RISK GENES IN HEAD AND NECK CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF LAST 5 YEARS

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INTRODUCTION

Head and Neck Carcinoma (HNC), of which the majority are squamous cell carcinomas of the head and neck (SCCHN), is the sixth most prevalent cancers in mankind and, presents high morbidity and low rates of survival.[1] It is known that the apoptotic and proliferation genes are involved in cancer development and these could be useful as a biomarker of this pathology. Systematic reviews and meta-analysis allow stronger and more generalized conclusions for identifying some models of risk markers. These models may help in screening, early diagnosis and/or therapy in the clinic.[2-5]

In recent decades, there has been increased interest in genetic predisposition studies in complex disease. This has led to the production of an enormous number of epidemiologic papers about the relationship between genetic polymorphism and disease. However, the magnitude of association between specific polymorphism and disease is still not established. The identification of a predictive model of risk polymorphisms could help in early diagnosis, and in understanding disease recurrence and/or progression in the subset of patients.

Vineis et al.[6]summarizedfive proposed models in the history of cancer research as follows: - *Mutational:* carcinogenic compounds such as tobacco produce mutations in the genes related to cell cycle regulation[7];*Genome Instability*: based on the tumor suppressor genes hypothesis and DNA repair (*mismatch repair*), and microsatellite instability[8]; *Non-Genotoxic*: based on modulators of cancer risk (epigenetic events) such as diet, obesity, hormones, etc.[9]; *Darwinian*: based on Darwin's theory and the work of researchers such as Greaves, 2007[10]. This model considers a clonally selection of cells that acquire advantages over others rather than mutations, but places the emphasis on the role of the macro- and micro-environment; *Tissue Organization*: focuses on the local micro-environment around the precancerous cells. There are two subtypes: focused on the micro-environment (focal proliferative lesions precede cancer) or morphostasis theory (morphostatic fields maintain the normal behavior of the cell and its tissue micro-architecture).[11]

The aim of this work was to identify risk genes related to the development and progression of squamous cell carcinoma head and neck (SCCHN) and do a meta-analysis of available estimates.

METHODS

Search strategy and selection criteria

This study was made according to the PRISMA reporting items for systematic reviews and meta-analysis guidelines. We conducted a systematic review and meta-analysis of case-control studies from the MEDLINE, Scopus, Cochrane, and CancerLit databases between January 2007 and January 2013. Language is not restricted. The search strategy included the following keywords

(variably combined): "oral cancer", "oral cancer polymorphism", "oncogene", "tumor suppressor gene", "squamous cell carcinoma", "head and neck cancer".

Data extraction

Data was collected of adult patients of both genders, with diagnosis of head and neck carcinoma according to the criteria of ICD-10C00-C14 WHO or another specific source, in whom genetic polymorphisms were identified. Original published papers that did not report genotyping by PCR (polymerase chain reaction), or studies of patients with systemic diseases or with syndromes, pregnancy or with indication of long-term medication were excluded.

Abstracts and titles of all the identified papers obtained by the electronic search were evaluated. All studies which met the inclusion criteria (presence/absence of mutation and/or polymorphism by PCR, Odd Ratios (OR) adjusted for alcohol and tobacco, 95% Confidence Intervals (CIs) were assessed in order to establish their validity and subsequent data extraction.

Evaluation of Quality of Studies

The case-control studies guidelines of the Scottish Intercollegiate Guidelines Network and MOOSE are followed. Two members of the team (AB, AMZ) evaluated complete articles independently and double-blinded, to establish their quality. Disagreements were resolved by reiteration, discussion and consensus with the participation of a third member (JLB).The papers were encoded and delivered independently to each reviewer. A search was made of combined electronic databases, and the bibliographies of all selected papers were searched to identify grey literature.

Statistical Analysis

Since the included polymorphisms are diallelic SNPs, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to assess the strength of association between each gene variant and HNC risk, based on meta-analysis of molecular association studies.[12]

Meta-analysis was performed using the random-effects (DerSimonian Laird) model, based on whether the homogeneity characteristics of the studies allowed us to assume that the effect size (HCN risk) varies between studies (studies represent a population of true effects), and the fixed effects by the Mantel Haenszel method (assumes that all studies belong to a common population, and that the effect size is not significantly different between studies.) To this end, heterogeneity was formally investigated by the Q-test and the I^2statistic $I^2 = \left(\frac{Q-df}{Q}\right) x100\%$. [13] The *meta* package of R software 2.15.3 (March 2013) was used.

Role of the funding source

The funders had no role in study design, data collection, analysis or interpretation of data, preparation of the report, or the decision to publish. All members of the analysis and writing committee had access to the raw data and are responsible for the final submission for publication.

RESULTS

Nineteen original reports were retrieved from 2285 potential reports that addressed the issue of DNA gene / polymorphisms and risk of SCCHN. Twelve of the studies were of unpaired case-control design, 6 studies were matched case-control, and 1 nested case-control (Table 1). All studies were adjusted for tobacco and alcohol. Clinical trials, chromosomal alterations or in vitro cell culture studies were not included. ORs and 95%CIs were estimated between case-control and presence/absence of SCCHN. Other aspects were also studied that are not included in this paper because they are not homogenous.

