ONLINE FIRST

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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

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DOI: 10.5603/RPOR.a2022.0109

Article type: Review paper

Published online: 2022-10-31

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

Running title: Genetic polymorphisms and HNSCC prognosis

10.5603/RPOR.a2022.0109

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Abstract

Background: Head and neck squamous cell carcinomas (HNSCCs) are associated with variable prognosis even with similar clinical characteristics and treatments. Gene polymorphisms have been suggested as prognostic factors for HNSCC which can justified this variable prognosis. So, the aim was to review literatures on gene polymorphisms and prognosis of HNSCCs.

Materials and methods: A systematic search was conducted using PubMed, Web of science, SCOPUS, Google Scholar and Cochrane library databases to find all related articles published up to December 2021 in the field of gene polymorphisms and HNSCC prognosis.

Results: Of 1029 initial searched articles, 71 articles were selected for inclusion in this systematic review. About 93 genes and 204 polymorphisms have been discussed in these articles. Among the most studied polymorphisms, the *XRCC1 Arg399Gln* and *Arg194Trp* polymorphisms were not associated with survival in most studies; the *ERCC1 C19007T*

polymorphism had no significant association in any of the studies. Different gene polymorphisms of glutathione s-transferase family, including *GSTM1 deletion*, *GSTT1 deletion* and *GSTP1 A313G,* were not associated with survival in included studies. There are conflicting results regarding the association between polymorphisms such as *ERCC2 A35931C*, *Asp312Asn*, *ERCC5 rs1047768* and *rs17655* with HNSCC prognosis. Less studied polymorphisms, such as *hOGG1 rs1052133* or the *VEGF rs699947*, were generally not associated with HNSCC prognosis.

Conclusion: Reviewed articles reported varied and contradictory results regarding the association of gene polymorphisms and HNSCC prognosis, which necessitates further studies along with meta-analysis on the results of such studies.

Key words: gene polymorphism; single nucleotide polymorphisms; head and neck squamous cell carcinoma; prognosis; survival

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world; HNSCC is associated with severe morbidity and mortality and has a five-year survival rate of approximately 25–60% [1–4].

Overall, survival (OS), disease-specific survival (DSS), progression-free survival (PFS), and disease-free survival (DFS) are among the most important patient's clinical outcomes. Prognosis of HNSCCs is dependent on multiple clinical factors, including stage, anatomic site, and patient's overall health status; other prognostic factors include age, gender, race, presence of comorbidities, alcohol drinking and tobacco consumption, tumor differentiation and lymph node metastasis. Human papillomavirus (HPV) infection, tumor markers, and genetic factors have also been correlated with prognosis and clinical outcomes [5, 6].

Studies have shown that HNSCCs are associated with variable prognosis even with similar clinical stages and treatments; at least part of this variable prognosis can be attributed to genetic variations. Genetic variations may cause differential radiosensitivity or chemosensitivity in HNSCC patients. Single nucleotide polymorphisms (SNPs) are among the most common genetic variations and study of SNPs as potential prognostic factors have become increasing in a wide variety of cancers [5–7].

So, the aim was to review literatures on gene polymorphisms and prognosis of HNSCCs.

Materials and methods

Literature search

The research question was defined based on PICO:

P — Population/Patient: HNSCC patients;

I — Intervention: presence of gene polymorphism;

C — comparator: HNSCC patients without gene polymorphism;

O — outcome: prognosis or survival.

A systematic search was conducted using PubMed, Web of science, SCOPUS, Google Scholar and Cochrane library databases to find articles related to the aim of this systematic review.

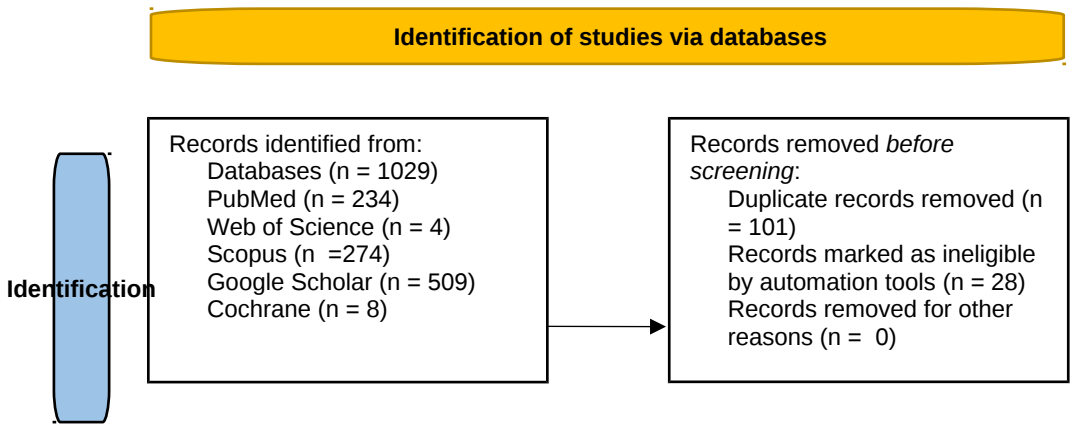
The search was performed on above databases according to MeSH terms as follows:

