

POLYMORPHISMS ASSOCIATED TO GENETIC SUSCEPTIBILITY AND HEAD AND NECK CANCER RISK: A SYSTEMATIC REVIEW

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INTRODUCTION

The head and neck, as a general anatomic region, is constituted by organs and cavities that, based on their anatomy and physiology, can be grouped under the name of upper aerodigestive tract (UADT). The UADT is covered by a mucosa where most cancers (85%) of the region originate; the remaining 15% represent tumors of the thyroid gland, skin, bones of the facial skeleton, cartilage, and soft tissue [1].

Head and neck cancer (HNC) are a heterogeneous neoplasm and usually begin in the squamous cells that line the mucosal surfaces inside the head and neck: oral cavity, pharynx, and larynx. These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck (HNSCC) [1, 2, 3]. Worldwide, HNSCC is the

seventh most prevalent type of cancer [4]. According to the “International Agency for Research on Cancer” (IARC GLOBOCAN) about 51.694 new cases were documented and more than 25.521 deaths were reported for South and Central America by 2020 [1, 4]. For the same year, in Colombia, nearly 3.148 new cases were recorded, with about 1.343 deaths from this neoplasm [4]. Also, this pathology has a higher incidence in men than in women, particularly in individuals between 45 and 70 years old.

It is well known the mechanisms of carcinogenesis of HNCSCC. Although most of these cancers still come from mutagenic environmental exposures [5, 6], it has been known that smoking and alcohol consumption are the strongest independent risk factors responsible of HNCSCC [7] and further have synergetic correlations [8]. Smokers have a 5 to 25-fold increased risk of developing head and neck cancers, more than general population [9]. Besides, exposure to secondhand smoke increases the risk of developing HNSCC as well [10].

Likewise, excessive alcohol consumption also represents a risk factor for HNSCC, mainly for hypopharyngeal cancers [11], and a low consumption of fruits and vegetables antioxidants may contribute to the development of this neoplasm too, largely associated with squamous cell carcinoma of the oropharyngeal and oral cavity [12].

Furthermore, the prevalence of oropharyngeal and nasopharyngeal cancer growth has shown causality with viral infection and its association to HNSCC varies according to the tumor site, HPV16 (tumors in the tonsils) [13] and Epstein-Barr virus (EBV) with

tumor involvement of the nasopharynx [14]. HPV has been associated with 20% of HNSCC and individuals with HPV positive tumors have a better prognosis for survival compared to those HPV- tumors [15, 16, 17, 18].

In addition, a widespread habit Betel-quin and areca-nut chewing are widely practiced in many parts of Asia and in Asian-migrant communities elsewhere in the world and it is considered a risk factor for the development of HNSCC, mainly oral cavity. Finally, oral hygiene, acid reflux disease and environmental exposures such as nickel refining, textile fibers and carpentry are also associated with HNSCC tumorigenesis [2].

Despite the impact of environmental factors on HNSCC risk, not all people exposed to carcinogens develop cancer suggesting the existence of inter-individual differences that can cause variation in the ability to metabolize carcinogens and modify cellular processes such as DNA repair, cell cycle control and alteration of the extracellular matrix, which may be associated with increased susceptibility to head and neck cancer [19, 20, 21].

This review identified variants that may contribute to genetic susceptibility and its association with the development of head and neck cancer due to exposure to mutagenic environments (smoking - alcohol consumption and radiation), viral infections, ethnicity, and dietary factors to establish potential biomarkers for future studies allowing the evaluation of HNC cancer risk and its response to treatments [22].

Key Words: Genetic susceptibility, head and neck cancer, oral cancer polymorphisms, mutations, genetic variants (SNPs).

REVIEW QUESTION/OBJECTIVE

The current scoping review sought to identify candidate genes SNP association studies related to genetic susceptibility, to summarize existing evidence on genetic variants (SNPs) for head and neck cancer risk and to ascertain knowledge gaps for future research on potential biomarkers for oral cancer development and treatments.

The review was guided by the following Research question:

¿What are the types of candidate genes, or genetic variants (SNPs) reported in association studies addressing genetic susceptibility and the risk of developing HNC?

INCLUSION CRITERIA

Types of participants

The current review considered studies that included participants over 18 years of age, regardless of their sex and ethnicity. Furthermore, we selected studies with individuals exposed to different mechanisms of carcinogenesis like mutagenic environmental exposures (tobacco and/or alcohol consumption, tobacco or Betel nut chewing habits), viral infections and ethnicity. participants diagnosed with head and neck cancer: oral squamous cell carcinoma, larynx, and nasopharynx carcinoma, according to the ICD10 classification.

Concept

The main outcome of interest for this review was to identify the candidate genes, or genetic variants (SNPs) reported in association studies addressing genetic susceptibility and the risk of developing HNC.

Context

This review included studies carried out in any geographic territory, with participants recruited from community, academic and healthcare organizations.

Types of studies

All eligible studies included in the review were case-control design limiting to genetic association studies for genetic susceptibility and the risk of developing HNC. Only published data in English or Spanish were considered for the review. Articles where the full text could not be acquired, and those based on pediatric population, animals and in vitro studies were excluded from the search.