A hundred and eight genotypes of 40 polymorphism/genes (Table 2) related to proliferation, apoptosis, carcinogenic metabolism, inflammatory and progression pathways were analyzed. The total number was 8540 cases and 9844 controls (Table 2). The number of males was higher than females. The average age range was between 50 and 60 years old, but the age ranged from 20 to 80, and was similar in both cases and controls. In two studies only males were enrolled.[14,15]

The following genes/polymorphisms were seen to have significant association with increased risk of SCCHN: miRNA499[15], TNFα[16], TNFβ[16], NFKB1[17], NFKBIA[17], CRYAB (Alpha B-Crystalline) [18], OGG1[19], CYP1B1[20], and GSTM1.[21,22] In contrast, the ADH7A92G[23], and DEC1[24]polymorphisms are associated with a diminished risk of SCCHN.TP53, GSTM1, and CYPA1were described in four, three, and two studies respectively, which were considered for meta-analysis.

The suppressor tumor gene TP53, Arg72Pro, rs1042522 (CC, GG, CG) polymorphism was evaluated in four studies for CC / GG genotypes, and in three studies for the CG genotype [24-27]. No study reported a significant association between this polymorphism and SCCHN risk. The studies reporting the genotype data were homogenous for the CC genotype (I^2=40.1%, Q-test=5.01, p-value=0.1714), GG genotype (I^2=0%, Q-test=2.69, p-value=0.447), and CG genotype (I^2=0%, Q-test=0.66, p-value=0.7171). For each genotype pooled, the OR observed was: CC genotype1.14, CIs95% [0.9195; 1.4208], p-value=0.2285; GG genotype 0.97, CIs95% [0.8837; 1.0707], p-value=0.5723; GC genotype 0.91, CIs95% [0.8191; 1.0058], p-value=0.0645.The meta-analysis showed no significant association between different allelic variants of Arg72Pro rs1042522 and SCCHN risk (Figure 1).

The GSTM1 polymorphism was evaluated in three studies[21,22,28]. No study reported a significant association between this polymorphism and SCCHN risk. For the positive genotype (I^2=87.4%, Q-test=15.87, p-value=0.0004) and null genotype (I^2=84%, Q-test=12.53, p-value=0.0019), heterogeneity was significant. Accordingly, there was no indication to meta-analyze the data.

The CYPA1 polymorphism was evaluated in two studies[21,28]. No single study reported a significant association between this polymorphism and SCCHN risk. The genotype data were homogenous for wilt/wilt genotype (I^2=73.3%, Q-test=3.74, p-value=0.0531) and wilt/m1 genotype (I^2=70.3%, Q-test=3.37, p-value=0.0665) (Figure 2). For the m1/m1 genotype (I^2=86.9%, Q-test=7.64, p-value=0.0057) heterogeneity was significant, which prevented meta-analyzing the data.

DISCUSSION

Despite the great molecular advances made in understanding the mechanism of SCCHN tumorigenesis, there are still numerous points that are unclear or unknown. The evaluation of diagnostic markers such as symptoms and genetic tests helps to increase the sensitivity or specificity of the determination of the presence/absence of malignancy.[2, 3,29]

Cancer is a complex pathology, and its incidence and survival index are closely related to social, cultural and socio-economic determinants of health.

Most of studies included in this paper are from the United States, but Europe, Asia and South America are also represented. Nonetheless, it is not possible to compare the prevalence of HNC among the countries, because this is influenced by variables such as ethnicity, geographic latitude and individual genetic background which are not included in all the studies.[1]Generally, low-income countries are more exposed to environmental risk factors such as, infections, tobacco, alcohol, unhealthy diet plus, in many situations, little access to health systems and health education.[30] Genes related to pathways of cell cycle regulation (proliferation, apoptosis, differentiation, proliferation, epigenetic) were included in this review and meta-analysis.

The p53, Mdm2, p73, and miRNA proteins are involved in proliferation control and cellular apoptosis. In this review, there was no reported significant association of TP53, Mdm2, and p73 polymorphisms with SCCHN.[24-27] It is known that the p53 suppressor tumor gene has a key role in stress cellular response, to preserve genome stability, and it is universally recognized as a human cancer marker when it is mutated.[2, 31-34]Actually, there is a TP53 polymorphism that produces a protein with an amino acid (arginine or proline) located at position72.[35]

Cellular functions of this polymorphism were studied in *in vitro* culture, and it was observed that the protein variant codon72 arginine (R72) has a suppressor function of malignancy and induces an increase in apoptotic activity in relation to the variant 72 proline (P72).[36,37] Authors such as Sarkar

et al.[38]have demonstrated that this polymorphism modulates the hyper-proliferative, apoptotic, and inflammatory phenotypes caused by HPV16 E6 and E7 oncoproteins. They also observed that it modifies the response to chemical carcinogens (e.g. 4NQO), suggesting that variant P72 could increase the risk of some cancers and that there is a tissue-specific difference in the response to environmental carcinogens. Epidemiological studies differ about the association of various cancers with this polymorphism R72P, with some reporting and others denying the association[39,40]. Furthermore the literature on this issue in relation to oral cancer is scarce.

