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Gene polymorphisms and risk of head and neck squamous cell carcinoma: a systematic review

Authors: Mahdieh Rajabi-Moghaddam, Hamid Abbaszadeh

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Gene polymorphisms and risk of head and neck squamous cell carcinoma: a systematic review

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Mahdieh Rajabi-Moghaddam[1], Hamid Abbaszadeh[2]

[1]*Department of Pathology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran*

[2]*Department of Oral and Maxillofacial Pathology, School of Dentistry, Birjand University of Medical Sciences, Birjand, Iran*

Corresponding author: Dr. Hamid Abbaszadeh, Oral and Maxillofacial Pathology Department, Faculty of Dentistry, Birjand, South Khorasan province, Iran, tel: +989158002580, fax: +985632381700; e-mail: hamidabbaszade@yahoo.com

Abstract

Background: Exposure to the same environmental factors in different people have resulted in different susceptibility to head and neck squamous cell carcinoma (HNSCC), which suggests genetic variation may be a risk factor for the development of HNSCC. So, the aim was to review literatures on the association between gene polymorphisms and risk of HNSCCs.

Materials and methods: This systematic review included all articles on the impact of gene polymorphisms on risk and susceptibility to HNSCC published till September 2021 using PubMed, Web of science, SCOPUS, Google Scholar and Cochrane library databases.

Results: Of 1163 initial searched articles, 77 articles were eligible to include in this review. Studies were categorized based on gene functions. In each category, studied gene polymorphisms related to growth control genes, cell cycle control, apoptosis, DNA repair genes, carcinogen-metabolizing enzymes, alcohol-metabolizing genes, antioxidant gene, inflammatory cytokine, transcription factor, tumor immunity, folate metabolism, and tumor

suppressor gene were discussed separately. Among the polymorphisms that are often significantly associated with HNSCC risk are: *GSTM1* null, *GSTT1* null, *CYP2D6* *4, *XRCC1* Arg194Trp and Arg399Gln, *ERCC1* C8092A, *XPD* Lys751Gln, *XRCC3* Thr241Met, *P53* codon 72 and *MTHFR* C677T polymorphisms.

Conclusion: Varied and contradictory results have been reported in different studies regarding the association of gene polymorphisms with HNSCC risk. To conclude about this association and to overcome these contradictions, it is necessary to use the results of existing meta-analyses or to perform new or updated meta-analyses.

Key words: gene polymorphism; single nucleotide polymorphisms; head and neck squamous cell carcinoma; risk; disease susceptibility

Introduction

Head and neck squamous cell carcinomas (HNSCCs) are the 6th most common cancer in the world with a five-year survival rate of approximately 25–60% [1–3]. The etiology of HNSCCs is multifactorial (no single factor has been implicated); both intrinsic and extrinsic factors are involved in the carcinogenesis process of HNSCCs. Extrinsic factors include tobacco smoking, smokeless tobacco chewing, alcohol consumption, sunlight (ultraviolet radiation), occupational exposures and environmental pollutants, bacteria, candida and oncogenic viruses. Intrinsic factors include vitamin/mineral deficiencies and dietary factors, such as malnutrition or iron-deficiency anemia, immunosuppression, oncogenes and tumor suppressor genes. Heredity has also a minor causative role. Some HNSCCs are associated with or preceded by a precancerous lesion. Tobacco and alcohol are among the most common etiologic factors of HNSCCs. In fact, HNSCC carcinogenesis involves an accumulation of mutations or epigenetic changes in genes resulting from harmful effects of environmental factors in a susceptible individual [2, 4, 5]. Exposure to the same environmental factors in different people have resulted in varied clinical presentation and different susceptibility to HNSCC that suggests genetic variation may be a major risk factor for the development of HNSCC [6].

Carcinogenesis processes in HNSCCs involve disruptions and deregulations of different pathways including DNA repair, metabolism of carcinogens, cell cycle, immunity and inflammation. Polymorphisms of genes involved in these pathways may play important roles in HNSCC development through alteration in activation and function of related proteins [2, 4, 5].

So, the aim was to review literatures on the association between gene polymorphisms and risk of HNSCCs.

Materials and methods

Literature search

The search strategy was based on the review question (PICO):

P — Population/Patient: HNSCC patients;

I — Intervention: presence of gene polymorphism;

C — comparator: patients without polymorphism;

O — outcome: risk or susceptibility.

A systematic search was done to find articles in the PubMed, Web of science, SCOPUS, Google Scholar and Cochrane databases.

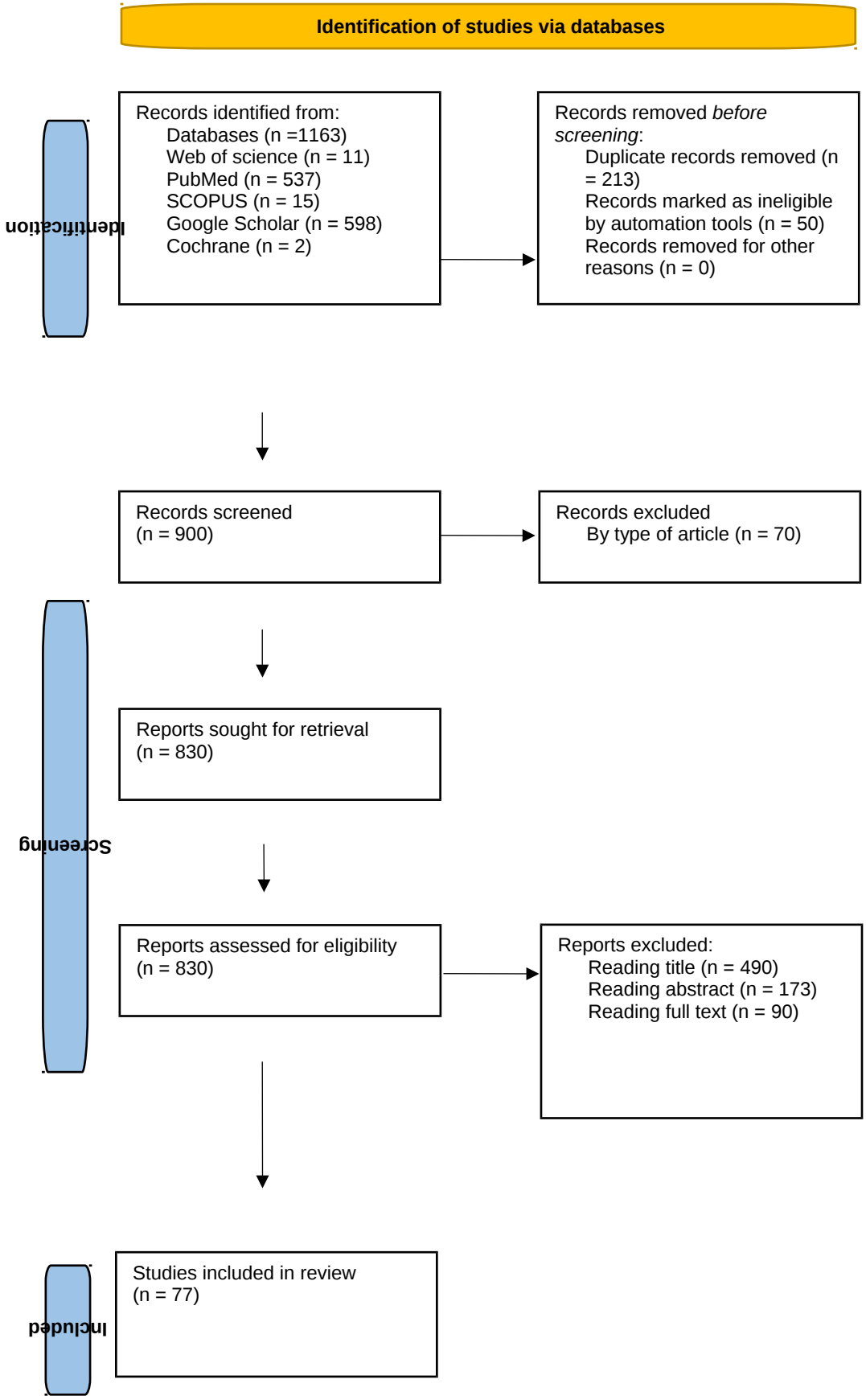
The search was performed in a similar way on above-mentioned databases based on the MeSH terms as follows:

(“Single nucleotide polymorphism” OR “genetic variation” OR “genetic polymorphism”) AND (“risk” OR “disease susceptibility”) AND (“squamous cell carcinoma of head and neck” OR “head and neck neoplasms”).

All searched articles were first assessed by title and duplicate articles were excluded manually and automatically (by EndNote). At later stage, we selected the articles by reading the abstracts. In next stage, related articles were selected based on assessing the full text. In the absence of access to the full text of the article and the lack of sufficient information in the abstract, that article would be excluded from the study. Two independent researchers made the search and extracted that data. Disagreements were resolved by consensus.

We used a PRISMA flow diagram for systematic search of articles and selecting the articles (Fig. 1).

Figure 1. PRISMA flow diagram showing the process of identification of studies via databases


Identification of studies via databases
Identification
Records identified from:
Databases (n =1163)
Web of science (n = 11)
PubMed (n = 537)
SCOPUS (n = 15)
Google Scholar (n = 598)
Cochrane (n = 2)
Records removed *before screening*:
Duplicate records removed (n = 213)
Records marked as ineligible by automation tools (n = 50)
Records removed for other reasons (n = 0)
Records screened
(n = 900)
Records excluded
By type of article (n = 70)
Screening
Reports sought for retrieval
(n = 830)
Reports assessed for eligibility
(n = 830)
Reports excluded:
Reading title (n = 490)
Reading abstract (n = 173)
Reading full text (n = 90)
Included
Studies included in review
(n = 77)

Inclusion and exclusion criteria

This review included all English language articles published since January 1995 till September 2021 which were about the impact of gene polymorphisms on risk of and susceptibility to HNSCC.

Exclusion criteria were as follows: studies evaluating neoplasms located in parts of the body other than head and neck area; studies evaluating neoplasms other than squamous cell carcinoma; cross-sectional studies without control group; case report articles, reviews and letters to the editor articles; studies which did not report the impact of gene polymorphism on risk and susceptibility; studies which included the impact of gene or protein expression on risk and susceptibility; studies which reported the impact of gene polymorphism on prognosis, toxicity, treatment response and resistance to therapies; studies which reported the impact of gene polymorphism on survival (overall survival, progression-free survival, disease-free survival, disease-specific survival, mortality); studies which reported the impact of gene polymorphism on recurrence of tumor; studies which reported the impact of gene polymorphism on cancer risk or susceptibility of second primary tumors; studies which included risk or susceptibility in cell lines.

Quality assessment

The Joanna Briggs Institute (JBI) checklist was used to evaluate the quality of the selected articles. Scoring of final articles was done based on JBI checklist. The acceptable score was 60% to include that article in this scoping review.

Results

Of 1163 initially searched articles, 77 articles were eligible to include in this review. Table 1 shows a summary of the studied gene polymorphisms in these articles.

Table 1. Studied gene polymorphisms in articles included in this systematic review

Gene category	**Gene**	**polymorphism**	**First author, year**

Carcinogen metabolizing enzymes	*GSTM1*	null	Fernández-Mateos, 2019 [4]; Trizna, 1995 [7]; Jahnke, 1996 [8]; Kihara, 1997 [9]; Cheng, 1999 [10]; Hanna, 2001 [11]; Gajecka, 2005 [12]; Ruwali, 2011 [13]; Yaghmaei, 2015 [14]; Maniglia, 2020 [15];
	GSTT1	null	Fernández-Mateos, 2019 [4]; Trizna, 1995 [7]; Jahnke, 1996 [8]; Cheng, 1999 [10]; Hanna, 2001 [11]; Gajecka, 2005 [12]; Ruwali, 2011 [13]; Yaghmaei, 2015 [14]; Maniglia, 2020 [15]
	GSTM3	A, B	Jahnke, 1996 [8]
	GSTP1	IIe105Val	Fernández-Mateos, 2019 [4]; Ruwali, 2011 [13]; Yaghmaei, 2015 [14]; Maniglia, 2020 [15]; Cho, 2006 [16]
		C341T	Maniglia, 2020 [15]
	CYP2D6	*1, *3, *6	Gajecka, 2005 [12]
		*4	Jahnke, 1996 [8]; Gajecka, 2005 [12]; Shukla, 2012 [17]
		*5	Jahnke, 1996 [8];
	CYP1A1	rs4646903	Jahnke, 1996 [8]; Kao, 2002 [18]
		rs1048943	Jahnke, 1996 [8], Kao, 2002 [18]
		*1, *2A, *2B, *4	Gajecka, 2005 [12]
	CYP2E1	1053C>T	Jahnke, 1996 [8]; Gajecka, 2005 [12]
	CYP3A5	rs776746	Fernández-Mateos, 2019 [4]
	NQO1	Trp139Arg	Cho, 2006 [16]
	NAT2	*4, *5B, *6A, *7B	Gajecka, 2005 [12]

