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Systematic Review: Genetic and epigenetic Changes involved in the Progression of Oral Squamous Cell Carcinoma

Shreya S Ingle[1], Shubhangi D Mishra[2], Yogita Dhengar[3], Mrunali Jambhulkar[4], Maya Nishad[4], Shreyasi Polley[4] Sapana Rupawate[1]

PG Student[1],

PG Guide & Associate Professor[2],

Head of Department and Professor[3],

Assistant Professor[4]

Department of Oral and Maxillofacial Pathology and Oral Microbiology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur, India.

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KEYWORDS

Oral Squamous Cell Carcinoma; Genetic alterations; Epigenetic modifications ; DNA methylation; MicroRNAs; Molecular biomarkers.

ABSTRACT:

Introduction: Oral squamous cell carcinoma (OSCC) remains one of the most prevalent malignancies worldwide, particularly in regions with high tobacco and areca nut consumption. Its pathogenesis is a multistep process influenced by both genetic predispositions and epigenetic modifications. Recent advances have identified key molecular alterations including DNA methylation, non-coding RNAs, and genetic polymorphisms that may serve as potential biomarkers for diagnosis, prognosis, and therapeutic targeting.

Objectives: This systematic review aims to comprehensively evaluate the genetic and epigenetic changes implicated in OSCC progression.

Materials and Methods: This review adhered to PRISMA guidelines. A systematic literature search was conducted in PubMed and Scopus databases, retrieving 625 and 321 articles respectively. After screening titles, abstracts, and full texts based on predefined inclusion criteria, 10 studies were included for qualitative synthesis. Data were extracted regarding study size, molecular markers evaluated, techniques employed, and key findings. Both observational and experimental studies involving OSCC tissues, cell lines, or clinical samples were considered.

Results: Among the 11 included studies, a diverse range of epigenetic and genetic markers were investigated. Notable findings include MIR146A polymorphism linked to OSCC susceptibility, promoter hypermethylation of tumor suppressor genes such as P15, P16, TP53, and VHL, and aberrant expression of miRNAs like miR-99b-3p, miR-100-5p, and miR-148a. Long non-coding RNAs (LINC00974) and circular RNAs (circ_0072387) were shown to modulate OSCC progression via interactions with miR-122 and miR-503-5p respectively. Epigenetic studies were more predominant compared to genetic analyses, reflecting a relative paucity of studies addressing genetic alterations. Most studies used PCR-based techniques, with tissue samples as the primary source.

Conclusion: This review underscores the significant role of both genetic and epigenetic mechanisms in the pathogenesis and progression of OSCC. Epigenetic markers, particularly miRNAs and DNA methylation changes, are consistently reported as potential diagnostic and prognostic tools. However, a noticeable gap exists in the literature regarding genetic studies in OSCC, indicating the need for more comprehensive investigations. Future research should focus on large-scale, multi-omics approaches and non-invasive biomarker discovery to facilitate early detection and improve patient outcomes.

Introduction

Oral squamous cell-carcinomas (OSCC) account for almost 90% of all oral cancers, making it one of the most prevalent cancers of the head-neck region. With especially high rates of morbidity and mortality in South and Southeast Asia, it is a major global public health concern. Due in significant part to late-stage

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detection, tumor heterogeneity and treatment resistance, the five-year survival rate for OSCC patients is still around 60% despite advancements in diagnostic techniques and therapeutic approaches.[1]

Alcohol and cigarette use are known risk factors for OSCC that may accelerate the growth of the tumor by raising the rate of DNA damage.[2] Understanding the molecular causes of OSCC, particularly the genetic and epigenetic processes that contribute to its onset and progression, has gained more attention in recent years. These molecular changes provide new targets for therapeutic intervention in addition to acting as possible indicators for prognosis and early identification.[2,3] Mutations in DNA repair genes, tumor suppressor gene-inactivation, oncogene-activation, and other associated variables are all part of the carcinogenesis process. Point mutations, deletions, amplifications, and methylation on the promoter of these genes are among the genetic alterations that result in the activation of oncogenes and the inactivation of tumor suppressor genes.[3]