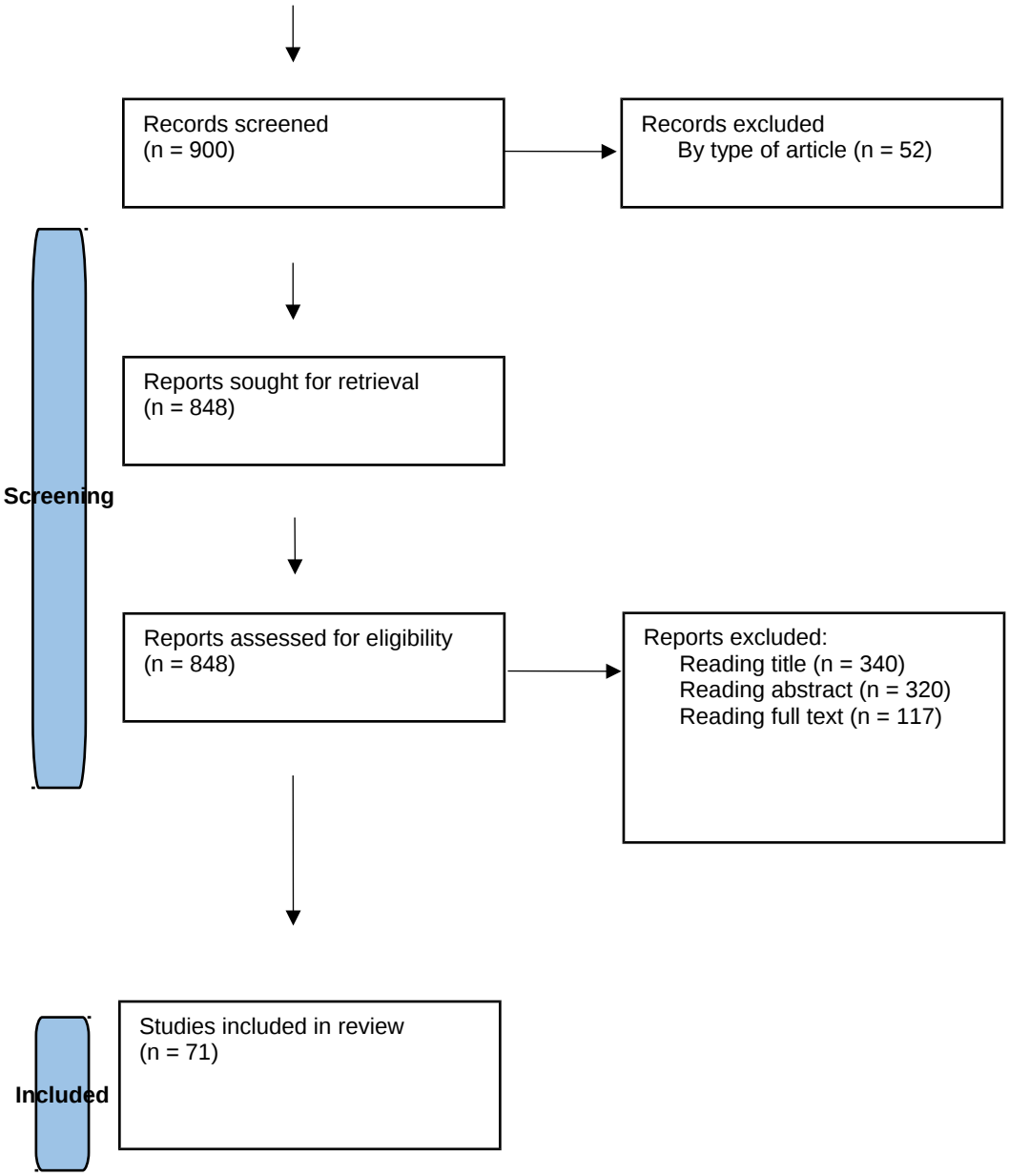
("Single nucleotide polymorphism" OR "genetic variation" OR "genetic polymorphism") AND ("prognosis" OR "survival" OR "disease-free survival" OR "progression-free survival") AND ("squamous cell carcinoma of head and neck" OR "head and neck neoplasms").

All articles were first assessed by title and duplicate articles were also excluded. Afterwards, we selected the articles by reading the abstracts. In the later stage, related articles were selected based on the full text. Two independent researchers made the search and extracted that data. Disagreements were resolved by consensus.

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

Figure 1. PRISMA flow diagram representing the process of identification of studies through databases





Inclusion and exclusion criteria

This systematic review included all original English-language research articles published from January 1998 to December 2021 regarding the association of gene polymorphisms with prognosis of HNSCCs. Prognosis in these articles was overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) or disease-specific survival (DSS).

Oral squamous cell carcinoma (OSCC), oropharyngeal SCC (OPSCC), hypopharyngeal SCC (HPSCC), nasopharyngeal SCC (NPSCC) and laryngeal SCC (LSCC) were regarded as HNSCCs.

Exclusion criteria were as follows: studies evaluating neoplasms located in other parts of the body than head and neck area; studies evaluating neoplasms other than squamous cell carcinoma; case report articles, reviews and letters to the editor articles; studies which did not report the association of gene polymorphisms with prognosis; studies which included the association of gene or protein expression with prognosis; studies which reported the association of gene polymorphisms with HNSCC risk, post-treatment toxicity and treatment response; studies which reported the association of gene polymorphisms with prognosis of second primary tumors.

Quality assessment

The Joanna Briggs Institute (JBI) checklist was used for evaluation of the quality of the selected articles. Scoring of final articles based on JBI checklist was done. The acceptable score (based on JBI checklist) was 60% for inclusion of the articles in this systematic review.