DNA repair gene	*XRCC1*	Arg194Trp	Fernández-Mateos, 2019 [4]; Sturgis, 1999 [19]; Olshan, 2002 [20]; Gajecka, 2005 [21]; Kietthubthew, 2006 [22]; Costa, 2016 [23]
		Arg399Gln	Fernández-Mateos, 2019 [4]; Sturgis, 1999 [19]; Olshan, 2002 [20]; Gajecka, 2005 [21]; Kietthubthew, 2006 [22]; Costa, 2016 [23]; Huang, 2005 [24]; Li, 2007 [25]; Jelonek, 2010 [26]; Kostrzewska-Poczekaj, 2013 [27]
		rs3213245	Costa, 2016 [23]
		rs25489	Costa, 2016 [23]
	ADPRT	Ala762Val	Li, 2007 [25]
	NBS1	Glu185Gln	Jelonek, 2010 [26]
	APE1	Asp148Gln	Li, 2007 [25]; Jelonek, 2010 [26]
	OGG1	rs1052133	Costa, 2016 [23]
	APEX1	rs1130409	Fernández-Mateos, 2019 [4]; Costa, 2016 [23]
	ERCC1	C8092A	Sturgis, 2002 [28]; Tejasvi, 2020 [29]
		rs11615	Fernández-Mateos, 2019 [4]; Tejasvi, 2020 [29]; Wang, 2020 [30]
		rs3212948, rs3212961, rs735482	Wang, 2020 [30]
	ERCC2	C22541A	Sturgis, 2000 [31]; Gajecka, 2005 [21]
		A35931C	Fernández-Mateos, 2019 [4]; Gajecka, 2005 [21]; Kietthubthew, 2006 [22]; Huang, 2005 [24]; Jelonek, 2010 [26]; Kostrzewska-Poczekaj, 2013 [27]; Sturgis, 2000 [31]
		G23591A	Jelonek, 2010 [26]; Sturgis, 2002 [28]
	XPA	G-4A	Jelonek, 2010 [26]
	XPC	rs2228000	Fernández-Mateos, 2019 [4]

		rs77907221, rs2228001	Kietthubthew, 2006 [22]
	ERCC5	rs751402	Zavras, 2012 [32]
	XRCC3	C18067T	Fernández-Mateos, 2019 [4]; Listyowati, 2019 [5]; Gajecka, 2005 [21]; Kietthubthew, 2006 [22]; Huang, 2005 [24]; Kostrzewska-Poczekaj, 2013 [27]; Werbrouck, 2008 [33]
		c.-1843, c.562-14	Werbrouck, 2008 [33]
		rs1799794	Fernández-Mateos, 2019 [4]
	RAD51	c.-3392 G>T	Werbrouck, 2008 [33]; Lu, 2007 [34]
		c.-98G>C, c.-61G>T	Lu, 2007 [34]
		c.-3429	Werbrouck, 2008 [33]
	MGMT	Leu84Phe	Kietthubthew, 2006 [22]; Huang, 2005 [24]
		Ile143Val	Huang, 2005 [24]
		Trp65Cys	Kietthubthew, 2006 [22]
	Lig4	c.26	Werbrouck, 2008 [33]
	Ku70	c. 1310	Fernández-Mateos, 2019 [4]; Werbrouck, 2008 [33]
	Ku80	c.2110-2408	Werbrouck, 2008 [33]
Tumor suppressor gene	*p53*	codon 72	Fernández-Mateos, 2019 [4]; Lu, 2007 [34]; Nagpal, 2001 [35]; Chen, 2007 [36]; Ji, 2008 [37]; Yu, 2011 [38]
	BRM	BRM-741, BRM-1321	Wang, 2013 [39]
	PTEN	rs2943773, rs9651495	Liu, 2019 [40]

Oncogene	*MDM2*	rs2279744	Fernández-Mateos, 2019 [4]; Yu, 2011 [38]; Alhopuro, 2005 [41]
		rs937283	Yu, 2011 [38]
	Pin1	rs2233678, rs2233679	Cao, 2012 [42]
	WISP1	rs62514004, rs16893344, rs2977530, rs2977537, rs2929970, rs2929973	Lau, 2017 [43]
	CHRNA 5	c.1192G>A	Rajesh, 2018 [44]
Anti- or pro-apoptotic regulators	*BAX*	-248 G>A	Fernández-Mateos, 2019 [4]; Chen, 2007 [36]
	BCL2	-938 C>A	Fernández-Mateos, 2019 [4]; Chen, 2007 [36]
	TERT	rs2736098	Liu, 2010 [45]
	CLPTM1 L	rs401681	Liu, 2010 [45]
	NOD2	rs2066844	Fernández-Mateos, 2019 [4]
Cell cycle control	*CCND1*	G870A	Jelonek, 2010 [26]; Zheng, 2001 [46]; Rydzanicz, 2006 [47]
	VDR	Taq I	Bektaş-kayhan, 2010 [48]
Antioxidant gene	*SOD1*	rs1804450, rs11556620	Liu, 2014 [49]
	SOD2	rs5746136, rs4880	Liu, 2014 [49]
	HO-1	$(GT)_n$ repeats	Chang, 2004 [50]
	NFE2L2 /NRF2	rs1303586, rs2706110	Fernández-Mateos, 2019 [4]
	KEAP1	rs1048290	Fernández-Mateos, 2019 [4]

Folate metabolism	*TS*	TS3'UTR, TSER	Zhang, 2004 [51]
	MTHFR	C677T	Vairaktaris, 2006 [52]; Rodrigues, 2010 [53]; Galbiatti, 2012 [54]
		A1298C	Galbiatti, 2012 [54]
Inflammatory cytokine	*TNF-α*	G-308A	Abakay, 2020 [55]; Liu, 2005 [56]
		238G/A	Fernández-Mateos, 2019 [4]; Liu, 2005 [56]
	IL-18	-607, -137	Asefi, 2009 [57]
	IL-10	rs1800896	Abakay, 2020 [55]; Hussain, 2016 [58]
		rs1800872	Fernández-Mateos, 2019 [4]; Abakay, 2020 [55]; Singh, 2017 [59]
		rs1800871	Abakay, 2020 [55]
	IL-6	rs1800795	Fernández-Mateos, 2019 [4]; Pasvenskaite, 2020 [60]
		rs2069840	Abakay, 2020 [55]
	IL-2	rs2069762	Fernández-Mateos, 2019 [4]
	IL-1B	rs16944	Fernández-Mateos, 2019 [4]
	IL1RAP	rs4624606	Pasvenskaite, 2020 [60]
	IL1RL1	rs1041973	Pasvenskaite, 2020 [60]
	MCP-1	A2518G	Chen, 2011 [61], Bektas-Kayhan, 2012 [62]
	CCR2	V64I	Chen, 2011 [61]; Bektas-Kayhan, 2012 [62]
	TGF-β1	rs1800470, rs1800471	Abakay, 2020 [55]
	IFN-γ	rs2430561	Abakay, 2020 [55]
	BLK	rs13277113	Pasvenskaite, 2020 [60]
Alcohol-metabolizing gene	*ADH1C*	*1/*2	Schwartz, 2001 [63]; Olshan, 2001 [64]; Peters, 2005 [65]; Asakage, 2007 [66]
	ADH1B	*1/*2	Asakage, 2007 [66]
	ALDH2	*1/*2	Asakage, 2007 [66]
Transcription factor	*NFKB1*	-94 insertion /deletion	Lin, 2006 [67]