The histological evaluation, which has not altered in decades and is centered on changes in cellular and tissue phenotypes, forms the foundation for both diagnostic processes and treatment choices.[4] Noncoding RNAs, such as microRNAs (miRNAs), may be employed as cancer biomarkers since they are implicated in the biology, evolution, and progression of cancer. Targeting oncogenes and tumor suppressor genes, altered expression of particular miRNAs contributes to the development of various cancer types. Tumor development, invasion, apoptosis, and immune response are all impacted by this.[5]

Research on epigenetic regulation especially through non-coding RNAs has become increasingly important. Tumor suppressors and oncogenes are two different functions of microRNAs (miRNAs), which are tiny non- coding RNAs that alter expression of genes after transcription. Numerous investigations have revealed that OSCC has changed miRNA profiles. Certain miRNAs, such miR-99b-3p and miR-100-5p, have been identified as potential markers of prognosis by Gombos et al. and Jakob et al., who showed different miRNA expression patterns in OSCC tissues compared to normal mucosa. [4,5]

Circular-RNAs (circ-RNAs) and long non-codingRNAs (lnc-RNAs) might also be important in regulating the progression of OSCC. Hanet al. demonstrated that hs a_circ_007 2387 suppresses OSCC growth, metastasis and glycolysis by down-regulating miR503 5p, indicating that circ-RNAs have a tumor-suppressive function in OSCC.[6] By downregulating miR-122 and upregulating RhoA, Tian et al. discovered that LINC00974 accelerates the progression of OSCC, highlighting the lncRNA–miRNA axis as a crucial regulatory mechanism. [7]

It has been estimated that about 60% of human genes are regulated by miRNAs. Numerous biological processes including the cell cycle, development, differentiation, metastasis, metabolism, and others are closely linked to the expression profiles of miRNAs.[8] Finding the impacted biological pathways enables the discovery of biomarkers that could predict the course of a tumor.[9]

Changes in DNA methylation are important drivers of OSCC at the epigenetic level.[10] RECK, or Reversion-inducing cysteine-rich protein with Kazal motifs, is a glycoprotein that is membrane-anchored. RECK stops invasion and metastasis by inhibiting MMP-2/-9 and stopping the extracellular matrix (ECM) from breaking down.[11]

Numerous studies have a narrow focus, looking at specific miRNAs or pathways without taking into account the larger genetic and epigenetic context. A comprehensive synthesis of these research is necessary to obtain a clearer knowledge of the molecular genesis of OSCC.

This systematic review aimed to gather the current information about the genetic and epigenetic changes that contribute to OSCC progression. Further it aims to illustrate the interaction between genetic and epigenetic alterations that propel OSCC progression and their potential as prognostic or therapeutic targets by examining important molecular pathways, gene expression patterns and regulatory RNAs.

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Aim and Objectives

Aim

To identify and evaluate key genetic and epigenetic markers associated with the progression.

Objectives

To systematically review published literature reporting on genetic and epigenetic modifications associated with OSCC progression.

To analyse molecular implications of genetic polymorphisms and epigenetic regulators in OSCC pathogenesis.

Material and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed in conducting this systematic review, and the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number [#CRD42025637017]. The eligibility criteria were based on PICO (population, intervention, comparators and outcomes) as follows:

Population(P):

Human participants diagnosed with OSCC, including studies utilizing tissue samples, blood, or cell lines derived from OSCC patients.

Intervention(I):

Investigations focusing on genetic alterations (e.g., gene polymorphisms, mutations, expression levels of oncogenes/tumor suppressor genes) and epigenetic mechanisms (e.g., DNA methylation, miRNA, lncRNA, circRNA expression, histone modifications, RNA-mediated silencing) associated with OSCC development, progression, or prognosis.

Comparators(C):

Comparisons between OSCC patients and healthy individuals or adjacent normal tissues.

Outcomes(O):

Identification and characterization of genetic and epigenetic markers linked to OSCC progression.