Results

Of 1029 initial searched articles, 71 articles were eligible for inclusion in this systematic review. A summary of the characteristics of the included studies are shown in Table 1.

Table 1. Characteristics of the studies included in this systematic review

First author, year	**Studied Genes (polymorphisms)**	**Primary outcome**
Matthias, 1998 [8]	*CCND1* (A870G)	DFS
Holley, 2001 [9]	*CCND1* (A870G, G1722C)	DFS
Sullivan, 2004 [10]	*p53* (Arg72Pro)	OS, PFS
Wang, 2004 [11]	*DNMT3B6* (C-149T)	OS
Streit, 2004 [12]	*FGFR4* (Gly388Arg)	OS
Monteiro, 2004 [13]	*CCND1* (A870G)	OS, DFS
Geisler, 2005 [14]	*GSTT1* (deletion), *GSTM1* (deletion), *GSTP1* (Ile105Val), *XRCC1* (Arg399Gln, Arg194Trp)	OS, DSS

Etienne-Grimaldi, 2005 [15]	*EGFR* (rs11568315)	DSS
Gal, 2005 [16]	*XRCC1* (Arg399Gln), *XRCC3* (Thr241Met), *XPD* (Lys751Gln), *MGMT* (Leu84Phe), *MGMT* (Val143Ile)	OS, DSS
Kondo, 2005 [17]	*MMP1* (1G 1607 2G)	OS
Wong, 2006 [18]	*CTLA-4* (A49G)	OS
Carles, 2006 [19]	*XPA* (rs1800975), *XPC* (Lys939Gln), *XPD* (Lys751Gln), *ERCC1* (Lys259Thr), *ERCC5* (His1104Asp, C581T), *XRCC5* (rs1051677, rs1051685), *XRCC1* (Arg399Gln)	OS
Matthias, 2006 [20]	*CCND1* (A870G), *TNFa* (TNFBID5)	DFS
Quintela-Fandino, 2006 [21]	*ERCC1* (C8092A), *XPD* (Asp312Asn, Lys751Gln), *XRCC1* (Arg399Gln)	OS
da Costa Andrade, 2007 [22]	*FGFR4* (Gly388Arg)	OS
Lehnerdt, 2009 [23]	*BCL2* (-938C>A)	DFS, OS
Lundberg, 2009 [24]	*TGFβ1* (rs1982073)	DFS, OS
Klinghammer, 2010 [25]	*EGFR* (R521K, CA-SSR)	PFS, OS
Lundberg, 2010 [26]	*TGFβ1* (rs1982073)	DFS, OS
Tanuma, 2010 [27]	*FGFR4* (Gly388Arg), *TP53* (Mutant)	OS
Corrêa, 2011 [28]	*TNF-α* (-308)	OS
Bergmann, 2011 [29]	*TLR4* (Asp299Gly, Thr399Ile)	DFS, OS
De Castro, 2011 [30]	*ERCC1* (T19007C)	OS
Hama, 2011 [31]	*VDR* (rs11568820), *FokI* (rs10735810), *BsmI* (rs1544410), *ApaI* (rs7976091), *TaqI* (rs731236)	PFS
Zhong, 2011	*ERCC2* (rs13181), *CCND1* (rs9344)	OS, DSS,

[32]		PFS, DFS
Wang, 2012 [33]	*KRAS* (rs1137282, rs712)	OS
Azad, 2012 [34]	*CCND1* (A870G), *TP53* (Arg72Pro), *DNMT3B* (C149T), *ERCC1* (C8092A, Lys259Thr), *ERCC4* (T2505C), *ERCC5* (C581T, His1104Asp), *MSH2* (C211þ9G), *ERCC2* (Asp312Asn, Lys751Gln), *XRCC1* (Arg399Gln), *XRCC3* (Thr241Met), *FGFR4* (Gly388Arg), *CTLA4* (A49G), *MMP3* (-1612insA), *GSTM1* (Deletion), *GSTT1* (Deletion), *CYP2D6* (*3, *4, *5)	OS, DFS
Lima, 2012 [35]	*ERCC1* (G19007A)	OS
Lundberg, 2012 [36]	*TGFβ1* (rs1800470)	OS, DFS
Stoehlmacher-Williams, 2012 [37]	*EGFR* (-216 G/T, -191 C/A, R497K G→A), *EGF* (61 A/G)	OS
Supic, 2012 [38]	*VEGF-A* (-2578C/A, -1154A/G, -634G/C, +936C/T)	OS
Liu, 2013 [39]	*FGFR4* (rs351855), *VEGF* (rs2010963, rs833061, rs3025039), *ERCC1* (rs3212986), *ERCC2* (rs1799793, rs13181), *XRCC1* (rs25487), *hOGG1* (rs1052133), *APEX1* (rs1130409), *ADPRT* (rs1136410), *MTHFR* (rs1801131, rs1801133), *ABCB1* (rs1045642, rs2032582), *MPO* (rs2243828), *MDM2* (rs2279744)	OS, PFS
Guan, 2013 [40]	Pre-microRNA (rs2910164, rs2292832, rs11614913, rs3746444)	OS, DSS, DFS
Jin, 2013 [41]	*IL-10* (rs1800871, rs1800872, rs1800896)	OS, DSS, DFS
Liu, 2013 [42]	*miR-196a2* (rs11614913)	DFS
Zhang, 2014 [43]	*TNF-α* (rs1800629, rs1799724, rs1800630, rs1799964)	DFS
Chung, 2014 [44]	*KRAS* (rs61764370)	OS, PFS
Lin, 2014 [45]	*hMLH1* (rs1800734, rs1540354)	OS, DFS
Su, 2014 [46]	*EGF* (A61G A>G), *EGFR* (R521K G>A, G-216T)	OS, PFS
Zhang, 2014 [47]	*TNF-α* (rs1800629, rs1799724, rs1800630, rs1799964)	DFS
Farnebo, 2015	*XPC* (A499V), *XPD* (K751Q), *XRCC1* (R399Q), *XRCC3*	OS