One of the miRNA polymorphisms has been associated with increased SCCHN risk. The miRNA are small portions of RNA, approximately 20-22 nucleotides, which may target a specific messenger RNA and generate feedback of its translation efficiency and stability[41-45]. 25% of all known human miRNAs are significantly deregulated in at least some kind of cancer such as HNC[46]. DEC1-606 polymorphism was related to a decrease of HNC risk. This gene is expressed in the majority of normal human tissues, but has been observed deregulated in some tumors such as breast, stomach, colon, lung, liver and adenocarcinoma of pancreatic duct, probably by hypoxia events[47].

The polymorphisms of genes TNF-α, TNF-β, NFKB1, and NFKBIA, involved in inflammatory pathways, have been seen to be associated with increased SCCHN risk[16]. For some years it has been known that cancer spreads uncontrollably from transformed cells, which ought to be recognized by the immune system before they become a tumor. Nevertheless, in a high number of cases, the transformed cells evade immune defenses. Authors such as Piva et al.[48]have observed inflammatory infiltrate in epithelial dysplasia with overexpression of NFKB and TNF-α, establishing a connection between the cancer and inflammation.

Nuclear factor κ is a transcription factor which activates in response to signals from T-cell receptors and is necessary for cytokine synthesis. These signals activate the kinase phosphorylation pathway and continue with the insertion of multiple copies of a small protein named ubiquitin that releases the NF-κB protein. This protein enters the cell nucleus and induces transcription of cytokine and receptor genes such as interleukin 2 (IL-2), tumor necrosis factor (TNF), and bacterial lipoproteins.[49] Some studies have reported the risk of Hodgkin's lymphoma, multiple myeloma, breast cancer, prostate cancer, stomach cancer, colorectal cancer and melanoma, associated with the polymorphic variation of NFKB1 and NFKBIA genes.[50] Only one of the studies included described a mutation related to increasing SCCHN risk. This study was about 8-oxiguanineDNA glycosylase gene (OGG1), which is involved in DNA repair mechanisms.[51,52]

The studies of Cordero et al.[21], Amtha et al.[28]andCha et al.[22] showed an association with SCCHN risk and the presence of CYP1A1, CYP1B1, and GSTM1 polymorphisms, related to carcinogenic metabolism.

It is widely known that tobacco is a risk factor of SCCHN and is closely related to the intensity and duration of this habit. Cigarettes contain carcinogens such as nitrosamines and polycyclic hydrocarbons. Those components have genotoxic effects and change the molecular profile of persons through the mutations they cause.[53] CYP1B1 belongs to family 1 of cytochrome P450 and has a significant role in the oxidation process of carcinogens such as the components of cigarette smoke.[54] Boyle et al.[55]compared the transcriptome of the oral mucosa and upper airway of smokers versus non-smokers, and observed an overexpression of CYP1A1 and CYP1B1 genes. Pickett et al.[56]also demonstrated a strong increase in CYP1A1 and CYP1B1 gene expression involved in xenobiotic and detoxification functions.

GSTM1 polymorphisms were also included in this study. This gene encodes glutathioneS-transferase Mu 1, which is critical to detoxification and the removal of electrophilic carcinogens. Deletions of this gene have been suggested as a risk factor in colorectal, pancreatic and esophagic cancers, among others.[57]

The ADH7A92G [23]polymorphism has been described as associated with diminished SCCHN risk. As well as smoking, alcohol consumption is another known cancer risk factor. In oral mucosa, alcohol acts as a dissolvent and promotes an increased exposure of oral mucosa to carcinogenic agents, enabling their cellular uptake. Acetaldehyde, an alcohol metabolite, may produce DNA adducts which interfere with synthesis and repair of DNA.[58] The evidence of carcinogenic effects of alcohol consumption on oral and pharyngeal cancers has been widely documented since 1988.[7] The risk of developing cancer increases according to the amounts of alcohol consumed. A meta-analysis of 7954 cases estimated the relative risk as 1.75 (1.70–1.82) in people who consumed 25 g/day and 2.85 (2.70–3.04) for a consumption of 50 g/day.[59]The AA genotype of the ADH1B R48H gene encodes an enzyme that is about 40 times more active than the enzyme encoded by AG and GG genotypes. The AA genotype is more frequent in Asia but is rare in Europe.[58,60]

CRYAB (Alpha B-Crystalline) C-802G polymorphism has been described as having an associated increase of HNC risk. This gene is related to an increase of tumor survival because it promotes angiogenesis and inhibits apoptosis. Lost or diminished CRYAB expression is recognized as a prognostic marker of such cancers as prostate and HNC.[61,62] Research by Su et al.[62]showed that allele G of CRYAB C-802G is correlated to breast cancer risk, and could be useful as a clinical marker for its early detection.