Inclusion Criteria:

1. Patients diagnosed with Head and Neck Squamous Cell Carcinoma
2. Studies exploring genetic alterations, including gene polymorphisms, mutations, and expression of oncogenes or tumor suppressor genes
3. Studies investigating epigenetic mechanisms, such as DNA methylation, miRNA, lncRNA, circRNA expression, histone modifications, and RNA-mediated gene silencing
4. Original Articles
5. Studies published in English language with full-text availability
6. Articles published from 2000 onward

Exclusion Criteria:

1. Patients diagnosed with Head and Neck Squamous Cell Carcinoma
2. Case reports, editorials, conference abstracts, or letters to the editor
3. Articles lacking molecular data related to genetic or epigenetic changes in OSCC
4. Studies involving non-human models, such as animal or in vitro studies
5. Non-English language publications

Information Sources

A thorough literature search was carried out, encompassing publications published from January 2000 to December 2024, across a number of electronic databases, including PubMed and Scopus. In order to find more relevant studies, the reference lists of pertinent papers were also manually examined.

Search Strategy

Search Strategy were based on PRISMA 2020 guidelines. Systematic literature search was performed across PubMed and Scopus database. The search included all relevant articles published up to December 2024. A combination of Medical Subject Headings (MeSH) terms and free text keywords was

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employed. These included “oral squamous cell carcinoma,” “OSCC,” “genetic alterations,” “epigenetic changes,” “miRNA,” “lncRNA,” “DNA methylation,” and “tumor suppressor genes,” among others. Boolean operators “AND” and “OR” were applied to maximize retrieval of pertinent studies.

Study Selection

Two major databases, PubMed (n = 625) and Scopus (n = 225), were used to conduct a thorough literature search, yielding 850 records in total. Eighty-six distinct records were left for screening after 764 duplicates and unnecessary records were eliminated. Forty-six papers were eliminated after being screened for titles and abstracts because they did not fit the requirements for inclusion. The full-text retrieval of the remaining 40 publications was sought. Following full-text examination, 28 papers were disqualified for review articles, conference abstracts (n = 4), in vitro research (n = 5), and animal studies (n = 9). Eleven papers were ultimately included in the final qualitative synthesis after fulfilling all eligibility requirements.

Data Extraction

To systematically gather pertinent data from each included study, a standardized data extraction form was created. This form included the study design, sample size, features, country in which the study was conducted, the author or authors and the year of publication, the type of genetic or

epigenetic alteration investigated, the analytical methods employed, and the key findings pertaining to the progression of oral squamous cell carcinoma (OSCC).

Risk of bias assessment

The QUADAS-2 technique, which assesses the risk of bias in diagnostic accuracy studies across four important dimensions was used to evaluate the methodological quality of the included research. selection of patients, by assessing the appropriateness of the patient spectrum and selection criteria; index test, by evaluating the conduct and interpretation of the genetic or epigenetic tests under review; reference standard, by determining the quality and applicability of the standard used to confirm OSCC; and flow and timing, by examining the interval between the index test and the reference standard, as well as the handling of patient flow throughout the study.

Result

Study characteristics

Ten studies published between 2000 and 2024 were included. These consisted of observational, case-control, and experimental studies conducted in diverse geographic locations [Table1]

In the majority of the studies reviewed, tissue samples were utilized for the investigation of genetic and epigenetic changes in OSCC. These samples served as the primary source for analyzing molecular alterations associated with the disease [2,4,5,10]. Among the various techniques employed, PCR- based methods were predominant, allowing for the amplification and detailed analysis of specific genetic sequences [3,4,5,6,8,9,11]. Immunohistochemistry followed as the next technique, enabling the visualization and localization of proteins of interest within tissue.