[48]	(T241M)	
Pfisterer, 2015 [49]	*AKT1* (rs2494738, rs2498804, rs3803304), *AKT2* (rs892119, rs8100018), *FRAP1* (rs11121704, rs2295080), *PIK3CA* (rs2699887, rs7640662), *PTEN* (rs12569998, rs2299939)	OS, PFS
Reuter, 2015 [50]	*PXR* (rs3814055, rs1523127, rs2472677, rs6785049, rs2276707, rs1054190, rs1054191)	OS
Stur, 2015 [51]	*XRCC1* (Arg194Trp, Arg399Gln), *XRCC3* (Thr241Met), *XPC* (Lys939Gln), *ERCC1* (Asn118Asn), *RAD51* (-98G>C)	DSS, DFS
Costa, 2016 [52]	*OGG1* (rs1052133), *APEX1* (rs1130409), *XRCC1* (rs3213245, rs1799782, rs25489, rs25487)	PFS, OS
Wang, 2016 [53]	Pre-microRNA (rs2910164, rs11614913, rs2292832, rs3746444)	OS, DSS, DFS
Agostini, 2017 [54]	*ATM* (5557G>A, IVS62 + 60G>A), *TP53* (215G>C), *BCL2* (-938C>A), *TGFβ* (-509C>T, 29C>T)	DFS, DSS
Braig, 2017 [55]	*EGFR* (EGFR-K_{521})	PFS
Chen, 2017 [6]	*FADS1* (rs174549)	PFS, OS
Lopes-Aguiar, 2017 [56]	*XPC* (c.2815A>C), *XPD* (c.934G>A, c.2251A>C), *XPF* (c.2505T>C), *ERCC1* (c.354C>T)	PFS, OS
Zhu, 2017 [57]	*ATM* (rs227091), *BRCA1* (rs12516, rs8176318), *PARP1* (rs8679), *LIG3* (rs4796030), *NBS1* (rs2735383, rs1063054, rs1063053), *RAD51* (rs7180135)	DFS
Magnes, 2018 [58]	*FCGR2A* (rs1801274), *FCGR3A* (rs396991)	PFS, OS
Nanda, 2018 [7]	*XRCC1* (Arg194Trp)	DFS, OS
Senghore, 2019 [59]	*MSH2* (rs3732183), *MSH3* (rs12515548, rs26279), *EXO1* (rs1047840), *MLH1* (rs1800734)	DFS, OS
Senghore, 2019 [60]	*ERCC5* (rs2094258, rs1047768, rs17655, rs873601), *ERCC2* (rs13181, rs1799793), *ERCC1* (rs735482, rs3212986, rs11615), *XPC* (rs2228001, rs2228000), *XPA* (rs1800975, rs10817938)	OS, DFS
Hirakawa, 2020 [4]	*ERCC1* (C8092A) , *XRCC1* (Arg399Gln)	OS
Butkiewicz, 2020 [61]	*VEGF* (rs2010963, rs699947, rs3025039), *VEGFR1* (rs9582036, rs7996030), *VEGFR2* (rs2071559, rs1870377), *ANGPT1* (rs2507800, rs1954727), *ANGPT2* (rs3739391, rs3020221), *TEK* (rs639225)	OS, DFS
Dutta, 2020 [62]	*XRCC1* (Arg399Gln)	OS, PFS