The model proposed in this work shows the genetic composition of individuals that could be at risk or protected against malignancy transformation. All genotypes are heterozygous or homozygous for polymorphic variant, not wild type. In our model, people have an increase of polymorphism expression related to inflammation (NFKB1-294-ATTG, TNFα308-A2A2/A2A1, and TNFβ252-B2B2/B2B1) or carcinogenic metabolism (GSTM1 null, and CYP1A1 m1/m1), representative of malignancy development. Furthermore, the increased expression of genes associated with the stabilization and repair of the cellular genome (OGG1- Asp267Asn, Ser279Gly Ile253Phe, 1578A>T, 1582C>T Ala399Glu (1542C>A) 1582insG 1543_1544delCT), and genes associated with the regulation of proliferation, apoptosis or tumor survival (miRNA499-CT/CC, CRYABC802G-CG/GG) are considered as risk factors. In this scheme, only the polymorphisms of ADH7A92G-GG and DEC1606-T/C genes are protective against malignancy transformation. Compared with the models described by Vineis et al.[6], the model proposed in this paper could fit models 1, 2, and 3 because it considers such epigenetic events as inflammation, mutational compounds such as tobacco and alcohol, and genomic stability and the cell cycle regulation process.

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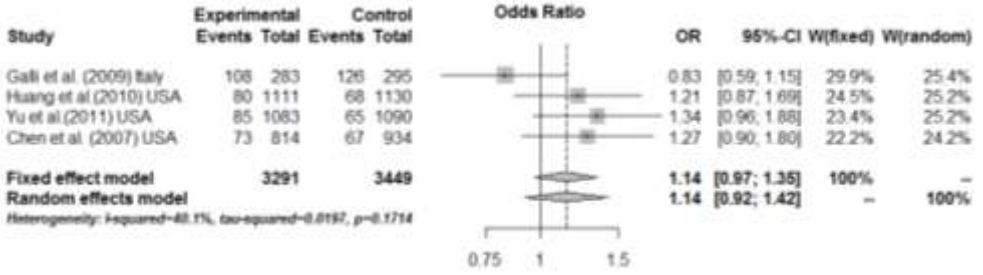
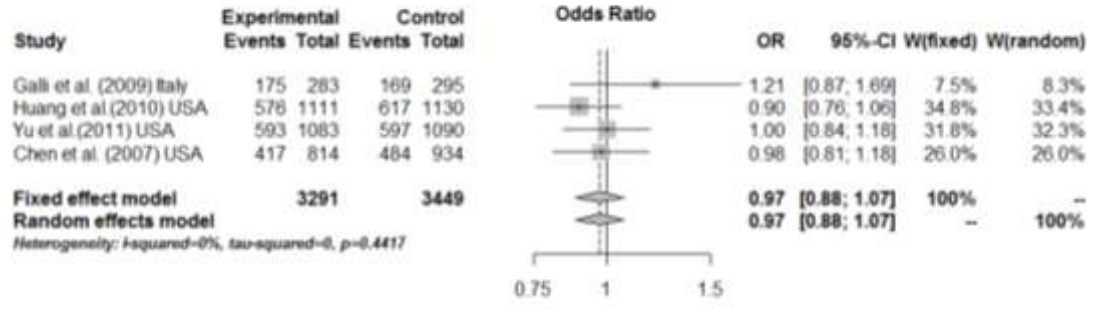
Contributors

MB conceived and coordinated the project, made all the analyses, and wrote the report. All authors contributed individual patient data from trials and commented on the initial surrogate-end point protocol and on drafts of the report.

Genotype CC



Genotype GG



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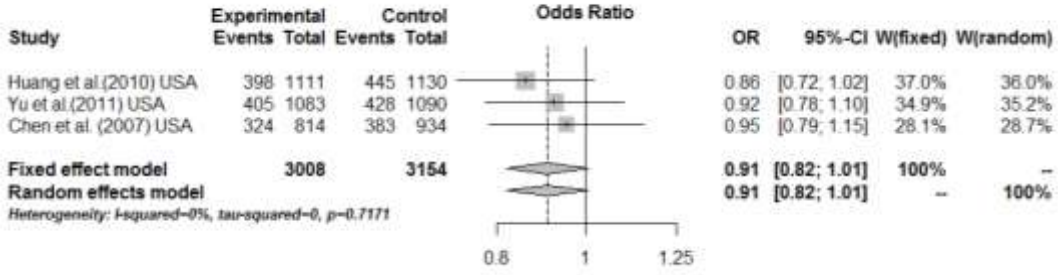
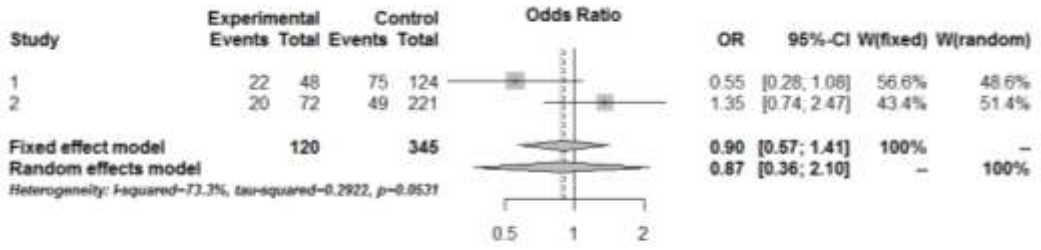


Figure 1. Meta-analysis of TP53 R72P polymorphism.