Search strategy

The search strategy aimed to find studies published within the last 10 years from 2009 to 2019 to identify genetic association studies of single nucleotide polymorphisms (SNPs) for HNC risk conducted world-wide. A three-step search strategy was utilized in this review. An initial limited search of PUBMED Database was undertaken followed by analysis of the text words contained in the titles and abstract keywords. A second search

using all identified abstracts keywords was undertaken across PUBMED and MEDLINE databases. Also, the reference lists of all identified reports and articles were searched for additional studies. We included literature in English and Spanish for this review. The following keywords were used: Genetic susceptibility, oral polymorphisms, mutations, genetic variants (SNPs), Aryl hydrocarbon receptor, and head and neck cancer (“oral polymorphisms” OR “mutations” OR “SNPs” OR “genetic variants” OR “Genetic susceptibility” AND “head and neck cancer”); (“Aryl hydrocarbon receptor” AND “head and neck cancer”).

METHODS

Data extraction

Relevant data were extracted from the 59 included studies to address the review question. The data extracted used the template developed in the protocol. The data included the following: first author, year of publication, population ethnicity, sample size, age of study subjects, gender of study subjects, clinical or pathological description of HNC subtype, genes or polymorphisms studied, methodology/ methods, function of the gene. A list of the data extracted is shown in Table 1 (online material).

RESULTS

A total of 716 articles were retrieved through databases searches on PubMed and MEDLINE using several combinations of keywords. To eliminate repeated and irrelevant papers, the titles and key words of all articles were read, and 539 studies were excluded.

177 articles related to genetic susceptibility and head and neck cancer were acquired for further inspection. A review of abstracts yielded 59 studies that met the eligibility criteria for final assessment (Fig. 1).

All eligible studies were cases and controls design. Heterogeneity existed among the studies in terms of sample size and reporting of results, with less emphasis on age and gender information from the participants. Table 1 summarizes key characteristics of the reviewed studies. Some of the reviewed studies had small sample sizes and thus were underpowered for reliably detecting risk alleles for genetic susceptibility associated to HNC. About 19 out of 59 included studies (32%) were small (n - cases < 200). More than half (64%) of the studies were conducted on Asian populations (32% Chinese, 15% Indian, 7% Pakistani, and less Taiwanese and Thai) followed by (36%) on Caucasians, Hispanics, African-Americans and others.

The most studied SNPs were in genes of carcinogen metabolism ($n = 17$ studies), cellular proliferation, Invasion, and metastasis ($n= 11$ studies), immune inflammatory ($n = 9$ studies), DNA repair ($n = 7$ studies), apoptosis ($n = 3$ studies), cell cycle control ($n = 2$ studies), antioxidative ($n=2$ studies) and extra-cellular matrix alteration ($n=1$) pathways. Also, there were some SNPs association studies related to HPV mediated oncogenesis ($n= 3$ studies), mtDNA mutations ($n= 1$), and epigenetics alterations ($n= 1$) that conferred genetic susceptibility to the development of HNC. Only two studies evaluated different candidate SNPs in genes within important carcinogenic pathways

(oncogenesis and tumor suppression, DNA repair, inflammation, oxidation, and apoptosis).

In terms of cancer type analyzed, 25 studies evaluated the Larynge- pharynx and oral cavity (HNC), 14 reports on oral cancer/ oral squamous cell carcinoma (OSCC), 15 studies reported on nasopharyngeal carcinoma (NPC), 3 reported on larynx-hypolaringe, and 2 more studies reported on tongue squamous cell carcinoma.

Suggestive markers of increased genetic susceptibility for HNC risk based on significant associations were reported by 51/59 studies worldwide within different mechanisms of carcinogenesis like DNA repair genes, Pro-inflammatory genes, apoptotic genes, cellular proliferation- Invasion-metastasis, carcinogen metabolism, extra-cellular matrix alteration, cell cycle control, HPV mediated oncogenesis, mtDNA mutations and epigenetics alterations (Fig. 2. Online material).

DNA repair genes associated to genetic susceptibility for HNC risk

The results of the analysis provided evidence of association between the SNP and head and neck cancer susceptibility, within these, the rs7213430 in BRIP1 gene was significantly associated with cancer risk (P trend = 0.021). Compared with the AA homozygotes, the G allele carriers had an increased risk of SCCHN (OR = 1.16, 95 % (CI 1.02–1.31)) [23].

Also, homozygous variant CC genotype of RAD51 135G/C was found to be associated with a 2.5-fold increased HNC risk (OR=2.5 (0.69-9.53) $p<0.02$), while RAD 51 172 G/T, heterozygous variant GT genotype was associated with a 1.68-fold (OR=1.68 (1.08-2.61) $p<0.02$) elevation when compared with controls. In the case of the Thr241Met polymorphism of XRCC3, it was observed a 16-fold (OR=16; 95% CI= 3.78-69.67; $p<0.0002$) increased HNC risk in patients compared to controls [24]. Furthermore, the XRCC1 Arg399Gln variant genotype was associated with an increased risk of NPC (399Gln/Gln: OR=1.96; 95% (1.02-3.78; $p=0.04$)) and Arg/Gln: OR=1.87; 95% (1.29-2.71; $p=0.001$)). However, APE1-141G/G may decrease risk of NPC in current smokers (OR=0.40;95% (0.18–0.89)). The combined effects of polymorphisms within BER genes of XRCC1 399Gln and APE1 148Gln may contribute to a high risk of nasopharyngeal carcinoma (OR=2.09; 95% (1.27-3.47; $p=0.004$)) in Chinese population [25].