Maniglia, 2020 [63]	*GSTT1* (Deletion), *GSTM1* (Deletion), *GSTP1* (A313G, C341T)	OS
Senghore, 2020 [64]	*XRCC1* (rs25487, rs25489, rs1799782), *OGG1* (rs1052133), *APEX1* (rs1760944), *MUTYH* (rs3219489)	OS, DFS
Yadav, 2021 [65]	*CYP2A6* (*4B, *4C, *9)	OS
Dimitrakopoulos, 2021 [66]	*VEGFA* (rs699947, rs12664104, rs34376996, rs144854329, rs35864111, rs833061, rs149983590, rs833062, rs1570360, rs28357093, rs13207351, rs79469752, rs59260042, rs3025039, rs149179279, rs112005313, rs187429037, rs111933757), *EDNRA* (rs5333, rs5334, rs10305924, rs17856670, rs112710542), *FAS* (rs1800682, rs34995925, rs2234768, rs150130637), *NBS1* (rs1805794, rs192240705, rs780661058, rs151070415, rs61754966, rs182756889)	OS
Guberina, 2021 [67]	*ERCC2* (rs1799793, rs13181, rs50871), *XRCC6* (rs2267437), *ERCC1* (rs11615), *ATM* (rs4988023), *ERCC5* (rs17655), *XRCC1* (rs25487)	OS, DFS
Duran, 2021 [68]	*ABCB1* (rs1045642, rs2032582), *ABCC1* (rs246221, rs45511401), *ABCC2* (rs717620), *ABCG2* (rs2231142), *ATP6V1C1* (rs2248718), *ATP7B* (rs1061472, rs1801244, rs2147363), *CDA* (rs2072671), *ND3* (rs2853826), *RRM1* (rs12806698), *SLC28A1* (rs2242047), *COX-2* (rs689466), *IL3* (rs1800925), *TGFB1* (rs1800469), *FGFR4* (rs351855), *GSTP1* (rs1695), *NQO1* (rs1800566), *MMP-2* (rs12934241), *SOD2* (rs4880), *RAD51* (rs1801320), *XRCC6* (rs2267437), *ERCC1* (rs11615, rs3212986), *ERCC4* (rs1799801), *XPC* (rs2228001), *ERCC2* (rs13181, rs1799793, rs238406), *ERCC5* (rs17655), *XRCC1* (rs25487), *XRCC2* (rs6464268), *XRCC3* (rs861539), *RPA34* (rs735482)	OS, DFS
Jović, 2021 [69]	*CCND1* (rs9344), *p21* (rs1801270, rs1059234)	OS, DFS
Lubiński, 2021 [70]	*SOD2* (rs4880), *CAT* (rs1001179), *GPX1* (rs1050450)	OS
Novais, 2021 [71]	*XRCC1* (rs25487), *HOGG1* (rs1052133), *CYP1A1* (rs1048943), *GSTM1* (rs4025935), *GSTT1* (rs71748309), *GSTP1* (rs1695), *NAT2* (*4)	OS, DFS
Pasvenskaite,	*IL-10* (rs1800871, rs1800872, rs1800896)	OS

2021 [72]		
Pasvenskaite, 2021 [73]	*IL-9* (rs1859430, rs2069870, rs11741137, rs2069885, rs2069884)	OS
Wei, 2021 [74]	*ERCC2* (rs13181)	OS, DFS
Zhu, 2021 [75]	*UCA1* (rs7255437)	DSS

OS — overall survival; PFS — progression-free survival; DFS — disease-free survival; DSS — disease-specific survival

Carcinogen-metabolizing enzymes

In general, different gene polymorphisms of glutathione-S-transferases (*GST*s), including *GSTM1 deletion*, *GSTT1 deletion*, *GSTP1 rs1695* and *GSTP1 rs749174*, were not associated with survival in HNSCCs [14, 34, 63, 68, 71]. In one study, the non-null variant of *GSTT1 deletion* polymorphism was significantly associated with poor OS and DSS [14]. In cytochrome P-450 (CYP) family, the *CYP2A6 *4B*, *4C* and *9* polymorphisms were associated with poor OS compared to common alleles [65].

DNA repair

In HNSCCs, in most studies, the *XRCC1 rs25487* polymorphism was not associated with survival [4, 14, 19, 39, 48, 51, 52, 62, 64, 67, 68, 71], although, in a few studies, this polymorphism was significantly associated with OS [16, 21, 34]; the results on the favorable variant in these studies were inconsistent so that the *GG* genotype was associated with worse OS compared to *GA + AA* genotypes in two studies [16, 21] and the *GA + AA* variant was associated with worse OS in one study [34]. In the same way, in most studies, the *XRCC1 rs1799782* polymorphism was not significantly associated with survival [7, 14, 51, 52]; in one study, *CT + TT* variant was significantly associated with OS, but not DFS, compared to *CC* genotype in OSCC patients [64]. The *ERCC1 rs11615* polymorphism was not significantly associated with survival [30, 35, 51, 56, 60, 67, 68]. In most studies, the *ERCC1 rs3212986* polymorphism was not associated with survival [21, 34, 60, 68]; in studies with a significant association, there is no agreement on the favorable variant so that in one study, the *CC* genotype was associated with poor PFS compared to *CA + AA* variant in NPC [39] while in another study, *CA + AA* variant was associated with worse OS compared to *CC* genotype in pharyngolaryngeal SCC (PLSCC) patients [4]. In two studies, the *ERCC1 rs735482* polymorphism was significantly associated with survival [19, 60]; the *CC* genotype was

significantly associated with poor DFS, but not OS, compared to *AC + AA* genotypes in OSCC [60]. There are conflicting results regarding the association between *ERCC2/XPD rs13181* and *rs1799793*, *ERCC5/XPG rs1047768* and *rs17655*, *XRCC3 rs861539*, *RAD51 rs1801320* polymorphisms with HNSCC prognosis; the *ERCC2 rs13181* polymorphism was significantly associated with survival in some studies [21, 32, 48, 67, 74]; the *AA* genotype was associated with poor OS compared to *AC + CC* genotypes [21]; the *AA* genotype was associated with worse OS in stage III–IV HNSCCs treated with radiation compared to *AC + CC* genotypes but it was associated with better survival in stage III–IV HNSCC patients who were not treated with radiation; also, this polymorphism was not associated with OS in stage I–II HNSCC patients [32]. In contrast, the *AA* genotype was associated with a significantly better OS and/ or DFS compared to *AC + CC* genotypes [48, 74]; the *CC* genotype was associated with worse OS and DFS compared to *AC + AA* genotypes [67]. In a few studies, the *ERCC2 rs1799793* polymorphism was significantly associated with survival [21, 67]; the *GG* genotype was the unfavorable variant in one study [21] and the favorable variant in another study [67]. In one study, the *ERCC5 rs1047768* polymorphism was significantly associated with OS [19]. In some studies, the *ERCC5 rs17655* polymorphism was significantly associated with survival [60, 67]; the *CC* genotype was significantly associated with worse DFS, but not OS, compared to *GC + GG* genotype in OSCC (60); in another study, the *GG* genotype was significantly associated with better DFS compared to *CG + CC* genotypes [67]. In one study, the *Thr* allele of *XRCC3 rs861539* polymorphism had significantly better DFS and DSS compared to the *Met* allele in irradiated LSCC [51]. The *RAD51 rs1801320* polymorphism was significantly associated with DFS in non-irradiated OSCC and OPSCC so that the *G* allele had a better DFS compared to *C* allele [51]. Each of the *hOGG1 rs1052133*, *XPC* rs2228001, *MSH2* rs3732183, hMLH1 *rs1800734*, *RAD51 rs7180135*, *BRCA1 rs12516* and *MUTYH rs3219489* polymorphisms was significantly associated with survival in HNSCCs in one study [45, 51, 52, 57, 59, 64].