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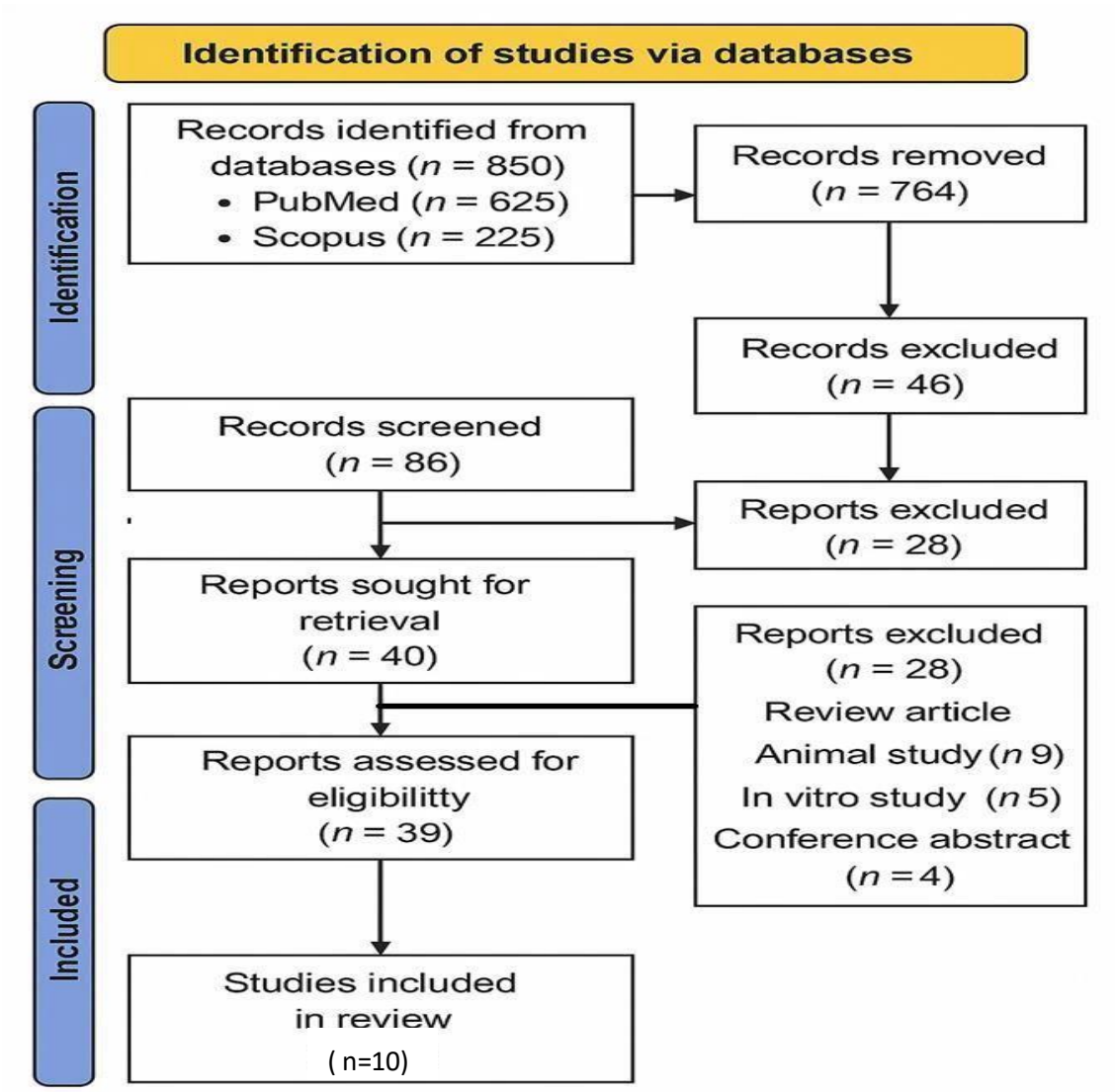
Additionally, studies incorporated in Palmieri et al. reported a significant association between the MIR146A polymorphism and increased susceptibility to OSCC, indicating a possible genetic predisposition[2]. Yeh et al. observed promoter hypermethylation of tumor suppressor genes such as *P15, P16, VHL*, and *TP53* in OSCC tissues, implicating epigenetic silencing in tumor development[3]. Jakob et al. found differential expression of miRNAs, where high *miR-99b-3p* expression was associated with improved survival results, while a worse prognosis was associated with higher expression of mi R100 5p[5].