Likewise, the 12p13.33 locus, encompassing rs10849605/RAD52, was identified as a significant somatic focal copy number amplification in upper aerodigestive tract (UADT) ($n = 374$, $q\text{-value} = 0.075$) tumors and correlated with higher RAD52 tumor expression levels ($p = 6 \times 10^{-48}$ in UADT). These results implicate increased RAD52 expression in genetic susceptibility and tumorigenesis of UADT tumors [26]. Further, BRCA2 SNP rs11571833 was associated with UADT cancers (odds ratio = 2.53, 95% (1.89 to 3.38, $P = 3 \times 10^{-10}$) and was present in European, Latin American, and Indian populations but extremely rare in Japanese populations. The association appeared more apparent in smokers (current or former) compared with never smokers ($P_{\text{het}}=.026$) [27].

Finally, it was reported that cumulative increased NPC risk associations with TERT-CLPTM1L and DSBK pathways contribute to genetic susceptibility to NPC (ORs per allele, 95% CI=1.37, 1.22,1.55, $p_{\text{Bonferroni}}=5.00 \times 10^{-6}$; 1.17, 1.09,1.26, $p_{\text{Bonferroni}}=4.58 \times 10^{-4}$, respectively, in TERT/ NHEJ pathways) [28].

On the other hand, the ERCC1 rs11615 ($p = 0.011$, OR = 0.288 (CI 95% = 0.110–0.751)) and ERCC2 rs13181 ($p = 0.046$, OR = 0.375 (0.143–0.982)) were associated with a lower risk of laryngeal cancer [21]. However, a marginal significance was found for SNP rs15869 in BRCA2 ($P = 0.053$) associated to HNC risk [23].

Pro-inflammatory genes associated to genetic susceptibility for HNC risk

It was found that “T” allele of IL1a+4845 SNP showed higher frequency in OSCC cases than controls (OR=2.0, (1.0–4.4)). Also, OSCC cases that smoke, and drink were more likely to carry either the “T” allele at the IL1b+3953 SNP (OR=10.4,1.1–93.2) or the “C” allele at the TNFa1031 SNP (OR=3.4, (1.0–11.4)) than controls. Thus, variants in inflammatory or immunomodulatory genes IL1a, IL1b, IL8, TNFa may influence susceptibility to OSCC in Thai population [29].

Also, carrying the IL-2 -330 G variant allele was associated with a decreased ability to produce IL-2, which may contribute to NPC susceptibility [30]. IL6 rs1800795 polymorphism was related to a higher risk of laryngeal cancer ($p = 0.002$, OR = 2.394 (1.376–4.163)), like the association found in CG+GG variants with increased oral cavity susceptibility ($p = 0.018$, OR = 2.265 (1.148–4.467)) [21]. The IL-10-1082, IL-10-819,

and IL-10-592 variants, and haplotypes GC and GT constitute biomarkers for early detection of HNC, especially NPC subtype. IL-10 -819T/C and TA haplotype may be used as biomarkers for early detection of LC [31].

The rs11556218 T/G polymorphism of IL-16 gene was significantly associated with the susceptibility to NPC (OR=1.67; 95% (1.18–2.36)). Therefore, IL-16 gene polymorphisms may be useful as genetic susceptibility markers for NPC [32]. For the IL-18, -137C/- 607A haplotype was associated with a significantly increased risk of NPC as compared with the -137G/-607C haplotype (OR=1.721; 95% (1.262–2.349); $p=0.001$) in Chinese population [33].

Furthermore, related to HLA-DRB1*0701 it was associated with an increased risk of developing NPC for Uyghur population. However, In Han population the HLA-DRB1*0101 polymorphism was associated with protection from disease progression [34]. Also, eight SNPs from the segment D6S211 to D6S510 within HLA complex were found to be significantly associated with NPC (most significant SNPs rs9260734 and rs2517716, located near to HLAA and HCG9 respectively). Thus, the segment from D6S211 to D6S510 in HLA complex region might contain NPC susceptibility loci [35].

Likewise, the HCGA9 rs6457110 polymorphism showed a tendency for an increased risk of NPC development among TT carriers with an almost of 2-fold increased risk (OR = 1.86; 95% (1.00–3.65)), which might represent a risk marker for NPC development in

Portuguese population [36], and the -308 TNFA AA genotype was associated with increased risk for the development of NPC (OR=2.46; 95% (0.98–6.17; p=0.047)); moreover, this effect was stronger in undifferentiated types, which are virtually 100% caused by the Epstein-Barr virus (OR=2.75; 95% (1.09–6.90; p=0.025)). Thus, -308 TNFA AA genotype can represent a risk marker for NPC development in Portuguese population and contributes for the definition of genetic susceptibility profiles for individuals at risk of development of a viral infection and associated neoplasia [37]. Finally, IL2 rs2069762 G variant was reported to be associated with a lower risk of oral cavity cancer (GG p = 0.039, OR = 0.300 (0.096–0.940)) [21].