Genotype wt/wt



Genotype wt/m1

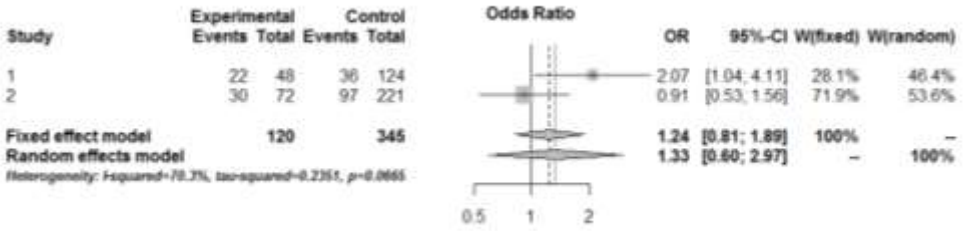


Figure 2. Meta-analysis of CYP1A1 polymorphism. Study 1: Cordero et al., 2010; study 2: Amtha et al., 2009

Table 1. Characteristics of Studies. **SCCHN**: squamous cell carcinoma head and neck; **OSCC**: oral squamous cell carcinma; **CC**: case-control study.**AF**: absolute frequency; **RF**: relative frequency. **M**: male; **F**: female.

Gene/Polymorphism	*Authors*	*Origin*	*Design*	*Diagnosis*	*Cases (place)*	*Controls (place)*	*Gender AF (RF)*	*Age (years) Average ±SD*
CYP1B1	Pradhan et al.(2011)[20]	India	CC matched	OSCC	51 Bangalore Institute of Oncology, Bangalore, India	51 R.L. Jalappa Hospital Research Center, India	both	
CYP1A1 GTSM1	Cordero et al.(2010)[21]	Chile	CC	OSCC	48 National Institute of Cancer	124 Santiago, Chile	Cases. 16 F 32 M Controls: 57 F 67 M	Cases. 62.3±10 Control 50.4±14
ADH1B R48H(rs1229984: G>A) ADH7A92G (rs1573496: C>G	Wei et al.(2010)[23]	USA	CC	SCCHN	1110 The University of Texas M. D. Anderson Cancer Center	1129 The University of Texas M. D. Anderson Cancer Center visitantes	Cases. 273 (24.6)F 837(75.4) M Controls 270 (23.9)F 859 (76.1)M	Cases. 57.2 (±11.1) Controls 56.8 (±11.0)
IGFBP7 702G>C, 418G>A,	Huang et al.(2010)[63]	USA	CC	SCCHN	1065 The University of Texas M. D. Anderson Cancer Center	1112 The University of Texas M. D. Anderson Cancer Center visitantes	Cases. 262 (24.6) F 803(75.4) M Controls 263 (23.7) F 849(76.4) M	Cases. 57.2 ±11.2 Controls 56.7±11.0
GSTM1 CYP1A1	Cha et al.(2007)	Korea	CC	OSCC	72 Department Oral and maxilofacial Surgery Yonsei University College of Dentistry	221 School or college of dentistry	Cases. 26 F 46 M Controls 108 F	Cases. 62.5+/-12.3 Controls 35.4+/-17.5

							113 M	
p53exon4 (Arg72Pro), intron 3 - 6 p73 G4C14 a-A4T14	Galli et al. (2009)[27]	Italy	CC	SCCHN	283 cases Hospital "A. Gemelli" the Università Cattolica Sacro Cuore	295 hospital controls	Cases. 234 (82.7)M Controls 177(60.0) M	Cases. 63.3 ± 11.2 Controls 63.5 ± 13.1
DEC1 21628 G>A 2606 T>C 2249T>C 2122 G>A c.179 C>T TP53 codon 72 (Arg72Pro)	Huang et al.(2010)[24]	USA	CC matched	SCCHN	1111 (100.0) The University of Texas. D. Anderson Cancer Center.	1130 (100.0)	Cases 274 (24.7) F 837(75.3) M Controls 270 (23.9) F 860(76.1) M	Cases 57.1 ± 11.1 Controls 56.8 ± 11.0
TAX1BP1 TT:wild homozygote; TA: heterozygote; AA:polymorphic homozygote	Ruiz et al.(2010)[65]	Brazil	CC	SCCHN	191	200	Cases 29 (15.2) F 162(84.8) M Controls 47(23.5) F 153(76.5) M	Cases 58.24±9.69 Controls 47.55±15.69
TNF-α-308G/A TNF-β 252G/A	Yapijakis et al.(2009)[16]	Greece Germany	CC matched	OSCC	160	153	Cases 128 M Controls 115 M	Cases 58.5±/10.1 Controls 56.1±/12.1
Alpha B-Crystallin CRYAB A-1215G (rs2228387), C-802G (rs14133) intron2 (rs2070894)	Bau et al.(2011)[18]	China Taiwan	CC nested	OSCC	496 China Medical University Hospital, Taichung, Taiwan, Republic of China	992	Cases 27 (5.4) F 469(94.6) M Controls 78 (7.9) F 914(92.1) M	Casos 63.8 ±8.4 Controls 66.1 ± 9.7
MDM2 309 GT + GG, 2164 AA, p53 codon 72 CC	Yu et al. (2011)[26]	USA	CC matched	SCCHN	1083 The University of Texas M. D. Anderson Cancer Center	1090	Cases 269 (24.8) F 814 (75.2)M Controls 258(23.7)F 832(76.3) M	Cases 57.1 Controls 56.7
NFKB1	Lin et al.	Taiwan	CC	OSCC	462	520	Cases	Cases

