzes the change of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine transformation to methionine [140]. Meta-analysis of the MTHFR SNP rs1801133 from 4 studies in Indian [136],[137], Taiwanese [138] and Brazilian [139] populations established a reduced danger of oral most cancers with CT genotype and an expanded threat of oral cancer with WT CC genotype.
- 6) *Cyclooxygenase-2*: COX-2 is concerned in prostaglandin biosynthesis in which arachidonic acid is transformed to prostaglandins, performs a imperative role in inflammation [143] and has been associated with angiogenesis, apoptosis and impairment of immune feature in most cancers [144]. The SNP rs20417 in COX-2 has been related to a threat of oral cancer in Indian [141],[142], Taiwanese [144] and American [145] studies. Meta evaluation of the records constituting indicated that the GC+CC genotype has an affiliation with a reduced risk of oral cancer and the WT+GG genotype with an increased risk of oral cancer, with the Indian studies showing the SNP association with extended chance and in the Taiwanese research with decreased chance of oral malignancy.

V. CONCLUSION

The relationship between genetic polymorphism and cancer risk has not been thoroughly investigated because the review of past studies on the subject have been doubtful. Moreover, additional study is necessary to establish a connection between carcinogens (chemicals found in tobacco, smoke, and other chemicals) and genetic polymorphism. Oral cavity organs are presented to numerous cancer-causing agents at high fixations. Although several polymorphisms in cancer-causing agent-using proteins or metabolizing enzymes have been identified, their detailed contribution to cancer susceptibility remains moderate.

For accurate assessments of the relationship between genetic polymorphism and oral malignant risk, many evidences highly suggested that age, sex, identity, diet, environmental exposure, and gene-gene interactions should be considered. As evaluated in the single series and meta-analysis of SNPs in multiple studies, inherent genomic variations expressed by SNPs play a role in susceptibility and, as a result, increased or decreased risk of oral cancer. The majority of the studies adhered to the basic characteristics of SNP disease association study, such as ensuring sufficient p values and replication in different samples and unrelated samples, along with avoiding population stratification. Future comprehensive studies will be challenged by the need for very large sample sizes and complex statistical methodologies.

VI. ACKNOWLEDGEMENT

The authors acknowledge the help provided by Department of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