Apoptotic genes associated to genetic susceptibility for HNC risk

The results showed a variant allele in CA+AA genotypes in BCL2 rs2279115 related with a higher risk of developing oral carcinoma (p = 0.010, OR = 2.753 (1.273–5.952)) [21]. For the ATG12 eQTL SNP rs26537 was found that it might contribute to an allele-specific effect on the expression of host gene ATG12 and explain a fraction of HNSCC genetic susceptibility [38].

Also, the FASL–844CT or TT genotype had a significantly decreased risk of developing laryngeal and hypopharyngeal SCC [odds ratio (OR) = 0.69; 95% confidence interval (CI) = 0.51–0.93; P = 0.016; or, OR = 0.41; 95% CI = 0.20–0.86; P = 0.009] compared with those carrying the CC genotype. However, joint gene-smoking and gene-drinking effects revealed an OR of CC genotype for smokers or drinkers equal to 5.15 (95% (3.24–8.97)) or 12.52 (95% (7.31–22.47)), respectively. Therefore, the FASL–844T > C

polymorphism is associated with genetic susceptibility of developing laryngeal and hypopharyngeal SCC in a Han Chinese population [39].

Finally, no significant difference was detected in the genotype frequencies of CASP8 polymorphisms (rs13016963) between the patients and control subjects. However, the AA genotype frequency of rs1306963 was associated with OSCC as a risk factor among non-smokers and non-drinkers. For CASP8, rs1045485 was not present in any of the patients with OSCC or control subjects. Thus, del allele of rs3834129 may play a protective role in the tumorigenesis of OSCC [40].

Cellular proliferation- Invasion-metastasis genes associated to genetic susceptibility for HNC risk

The results evidenced that miRNA-605 rs2043556 [dominant model: (OR = 0.71, 95% (0.58–0.88); additive model: (OR = 0.74, 95% (0.62–0.89))] and miRNA-196a2 rs11614913 [dominant model: OR = 1.36, 95% (1.08–1.72); additive model: (OR 1.28, 95% (1.10–1.48))] were significantly associated with the risk of oral squamous cell carcinoma (OSCC). Furthermore, when these two loci were evaluated together (rs2043556 A and rs11614913 G), a significant locus-dosage effect was noted on the risk of OSCC (P trend < 0.001) [41]. For miR-499 rs3746444, CC genotype increased risks of oral cancer compared with the wild TT genotype (OR = 3.154, 95% (1.555±6.397), P value = 0.001) [42]. Also, variant of MIR548H4 (rs7834169), was associated to overall HNSCC risk as well as risk of oral cavity cancer. Four other variants (rs16914640, rs1134367, rs7306991 and rs1373756) were specifically associated with

oral cavity cancer risk. The 3'UTR variant of HADH, rs221347 and rs4975616, located within known cancer risk locus 5p15.33, were specific to risk of laryngeal cancer [43].

Further, it was found that A/G heterozygotes allele of SDF-1 had a higher risk of 1.86-fold for carriers' individuals to develop oral cancer when compared with those with G/G wild type homozygotes. Furthermore, patients with oral cancer with at least 1 mutant T allele of CXCR4 gene had a risk of 2.66-fold to progress to stage III or IV. These gene polymorphisms may be considered as factors of increased susceptibility to oral cancer in Taiwanese population [44]. Besides, the SNPs rs217727 and rs2839701 for the lncRNA H19 gene, were found to be associated with the risk of OSCC [rs217727: (OR) = 1.32, 95% (1.11–1.58), $P = 0.002$; rs2839701: OR = 1.23, 95% (1.04–1.46), $P = 0.019$]. Also, it was found that rs2839701 C>G inhibited the transcription activity and was correlated with the decreased expression of downstream gene MRPL23-AS1 which is downregulated in OSCC [45]. Genetic variants in NF κ B1 (rs28362491del>ins ATTG: OR = 1.30, 95% (1.09–1.55), $P = 2.80 \times 10^{-3}$), in I κ B α (rs696G>A: OR = 1.41, 95% (1.20–1.66), $P = 2.28 \times 10^{-5}$) and their synergistic effect might contribute to NPC predisposition [46]. The results showed a variant allele in MDM2 rs2279744 associated with higher risk of laryngeal cancer ($p = 0.029$ OR = 2.413 (1.094–5.323)) [21].

The SNP rs6554198 [OR=0.85, 95% (0.74–0.97), $P=0.019$] and two intron SNPs rs2237025 (OR=0.82, 95% (0.70–0.95), $P=0.007$), and rs17084687 (OR=0.85, 95% (0.73–0.99), $P=0.042$) of KIT were significantly associated with decreased risk of HNSCC. Also, combined analysis of the three SNPs showed that subjects carrying the

protective alleles had decreased risk of HNSCC in a dose-response manner ($P_{\text{trend}}=0.001$). Furthermore, there was found a significant multiplicative interaction between rs17084687 and drinking on HNSCC risk ($P=0.012$), where allele “A” of potentially functional rs6554198 led to significantly lower transcription activity of KIT compared to the risk allele G. Thus, SNPs in KIT gene may play a role in genetic susceptibility to HNSCC [47].

