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Genetic Polymorphism and Susceptibility to Oral Cancer

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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 benzepyrene 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 benzepyrene 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-specificnitrosamines (TSNs) 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (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'nitrosonornicotine (NNN) and 4 (methylnitrosoamino)-1-(3pyridyl)-1butanone (NNK), and areca nut alkaloids-arecoline and arecaidine, 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'nitrosonornicotine (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 oral 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.

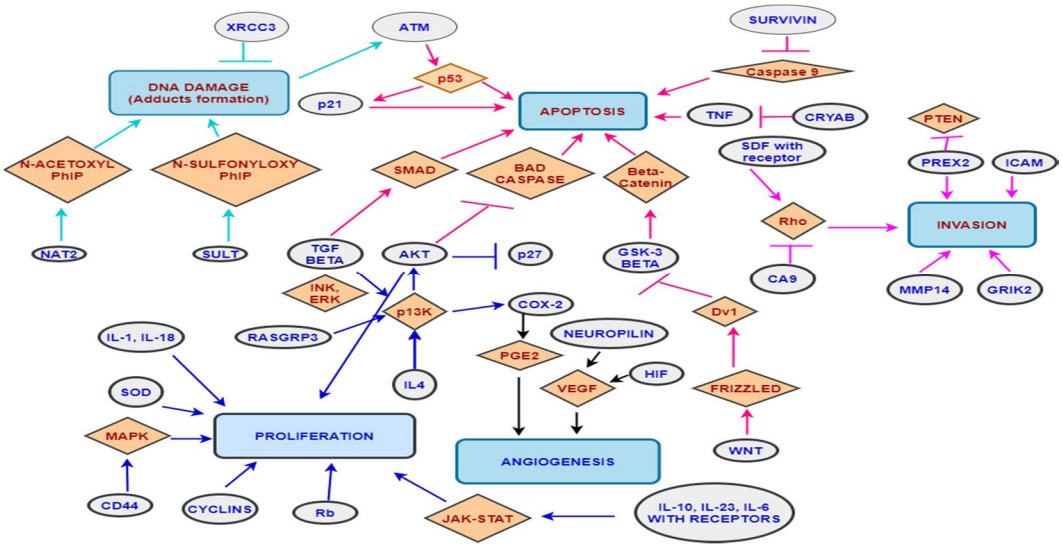

Fig.1: Basic functions of SNP containing genes in oral carcinogenesis. The basic natural elements of DNA damage, cell proliferation, invasion, angiogenesis and apoptosis of genes containing the significant SNPs in oral carcinogenesis are shown. The genes holding the SNPs (*light blue circles*) and related 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-β1 [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-β1/17A/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-β1 (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-β1(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-1β(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 Gl to the S phase [54]. The main cyclins linked to cyclin-dependent kinases are CyclínD-1(CCND1) [55] In this process, CCNDI represents a major metabolic protein, which plays a key role in the cell cycle transition from Gl to S phase. During the G1 phase, CCNDI movement is maximum and CDK4 and CDK6 are associated with mid to late Gl phase. CCND1 shows a common A/G polymorphism(G870A). The A/A genotype of the CCNDI 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 CCNDI 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 (CYPIA1, CYPIA2, CYP2A6, CYP2CI9, CYP2D6) being the most studied., The one of the most studied CYP IS CYPIA1, considered to perform a key role in the formation of poly aromatic hydrocarbon compounds (PAH) such as benzo(a)pyrene [30]. CYPIA1 metabolizes benzo(a)pyrene in tobacco smoke to a significant cancer-causing agent, 7β,8α-dihydroxy-9α,10α-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene. CYPIAI contains two polymorphisms. The CYPIAI Ile462val polymorphism is a result of A (CYPIAI*IA) to G (CYPIAI*2C) exchange in exon7, causing a change in an amino acid heme-binding region [31]. The other CYPIAI polymorphism (Mspl polymorphism) is a T (CYPIAI*IA) to C (CYPIAI*2A) transition 1197bp downstream of exon 7 [33]. The Mspl polymorphism of the CYPIAI 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 CYPIA1 Mspl homozygous variation [37]. As of late, another polymorphism of CYPIAI 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 GSTMI, GSTTI, GSTP1 and GSTM3. GSTMI, GSTTI and GSTPI have been assessed frequently. The null genotype of GSTMI and GSTTI was related with an increased threat of oral cancer [80], and the GSTMI null genotype was one of the main factor that 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 GSTPI 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 GSTPI. The GSTPI 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 GSTPI 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). Xray repair cross complementing Protein l (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 Xray 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 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-β1 (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-β1 (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-αactivated 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.