REFERENCES

- [1] <http://www.cancercenter.com/oral-cancer/risk-factors/>
- [2] Hung HC, Chuang J, Chien YC, et al. Genetic polymorphisms of CYP2E1, GSTM1, and GSTT1; environmental factors and risk of oral cancer. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 901–905.
- [3] Maier H, De Vries N & Snow GB (1991): Occupational factors in the etiology of head and neck cancer. *Clin Otolaryngol Allied Sci* 16:406–412.
- [4] Wang B, Zhang S, Yue K, Wang X-D. The recurrence and survival of oral squamous cell carcinoma: a report of 275 cases. *Chin J Cancer*. 2013; 32:614–618.
- [5] Krishna Rao SV, Mejia G, Soberts-Homson K, Logan R (2013) Epidemiology of oral cancer in Asia in the past decade--an update (2000-2012). *Asian Pac J Cancer Prev* 14: 5567-5577.
- [6] Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ. Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. *Oral Dis* 1995;1:54-8.
- [7] Warnakulasuriya KA, Johnson NW, Linklater KM, Bell J. Cancer of mouth, pharynx and nasopharynx in Asian and Chinese immigrants resident in Thames regions. *Oral Oncol* 1999;35:471-5.
- [8] Scully C, Field JK, Tanzawa H Genetic aberrations in oral or head and neck squamous cell carcinoma (SCCHN): 1. Carcinogen metabolism, DNA repair and cell cycle control. *Oral Oncol* 2000;36:256-63.
- [9] Axell T Occurrence of leukoplakia and some other oral white lesions among 20,333 adult Swedish people. *Community Dent Oral Epidemiol* 1987;15:46-51.
- [10] Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer* 2003;3:733-44.
- [11] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some areca-nut-derived nitrosamines. Vol. 37. Lyon: IARC; 1985. p. 188.
- [12] Jafarey NA, Mahmood Z, Zaidi SH. Habits and dietary pattern of cases of carcinoma of the oral cavity and oropharynx. *J Pak Med Assoc* 1977;27:340-3.
- [13] Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. *Community Dent Oral Epidemiol* 1985;13:340-1.
- [14] Negri E, Franceschi S, Bosetti C, Levi F, Conti E, Parpinel M, et al. Selected micronutrients and oral and pharyngeal cancer. *Int J Cancer* 2000;86:122-7.
- [15] Sankaranarayanan R, Mathew B, Varghese C, Sudhakaran PR, Menon V, Jayadeep A, et al. Chemoprevention of oral leukoplakia with vitamin A and beta carotene: An assessment. *Oral Oncol* 1997;33:231-6.
- [16] Hecht SS, hoffmann D (1988) Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 9: 875-884. 6.
- [17] Notani PN (1988) Role of alcohol in cancers of the upper alimentary tract: use of models in risk assessment. *J Epidemiol Community Health* 42: 187-192. 7.
- [18] D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR (1998) Detection of HPV-16 genome in human oral cancers and potentially malignant lesions from India. *Oral Oncol* 34: 413-420.
- [19] Blot WJ (1992) Alcohol and Cancer. *Cancer Res* 52: 2119-2123.
- [20] Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, et al. (2003) Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 95: 1772-1783.
- [21] Parkin DM, Bray F (2006) Chapter 2: The burden of HPV-related cancers. *Vaccine* 24 Suppl 3: S3/11-25.
- [22] Petti S (2009) Lifestyle risk factors for oral cancer. *Oral Oncol* 45: 340-350.
- [23] Multani S, Saranath D (2016) Genotypic Distribution of Single Nucleotide Polymorphisms in Oral Cancer: Global Scene. *Tumor Biol. In Press*.
- [24] D' Souza W, Saranath D. Clinical implications of epigenetic regulation in oral cancer. *Oral Oncol*. 2015;51:12:1061-68.
- [25] Gasche JA, Goel A. Epigenetic mechanisms in oral carcinogenesis. *Future Oncol*. 2012;8:1407–25.
- [26] Rai R, Kulkarni V, Saranath D. Genome wide instability scanning in chewing-tobacco associated oral cancer using inter simple sequence repeat PCR. *Oral Oncol*. 2004;40:1033–9.
- [27] Bhatnagar R, Dabholkar J, Saranath D. Genome-wide disease association study in chewing tobacco associated oral cancers. *Oral Oncol*. 2012;48:831–5.
- [28] The International HapMap Project. 2003;426:789–96.
- [29] Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, et al. A second generation human haplotype map of over 3.1million SNPs. *Nature*. 2007;449:851–61.
- [30] Chien MH, Yang JS, Chu YH, Lin CH, Wei LH, Yang SF, et al. Impacts of CA9 gene polymorphisms and environmental factors on oral-cancer susceptibility and clinicopathologic characteristics in Taiwan. *PLoS One*. 2012;7:5–12.
- [31] Bau DT, Chang CH, Tsai MH, Chiu CF, Tsou YA, Wang RF, et al. Association between DNA repair gene ATM polymorphisms and oral cancer susceptibility. *Laryngoscope*. 2010;120:2417–22.