Also, the association of SP1 rs1353058818 and STAT3 rs1053004 gene polymorphisms with human tongue squamous cell carcinoma (TSCC) was evaluated. According to the study, the SP1 rs1353058818 locus deletion allele confers a high-risk factor for TSCC development (OR = 2.997, 95%CI: 1.389-6.466, $P = 0.003$). In the other hand the STAT3 rs1053004 locus A allele showed a protective factor for TSCC (OR = 0.604, 95% CI: 0.460-0.793, $P < 0.001$). Also, the analysis of SP1 mRNA and hsa-miR-149-5p in tumor and adjacent normal tissues revealed a negative correlation between them ($r = -0.81$, -0.77), and the evaluation of the expression of SP1 protein in tumor tissues was significantly higher in those with the SP1 rs1353058818 locus [DD] genotype rather than in tissues with the [ID] and [II] genotypes. In contrast to SP1 mRNA, the STAT3 mRNA was positively correlated with hsa-miR-21-5p in tumor and adjacent normal tissues ($r = 0.75$, 0.78). Finally, the expression level of STAT3 protein in tumor tissues of patients with STAT3 rs1053004 locus GG genotype was significantly higher than in patients with type GA, and it was the lowest in patients with type AA. According to the study, polymorphisms in the SP1 rs1353058818 and STAT3 rs1053004 loci are associated with the risk of human TSCC [48].

Taken together candidate genes that might be important in NPC pathogenesis, it was observed an association between combined common and rare variants in CDKN2A/2B rs1412829 ($P=1.3 \times 10^{-4}$), PRKDC rs78231671 ($P = 4.7 \times 10^{-4}$), BRD2 rs76146382 ($P=1.6 \times 10^{-3}$), TNFRSF19 rs9510787 ($P=4.0 \times 10^{-3}$) and CLPTM1L/TERT rs31489 ($P=5.4 \times 10^{-3}$), HNRNPU ($P=3.8 \times 10^{-3}$) with the development of sporadic NPC. Also, some NPC-associated genes, including CLPTM1L/TERT, BRD2, and HNRNPU, suggest a role for telomere length maintenance in NPC etiology [49].

Carcinogen metabolism genes associated to genetic susceptibility for HNC risk

According to the information analyzed, GSTM1 or GSTT1 null genotypes have been reported as significantly higher risk of oral cancer (OR = 3.019 (1.861-4.898) and 3.011(1.865-4.862), respectively), which further increased when either one or both null genes were present in combination (OR = 3.627 (1.981-6.642) and 9.261 (4.495-19.079), respectively) [50]. Thus, GSTM1 and GSTT1 null genotypes may act as biomarkers to determine genetic susceptibility to HNSCC patients [51].

Besides those genes, CYP1A1m1/m1 (OR = 8.12, 95% (3.27–21.30)) and CYP1A1w1/m1 genotype showed elevated risk when compared with CYP1A1w1/w1 genotype. Likewise, CYP1A1w2/m2 (OR = 1.58, 95% (0.94–2.67)) and CYP1A1m2/m2 (OR = 6.31, 95% (2.74–18.69)) genotypes also showed elevated risk when compared with CYP1A1w2/w2. individuals carrying at least one CYP1A1 m1 or m2 variant allele were at a 2-fold elevated risk for head and neck cancer [52]. CYP1A1 rs4646903 gene in the presence of GSTM1 and/or GSTT1 null genotypes increased the association (ORs

= 4.576 (2.038-10.273), 5.593 (2.530-12.362) and 16.10 (3.854-67.260) for risk of oral cancer susceptibility [50]. Also, significant associations between metabolizing phase I genes (CYP1A1 and CYP2A6), phase II genes (GSTA2) and upper aerodigestive tract cancers were found suggesting that the less rapid alcohol metabolizers are more susceptible to upper aerodigestive tract cancer risk [52]. Last, interaction of combined genotypes of carcinogen-metabolizing genes with environmental factors might modulate susceptibility of HNC [53].

Additionally, the NQO1 polymorphism was associated with a significantly higher risk of NPC among smokers (two-fold higher NPC risk in ever-smokers carrying the CT or TT genotype: OR = 1.95, 95% (1.20–3.19); interaction $p = 0.007$)) [54]. Moreover, Individuals with the mutant genotype ADH1B Arg48His, who consume alcohol >30 g/L/day have more than four times the risk for HNC (OR = 4.42; 95% (1.21–16.11)) [55]. However, the mutant genotype ADH1B Arg48His confers protection for HNC (OR = 0.42; 95% (0.21–0.85)) showing higher frequency in controls (12.7%) than HNC patients (5.8%), and combined Arg/His and His/His genotypes of the ADH1B Arg48His were also associated with a reduced risk of SCCHNC (OR: 0.203; 95% (0.052-0.796)) [56].

Extra-cellular matrix alteration genes associated to genetic susceptibility for HNC risk

Among allelic discrimination it was found that TIMP3 C>T polymorphic rs9862 allele was more susceptible to oral cancer [OR = 1.6; 95% (1.2-2.1)] after adjustment for betel quid chewing, alcohol, and tobacco consumption. Also, a significant association between

rs9862 variants and large tumors (OR, 1.5; 95% CI, 1.0–2.3) development was found [57].