Han et al. demonstrated that the circular RNA *circ_0072387* inhibits OSCC cell proliferation and metastasis by downregulating *miR-503-5p*, highlighting a regulatory axis involved in tumor suppression[6]. Tian et al. reported that the long non-coding RNA *LINC00974* promotes OSCC progression through modulation of the *miR-122/RhoA* signaling axis[7]. Jia et al. showed significant downregulation of *miR-148a* in OSCC tissues, where restoration of its expression inhibited cell proliferation and migration[8].Both genetic changes and epigenetic changes play important roles in the pathogenesis and progession of OSCC.



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	Author (Year)	Study Design	Sample Size	Population	Key genetic and epigenetic	Comparator	Outcome Measures	Key Findings	Country
1.	Palmieri et al. (2014)	Case-Control Study	Not specified	OSCC patients and healthy controls	MIR146A Polymorphism	Healthy controls	Association between MIR146A polymorphism and OSCC risk	MIR146A polymorphism is significantly associated with increased susceptibility to OSCC, suggesting a genetic predisposition.	Italy
2	Yeh et al. (2003)	Observational Study	Not specified	OSCC tissue samples	Promoter Hypermethylation of P15, P16, VHL, TP53	Adjacent normal tissues	Methylation status of tumor suppressor genes	Methylation-induced silencing of tumor suppressor genes contributes to OSCC pathogenesis.	Taiwan
3	Gombos et al. (2013)	Observational Study	29 OSCC tumors and 7 normal tissues	OSCC patients	miRNA Expression Profiling	Normal oral mucosa	Differential expression of miRNAs	Identified unique miRNA profiles in OSCC tissues, suggesting roles in tumor development and progression.	Hungary
4	Jakob et al. (2019)	Observational Study	36 OSCC tissue	OSCC patients	miR-99b-3p and miR-	Healthy oral mucosa	Correlation of miRNA	High miR-99b-3p expression	Germany

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			s and 17 normal tissues		100-5p Expression		expression with clinical variables	associated with better survival; high miR-100-5p expression correlated with poorer survival.	
5	Han et al. (2021)	Experimental Study	Not specified	OSCC cell lines	circ_0072387 and miR-503-5p Interaction	N/A	Cell proliferation, metastasis, and glycolysis assays	circ_0072387 suppresses OSCC cell proliferation and metastasis by downregulating miR-503-5p.	China
6	Tian et al. (2021)	Experimental Study	Not specified	OSCC cell lines and tissues	LINC00974 / miR-122 / RhoA Axis	N/A	Tumor progression assays	LINC00974 promotes OSCC progression by sponging miR-122, leading to upregulation of RhoA.	China
7	Jia et al. (2020)	Observational Study	110 OSCC patients	OSCC patients	miR-148a / IGF-IR Interaction	N/A	miR-148a expression levels and clinical characteristics	miR-148a is significantly downregulated in OSCC tissues; restoration inhibits cell proliferation and migration.	China

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8	Chamorro Petronacci et al. (2019)	Observational Study	8 OSCC patients and 8 healthy controls	OSCC patients and healthy controls	miRNA Biomarkers	Healthy controls	miRNA expression profiles	Identified deregulated miRNAs in OSCC; potential as diagnostic and prognostic biomarkers.	Spain
9	Jäwert et al. (2013)	Observational Study	Not specified	OSCC tissue samples	5hmC and TET2 Expression	Adjacent normal tissues	Levels of 5hmC and TET2	Loss of 5hmC and TET2 expression indicates epigenetic dysregulation in OSCC.	Germany
10	Pramanik et al. (2016)	Experimental Study	Not specified	OSCC cell lines and tissues	RECK / GSK3 Signaling Pathway	N/A	RECK expression and cell invasion assays	Aberrant GSK3 activity downregulates RECK, enhancing OSCC invasion and angiogenesis.	India

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for the risk of bias and assessment of the applicability of the studies included in the review

Table: 2-

References	Risk of bias				Applicability concerns		
	Data selection	Index test	Reference standard	Flow & timing	Data selection	Index test	Reference standard
Fredrik Jawert et al 2013	+	−	?	?	+	+	?