- [32] Murali A, Nalinakumari KR, Thomas S, Kannan S. Association of single nucleotide polymorphisms in cell cycle regulatory genes wit oral cancer susceptibility. *Br J Oral Maxillofac Surg.* 2014;52:652–8.
- [33] Gaur P, Mittal M, Mohanti BK, Das SN. Functional genetic variants of TGF- β 1 and risk of tobacco-related oral carcinoma in high-risk Asian Indians. *Oral Oncol.* 2011;47:1117–21.
- [34] Al-Hadyan KS, Al-Harbi NM, Al-Qahtani SS, Alsbeih GA. Involvement of single-nucleotide polymorphisms in predisposition to head and neck cancer in Saudi Arabia. *Genet Test Mol Biomarkers.* 2012;16:95–101.
- [35] Gaur P, Mittal M, Mohanti BK, Das SN. Functional variants of IL4 and IL6 genes and risk of tobacco-related oral carcinoma in highrisk Asian Indians. *Oral Dis.* 2011;17:720–6.
- [36] Li N, Zhang C, Chen Z, Bai L, Nie M, Zhou B, et al. Interleukin 17A and interleukin 17F polymorphisms are associated with oralsquamous cell carcinoma susceptibility in a Chinese population. *J Oral Maxillofac Surg.* 2015;73:267–73.
- [37] Chien M-H, Hsin C-H, Chou LS-S, Chung T-T, Lin C-H, Weng MS, et al. Interleukin-23 receptor polymorphism as a risk factor for oral cancer susceptibility. *Head Neck.* 2012;34:551–6.
- [38] Lakhanpal M, Yadav DS, Devi TR, Singh LC, Singh KJ, Latha SP, et al. Association of interleukin-1 β -511 C/T polymorphism with tobacco-associated cancer in Northeast India: a study on oral and gastric cancer. *Cancer Genet.* 2014;207:1–11.
- [39] Singh PK, Ahmad MK, Kumar V, Hussain SR, Gupta R, Jain A, et al. Effects of interleukin-18 promoter (C607A and G137C) gene polymorphisms and their association with oral squamous cell carcinoma(OSCC) in northern India. *Tumor Biol.* 2014;35:12275–84.
- [40] Su S, Chien M, Lin C, Chen M, Yang S. RAGE gene polymorphism and environmental factor in the risk of oral cancer. *J Dent Res.* 2015;94:403–11.
- [41] Teng Y-H, Liu T-H, Tseng H-C, Chung T-T, Yeh C-M, Li Y-C, et al. Contribution of genetic polymorphisms of stromal cell-derived factor-1 and its receptor, CXCR4, to the susceptibility and clinicopathologic development of oral cancer. *Head Neck.* 2009;31:1282–8.
- [42] Jha R, Gaur P, Sharma SC, Das SN. Single nucleotide polymorphism in hMLH1 promoter and risk of tobacco-related oral carcinoma in high-risk Asian Indians. *Gene.* 2013;526:223–7.
- [43] Wang Y, Lin L, Xu H, Li T, Zhou Y, Dan H, et al. Genetic variants in AKT1 gene were associated with risk and survival of OSCC in Chinese Han. Population. 2015:45–50.
- [44] Weng CJ, Hsieh YH, Chen MK, Tsai CM, Lin CW, Yang SF. Survivin SNP-carcinogen interactions in oral cancer. *J Dent Res.* 2012;91:358–63.
- [45] Bau DT, Tsai CW, Lin CC, Tsai RY, Tsai MH. Association of alpha B-crystallin genotypes with oral cancer susceptibility, survival, and recurrence in Taiwan. *PLoS One.* 2011;6:3–7.
- [46] Ma L, Chen J, Song X, Yuan H, Wang Y, Wu Y, et al. Evidence that the genetic polymorphism rs1412115 on chromosome 10 is associated with risk for oral squamous cell carcinoma. *Gene.* 2015;560:137–9.
- [47] Weng C-J, Chen M-K, Lin C-W, Chung T-T, Yang S-F. Single nucleotide polymorphisms and haplotypes of MMP-14 are associate with the risk and pathological development of oral cancer. *Ann Surg Oncol.* 2012;19(Suppl 3):S319–27.