Antioxidative genes associated to genetic susceptibility for HNC risk

The results showed that SOD2 rs4880 may be involved in the tumorigenesis of OSCC and may be useful as a genetic susceptibility marker for OSCC (CT genotype of SOD2 SNP rs4880 was found to be higher in the patients than in normal subjects [CT vs. TT; $P=0.045$; AOR=1.484; 95% (1.009-2.182)]. Also, for those who smoked, the incidence of the CT genotype of rs4880 increased markedly in the patients compared with the controls (CT vs. TT; $P=0.003$; OR=2.325; 95% (1.330-4.064)) [58].

On the other hand, variant genotypes rs1303586 GA+AA and rs2706110 CT+TT, both in the NRF2 gene, were associated with a lower risk of laryngeal carcinoma ($p = 0.035$, OR = 0.478 (0.240–0.949) and $p = 0.518$, OR = 0.518 (0.299–0.900), respectively). Related to pharyngeal cancer, only NRF2 rs2706110 allele genotypes CC+CT were related with a lower risk of developing pharyngeal carcinoma ($p = 0.043$, OR = 0.552 (0.311–0.982)) [21].

Cell cycle control genes associated to genetic susceptibility for HNC risk

For the Rb1/105 gene were found five missense mutations g77082G>C, g77083G>A, g170220A>T, g170221G>C, g170228T>A, two frameshift mutations, two stop codon and two intronic substitutions with an overall frequency of 0.71 related to HNC. Within

these, novel missense mutations Lys462stop and Ser834stop were reported in HNC Pakistani patients [59] which can be evaluated in future studies in other populations.

Also, it was reported the TP53 rs78378222AC genotype or C allele as a possible protection against SCCHN ($P = 0.008$ and 0.008 respectively), compared with the AA genotype or A allele [60]. Beside this, TP53 rs1042522 mutant allele was associated with a decreased risk of developing laryngeal cancer as well ($p = 0.002$, OR = 0.286 (0.119–0.607)); and pharyngeal cancer ($p = 0.001$, OR = 0.124 (0.035–0.476)) [21].

Furthermore, it has been evaluated the contribution of TP53Pro allele to the incidence of laryngeal cancer. According to the study, TP53 Pro/Pro genotype frequency was about 2-fold higher in patients than in controls. Also, the frequency of the heterozygous genotype TP53 Arg/Pro in patients was higher than in controls. According to the authors, patients with the Pro/Pro and Arg/Pro TP53 genotypes showed a 1.755-fold increased risk of laryngeal cancer (95% CI = 1.149-2.680, $P=0.0099$). This suggests the possible contribution of the TP53Pro variant to laryngeal cancer development [61].

HPV mediated oncogenesis of HNC and genetic susceptibility

It was found that SLC23A2 gene (Wild-type allele) modifies the risk of HNSCC associated with HPV16 infection. It was evidenced that individuals with wild-type allele, HPV16-positive serology, and high citrus intake (OR 5 7.4; 95% CI 5 3.6– 15.1) increased risk of this type of cancer [62].

Furthermore, it was identified a variant in the DFNA5 region (rs2237306), associated with Benzo(a)pyrene, as a protective factor (odds ratio = 0.33; $p = 0.009$) and four harmful (odds ratio.2.5; $p < 0.05$) intronic variants, rs182361, rs290974, and rs169724 in SYK and rs1670661 in NELL1 region, involved in genetic susceptibility to tobacco- and HPV mediated oral oncogenesis [60]. However, the variant T genotype of the TMC8 gene was associated with a reduced risk of HNSCC ($OR_{AT} = 0.63$, 95% (0.45–0.89)), ($OR_{TT} = 0.54$, 95% (0.36–0.81)), even among subjects seronegative for all HPV types (OR_{AT} : 0.71, 95% CI 0.45–1.11, OR_{TT} : 0.54, 95% CI 0.31–0.93) [63].

mtDNA mutation associated to genetic susceptibility for HNC risk

Based on mtDNA variations of hypervariable sequence I (HVSI) and comparison of mtDNA haplogroups between tongue cancer and control groups, it was found that mitochondrial DNA may play a crucial role for the maternal genetic susceptibility of tongue cancer in patients from Hunan, central of China [64].

Epigenetics alterations genes associated to genetic susceptibility for HNC risk

The results evidenced that DNMT3B -149C/T polymorphism was found to be associated with a genetic susceptibility for developing Laryngeal Squamous Cell Carcinoma in a Chinese population. After reviewing the information, 7 studies reported null associations for some SNPs related to genetic susceptibility and HNC risk. It was found that miR-101 SNPs were not associated with HNSCC risk. However, in the stratification analysis by tumor sites, rs578481 and rs705509 in pri-miR-101-1 were significantly associated with risk of OSCC (rs578481: $OR = 1.19$, 95 % (1.01–1.39), $P=0.036$; rs705509: $OR=0.85$,

95 % (0.73–0.98), $P=0.030$) [65]. Also, miRNA-149rs2292832, miRNA-146a rs2910164, and miRNA-608 rs4919510 did not show significant association to HNSCC risk [41].