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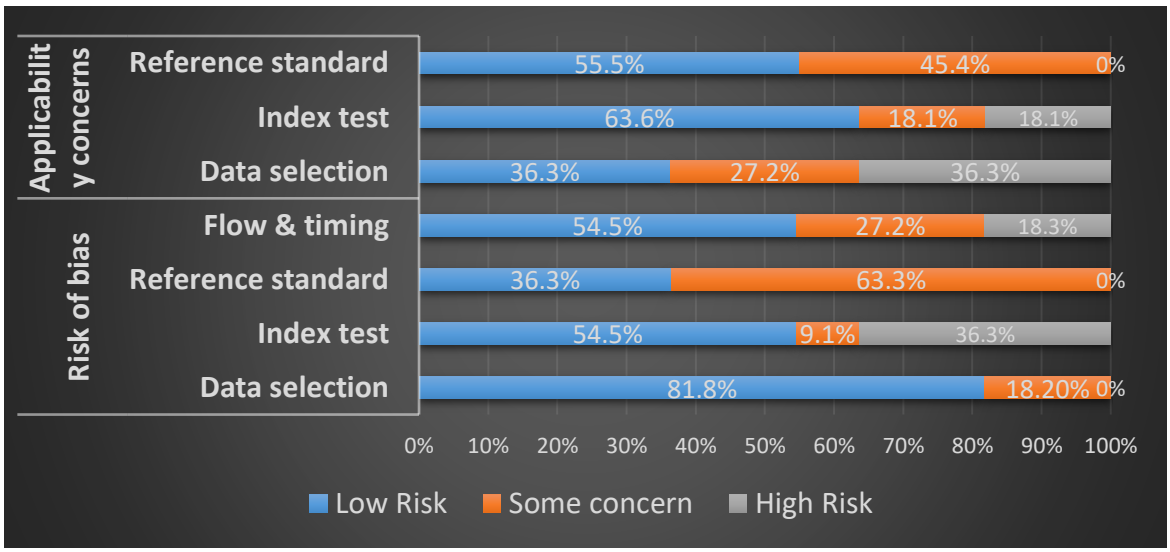
Katalin Gombos et al 2013	+	+	?	+	?	+	+
Palmieri A. et al 2014	+	−	?	+	−	+	+
Cintia M C Petronacci et al 2019	+	+	+	−	?	−	?
Long Han et al 2020	+	+	+	+	+	?	+
Yanyan Tian et al 2019	?	+	?	?	+	+	?
Kamdeo Pramanik et al 2016	+	+	+	+	+	−	+
Tingting Jia et al 2020	?	?	?	?	−	?	?
Mark Jacob et al 2019	+	−	?	+	−	+	+
Kung Tu Yeh et al 2003	+	−	?	+	−	+	+
Hyunga Sung et al 2021	+	+	+	−	?	−	?

+/green color: low risk of bias; ?/yellow color: some concerns; −/red color: high risk of bias



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Quality assessment of the studies

The quality of the various studies varied greatly, with scores ranging from 10 to 40 out of a possible 42 for the QATSDD. 28.0 (6.1) was the average score. The mean score for each of the 14 quality assessment categories is displayed in the table. A total potential score of 3 means that all of the papers fully met the criteria, while a mean score of 0 indicates that none of the papers met all of the criteria's components.

Quality Criteria	Mean Score (SD, Range)
Evidence of user involvement in design	**1.1 (0.2, 0-0.9)**
Explicit theoretical framework	**1.4 (0.4, 0.3-1.6)**
Evidence of sample size considered in terms of analysis	**1.1 (1.1, 0-3)**
Statistical assessment of reliability and validity of measurement tools	**1.3 (0.9, 1-3)**
Strength and limitations critically discussed	**1.9 (1.3, 0-3)**
Good justification for method of analysis	**2.2 (1.2, 0-3)**
Clear description of research setting	**1.9 (1.6, 1-3)**
Description of procedure for data collection	**2.6 (1.1, 1-3)**
Statement of aims/objectives in body of report	**2.4 (0.9, 1-3)**
Detailed recruitment data	**1.8 (1.3, 1-3)**
Representative sample of reasonable size	**2.7 (0.9, 1-3)**
Rationale for choice of data collection tool	**2.5 (1.1, 1-3)**
Fit between research question and method of analyis	**2.6 (1.2, 1-3)**
Fit between research question and method of data analysis	**2.5 (1.1. 1-3)**