Tumor immunity	*CTLA-4*	+49 A/G	Ka¨mmerer, 2010 [68]; Wong, 2006 [69]
		-1661 A/G	Ka¨mmerer, 2010 [68]
	ICOS	+637, +1599	Ka¨mmerer, 2010 [68]
	CD28	0, +3160	Ka¨mmerer, 2010 [68]
	OX40	rs17568, rs229811	Faghih, 2019 [3]
Growth control	*VEGF*	rs1570360	Ka¨mmerer, 2010 [70]; Supic, 2012 [71]
		rs2010963	Ka¨mmerer, 2010 [70]; Supic, 2012 [71]
		rs3025039	Ka¨mmerer, 2010 [70]; Supic, 2012 [71]
		rs699947	Ka¨mmerer, 2010 [70]; Supic, 2012 [71]
		rs833061	Ka¨mmerer, 2010 [70]
	FGFR4	rs351855	Chou, 2017 [72]; Ansell, 2009 [73]
		rs2011077, rs7708357, rs1966265	Chou, 2017 [72]
	KRAS	rs712, rs1137282	Wang, 2012 [74]
		rs61764370	Fernández-Mateos, 2019 [4]
	EGFR	rs2227983	Fernández-Mateos, 2019 [4]
MircroRNA	*miRNA*	hsa-mir-499, hsa-mir-146a, hsa-mir-149, hsa-mir-196a2	Liu, 2010 [1]
Connective tissue remodeling	*MMP-2*	-1306 C/T	Hajihoseini, 2011 [75]
	MMP-9	-1562 C/T	Hajihoseini, 2011 [75]
	TIMP3	rs9621532	Pasvenskaite, 2020 [60]
Autophagy	*ATG10*	rs1864183	Fernández-Mateos, 2017 [2]
	ATG2B	rs3759601	Fernández-Mateos, 2017 [2]

	ATG16L1	rs2241880	Fernández-Mateos, 2017 [2]
	ATG5	rs2245214	Fernández-Mateos, 2017 [2]
Tissue regeneration	*REG1A*	2922C/T, 14C/T, 20C/T, 369G/T, 1201A/G	Xing, 2020 [6]
Immune tolerance	*HLA-G*	14-bp insertion/deletion, HLA-G*01:05 N	Barakat, 2021 [76]
Regulators of cellular homeostasis	*TRIM21*	rs4144331, rs915956	Chuang, 2021 [77]

Carcinogen-metabolizing enzymes
Glutathione S-transferase (GST)

Glutathione S-transferase M1 (GSTM1)

Heterozygote *GSTM1* A/B genotype was significantly higher in the control group compared to the laryngeal SCC group [8]. In some studies, frequency of *GSTM1* null genotype was significantly higher in the HNSCC group compared to the control group and null genotype was associated with increased risk of HNSCC [7, 10, 11, 13, 14] but in other studies the difference between the frequency of null genotype in HNSCC patients and control individuals was not significant [4, 8, 12, 15]. In Kihara et al. study, *GSTM1* null genotype was significantly higher in the HNSCC smoking patients compared to the control group, but this was not the case for non-smoking HNSCC patients; in smoking patients, the frequency was significantly higher in non-laryngeal cancer; in laryngeal cancers, the frequency of this variant was higher in patients < 60 years old compared to patients ≥ 60 years old [9]. In contrast, in Cheng et al. study, HNSCC patients > 65 years of age, never-smoking patients and never-drinking patients showed the highest frequencies of null genotype of *GSTM1* [10].

Combined genotypes of null variant of *GSTM1* gene and homozygous A/A variant of *XPD* A35931C (Lys751Gln) polymorphism were associated with elevated risk of laryngeal SCC [12].

GSTM3

Homozygote *GSTM3* B/B genotype was significantly higher in control group compared to laryngeal SCC group (8)

GSTT1

In some studies, frequency of *GSTT1* null genotype was significantly higher in the HNSCC group compared to the control group and null genotype was associated with HNSCC risk [7, 8, 10, 13, 14] but in other studies the difference of this frequency between these two groups was not significant [4, 11, 12, 15]. In Cheng et al. study, HNSCC patients ≤ 45 years old, never-smoking patients and former alcohol drinkers showed higher frequency of null genotype of *GSTT1* [10].

The interaction of alcohol drinking or tobacco smoking with *GSTT1* or *GSTM1* gene polymorphisms was also associated with significantly increased risk of HNSCC [13].

GSTP1

In one study, A/G and A/G+ G/G genotypes of *GSTP1* Ile105Val (rs1695) polymorphism were associated with significantly decreased risk of HNSCC [13]. In contrast, in other studies, there were not significant differences between the frequency of alleles and genotypes of this polymorphism between the HNSCC group and control group [4, 14–16]. The GA + GG genotypes of this polymorphism were significantly higher in heavy smoking HNSCC patients compared to non-smokers and light-smokers and were associated with HNSCC risk in a tobacco dose-dependent manner [16].

The haplotype analysis of the A313G and C341T *GSTP1* polymorphisms showed a significantly higher frequency of the AC and AT haplotypes in the HNSCC group than in the control group; GC haplotype was significantly higher in the control group [15].

Cytochrome P-450 (CYP)

CYP2D6

In Jahnke et al. study, variant genotypes of *CYP2D6* *4 gene polymorphism showed no significant differences between the HNSCC group and control group [8]. In contrast, in Shukla et al. and Gajecka et al. studies, variant genotypes of *CYP2D6**4 were associated with a significant increase in HNSCC risk [12, 17]. The *CYP2D6**4/*4 genotype and the

*CYP2D6**4 allele were significantly more frequent in the laryngeal SCC group than the control group [12].

Variant genotypes of *CYP2D6**10 polymorphism were associated with a significant increase in HNSCC risk [17]. Tobacco smoking or chewing and alcohol drinking significantly increased the risk of HNSCC in interaction with *CYP2D6* genotypes [17].

CYP1A1

Variant genotypes of *CYP1A1* rs1048943 (Ile462Val) polymorphisms showed no significant differences between the HNSCC group and control group [8]; in contrast, in Kao et al. study, the frequency of A/G genotype and G/G genotype of this polymorphism were significantly higher in the OSCC group than control group (G allele was associated with increased risk for OSCC); the frequency of *CYP1A1* A/G genotype was higher in younger oral SCC patients than A/A genotype [18].

The *CYP1A1**1/*4 genotype of *CYP1A1* C4887A (Thr461Asn) polymorphism and the *CYP1A1**4 allele were significantly more frequent in the laryngeal SCC group than control group [12].

NAD(P)H quinone dehydrogenase 1 (NQO1)

The CT + TT genotypes of *NQO1* Trp139Arg polymorphism was significantly higher in heavy smoking HNSCC patients compared to non-smokers and light-smokers and were associated with HNSCC risk in a tobacco dose-dependent manner [16].

Arylamine N-acetyltransferase (NAT)

The *NAT2**4/*6A genotypes and the *NAT2**4 allele were significantly more frequent in the laryngeal SCC group than control group. *NAT2**6A/*6A and *NAT2**5B/*6A genotypes were significantly more frequent in the control group than laryngeal SCC group (considered as protective variants) [12].

DNA repair genes

X-Ray repair cross-complementing group-1 (XRCC1)

*In one s*tudy, the CC genotype of *XRCC1* Arg194Trp (rs1799782) polymorphism was a significant risk factor for HNSCCs, especially for oral and pharyngeal SCCs [19]; in contrast, in other studies, there were an elevated risk for oral and oropharyngeal SCC in CT/TT genotypes; this increase was significant in Costa et al. study and was borderline in

Kietthubthew et al. study [22, 23]; in Olshan et al. study, the CT genotype was associated with a slight increase of HNSCC risk in white patients [20]; in Gajecka et al. study, all genotypes of *XRCC1* Arg194Trp polymorphism were not associated with increased or decreased risk of HNSCC [21].