Moreover, there was not association between polymorphisms in CHRN gene including rs16969968 (CHRNA5), rs578776 (CHRNA3), rs1229984 (ADH1B), rs698 (ADH1C), rs1573496 (ADH7), and rs4767364 (ALDH2) which encodes for alcohol metabolism, and oral cancer in the Indian population [66, 67]. Also, The XRCC1 and hOGG1 genes were unlikely to play a role in the susceptibility to NPC in North Africans [68]. The APE1 polymorphisms did not showed a significantly correlate with development of oral cancer either 38, non the TGF- β 1 C-509T and T869C with the development of NPC (TGF- β 1 C-509T: OR = 0.74; 95 % CI 0.46 – 1.18; for TGF- β 1 T869C: OR = 0.86; 95 % CI 0.56 – 1.31) [69].

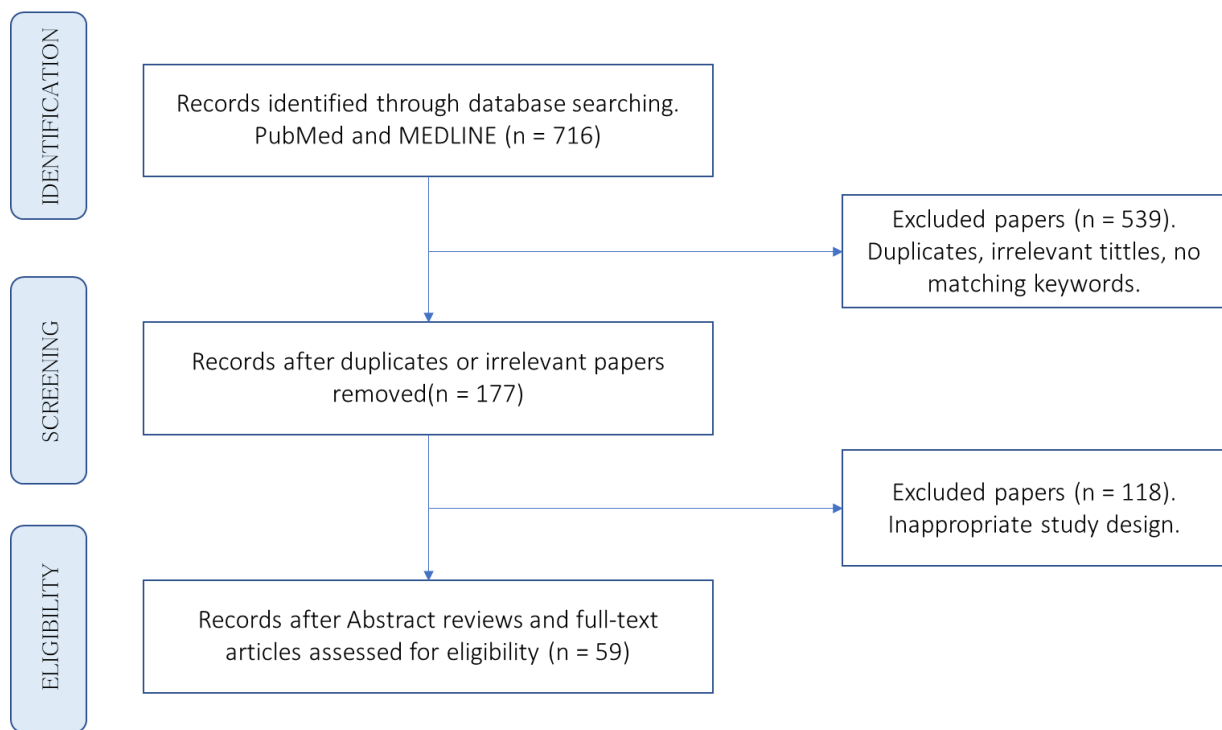


Figure 1. Flow chart of inclusion and exclusion criteria for selection of genetic association studies and the risk of developing HNC. (up to April 2022).

DISCUSSION

SNPs association studies have provided evidence that individual susceptibility to cancer is mediated by both genetic and environmental factors. The role of genetic polymorphisms in HNC has permitted establish important genes encoding for different pathways like carcinogen metabolism, DNA repair, cell cycle control, extra-cellular matrix alteration, immune inflammation, among others.

This review of 59 studies was conducted to identify the candidate genes, or genetic variants (SNPs) reported in association studies addressing genetic susceptibility and the risk of developing HNC.

The most studied genes were those encoding enzymes that metabolize carcinogens and include GSTM1, GSTT1, CYP1A1 and ADH1B [50, 52, 55 respectively]. It is well recognized that some individuals are more susceptible to certain types of cancers within similar environmental conditions. Therefore, these genes are responsible for the expression of carcinogen metabolizing enzymes, environmental exposure (such as tobacco use and alcohol consumption) and dietary and lifestyle habits of the individuals, and different factors or polymorphisms might be involved in the genetic susceptibility associated to the initiation of carcinogenesis [52]. the lack of GSTM1 activity would make the oral tissues more susceptible to action of tobacco carcinogens and to the development of a high-grade level of dysplasia in oral leukoplakia and thereby increases the susceptibility of lesion to undergo malignant changes [55].