294ATGG1/ATGG2, 294 ATGG2/ATGG2, NFKBIA 2826 T (CT+TT) 2881 G (AG+GG)	(2012)[17]				Chung Shan Medical University Hospital Taichung and Changhua Christian Hospital and Show Chwan Memorial	Chung Shan Medical University Hospital Taichung and Changhua Christian Hospital and Show Chwan Memorial	18 F 444 M Controls 94 F 426 M	54.46±11.4 Controls 52.46±14.7
GSTM1, GSTT1 CYP1A1	Amtha et al.(2009)[28]	Indonesia	CC	OSCC	81 hospital Jakarta	162 hospital Jakarta	Cases 31 (38.3) F 50 (61.7) M Controls 62 (38.3) F 100(61.7) M	Cases 47.4 ±12.4
RECK gene rs10814325, rs16932912, rs11788747 rs10972727	Chung et al.(2011)[14]	Taiwan	CC	SCCHN	341 Chung Shan Medical University Hospital Taichung Changhua Christian Hospital y Show Chwan Memorial	415 Show Chwan Memorial Hospital, Changhua Christian Hospital Chung Shan Medical University Hospital	Cases 341M Controls 415M	
OGG1 (mutations) Asp267Asn, Ser279Gly Ile253Phe, 1578A>T, 1582C>T Ala399Glu (1542C>A) 1582insG 1543_1544delCT	Mahjabeenet al.(2011)[19]	Pakistan	CC matched	SCCHN	300 National Oncology Radiotherapy Institute (NORI) Pakistan Institute of Medical Sciences (PIMS).	300 National Oncology Radiotherapy Institute (NORI) Pakistan Institute of Medical Sciences (PIMS).		
L-MYC	Bektas-Kayhan et al.(2009)[64]	Turkish	CC matched.	OSCC	80 Estambul University Medical Faculty Department of Otorhinolaryngology and Department of Radiation Oncology	60	no consigna	Cases 54.9±13.21 Controls 50.82±11.11
BAX (_248 G.A)	Chen et al.	USA	CC	SCCHN	814	934	Cases	Cases

BCL2 (_838 C.A) TP53 (Arg72Pro)	(2007)[25]				University of Texas M. D. Anderson Cancer Center.	University of Texas M. D. Anderson Cancer Center	194 (23.8) F 620(76.2) M Controls 233 (25.0) F 701(75.0) M	57.0 ± 11.0 Controls 55.9 ± 11.2
CBS 844ins68	Galbiatti et al.(2010)[66]	Brazil	CC	SCCHN	322 Hospital de Base, a Public Institution, Sao José do Rio Preto, Sao Paulo,Brazil	531	Cases 13.3% F 86.7% M Controls 27.7% F 72.3% M	Both 52.5 ±13.7
MicroRNA miRNA146a,miRNA196, miRNA499 miRNA149	Chu et al. (2012)[15]	Taiwan	CC	OSCC	470 Chung Shan Medical University Hospital-Taichung Changhua Christian Hospital Show Chwan Memorial Hospital - Changhua	425 From three hospitals	M 100% Cases /controls	

Table 2. Polymorphisms studied.(*)OR adjusted by habits, age, and gender. [a] Reference category. **NA**: not calculated. **SCCHN**: squamous cell carcinoma head and neck; **OSCC**: oral squamous cell carcinoma. **Bold:** OR-CI95% significant association.