In Sturgis et al. study, the frequency of AA genotype of Arg399Gln (rs25487) *XRCC1* polymorphism was significantly higher in the HNSCC group compared to the control group [19]; in contrast, in four studies, AA genotype was associated with a significantly decreased risk of HNSCCs [20, 22, 24, 27]; in other studies, all genotypes were not associated with increased or decreased risk of HNSCCs [4, 21, 23, 25, 26].

In Sturgis et al. study, coexistence of genotypes with lack of T allele of *XRCC1* Arg194Trp and presence of A allele of *XRCC1* Arg399Gln significantly increased the risk of HNSCCs [19]. The *XRCC1* TTGG haplotype (from c.-77T>C, Arg194Trp, c.839G>A and Arg399Gln polymorphisms) was more frequent in the oropharyngeal SCC group than in control group [23]. In Olshan et al. study, an interaction between *XRCC1* Arg194Trp and Arg399Gln polymorphisms and tobacco use was proposed [20].

Variants with *XRCC1* 194Trp (CT/TT genotypes) had interaction with tobacco smoking and alcohol drinking to further increase oral SCC risk; non-betel chewer with these variants were associated with significantly increased oral SCC risk [22].

ADP-ribosyltransferase (ADPRT)

The *ADPRT* 762Ala/Ala genotype and combined *ADPRT* 762Ala/Val and Ala/Ala genotypes were associated with a decreased risk of HNSCCs (25).

Nijmegen breakage syndrome 1 (NBS1)

NBS1 Glu185Gln gene polymorphism was associated with HNSCC risk; Glu/Glu homozygotes were more frequent in HNSCC patients and Gln/Gln homozygotes were more frequent in control individuals [26].

Excision repair cross complementary gene 1 (ERCC1)

The CC genotype of *ERCC1* C8092A (rs3212986) polymorphism was associated with increased risk of HNSCC but this increase was not significant; combination of CC genotype of *ERCC1* C8092A and GA/AA genotypes of Xeroderma pigmentosum complementation group D (*XPD*) G23591A polymorphism was associated with a significantly increased risk of

HNSCC (28); in contrast, in Tejasvi et al. study, CA genotype of *ERCC1* C8092A was associated with a significantly increased risk of oral SCC [29].

The CC genotype of *ERCC1* rs11615 (C118T) was associated with decreased risk of laryngeal SCC [4]; in Tejasvi et al. study, the CT and TT genotypes were associated with increased risk of oral SCC [29].

Xeroderma pigmentosum complementation group D (XPD)/Excision repair cross complementary group 2 (ERCC2)

In Gajecka et al. and Kietthubthew et al. study, the CA genotype of *XPD* C22541A (Arg156Arg) polymorphism was present in significantly higher frequency in the laryngeal and oral SCC group than control group [21, 22]; although this increase was not significant in Kietthubthew et al. study, female oral SCC patients with variant genotypes (CA/AA genotypes) had significantly higher risk for oral SCC [22].

In some studies, *XPD* A35931C (rs13181) polymorphism was not significantly associated with HNSCC risk [22, 24, 27, 31]; in contrast in other studies, this polymorphism was associated with HNSCC risk [4, 21, 26]; in Jelonek et al. study, Gln/Gln genotype was more frequent in HNSCC patients and Lys/Lys genotype was more frequent in control individuals [26]; in Fernández-Mateos et al. study, the CC genotype was associated with decreased risk of laryngeal SCC [4]; in Gajecka et al. study, AC genotype of was present in significantly higher frequency in the laryngeal SCC group than control group [21]. In Sturgis et al. study, frequency of CC variant was higher in the HNSCC group compared to the control group but this increase was borderline (not significant); this increased risk was significantly higher in smokers, drinkers and older age [31].

Excision repair cross complementing group 5 (ERCC5)

CC genotype of *ERCC5* rs751402 polymorphism was significantly associated with reduced risk of oral SCC while the T allele was associated with increased risk of oral SCC [32].

X-ray repair cross-complementing group 3 (XRCC3)

In most of studies, variant genotypes of *XRCC3* C18067T (rs861539) polymorphism were associated with increased risk of HNSCC [5, 21, 22, 27, 33]; in four of them, CT genotype was associated with an increased risk [21, 22, 33, 27] although this increase was non-significant in Gajecka et al. study (for laryngeal SCC) [21]. In Listyowati et al. study, TT genotype was significantly associated with increased risk of HNSCC [5]; in Listyowati et al.

and Kietthubthew et al. studies, 241Met (T) allele (CT/TT genotypes) was associated with increased oral SCC risk [5, 22]. In Fernández-Mateos et al. and Huang et al. studies, variant genotypes of this polymorphism were not associated with HNSCC risk [4, 24].

Combination of three variants including genotypes with *XRCC3* 241Met, variants with *XRCC1* 194Trp and *XPD* exon 6 was associated with a significantly increased risk for oral SCC [22].

RAD51 recombinase (RAD51)

The TT homozygotes of *RAD51* 172 G>T (rs1801321) polymorphism were associated with a decreased risk for HNSCCs compared with other genotypes, especially in *P53* Arg72Arg homozygotes [34]. In contrast, in Werbrouck et al. study, this polymorphism was not associated with HNSCC risk [33].

RAD51 135G>C (rs1801320) polymorphism was not associated with HNSCC risk [34]. In contrast, GC and GC + CC variants were associated with decreased risk for HNSCCs [33].

O^6-methylguanine-DNA-methyltransferase (MGMT)

Phe_{84} and Val_{143} alleles of Leu84Phe and Ile143Val *MGMT* polymorphisms were associated with a decreased risk for HNSCC. There was also a significant difference between the HNSCC group and control group with regard to *MGMT* haplotype distribution [24]. On the other hand, it has been reported that *MGMT* Trp65Cys and *MGMT* Leu84Phe polymorphisms are not associated with oral SCC risk [22].

DNA Ligase 4 (Lig4)

Lig4 c.26 polymorphism was associated with a significantly decreased risk for HNSCC [33].

Tumor suppressor gene

P53

Pro/Pro genotype of *p53* codon 72 polymorphism (rs1042522 or *TP53* Arg72Pro) was associated with decreased risk of HNSCC. This decreased risk was for human papillomavirus (HPV)-positive oral SCCs in Nagpal et al. study and for laryngeal and pharyngeal SCCs in Fernández-Mateos et al. study [4, 35]. In Nagpal et al. study, Arg/Arg genotype had higher susceptibility to HPV infection and oral SCC [35]. On the other hand, in Ji et al. study, Arg/Pro and Pro/Pro genotypes were associated with increased risk of HPV-associated oropharyngeal SCC in never-smokers [37].

Brahma (BRM)

The homozygous genotypes of *BRM*-741 and *BRM*-1321 polymorphisms were significantly associated with elevated risk of HNSCC. Homozygosity for both *BRM* polymorphisms was associated with even more increased risk. The most increased risk was associated with the HPV-positive oropharyngeal SCC patients who were homozygous for both polymorphisms [39].