- [48] Andrade Filho PA, Letra A, Cramer A, Prasad JL, Garlet GP, Vieira AR, et al. Insights from studies with oral cleft genes suggest associations between WNT-pathway genes and risk of oral cancer. *J Dent Res.* 2011;90:740–6.
- [49] Li L. Correlation between superoxide dismutase 1 and 2 polymorphisms and susceptibility to oral squamous cell carcinoma. *Exp Ther Med.* 2013:171–8.
- [50] Chung YT, Hsieh LL, Chen IH, Liao CT, Liou SH, Chi CW, et al. Sulfotransferase 1A1 haplotypes associated with oral squamous cell carcinoma susceptibility in male Taiwanese. *Carcinogenesis.* 2009;30:286–94.
- [51] Chou Y-E, Hsieh M-J, Hsin C-H, Chiang W-L, Lai Y-C, Lee Y-H, et al. CD44 gene polymorphisms and environmental factors on oral cancer susceptibility in Taiwan. *PLoS One.* 2014;9:e93692.
- [52] Lin CW, Chuang CY, Tang CH, Chang JL, Lee LM, LeeWJ, et al. Combined effects of ICAM-1 single-nucleotide polymorphisms and environmental carcinogens on oral cancer susceptibility and clinicopathologic development. *PLoS One.* 2013;8:1–8.
- [53] Multani S, Pradhan S, Saranath D. Gene polymorphisms and oral cancer risk in tobacco habitués. *Tumor Biol.* 2015.
- [54] Sherr CJ (1996):Cancer cell cycles, *Science* 274: 1672-1677.
- [55] Sherr CJ (1995):D-type cyclins. *Trends Biochem Sci* 20:187-190.
- [56] Zheng Y, Shen H, Sturgis EM, Wang LE, Eicher SA, Strom SS, Frazier ML, Spitz MR & Wei Q (2001): Cyclin D1 polymorphism and risk for squamous cell carcinoma of the head and neck: a case-control study. *Carcinogenesis* 22:1195-1199.
- [57] Huang M, Spitz MR, Gu J, Lee JJ, Lin J, Lippman SM & Wu X (2006): CyclinD1 gene polymorphism as a risk factor for oral premalignant lesions. *Carcinogenesis* 27:2034-2037.
- [58] Holley SL, Matthias C, Jahnke V, Fryer AA, Strange RC & Hoban PR (2005):Association of cyclin D1 polymorphism with increased susceptibility to oral squamous cell carcinoma. *Oral Oncol* 41:156-160.
- [59] Maier H, Dietz A, Gewelke U, Heller WD, Weidauer H(1992):Tobacco and alcohol and risk of head and neck cancer. *Clin Investig* 70:320-327.
- [60] Kiyohara C, Hirohata T & Inutsuka S (1996):The relationship between aryl hydrocarbon hydroxylase and polymorphisms of the CYP1A1 gene. *Jpn J Cancer Res* 87:18-24..
- [61] Hemminki K, Dickey C, Karlsson S, Bell D, Hsu Y, Tsai WY, Mooney LA, Savelle K & Perera FP (1997):Aromatic DNA adducts in foundry workers In relation to exposure, lifestyle and CYP1A1 and glutathione transferase M1 genotype, *Carcinogenesis* 18:345-350.
- [62] Tanimoto K, Hayashi S, Yoshiga K & Ichikawa T (1999):Polymorphisms of the CYP1A1 and GSTM1 gene involved in oral squamous cell carcinoma in association with a cigarette dose. *Oral Oncol* 35:191-196.
- [63] Hashibe M, Brennan P, Strange RC et al (2003):Meta- and pooled analyses of GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes and risk of head and neck cancer, *Cancer Epidemiol Biomarkers Prev* 12:1509-1517.
- [64] Hinvonen A, Husgafvel-Pursiainen K, Anttila S & Vainio H (1993):The GSTM1 null genotype as a potential risk modifier for squamous cell carcinoma of the lung. *Carcinogenesis* 14:1479-1481
- [65] Morita S, Yano M, Tsujinaka T et al (1999):Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma, *Int J Cancer* 80:685-688