Tumor suppressor genes/oncogenes

Given the key role of *TP53* in the carcinogenesis process, it is not surprising that *TP53* mutations can reduce the survival rate of HNSCC patients [27]. In two studies, the *TP53 Arg72Pro* (*rs1042522*) polymorphism was significantly associated with survival [10, 34]; HNSCC patients with a *wild-type p53* allele had better OS and PFS compared to patients without *wild-type* allele; the OS and PFS were significantly different among patients with a

wild-type *72R* (*Arg*) allele, with a wild-type *72P* (*Pro*) allele and with both wild-type alleles so that *72R* allele had the best OS and PFS (10); this polymorphism was associated with DFS in patients with stage I and II radiation-treated HNSCC so that the DFS was worse for each *Pro* allele when compared with the reference (*Arg/Arg*) [34]. The *GT/GG* variant of *MDM2 rs2279744* polymorphism was significantly associated with poor PFS compared to *TT* genotype in NPC patients [39].

Anti- or pro-apoptotic regulators

The *CC* genotype of *BCL-2 -938C>A* polymorphism was significantly associated with worse survival compared to the *AA + CA* genotypes [23, 54].

Cell cycle control

Results on the association between *CCND1 rs603965* polymorphism and HNSCC prognosis were contradictory; in most studies, the *GG* genotype of this polymorphism was significantly associated with poor DFS compared to *AA* genotype in HNSCC patients [8, 9, 13, 20]; the *AA* genotype was significantly associated with better DFS and OS in LSCC compared to *AG + GG* genotypes [13]. In contrast, the *GG* genotype was associated with better OS in stage III–IV HNSCC patients who were not treated with radiation [32]. With regard to *CCND1 rs678653* polymorphism, the *CC* genotype was significantly associated with poor DFS compared to *GG* genotype in one study [9]. The *VDR FokI (rs10735810)* [31], *AKT2* rs8100018, *AKT1 rs3803304* and *PTEN rs12569998* (49) polymorphisms were significantly associated with survival. The *TT* genotype of *VDR rs10735810* polymorphism was associated with poor PFS [31]. The *GG* genotype of *AKT2 rs8100018* polymorphism was associated with a significantly worse OS and PFS compared to *CC* genotype. The *CG+GG* genotypes of *AKT1 rs3803304* polymorphism had significantly better OS compared to *CC* genotype (49).

Antioxidant gene

The *SOD2 rs4880*, *CAT rs1001179* and *GPX1 rs1050450* polymorphisms were not associated with survival [68, 70].

Inflammatory mediators

Results on the association between *TNF-α* polymorphisms and HNSCC prognosis were contradictory; in one study, the *GG* genotype of *-308G>A* polymorphism was associated with

a significantly worse DFS compared to corresponding variant genotypes [47]; also, in one study, the *TNF-α -857* and *-1031* polymorphisms were significantly associated with DFS so that the *-857 CC* and *-1031 TT* genotypes had significantly worse DFS compared to corresponding variant genotypes [43]. The *TNF-α -863* polymorphism was significantly associated with DFS so that the *CC* genotype was associated with a significantly worse DFS compared to corresponding variant genotypes [43, 47]. The *BID5+* variant of *TNFα TNFBID5* polymorphism was significantly associated with poor DFS [20]. The *IL-9 rs1859430* polymorphism was significantly associated with OS so that the *AA* genotype was associated with poor OS compared to *AG + GG* genotypes [73]. Results on the association between *IL-10* polymorphisms and HNSCC prognosis were contradictory; in one study, the *CC* genotype of *IL-10 rs1800871* polymorphism (compared to *CT + TT* genotypes) and the *CC* genotype of *IL-10 rs1800872* polymorphism (compared to *CA + AA* genotypes) were associated with a significantly better survival in $HPV16^{+}$ OPSCC patients [41]. In HNSCC patients who received chemoradiotherapy without surgical treatment, the *CC + CT* genotypes of *TGFβ1 rs1982073* polymorphism were significantly associated with a better DFS and OS in comparison with *TT* genotype [24, 26]. The *TGFβ1 rs1800470* polymorphism was significantly associated with survival [36, 54]; the *TT + CT* genotypes were associated with a better OS compared to the *CC* variant [36]; in irradiated LSCCs, the *TC+TT* genotypes had a better DFS compared to the *CC* genotype [54]. The *TGF β1 rs1800469* polymorphism was significantly associated with DSS in irradiated OSCC/OPSCC patients so that the *CC* genotype had better DSS compared to *TC+TT* genotypes [54].