The BRIP, rad51/52, BER genes [6, 56, respectively], are implicated in the DNA cross-link repair. Deficiency or genetic variants related to these genes may increase cancer risk in the head and neck and gynecological system. The SNP rs7213430 in the 3' -UTR of BRIP1 might contribute to SCCHN susceptibility by affecting the binding activity of miR-101 and resulting in a decreased BRIP1 expression. The findings evidenced a future potential clinical relevance for improvement of therapeutic regimens for HNC patient treatments involving DNA-damaging agents.

Cell cycle control is regulated by several candidate genes, among which were reported by the literature RB1/105 and TP53 [70] [68], Mutations in Rb1 gene were detected, among its exons and two in intronic region. As these alterations are in a pocket domain

and C terminus of gene, they might have a causal effect in the loss of Rb1 function [35, 36]. Functional inactivation of gene by genomic mutation or by transforming oncoprotein may provide the cell with growth advantage resulting in tumor formation.

The TIMP3 gene is related to the extra-cellular matrix alteration. Tissue inhibitor of metalloproteinase-3 acts as a tumor suppressor gene in many cancers by inhibiting tumor growth, angiogenesis, invasion, and metastasis. Moreover, a TIMP3 expression loss correlates with poor prognosis and survival in cancer patients.^{23,24} The TIMP3 SNP rs9862 was associated with oral cancer susceptibility and betel quid chewing or tobacco consumption contributes to the tumor growth [57].

Cellular proliferation- Invasion-metastasis genes associated to genetic susceptibility for HNC risk were found from the studies. Among these, miRNA605/499, SDF1, KIT, NF κ B1 [71, 72, 73] [69, 70, 71]. MiRNAs may act as regulators of gene expression and be involved in many cellular processes. Therefore, functional genetic polymorphisms of miRNAs may lead to individual variations in many cellular processes, leading to modification of the risk of cancers. Such increased or decreased expression of microRNAs may be associated with the development, progression, and prognosis of oral cancer. High expression of miR-605 could result in a significant reduction in cell viability, clonogenicity, and cell migration in TP53-mutant cell types. From this review miR-605 rs2043556 was associated with a significant overall risk of human cancer. Several tumor types have been associated with the aberrant activation of KIT through its overexpression or activating mutations [73]. As a key oncogenic driver, KIT plays a vital

role in promoting cellular proliferation, angiogenesis, cellular migration, and invasion by triggering multiple signal transduction pathways, such as PI3K/Akt, Ras-MAPK, and JAK-STAT pathways [73]. The review provided evidence that KIT polymorphisms might play a role in the development of HNSCC among Chinese population.

Among the apoptotic genes, the BCL₂ and CASP8 [21, 41] were found from the studies. Variations on these genes may produce dysregulation of apoptosis. Alterations on this mechanism is crucial for cancer progression because cells with unreparable DNA damage cannot be eliminated. A significant association between the anti-apoptotic gene BCL2 SNP and oral cavity cancer susceptibility was reported. On the other hand, CASP8 -652 6 N ins/del polymorphism found in this review may affect patient susceptibility to OSCC and may be used as a biomarker for this disease.

Finally, the pro-inflammatory genes associated to genetic susceptibility for HNC risk were IL1/2/16/18, HLA DRB1 and TNFA [29, 30, 32, 34, 37] demonstrating the involvement of pro-inflammatory cytokine genes in the development of OSCC. Further, the role of the -308AA genotype was clear on the development of NPC. According to the study, this variant was associated with EBV infection in over 95% of the cases. If the A allele induces higher expression of TNF- α , the increase of angiogenesis will favor the growth of infected cells and therefore provide a favorable environment for the viral infection to spread, and the final progression of HNC [14].

All eligible studies included in the review were case-control design. Regarding genotyping methods, 30% of the studies (18/59) used Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). The rest used RT-PCR direct sequencing (n = 11), Illumina assays (n = 5), PCR conventional (n=4), Affymetrix SNP Array (n=4), multiplex PCR (n = 4), Exonuclease assay (n= 2) and ELISA assay (n = 1). Few studies (n = 10) used more than one method for different SNPs such as PCR conventional + RT-PCR. Studies that utilized more than one method on a subset or on all samples confirmed the validity of the different methods of genotyping (Fig. 3. Online material).

The reviewed studies on HNC were subject to several limitations. Some studies lacked enough sample size, and hence power to detect moderate risk associations, and might have overestimation of true. Thus, it was not possible to indicate strong inference for any SNP identified to date in any population. Most authors of the reviewed studies highlighted the need of future studies with higher sample sizes and different populations (most were Asian populations) to corroborate their findings.

ETHICAL STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of Universidad Cooperativa de Colombia (INV2085), and Universidad Industrial de Santander (4110).

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AUTHOR'S CONTRIBUTION

The authors confirm contribution to the paper as follows: study conception and design: CCL, VCC, TPN; data collection: TPN and CCL; analysis and interpretation of results: CCL, VCC, TPN; draft manuscript preparation: CCL, VCC, TPN. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

COMPETING INTERESTS

No competing interests were disclosed.

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