- [66] Anantharaman D, Chaubal PM, Bhisey RA, Mahimkar MB. Susceptibility to oral cancer by genetic polymorphisms at CYP1A1, GSTM1 and GSTT1 loci among Indians: tobacco exposure as a risk modulator. 2007;28:1455–62
- [67] Anantharaman D, Samant TA, Sen S, Mahimkar MB. Polymorphisms in tobacco metabolism and DNA repair genes modulate oral precancer and cancer risk. Oral Oncol. 2011;47:866–72.
- [68] Shukla D, Kale AD, Hallikerimath S, Vivekanandhan S, Venkatakanthaiah Y. Genetic polymorphism of drug metabolizing enzymes (GSTM1 and CYP1A1) as risk factors for oral premalignant lesions and oral cancer. Biomed Pap. 2012;156:253–9.
- [69] Balaji L, Singh KB, Bhaskar LVKS. CYP1A1 genotypes and haplotypes and risk of oral cancer: a case-control study in South Indians. Genet Mol Biol. 2012;35:407–12.
- [70] Singh R, Haridas N, Shah F, Patel J, Shukla S, Patel P. Gene polymorphisms, tobacco exposure and oral cancer susceptibility: a study from Gujarat, West India. Oral Dis. 2014;20:84–93.
- [71] Atoh TK, Aneko SK, Ohshi KK, UnakaMM, ItagawaKK, Unugita NK, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and oral cavity. Cancer. 1999;609:606–9.
- [72] Sato M, Sato T, Izumo T. Genetic polymorphism of drugmetabolizing enzymes and susceptibility to oral. Cancer. 1999;20:1927–31
- [73] Tanimoto K, Hayashi S, Yoshiga K, Ichikawa T. Polymorphisms of the CYP1A1 and GSTM1 gene involved in oral squamous cell carcinoma in association with a cigarette dose. Oral Oncol.1999;35:191–6.
- [74] Sato M, Sato T, Izumo T, Amagasa T. Genetically high susceptibility to oral squamous cell carcinoma in terms of combined genotyping of CYP1A1 and GSTM1 genes. Oral Oncol. 2000;36:267–71.
- [75] Amtha R, Ching CS, Zain R, Razak IA, Basuki B, Roeslan BO,et al. GSTM1, GSTT1 and CYP1A1 polymorphisms and risk of oral cancer: a case-control study in Jakarta, Indonesia. 2009;10:21–6.
- [76] Kao S, Wu C, Lin S. Genetic polymorphism of cytochromeP4501A1 and susceptibility to oral squamous cell carcinoma and oral precancer lesions associated with smoking/betel use.2002;505–11.
- [77] Xie H, Hou L, Shields PG, Winn DM, Gridley G, Bravo-otero E,et al.Metabolic polymorphisms, smoking, and oral cancer in Puerto Rico. 2004;14:315–20.
- [78] Marques CFS, Koifman S, Koifman RJ, Boffetta P, Brennan P,Hatagima A. Influence of CYP1A1, CYP2E1, GSTM3 and NAT2genetic polymorphisms in oral cancer susceptibility: results from a case-control study in Rio de Janeiro. Oral Oncol. 2006;42:632–7.
- [79] Hung HC, Chuang J, Chien YC, Chern IID, Chiang CP, Kuo YS, Hildesheim A & Chen CJ (1997): Genetic polymorphisms of CYP2E1, GSTM1, and GSTT1; environment factors and risk of oral cancer. Cancer Epidemiol Biomarkers Prev 6:901-905
- [80] Sreelekha TT, Ramadas K, Pandey M, Thomas G, Nalina kumari KR & Pillai MR (2001):Genetic polymorphism of CYP1A1, GSTM1 and GSTT1 genes in Indian oral cancer. Oral Oncol 37:593- 59
- [81] Sato M, Sato T, Izumo T & Amagasa T (2000):Genetically high susceptibility to oral squamous cell carcinoma in terms of combined genotyping of CYP1A1 and GSTM1 genes. Oral Oncol 36:267-271 47.Drumfnd SN, De Marco L, Noronha JC & Gomez RS (2004):GSTM1 polymorphism and oral squamous cell carcinoma. Oral Oncol 40:52-55
- [82] Buch SC, Notani PN, Bhisey RA. Polymorphism at GSTM1,GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population at GSTM1, GSTM3 and GSTT1 gene loci on oral cancer tobacco, bidi or cigarette. DNA extracted from white blood cells of 297 cancer patients and 4. 2002;23:803–7
- [83] Sikdar N, Paul RR, Roy B. Glutathione S-transferase M3 (A/A)genotype as a risk factor for oral cancer and leukoplakia among Indian tobacco smokers. Int J Cancer. 2004;109:95–101.
- [84] Masood N, Kayani MA, Malik FA, Mahjabeen I, Baig RM, Faryal R. Genetic variation in carcinogen metabolizing genes associated with oral cancer in pakistani population. Asian Pac J Cancer Prev.2011;12:491–5.
- [85] Park JY, Schantz SP, Stern JC, Kaur T & Lazarus P (1999);Association between glutathione S-transferase P1 genetic polymorphisms and oral cancer risk. Pharmacogenetics 9: 497-504
- [86] Katoh T, Kaneko S, Takasawa S, Nagata N, Inatomi H, Ikemura K. Itoh H, Matsumoto T, Kawamnoto T & Bell DA (1999):Human glutathione S-transferase P1 polymorphism and susceptibility to smoking related epithelial cancer; oral, lung, gastric, colorectal and urothelial cancer. Pharmacogenetics 9:165-169.
- [87] Thompson LH (1996):Evidence that mammalian cells possess homologous recombinational repair pathways. Mutat Res 363:77-88
- [88] Sturgis EM, Castillo EJ, Li L, Zheng R, Eicher SA, Clayman GL, Strom SS, Spitz MR & Wei Q (1999): Polymorphisms of DNA repair gene XRCCI in squamous cell carcinoma of the head and neck. Carcinogenesis 20:2125-2129
- [89] Tae K, Lee HS, Park BJ, Park CW, Kim KR, Cho HY, Kim LH, Park CW, Kim KR, Cho HY, Kim LH, Park BL &Shin HD(2004):Association of DNA repair gene XRCC1 polymorphism with head and neck cancer in Korean population. Int J Cancer 111:805-808.
- [90] Yen C-Y, Liu S-Y, Chen C-H, Tseng H-F, Chuang L-Y, Yang C-H,et al. Combinational polymorphisms of four DNA repair genes XRCC1, XRCC2, XRCC3, and XRCC4 and their association with oral cancer in Taiwan. J Oral Pathol Med. 2008;37:271–7.
- [91] Tsai C, Chang W, Liu J, Tsai M, Lin C, Bau D. Contribution of DNA double-strand break repair gene XRCC3 genotypes to oral cancer susceptibility in Taiwan. 2014;2956:2951–6.
- [92] Kietthubthw S, Sriplung H, WW A, Ishida T. Polymorphism in DNA repair genes and oral squamous cell carcinoma in Thailand. Int J Hyg Environ Health. 2006;209:21–9.
- [93] Bisarro M, Losi-guembarsovski R, Maria E, Fonseca DS, Morita MC, Henrique G, et al. Allelic variants of XRCC1 and XRCC3 repair genes and susceptibility of oral cancer in Brazilian patients.2013;180–5.
- [94] Roy B, Beamon J, Balint E & Reisman D (1994):Transactivation of the human p53 tumor suppressor gene by c-Myc/Max contributes to elevated mutant p53 expression in some tumors, Mol Cell Biol 14: 7805-7815
- [95] Tandle AT, Sanghvi V & Saranath D (2001):Determination of p53 genotypes in oral cancer patients from India. Br J Cancer 84:739-742
- [96] Kuroda Y, Nakao H, Ikemura K & Katoh T (2007):Association between the TP53 codon72 polymorphism and oral cancer risk and prognosis, Oral Oncol 43:1043-1048.
- [97] Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A & Fraumeni JF Jr (1988):Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 48: 3282-328