Angiogenesis

The *CC* genotype of *VEGF rs2010963* polymorphism was significantly associated with poor OS and metastasis-free survival (MFS) compared to *CG/GG* genotypes [61]. The *AA* genotype of *VEGF rs699947* polymorphism was significantly associated with poor local recurrence-free survival (LRFS), but not OS, compared to *AC/CC* genotypes [61]. The *GG* genotype of *VEGF-A rs1570360* polymorphism was significantly associated with decreased OS in OSCCs [38]. The *AA* genotype of *VEGFA rs13207351* polymorphism was significantly associated with poor OS compared to *GG* genotype in LSCC patients [66]. The *TT* genotype of *VEGFR2 rs1870377* polymorphisms was significantly associated with poor DFS, but not OS, compared to *TA+AA* genotypes [61]. The *GA/AA* genotypes of *ANGPT2 rs3739391*

polymorphism and the *CC* genotype of *ANGPT2 rs3020221* polymorphism were significantly associated with poor OS, but not DFS, compared to corresponding variants [61].

Growth control

In some studies, the *FGFR4 rs351855* polymorphism was significantly associated with OS in HNSCC patients (12, 22, 27); the *Gly/Arg + Arg/Arg* genotypes (*Arg388* allele) were associated with poor OS compared to *Gly/Gly* genotype [12, 22, 27]. The *TG/GG* genotypes of *KRAS rs61764370* polymorphism were significantly associated with poor PFS compared to the *TT* genotype in HNSCC patients who were treated with cisplatin + placebo or cetuximab [44]. In one study, the *G/G* genotype of *EGF A61G* polymorphism was significantly associated with poor OS and PFS compared to *G/A* or *A/A* genotypes in PLSCC but this association did not exist for OSCC [46]. There are conflicting results regarding *EGFR R521K* polymorphism; in some studies, the *K*-allele carriers had shorter OS/PFS compared to HNSCC patients with *RR* genotype [37, 55]; in one study, the *RR*/*RK* genotypes were significantly associated with poor PFS compared to *KK* genotype in PLSCC but this association did not exist for OSCC [46].

Non-coding RNA

Results on the association between miRNAs polymorphisms and HNSCC prognosis are contradictory; in one study, the *hsa-mir-146a rs2910164* polymorphism was significantly associated with DSS and DFS in OPSCC so that the *GG* genotype had better DSS and DFS compared to the *CG + CC* variant [40]; also, in one study, the *hsa-mir-149 rs2292832* polymorphism was significantly associated with survival so that the *CC* genotype had better OS, DSS and DFS compared to the *CT/TT* genotypes in non-OPSCCs [53]. The *hsa-mir-196a2 rs11614913* polymorphism was significantly associated with survival in OPSCC so that the *CT + TT* variant had better OS, DSS and DFS compared to the *CC* genotype [40]; the *TT* genotype of this polymorphism was associated with poor DFS in OSCC patients compared to the *CT + CC* genotypes [42]. In one study, the *hsa-mir-499 rs3746444* polymorphism was significantly associated with survival so that the *TT* genotype had better OS, DSS and DFS compared to the *CT/CC* genotypes in non-OPSCCs [53]. The *NEAT1 rs3741384* and *UCA1 rs7255437* polymorphisms were significantly associated with DSS in OSCC patients so that the *GG* genotype of *NEAT1 rs3741384* polymorphism and *TC + TT* genotypes of *UCA1 rs7255437* were associated with poor DSS [75].

Invasion and metastasis

The *1G/1G* genotype of *MMP-1 −1607 1G/2G* polymorphism was significantly associated with better OS compared to *1G/2G+2G/2G* genotype in NPSCC [17]. The *MMP-2 rs12934241* polymorphism was significantly associated with OS and DFS; the *CT+TT* genotypes were associated with poor OS and DFS compared to *CC* genotype [68].

Regulation of immune response

In HNSCCs, the *Asp/Gly* variant of *TLR4 Asp299Gly* polymorphism was significantly associated with reduced DFS and OS. The *Thr/Ile* variant of TLR4 *Thr399Ile* polymorphism was significantly associated with reduced DFS [29]. The *AA* genotype of *CTLA4 A49G* polymorphism was significantly associated with poorer OS [18]. In another study, the *GG+AG* genotypes of this polymorphism had poorer OS compared with the *AA* genotype [34]. HNSCC patients with *131H/H* genotype of *FCGR2A H131R* polymorphism and/or *157V/V* genotype of *FCGR3A V157F* polymorphism had significantly better PFS compared to patients carrying *131R* and *157F* alleles [58].

Multidrug resistance

The *AT/AA* variant of *ABCB1 rs2032582* polymorphism was significantly associated with poor PFS compared to other variants in NPC patients [39]. The *ABCC2 rs717620* polymorphism was significantly associated with OS and DFS so that the *GA+AA* variant was associated with poor OS and DFS compared to the *GG* genotype [68]. The *SLC28A1/CNT1 rs2242047* polymorphism was significantly associated with OS and DFS so that the *GA+AA* variant was associated with better OS and DFS compared to the *GG* genotype [68].