Phosphatase and tensin homolog deleted on chromosome ten (PTEN)

The CC genotype of *PTEN* rs9651495 was significantly associated with increased oral SCC risk; the TT genotype was significantly associated with decreased risk of oral SCC [40].

Oncogene

Murine double minute 2 (MDM2) gene

In two studies, *MDM2* rs2279744 (T309G) and rs937283 (A2164G) gene polymorphisms were not associated with HNSCC risk [38, 41]; in contrast, in Fernández-Mateos et al. study, GG genotype was associated with increased risk of laryngeal SCCs [4].

Combined genotypes of *MDM2* 309, *MDM2* A2164G and *p53* codon 72 were not associated with HNSCC risk; in subgroups, combination of these genotypes significantly increased the risk of non-oropharyngeal cancer; this increased risk was greater among young individuals, men, cigarette-smokers, and alcohol drinkers [38].

***PIN1* (protein interacting with NIMA [never in mitosis A]-1)**

Variant genotypes of rs2233678 *Pin1* polymorphism were associated with increased risk of laryngeal SCC [42].

WNT1-inducible signaling pathway protein 1 (WISP1)

Presence of at least one G allele of *WISP1* rs2929970 polymorphism was associated with increased oral SCC risk [43].

Anti- or pro-apoptotic regulators

BCL2 associated X (BAX)

BAX -248 G>A (rs4645878) polymorphism was not associated with an increased or decreased risk of HNSCCs [4, 36]; although in *TP53* heterozygotes, the AA genotype of *BAX* -248 G>A polymorphism was associated with an increased risk of HNSCCs [36].

B-cell lymphoma 2 (BCL2)

BCL2 -938 C>A (rs2279115) polymorphism was not associated with an increased risk of HNSCCs, although in *TP53* heterozygotes, AA, CA and AA+CA genotypes of *BCL2* -938 C>A polymorphism was associated with a decreased risk of HNSCCs (36). In contrast, in Fernández-Mateos et al. study, CA genotype of *BCL2* rs2279115 was associated with increased risk of oral SCC [4].

Telomerase reverse transcriptase (TERT)

CT+TT genotype of rs2736098 *TERT* gene polymorphism was associated with a slightly decreased risk of HNSCCs. The combination of variant genotypes of the two polymorphisms of rs2736098 *TERT* and rs401681 cleft lip and palate transmembrane 1-like (*CLPTM1L*) was associated with a moderately decreased risk of HNSCC. This decreased risk was more pronounced in smokers, alcoholics, and patients with oropharyngeal cancer [45].

Cleft lip and palate transmembrane 1-like (CLPTM1L)

CT+TT genotype of rs401681 *CLPTM1L* polymorphisms was associated with a slightly decreased risk of HNSCCs [45].

Cell cycle control

Cyclin D1 (CCND1)

The frequency of allele A of the G870A cyclin D1 gene polymorphism was slightly higher in HNSCC patients than in the control group, but this difference was not significant and was borderline [46, 47]. The GA genotype was associated with an increased risk for HNSCC, but this increase was not significant; AA genotype was associated with a significant increase in risk; in subgroups, AA genotype was associated with increased risk in people ≤ 50 years old, females, non-smokers and non-alcoholics [46]. On the other hand, another study reported that GA genotype and a combination of GA and AA genotypes were associated with a significant increased risk of laryngeal cancer [47]. In Jelonek et al. study, *CCND1* A870G polymorphism was not associated with HNSCC risk [26].

Vitamin D receptor (VDR)

There was a significant difference in the frequency of *VDR* Taq I genotypes between oral SCC patients and control individuals; *VDR* Tt genotype was associated with a significantly increased risk of oral SCC risk, especially in females [48].

Antioxidant gene

Superoxide dismutase-2 (SOD2)

Frequency of CT genotype of rs4880 *SOD2* polymorphism was higher in the oral SCC group than control group and it was associated with oral SCC risk; this increased risk was higher in smoking patients [42].

Heme oxygenase-1 (HO-1)

Long (L) $(GT)_n$ repeat allele of *HO-1* promoter was associated with increased risk for areca (betel)-induced oral SCC, especially buccal SCC; medium (M) $(GT)_n$ repeat allele of *HO-1* promoter was protective against oral SCC, especially non-buccal SCC [50].

Nuclear factor erythroid-derived 2-like 2 (NFE2L2/ NRF2)

GA genotype of *NFE2L2* rs1303586 polymorphism and CT genotype of *NFE2L2* rs2706110 polymorphism were associated with decreased laryngeal and pharyngeal SCCs (4).

Folate metabolism

Thymidylate synthase (TS)

The 0bp/0bp genotype of thymidylate synthase in the 3'-untranslated region (*TS3'UTR*) polymorphism had a significantly reduced risk for HNSCC in comparison with 6bp/6bp genotype, but the thymidylate synthase in the 5'-untranslated enhanced region (*TSER*) polymorphism was not associated with a significant impact on HNSCC risk. When considering two polymorphisms together, combined genotype of *TSER* 3R3R and *TS3'UTR* 0bp/0bp had a significantly reduced risk for HNSCC. The *TS3'UTR* 0bp allele (6bp/0bp and 0bp/0bp genotypes**)** was associated with a reduced risk for stage IV oral SCCs. The *TSER* 3R and *TS3'UTR* 0bp alleles together were introduced as protective alleles against HNSCCs and the 0bp allele was especially protective against oral SCC [51].

Methylenetetrahydrofolate reductase (MTHFR)

In one study, the frequency of heterozygote genotype of *MTHFR* C677T polymorphism was significantly higher in the oral SCC group compared to control group and this polymorphism was considered as a minor risk factor for oral SCCs [52]. In contrast, in other studies, variant genotypes were not associated with HNSCC risk [53, 54]; T allele was associated with increased risk of HNSCC. AC or CC genotypes of *MTHFR* A1298C gene polymorphism and 1298C allele were associated with increased risk of HNSCC. Combined genotype of *MTHFR* C677T and A1298C polymorphisms were associated with increased risk of HNSCCs [54].

Inflammatory cytokine

Tumor necrosis factor (TNF)

In Liu et al. study, oral SCC patients had a higher frequency of the GG genotype of *TNF-α* G-308A (rs1800629) polymorphism; GA genotype was lower in oral SCC patients (56). In contrast, in Abakay et al. study, GA genotype was significantly higher in laryngeal SCC patients than controls [55].

GA genotype of *TNF-α*-238G/A (rs361525) gene polymorphism was lower in oral SCC patients [56]. In contrast, in Fernández-Mateos et al. study, variant genotypes were not associated with HNSCC risk [4].

Interleukin (IL)

Interleukin-10 (IL-10)

The AG genotype of *IL-10* A1082G (rs1800896) polymorphism was significantly associated with increased risk of oral SCC but GG genotype was not significantly associated with oral SCC risk. G mutant allele was associated with increased risk of oral SCC and there was an interaction between this allele and tobacco chewing [58]. In contrast, in Abakay et al. study, variant genotypes were not associated with laryngeal SCC risk [55].