- [98] Ybkoyama A, Muramatsu T, Omori T, YOkoyama T, Matsushita S, Higuchi S, Maruyama K & IshiiH (2001):Alcohol and aldehyde dehydrogenase gene polymorphisms and oropharyngolaryngeal, esophageal and stomach cancers in Japanese alcoholics. *Carcinogenesis* 22:433-439
- [99] Hashimoto T, Uchida K, Okayama N, Imae Y, Suehiro Y, Ueyama Y, Yamashita H & Hinoda Y (2006): ALDH2 1510 G/A (Gln487fys) polymorphism interaction with age in head and neck squamous cell carcinoma. *Tumor Bio* 127:334-338
- [100] Nomura T, Noma H, Shibahara T, Yokoyama A, Muramatsu T & Ohmori T (2000):Aldehyde dehydrogenase 2 and glutathione S-transferase M1 polymorphisms in relation to the risk for oral cancer in Japanese drinkers. *Oral Oncol* 36:42-46
- [101] Harty LC, Caporaso NE, Hayes RB et al (1997):Alcohol dehydrogenase3 genotype and risk of oral cavity and pharyngeal cancers. *J Natl Cancer Inst* 89:1698-1705
- [102] Schwartz SM, Doody DR, Fitzgibbons ED, Ricks S, Porter PL & Chen C (2001):Oral squamous cell cancer risk in relation to alcohol consumption and alcohol dehydrogenase-3 genotypes, *Cancer Epidemiol Biomarkers Prev* 10: 1137-1144
- [103] Solomon PR, Selvam GS & Shanmugam G (2008):Polymorphism in ADH and MTHFR genes in oral squamous cell carcinoma of Indians, *Oral Dis* 14:633-639
- [104] Olshan AF, Weissler MC, Watson MA & Bell DA (2000):GSTM1, GSTT1, GSTP1, CYP1A1, and N!vr1 polymorphisms, tobacco use, and the risk of head and neck cancer. *Cancer Epidemiol Biomarkers Prev* 9:185-191
- [105] Katoh T, Kaneko S, Boissy R, Watson M, Ikemura K & Bell DA (1998):A pilot study testing the association between N-acetyltransferases 1 and 2 and risk of oral squamous cell carcinoma in Japanese people. *Carcinogenesis* 19: 1803-1807.
- [106] Casciari JJ, Sato H, Durum SK, Fiege J, Weinstein JN. Reference databases of cytokine structure and function. *Cancer Chemother Biologic Response Modifiers* 1996;16:315-46.
- [107] Balkwill FR, Burke F. The cytokine network. *Cell Biol Int* 2000;24(9):299-304.
- [108] Dinarello CA. Interleukin-18, a proinflammatory cytokine. *Euro Cytokine Netw* 2000;11(3):483-6.
- [109] Akira S. The role of IL-18 in innate immunity. *Curr Opin Immunol* 2000;12(1):59-63.
- [110] Elias JA, Zitnik RJ. Cytokine-cytokine interactions in the context of cytokine networking. *Am J Respir Cell Mol Biol* 1992;7:365-7.
- [111] Salazar-Onfray F, Lopez MN, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. *Cytokine Growth Factor Rev* 2007;18(1-2):171-82.
- [112] Liu CJ, Wong YK, Chang KW, Chang HC, Liu HF, Lee YJ. Tumor necrosis factor- α promoter polymorphism is associated with susceptibility to oral squamous cell carcinoma. *J Oral Pathol Med* 2005; 34:608-12.
- [113] Vairaktaris E, Yiannopoulos A, Vylliotis A, Yapijakis C, Derka S, Vassiliou S, et al. Strong association of interleukin-6 174 G>C promoter polymorphism with increased risk of oral cancer. *Int J Biol Markers* 2006;21(4):246-50.
- [114] Vairaktaris E, Yapijakis C, Serefoglou Z, Derka S, Vassiliou S, Nkenke E, et al. The interleukin-8 (-251A/T) polymorphism is associated with increased risk for oral squamous cell carcinoma. *Eur J Surg Oncol* 2007;33(4):504-7.
- [115] Vairaktaris E, Yapijakis C, Serefoglou Z, Derka S, Vassiliou S, Nkenke E, et al. Gene expression polymorphism of interleukin10 is associated with risk for oral squamous carcinoma. *Anticancer Res* [in press].
- [116] Yapijakis C, Vairaktaris E, Serefoglou Z, Vylliotis A, Ries J, Nkenke E, et al. Association of tumor necrosis factor alpha -308 G/A and beta 252 G/A polymorphisms with increased risk for oral cancer. *Int J Biol Markers* [in press].