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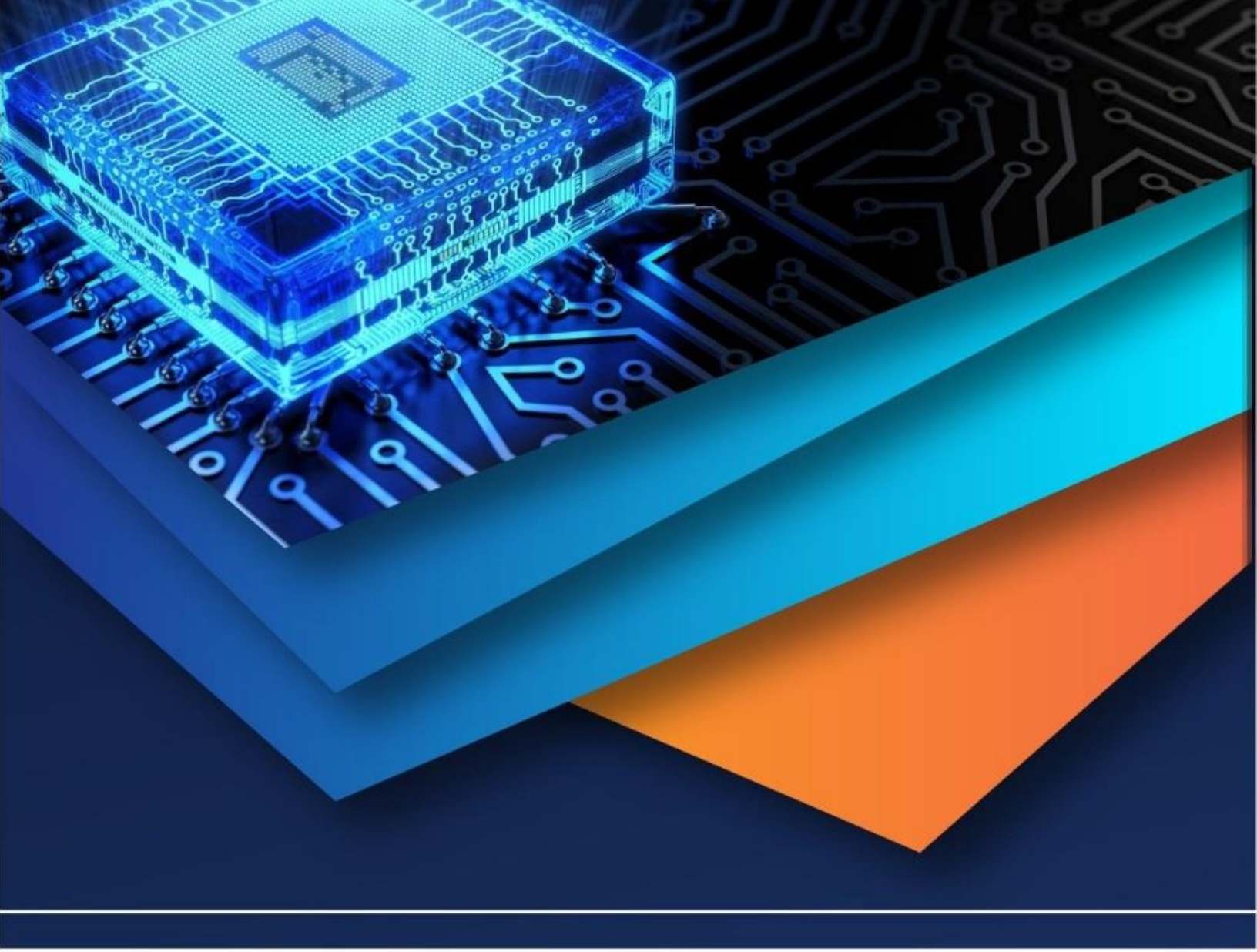

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