Author	Country	Diagnosis	Polymorphism	Genotype	OR(*)	CI95%	Cases	Controls
Cordero et al.(2010)[21]	Chile	OSCC	CYP1A1	wt/wt	1.00[a]		22	75
				wt/m1	2.08	1.00-4.29	22	36
				m1/m1	1.04	0.30-3.56	4	13
			GTSM1	Positive	1.00[a]		24	100
				Null	**4.16**	**1.95-8.89**	24	24
Wei et al.(2010)[23]	USA	SCCHN	ADH1B	GG	1.00[a]		1059	1075
			R48H	AG	1.33	0.88-2.02	51	52
			(rs1229984: G>A)	AA	NA	NA	0	2
				AG+AA	0.96	0.65-1.42	51	54
			ADH7A92G	CC	1.00[a]		948	902
			(rs1573496: C>G	CG	0.79	0.62-1.00	156	206
				GG	**0.32**	**0.13-0.82**	6	21
				CG+GG	**0.74**	**0.59-0.94**	162	227
Huang et al.(2010)[63]	USA	SCCHN	IGFBP7	GG	1.00[a]		395	369
			418G>A	AG	**0.82**	**0.67-0.99**	506	571
			(rs 4075349)	AA	0.85	0.65-1.11	164	172
				AG+AA	**0.82**	**0.69-0.99**	670	743
			IGFBP7	GG	1.00[a]		794	791
			702G>C	CG	0.83	0.68-1.02	251	301
			(rs 11573014)	CC	0.91	0.47-1.74	20	20
				CG+CC	0.83	0.68-1.02	271	321
Cha et al.(2007)[22]	Korea	OSCC	GSTM1	Positive	1.00[a]		35	86
				Null	0.7	0.4-1.3	37	123
			CYP1A1	wt/wt	1.00[a]		20	49
				wt/m1	0.8	0.4-1.4	30	97
				m1/m1	**3.3**	**1.4-10**	22	17
Galli et al.(2009)[27]	Italy	SCCHN	p53intron 3	wt	1.00[a]		191	209
			(rs1788332)	M	1.30	0.81-2.10	92	86
			p53exon4 Arg72Pr	Arg Arg	1.00[a]		175	169
			(rs1042522)	Pro	1.07	0.68-1.67	108	126
			p53intron 6	GG	1.00[a]		194	192

			(rs 1625895)	C	0.99	0.63-1.58	89	86
			p73exon2 G4A	GG/GC	1.00		187	214
			(rs1801173/rs2273953)	AT	1.51	0.94-2.43	96	81
Huang et al.(2010)[24]	USA	SCCHN	DEC1 -1628	GG	1.00[a]		1008	1021
			G>C (rs1591420)	CG	1.03	0.75-1.42	89	90
				CC	0.33	0.03-3.16	1	4
				CG+CC	1.00	0.73-1.37	90	94
			DEC1 -606	TT	1.00[a]		529	537
			T>C (rs4978620)	CT	0.95	0.79-1.14	492	481
				CC	**0.71**	**0.52-0.99**	89	112
				TT+CT	**0.73**	**0.54-0.99**	1021	1018
			DEC1T>C,(Ala→Val,	TT	1.00[a]		403	429
			rs2269700)	CT	1.11	0.92-1.35	522	499
				CC	0.87	0.66-1.44	144	177
				TT+CT	0.82	0.64-1.05	925	928
			DEC1G>A	GG	1.00[a]		859	882
			(rs3750505)	AG	1.10	0.88-1.36	221	222
				AA	1.46	0.70-3.03	18	11
				AG+AA	1.12	0.90-1.38	239	236
			TP53 codon 72	GG	1.00[a]		576	617
			(rs 1042522; G>C)	CG	0.96	0.79-1.15	398	445
				CC	1.28	0.89-1.83	80	68
Ruiz et al.(2010)[65]	Brazil	SCCHN	TAX1BP1	TT	1.00[a]		34	94
				TA+AA	0.82	0.36-1.87	11	26
Yapijakis et al.(2009)[16]	Greece	OSCC	TNF-α-308G/A	A1/A1	1.00[a]		36	121
	Germany			A2/A2	**17.51**	**8.6-35.6**	75	13
				A1/A2	**8.33**	**4.04-17.15**	49	19
			TNF-β-252G/A	B1/B1	1.00[a]		28	108
				B2/B2	**40.83**	**13.8-120.8**	82	3
				B1/B2	**5.09**	**2.69-9.64**	50	42
Bau et al.(2011)[18]	China	OSCC	CRYAB A-1215G	GG	1.00[a]		491	981
	Taiwan		(rs2228387)	AG	0.91	0.31-2.63	5	11
				AA	NA	NA	0	0
			CRYAB C-802G	CC	1.00[a]		301	703
			(rs14133)	CG	**1.51**	**1.18-1.92**	158	245
				GG	**1.96**	**1.24-3.10**	37	44