- [117] Chiu CJ, Chiang CP, Chang ML, Chen HM, Hahn LJ, Hsieh LL, et al. Association between genetic polymorphism of tumor necrosis factor-alpha and risk of oral submucous fibrosis, a precancerous condition of oral cancer. *J Dent Res* 2001;80(12): 2055-9.
- [118] Yapijakis C, Vairaktaris E, Vassiliou S, Vylliotis A, Nkenke E, Nixon AM, et al. The low VEGF production allele of the +936C/T polymorphism is strongly associated with increased risk for oral cancer. *J Cancer Res Clin Oncol* 2008;133(10):787-91.
- [119] Vairaktaris E, Yannopoulos A, Vassiliou S, Serefoglou Z, Vylliotis E, Nkenke E, et al. Strong association of interleukin-4 (-590 C/T) polymorphism with increased risk for oral squamous cell carcinoma in Europeans. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;104(6):796-802.
- [120] Vairaktaris E, Yapijakis C, Serefoglou Z, Avgoustidis D, Critselis E, Spyridonidou S, et al. Gene expression polymorphisms of interleukins-1 β , -4, -6, -8, -10, and tumor necrosis factors- α , - β : regression analysis of their effect upon oral squamous cell carcinoma. *J Cancer Res Clinic Oncology* [in press].
- [121] Miettinen M, Vuopio-Varkila J, Varkila K. Production of human tumor necrosis factor alpha, interleukin-6, and interleukin-10 is induced by lactic acid bacteria. *Infect Immun* 1996;64: 5403-5.
- [122] Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA. Correlations and interactions in the production for interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppress IL-1 and TNF. *Blood* 1990;75:40-7.
- [123] Yoshida S, Ono M, Shono T, Izumi H, Ishibashi T, Suzuki H, et al. Involvement of interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor in tumor necrosis factor alpha-dependent angiogenesis. *Mod Cell Biol* 1997;17(7):4015-23.
- [124] Erdei E, Luo L, Sheng H, Maestas E, White KA, Mackey A, et al. Cytokines and tumor metastasis gene variants in oral cancer and precancer in Puerto Rico. *PLoS One* 2013;8:e79187.
- [125] Vairaktaris E, Yapijakis C, Serefoglou Z, Avgoustidis D, Critselis E, Spyridonidou S, et al. Gene expression polymorphisms of interleukins-1 beta, -4, -6, -8, -10, and tumor necrosis factors-alpha, -beta: regression analysis of their effect upon oral squamous cell carcinoma. *J Cancer Res Clin Oncol* 2008;134:821-32.
- [126] Yao JG, Gao LB, Liu YG, Li J, Pang GF. Genetic variation in interleukin-10 gene and risk of oral cancer. *Clin Chim Acta* 2008;388:84-8.
- [127] Yapijakis C, Serefoglou Z, Vylliotis A, Nkenke E, Derka S, Vassiliou S, et al. Association of polymorphisms in tumor necrosis factor alpha and beta genes with increased risk for oral cancer. *Anticancer Res* 2009;29:2379-86.
- [128] Brailo V, Vucicevic-Boras V, Cekic-Arambasin A, Alajbeg IZ, Milenovic A, Lukac J. The significance of salivary interleukin 6 and tumor necrosis factor alpha in patients with oral leukoplakia. *Oral Oncol* 2006;42:370-3.
- [129] Carrozzo M, Ubaldi de Capei M, Dametto E, Fasano ME, Arduino P, Brocchetto R, et al. Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. *J Invest Dermatol* 2004;122: 87-94.
- [130] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signaling and its regulation. *Biochem J* 2003;374: 1-20
- [131] Wang YF, Chang SY, Tai SK, Li WY, Wang LS. Clinical significance of interleukin-6 and interleukin-6 receptor expressions in oral squamous cell carcinoma. *Head Neck* 2002;24:850-8.