Discussion

Various factors have been attributed to prognosis of HNSCCs including staging, grading, tumor site, health status, age, gender, race, comorbidities, alcohol drinking and tobacco consumption, lymph node metastasis and HPV positivity [5, 6]. Even with relatively similar clinical features and treatments, the prognosis of HNSCCs may vary widely. In recent years, gene polymorphisms have been suggested as at least parts of the source of this variable prognosis. In a polygenic mechanism, these polymorphisms with their corresponding alleles

can contribute to varied prognosis; in fact, these alleles are low-penetrance alleles (each with a small risk) that combine together to cause varied cancer prognosis. Some believe that since the frequency of these polymorphic alleles is relatively high, the role of them in cancer prognosis can be quite high, even if their penetrance is low. Also, the importance of gene polymorphisms in cancer prognosis may become more pronounced when these polymorphisms are analyzed in specific subgroups of the population. The gene polymorphisms may cause variable prognosis through the differential response of tumors to treatment or through involvement in various carcinogenesis pathways [5–7]. For example, it has been reported that carriers of *C* allele of *TGFβ1 rs1982073* polymorphism have elevated serum concentrations of *TGF-β1* in comparison with *TT* genotype; the better survival of the *C* allele carriers after chemoradiotherapy can be justified by the fact that the elevated serum concentration of *TGF-β1* may sensitize cancer cells to chemoradiotherapy [24, 26, 36]. Arginine to lysine substitution in R521K *EGFR* polymorphism leads to an *EGFR* variant that shows less affinity to its related ligand and less mitogenic activity. So, it has been hypothesized that *EGFR* gene polymorphisms may affect sensitivity to anti-*EGFR* treatment and prognosis [25, 37]. Sometimes, a dual function has been described for gene polymorphisms; for example, the *ERCC1* gene and associated protein (as a part of DNA repair pathway) regulates cell sensitivity to cisplatin (cisplatin causes cytotoxicity through formation of DNA adducts which blocks nucleotide replication and transcription) which has been correlated with chemo-radiation-resistance. Lower *ERCC1* expression (as a result of functional gene polymorphism in *ERCC1* gene) has been reported to correlate with better prognosis in some cancers; at the same time it may be associated with the accumulation of DNA damage and results in a more aggressive behavior of tumor which implicates a dual effect in terms of prognosis [4, 30, 35, 60]. Invasion and metastasis affect clinical outcome of HNSCC. Invasion and metastasis are dependent on angiogenesis. *VEGF*/*VEGFR* genes and *ANGPT*/ *TEK* genes play key roles in angiogenesis and are overexpressed in different human cancers including HNSCC. Functional SNPs in these genes are associated with high or low expression level of their related proteins. For example, the *-2578C*, *-1154A* or *-634G* variant alleles have been linked with the low *VEGF* expression. Consequently, it can affect the angiogenesis process and may result in variations of tumor progression and clinical outcomes [38, 61, 66]. Function of some growth control genes like *FGFR4* also involves up-regulation of proteolytic enzymes required for cell migration; overexpression of these genes has been suggested as a possible mechanism in cancer progression. Some variant alleles (like the

Arg388 allele of *FGFR4 Gly388Arg* polymorphism) increase the gene expression (e.g. *FGFR4*) and may increase the aggressive behavior of cancer cells and, consequently, may affect HNSCC prognosis [27]. Polymorphisms in the promoter region of the genes related to inflammatory mediators (like *TNF-α* gene) are implicated in the regulation of expression level of its related cytokine. Such a polymorphism has been proposed to be linked with the prognosis in cancers (such as gastric and colorectal cancers) [28, 43, 47]. *GST*s are a group of phase II detoxification enzymes. Genetic polymorphisms of *GST*s have probably some impact on HNSCC risk by regulating the efficacy of detoxification of carcinogens derived from cigarette smoking. Based on these evidences, it has been hypothesized that polymorphism of these genes may also be involved in HNSCC prognosis [14, 34]. Expression of anti-apoptotic proteins (like *BCL-2*) has been associated with better local control and survival in HNSCCs. A regulatory polymorphism (like *BCL2 -938C>A*) in gene promoter produces different promoter function and activity which may be associated with outcome in HNSCC patients (23). Variants of cell cycle regulatory genes like *CCND1* may promote alternative splicing of transcript which produces truncated proteins that lack regulatory motifs. This results in protein degradation and nuclear export which may have some impact on cancer survival [32]. The importance of the epigenetic changes in tumors including HNSCCs is apparent. DNA methylation (as an epigenetic change) is regulated by a family of enzymes called DNA methyltransferases (*DNMT*s). The *DNMT* gene polymorphism may be associated with aberrant DNA methylation in HNSCCs and, consequently, affects survival as reported in a study by Supic et al. [77]. Research has suggested miRNAs (*miR*), such as *miR-149*, suppress tumor cell mobility. The *pre-miR* gene polymorphism may affect the processing of *miR* (for example, T variant of *pri-mir-149* polymorphism shows a low processing efficacy) which results in a lower frequency of the mature form of miRNA, which consequently regulates tumor progression and HNSCC survival [78].

Conclusion

HNSCC prognosis may be affected by deregulations of different pathways and several studies have assessed the gene polymorphisms involved in these pathways which have been associated with different and sometimes contradictory results. In order to analyze the association between gene polymorphisms and HNSCC prognosis and to overcome these contradictory results, further studies along with conducting meta-analyses are necessary.

Declaration

All authors have viewed and agreed to the submission.

Conflict of interest

None declared

Funding

None declared.

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