In Singh et al. study, AC and CC genotypes of *IL-10* rs1800872 (-A592C) gene polymorphism was significantly associated with increased risk of oral SCC. The -592 C allele was significantly associated with elevated oral SCC risk [59]. In contrast, in Fernández-Mateos et al. and Abakay et al. studies, variant genotypes were not associated with HNSCC risk [4, 55].

Interleukin-6 (IL-6)

The CG genotype of *IL-6* rs1800795 was associated with increased risk of laryngeal and oral SCCs [4]. In contrast, in Pasvenskaite et al. study, variant genotypes were not associated with laryngeal SCC risk [60].

Interleukin-2 (IL-2)

The GG genotype of *IL-2* rs2069762 was associated with decreased oral SCC risk [4].

Interleukin 1 receptor accessory protein (IL1RAP)

In Pasvenskaite et al. study, a significant increase in laryngeal SCC risk was observed with variant genotypes and allele of *IL1RAP* rs4624606 polymorphism in different genetic models [60].

Monocyte chemoattractant protein-1 (MCP-1)

The G allele and GG genotype of *MCP-1* A2518G polymorphism was associated with significantly elevated risk of oral SCC [62]. In contrast, in another study, this polymorphism was not associated with oral SCC risk [61].

CC chemokine receptor 2 (CCR2)

The A allele (64I allele) and GA genotype (wt/64I genotype) of *CCR2* V64I gene polymorphism were associated with significantly elevated risk of oral SCC (61, 62); *CCR2* GG genotype (wt/wt genotype) plays a protective role against oral SCC. *MCP-1* G: *CCR2* 64I haplotype was significantly higher in oral SCC patients compared to the control group [62].

Transforming growth factor-β1 (TGF-β1)

The GC genotype and C allele of *TGF-β1* rs1800471 (codon 25) polymorphism were significantly associated with increased risk of laryngeal SCC. The GG genotype and G allele were significantly associated with decreased risk of laryngeal SCC [55]. The TC genotype of *TGF-β1* rs1800470 (codon 10) polymorphism was significantly associated with increased risk of laryngeal SCC [55].

Interferon gamma (IFN-γ)

In Abakay et al. study, frequency of AA genotypes of *IFN-γ* rs2430561 polymorphism was significantly lower in laryngeal SCC patients than controls [55].

Alcohol-metabolizing gene

Alcohol dehydrogenase-1C (ADH1C/ADH3)

The *ADH1C* *2 allele was associated with increased impact of alcohol on oral SCC risk. The *ADH1C* *2-2 genotype in heavy alcohol drinkers caused more susceptibility to HNSCC in comparison with *ADH1C**1/*2 and *ADH1C**1/*1 genotypes [21, 63]. In contrast, other studies could not find any role for *ADH1C**1 polymorphism in increasing the HNSCC risk; there was no significant difference between *ADH1C**1-1 or *ADH1C**1-2 genotypes in comparison with *ADH1C**2-2 genotype with regard to HNSCC risk [64, 66].

Alcohol dehydrogenase 1B (ADH1B)

*ADH1B**1/*1 genotype was associated with significantly increased risk of HNSCCs (including all oral and pharyngeal SCCs), hypopharyngeal SCCs, and oral/oropharyngeal SCCs in moderate to heavy alcohol drinkers [66].

Aldehyde dehydrogenase 2 (ALDH2)

*ALDH2**1/*2 genotype was associated with increased risk of HNSCCs (including all oral and pharyngeal SCCs) and hypopharyngeal SCCs in moderate to heavy alcohol drinkers; *ALDH2* genotypes were not associated with the risk of oral/oropharyngeal SCCs [66].

Transcription factor

Nuclear factor kappa-B, subunit 1 (NFKB1)

Oral SCC patients older than 50 years had significantly higher frequency of insertion allele of *NFKB1* polymorphism compared to controls. Frequency of deletion/insertion, insertion/insertion and deletion/insertion + insertion/insertion genotypes was also significantly higher in oral SCC patients older than 50 years compared to controls. Presence of both *NFKB1* insertion and *HO-1* L alleles significantly increased the risk of oral SCC. Oral SCC patients with lymph node metastasis or stage IV were associated with significantly higher frequency of *NFKB1* insertion and *HO-1* L alleles [67].

Tumor immunity

Cytotoxic T lymphocyte antigen-4 (CTLA-4)

Frequency of *CTLA-4* -1661 A/G polymorphism was significantly different between the oral SCC patients and control individuals. The allele *CTLA-4* -1661 G was more frequent in oral SCC group. The combinations *CTLA-4* -1661 G/G and *CTLA-4* +49 A/G were seen in the patient group only [68].

Growth control

Vascular endothelial growth factor (VEGF)

In Kammerer et al. study, T allele of *VEGF* +936C/T (rs3025039) polymorphism and variant genotype of *VEGF* -2578 C/A polymorphism were more frequent in oral SCC patients and significantly associated with oral SCC risk. The combination of these polymorphisms with other *VEGF* polymorphisms (+936 C/T and +405 G/C [rs2010963], -2578 C/A [rs699947] and -1154 G/A [rs1570360], 460 C/T [rs833061] and -2578 C/A [rs699947]) were also associated with oral SCC risk **(**70**).** In contrast, in Supic et al. study, variant genotypes of *VEGF-A* polymorphisms (rs699947, rs1570360, rs2010963, rs3025039) were not associated with oral SCC risk; although *VEGF-A* haplotypes were associated with oral SCC risk. For example, CAG haplotype for *VEGF* rs699947, rs1570360, rs2010963 (-634G/C) polymorphisms was associated with an elevated oral SCC risk and CGG haplotype was associated with a reduced risk of oral SCC (7).

Fibroblast growth factor receptor (FGFR)

In Ansell et al. study, GG genotype of *FGFR4* Gly388Arg (rs351855) polymorphism was associated significantly with increased HNSCC risk and this genotype was even associated with a higher risk in HNSCC male patients [73]. In contrast, in Chou et al. study, GA genotype and a combination of GA and AA genotypes were associated with increased oral SCC risk [72].

Kirsten rat sarcoma virus (KRAS) gene

G/T and T/T genotypes of *KRAS* rs712 polymorphism were associated with a decreased risk of oral SCC [74].

MicroRNAs (miRNAs)

The AG and GG genotypes of homo sapiens miRNA-499 (*hsa-mir-499*) gene polymorphism were associated with a decreased risk of HNSCC. Combination of variant genotypes of four

polymorphisms in pre-miRNAs genes (*hsa-mir-146a* [rs2910164], *hsa-mir-149* [rs2292832], *hsa-mir-196a2* [rs11614913], *hsa-mir-499* [rs3746444]) were associated with a moderately elevated risk of HNSCCs [1].

Connective tissue remodeling

Matrix metalloproteinases (MMP)

Variant genotypes of *MMP-2* -1306 C/T gene polymorphism were significantly different between HNSCC patients and control group; the C allele was associated with increased HNSCC risk. Variant genotypes of *MMP-9* -1562 C/T gene polymorphisms were signifiantly different between the HNSCC patients and the control group, and TT genotype significantly increased the risk of HNSCC [75].