- [132]Hsu H, Yang Y, Shieh T, Chen C. TGF- β 1 and IL-10 single nucleotide polymorphisms as risk factors for oral cancer in Taiwanese. *Kaohsiung J Med Sci*. 2014;1–7.
- [133]Couper K, Blount D, Riley E. IL-10: the master regulator of immunity to infection. *J Immunol*. 2008;180:5771–7.
- [134]Tsai C, Chang W, Lin K, Shih L, Tsai M. Significant association of interleukin-10 genotypes and oral cancer susceptibility in Taiwan. 2014; 3738: 3731–7.
- [135]Yao J-G, Gao L-B, Liu Y-G, Li J, Pang G-F. Genetic variation in interleukin-10 gene and risk of oral cancer. *Clin Chim Acta*. 2008; 388: 84–8.
- [136]Sailasree R, Nalina kumari KR, Sebastian P, Kannan S. Influence of methylenetetrahydrofolate reductase polymorphisms in oral cancer patients. *J Oral Pathol Med*. 2011;40:61–6
- [137]Addala L, Kumar, CHK, Reddy N M, Kumar Reddy TP, Md S. Association of the C677T polymorphism in the MTHFR gene with risk of oral squamous cell carcinoma in South Indian population. *Am J Cancer Res Clin Oncol*. 2013;1–11.
- [138]Tsai C, Hsu C, Tsai M, Tsou Y, Hua C. Methylenetetrahydrofolate reductase (MTHFR) genotype, smoking habit, metastasis and oral cancer in Taiwan. 2011;2400:2395–9.
- [139]Weinstein SJ, Gridley G, Harty LC, Diehl SR, Brown LM, Winn DM, et al. Folate intake, serum homocysteine and methylenetetrahydrofolate reductase (MTHFR) C677T genotype are not associated with oral cancer risk in Puerto Rico. 2002;762
- [140]Curtin K. MTHFR C677T and A1298C polymorphisms: diet, estrogen, and risk of colon cancer. *Cancer Epidemiol Biomarker Prev*. 2004;13: 285–92.
- [141]Mittal M, Kapoor V, Mohanti BK, Das SN. Functional variants of COX-2 and risk of tobacco-related oral squamous cell carcinoma in high-risk Asian Indians. *Oral Oncol*. 2010;46:622–6.
- [142]Lakshmi A, Muralidhar S, Kumar CK, Kumar AP, Chakravarthy PK, Anjaneyulu V, et al. Cyclooxygenase-2-765G>C functional promoter polymorphism and its association with oral squamous cell carcinoma. *J Investig Clin Dent*. 2012;3:182–8.
- [143]Dubois RN, Abramson SB, Crofford L, Gupta RA, Simo
- [144]Soslow RA, Dannenberg AJ, Rush D, Woerner BM, Nasir Khan K, Masferrer J, et al. COX-2 is expressed in human pulmonary, colonic, and mammary tumors. *Cancer*

10.22214/IJRASET

45.98

IMPACT FACTOR:
7.129

IMPACT FACTOR:
7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Call : 08813907089 (24*7 Support on Whatsapp)