			CRYAB intron2	CC	1.00[a]		325	688
			(rs2070894)	CT	1.18	0.93-1.51	150	268
				TT	1.23	0.71-2.15	21	36
Yu et al.(2011)[26]	USA	SCCHN	Mdm2 309(T>G;	TT	1.00[a]		463	488
			rs2279744)	GT	1.11	0.92-1.34	486	472
				GG	1.08	0.81-1.43	134	136
				GT/GG	1.10	0.92-1.32	620	602
			Mdm2 A2164G	AA	1.00[a]		369	355
			(rs937283)	AG	0.98	0.81-1.20	522	529
				GG	0.83	0.64-1.07	187	205
				AG/GG	0.95	0.79-1.14	709	734
			TP53 codon 72	GG	1.00[a]		593	597
			(rs 1042522; G>C)	CG	0.95	0.79-1.14	405	428
				CC	1.30	0.91-1.86	85	65
				CG+CC	1.00	0.83-1.19	490	493
Lin et al. (2012)[17]	Taiwan	OSCC	NFKB1 -294 ATTG	Del/Del	1.00[a]		100	168
				Del/Ins	**1.8**	**1.1-2.7**	246	271
				Ins/Ins	**2.2**	**1.2-4.2**	116	81
				Del/Ins+ Ins/Ins	**1.8**	**1.2-2.8**	362	352
			NFKBIA -519 T	CC	1.00		381	432
				CT	1.3	0.9-2.2	78	86
				TT	5.4	0.4-74.1	3	2
				CT+TT	1.4	0.9-2.2	81	88
			NFKBIA-826	CC	1.00[a]		351	438
				CT	1.6	1.0-2.6	101	78
				TT	3.4	0.6-18.3	10	4
				CT+TT	**1.7**	**1.2-2.7**	111	82
			NFKBIA -881	AA	1.00[a]		351	438
				AG	1.6	1.0-2.6	101	78
				GG	3.4	0.6-18.3	10	4
				AG+GG	**1.7**	**1.2-2.7**	111	82
Amtha et al.(2009)[28]	Indonesia	OSCC	GSTM1	Wt	1.00[a]		32	72
				Null	1.19	0.70-2.02	49	90
			GSTT1	Wt	1.00[a]		44	95
				Null	1.19	0.72-2.05	37	67
			CYP1A1	Wt	1.00[a]		45	77

				Polymorphism	0.70	0.39-1.25	36	85
Chung et al.(2011)[14]	Taiwan	SCCHN	RECK rs10814325	TT	1.00[a]		95	120
				TC	0.80	0.49-1.31	143	189
				CC	1.13	0.65-1.99	103	106
				TC+CC	0.89	0.57-1.38	246	295
			RECK rs16932912	GG	1.00[a]		155	214
				GA	1.27	0.84-1.93	155	169
				AA	0.97	0.44-2.13	31	32
				GA+AA	1.21	0.82-1.80	186	201
			RECK rs11788747	AA	1.00[a]		208	237
				AG	0.79	0.51-1.23	106	153
				GG	1.10	0.49-2.46	27	25
				AG+GG	0.82	0.55-1.22	133	178
			RECK rs10972727	TT	1.00[a]		208	236
				TA	0.83	0.54-1.28	111	152
				AA	0.82	0.35-1.92	22	27
				TA+AA	0.81	0.54-1.21	133	179
Mahjabeenet al.(2011)[19]	Pakistan	SCCHN	OGG1 Asp267Asn	mutation	**8.79**	**4.91-15.8**	49	
			OGG1Ser279Gly	mutation	**8.94**	**5.09-15.7**	53	
			OGG1Ile253Phe, 1578A>T, 1582C>T	mutation	**8.00**	**3.54-18.1**	24	
			OGG11582insG	mutation	**8.83**	**4.95-15.8**	50	
			OGG1Ala399Glu1543_ 1544delCT	mutation	**9.27**	**5.48-15.7**	62	
Bektas-Kayhan et al.(2009)[64]	Turkish	OSCC	L-MYC	LL			31	22
				LS			30	27
				SS			19	11
Chen et al. (2007)[25]	USA	SCCHN	BAX	GG	1.00[a]		627	723
			-248 G>A;rs4645878)	AG	0.99	0.78-1.26	170	200
				AA	2.01	0.91-4.47	17	11
				AG+AA	1.04	0.82-1.32	187	211
			BCL2	CC	1.00[a]		226	257
			(-838 C>A; rs2279115)	AC	0.97	0.76-1.22	382	446
				AA	1.03	0.78-1.35	206	231
				AC+AA	0.99	0.79-1.23	588	677
			TP53 codon 72	GG	1.00[a]		417	484

			(rs 1042522; G>C)	CG	1.02	0.83-1.26	324	383
				CC	1.21	0.83-1.76	73	67
				CG+CC	1.05	0.86-1.28	397	450
Galbiatti et al.(2010)[66]	Brazil	SCCHN	CBS 844ins68	NN	1.00[a]		258	443
				IN	1.15	0.74-1.79	56	78
				II			8	10
Chu et al. (2012)[15]	Taiwan	OSCC	miRNA146a, rs	CC	1.00[a]		174	175
			2910164	CG	1.18	0.82-1.70	242	196
				GG	0.59	0.32-1.08	54	54
			miRNA149, rs 2292832	TT	1.00[a]		345	315
				CT	0.76	0.49-1.17	88	84
				CC	1.45	0.75-2.83	37	26
			miRNA196, rs	TT	1.00[a]		136	132
			11614913	CT	1.14	0.78-1.68	277	206
				CC	0.74	0.42-1.30	87	57
			miRNA499, rs3746444	TT	1.00[a]		339	356
				CT	**1.79**	**1.16-2.75**	119	66
				CC	**4.52**	**1.24-16.48**	12	3