Tissue inhibitor of metalloproteinase (TIMP)

TIMP3

In Pasvenskaite 2020 et al. study, a significant decrease in laryngeal SCC risk was observed with variant genotypes and allele of *TIMP3* rs9621532 polymorphism in different genetic models [60].

Autophagy-related genes (ATG)

The *ATG10* rs1864183, *ATG2B* rs3759601 and *ATG16L1* rs2241880 polymorphisms were associated with increased laryngeal, pharyngeal and oral SCC risk, respectively [2].

Tissue regeneration

Regenerating gene 1A (REG1A)

Variant genotypes of *REG1A* 2922C/T were associated with increased risk of nasopharyngeal carcinoma [6].

Immune tolerance

Human leucocyte antigen — G (HLA-G)

The −14/-14 and −14/ +14 genotypes of *HLA-G* 14-bp insertion/deletion polymorphism were significantly higher in the laryngeal SCC group. There was a significant association between *HLA-G* 14-bp deletion allele and susceptibility to laryngeal SCC [76].

Regulators of cellular homeostasis

Tripartite motif 21 (TRIM21)

The GT or TT genotypes of *TRIM21* rs4144331 polymorphism with betel-nut chewing had a significantly higher risk for oral SCC than non-betel-nut chewing with GG genotype. The GA or AA genotypes of *TRIM21* rs915956 polymorphism with betel-nut chewing had a significantly higher risk for oral SCC than non-betel-nut chewing with GG genotype [77].

Discussion

Development of sporadic cancers (non-hereditary) can be explained based on polygenic mechanism in which a large number of low-penetrance alleles (each with a small risk of developing cancer) combine together to cause cancer susceptibility. In fact, development of most of sporadic cancers occurs in genetically predisposed people and this predisposition results from multiple low penetrance genes (cancer susceptibility genes) rather than a single gene mutation [78, 79].

The role of low penetrance susceptibility genes in head and neck cancer development is still to be clarified. Some evidence from previous literatures has shown that specific polymorphic alleles of cancer susceptibility genes (such as *CYP2D6*, *GSTM1*, *NAT2* and etc.) may be associated with cancer risk [80, 81]. For example, in Xu et al. meta-analysis, the *GSTM3* A/B polymorphism was associated with a decreased risk of head and neck cancers, especially in laryngeal cancer and Caucasian populations [82] or in Hashibe et al. meta-analysis, *GSTM1* and *GSTT1* polymorphisms were associated with increase in HNSCC risk [83]. These polymorphisms sometimes play a more important role in certain ethnic groups [84].

As mentioned in the introduction, HNSCC carcinogenesis involves dysregulation of different pathways, including DNA repair, carcinogens' metabolism, cell cycle control and so on. Gene polymorphisms can affect the ability of different individuals to differentially metabolize carcinogens, repair DNA damage, and induce apoptosis, which, in turn, can affect individual susceptibility to HNSCCs [6, 31].

Since tobacco smoking and alcohol drinking are among the most important etiologic factors of HNSCCs, any factor that can affect the metabolism of tobacco derivatives or alcohol may also affect the risk of head and neck cancers. *GSTs* or *CYP*s like *CYP2El* or *CYP2D6* are induced by ethanol and are involved in metabolizing of chemicals derived from tobacco (e.g.

nitrosamines). Therefore, functional polymorphisms in genes related to carcinogen metabolizing enzymes, such as *GST*s or *CYP*s, which affect the expression of the corresponding protein and have impact on the efficacy of detoxification of carcinogens derived from cigarette smoking, can become the basis for development of head and neck cancer [8, 12, 17, 18].

Tobacco smoke as the main etiologic factor for HNSCC development has numerous carcinogens that induce DNA damage. This damage is removed by DNA repair genes through different pathways. It is probable that polymorphisms in DNA repair genes (like *XRCC*, *ADPRT*, *APE1*, etc.) result in amino acid differences in DNA repair enzymes which in turn impair their functions in repairing the damage to DNA. This results in reduced DNA repair capacity. Thus, DNA repair gene polymorphisms may predispose people to HNSCCs, especially those which are induced in response to damage to DNA. A similar mechanism can be true for head and neck cancers caused by DNA damage due to sunlight and ultraviolet radiation [19, 20, 25].

Polymorphisms of cell cycle control genes, like cyclin D1 gene, can alter mRNA' splice site which subsequently influence their related proteins. It has been hypothesized that cells with DNA damage and these gene polymorphisms may pass more easily through the G1/S checkpoint in the cell cycle. This reduces the DNA repair capacity, which, in turn, can increase the susceptibility to HNSCC [26, 46, 47].

Oxidative response proteins are protective mechanisms against oxidative stresses like heat shock, ultraviolet radiation, etc. Pathogenesis of HNSCC has been attributed, to some extent, to oxidative stresses. It has been hypothesized that polymorphisms of these proteins (like *HO-1*) regulate gene transcription. Therefore, it can affect the HNSCC risk [50].

Changes in immune functions of HNSCC patients have been reported. Inflammatory mediators (like *TNF-α*) have sometimes been suggested as tumor promoters. So, polymorphisms of genes related to inflammatory mediators have been proposed as risk factors for HNSCC [4, 55, 56].

Interaction of tobacco with alcohol elevates HNSCC risk. Removal of alcohol is done via oxidation by alcohol dehydrogenase (*ADH*) enzyme. The polymorphisms of *ADH*s genes may affect the metabolism of alcohol. For example, it has been suggested that the inactive *ALDH2* coded by *ALDH2**1/*2 genotype and the less-active *ADH1B* coded by *ADH1B**1/*1 genotype could increase the risk of HNSCC in alcohol drinkers. So, polymorphism of *ADH*s

gene can be considered as a factor that modulates alcohol-related HNSCC risk; this is probably through regulating effective dose of alcohol [63–66].

If the cell cannot repair DNA damage, it takes the path of apoptosis, which involves tumor suppressor genes/oncogenes such as P53 or pro-apoptotic/anti-apoptotic molecules in inducing or preventing apoptosis. Dysregulation in any of the components of the apoptosis pathway can lead to head and neck cancer. Among the things that can affect the apoptosis pathway is the polymorphism of tumor suppressor genes or anti-apoptotic molecules [4, 36, 45].

The function of miRNAs is not clear but studies have reported they may act as tumor suppressors or oncogenes. Polymorphisms in pre-microRNAs (miRNAs) genes can change the expression of miRNAs and this may help in the process of HNSCC carcinogenesis [1].

Conclusion

HNSCC carcinogenesis processes involve disruptions and deregulations of different pathways; numerous studies have examined the gene polymorphisms involved in these pathways, which have been associated with different and sometimes contradictory results. Among the polymorphisms that are often significantly associated with HNSCC risk are: *GSTM1* null, *GSTT1* null, *CYP2D6* *4, *XRCC1* Arg194Trp and Arg399Gln, *ERCC1* C8092A, *XPD* Lys751Gln, *XRCC3* Thr241Met, *P53* codon 72 and *MTHFR* C677T polymorphisms.

Conflict of interest

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