The included studies adequately addressed a number of quality criteria, particularly the alignment between the study topic and the data collecting and analyticed methodology. However, there was no proof of user input in the design in any of the included articles, and most of the investigations lacked a clear theoretical foundation. The methods used to estimate the sample size and evaluate the validity and reliability of the measurement instruments were two additional areas that received less attention Overall agreement amongst independent reviewers of 241 out of 280 (86.07%) quality criteria scores was found for the quality assessment. However, a weighted kappa was also used to determine relative concordance across reviewers because quality rating was an ordered variable. Individual variances in quality scores were believed to be equal. Significant to perfect agreement was shown by the inter-rater agreement (kappa with linear weighting), which was 0.835 (95% CI, 0.74–0.92)

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Discussion

Current research on the genetic and epigenetic changes linked to the Progression of oral squamous cell carcinoma (OSCC) is compiled in this comprehensive review. The comparatively poor survival rate among patients with OSCC is largely due to its strong tendency to spread through the lymphatic system [13,21-23].The results show the complex relationship between genetic and epigenetic changes, underscoring the diverse character of OSCC etiology. A significant contributing factor to the development of OSCC is genetic predisposition. The impact of genetic polymorphisms was examined by Palmieri et al. with a focus on microRNA (miRNA) genes, which are important post-transcriptional regulators of gene expression.[2]

The MIR146A polymorphism's function in regulating inflammation and carcinogenesis was emphasized by their investigation. Significantly higher vulnerability to OSCC was shown to be connected with the MIR146A polymorphism, indicating a genetic predisposition that interacts with environmental carcinogens.[2]

Epigenetic mechanisms which control gene expression without changing the DNA sequence have received attention. The strategies include RNA-mediated gene silencing, histone changes and DNA methylation. The most thoroughly researched of these is DNA methylation. Tumor suppressor genes like P15, P16, VHL and TP53 were found to be silenced by methylation in OSCC samples in a seminal work by Yeh et al. It has been demonstrated that these epigenetic changes interfere with important processes related to DNA repair, apoptosis and cell cycle regulation which promotes malignant transformation.[3] Among the most thoroughly studied DNA methylation events in head and neck carcinogenesis are are p16, DAPK, and TIMP3 abnormal methylations. P16 plays a key role in regulating cell growth, and it has been proposed that p16 methylation could be involved in the early phases of the development of head and neck cancer.[12] This is corroborated by the discovery of p16 methylation in both tumor-derived and immortalized non-tumor cell lines. Consequently, it has been suggested that the high recurrence rates in patients with HNSCC may be explained by p16 methylation in distant mucosal areas.[12]

The epigenetic landscape of OSCC was further elucidated by microRNA expression profiling. Several miRNAs were reported to be highly disrupted in a study by Gombos et al. to evaluate differential miRNA expression in OSCC tissues. While some of these miRNAs were downregulated and often suppressed oncogenic pathways, others were upregulated and inhibited tumor suppressor genes, acting as oncogenes. These results highlighted how, depending on the biological setting, miRNAs can function as both tumor suppressors and oncogenes.[4]

In keeping with this review, Jakob et al. discovered that hsa-miR-99b-3p and hsa-miR-100-5p may be predictive biomarkers for OSCC. When compared to normal mucosa, their expression was shown to be significantly lower in OSCC tissues and lower expression levels were linked to a shorter overall survival rate. These miRNAs are attractive candidates for targeted treatment approaches and prognosis tools because they may control pathways related to cellular proliferation and differentiation.[5]

Circular RNAs (circRNAs), in addition to miRNAs, have become important regulators in the biology of cancer. In investigation of hsa_circ_0072387's function in OSCC, Han et al. discovered that it was downregulated in tumor tissues.[6] Through the downregulation of miR-503-5p, a known oncogenic miRNA, functional experiments showed that this circRNA decreased OSCC cell proliferation, metastasis and glycolysis. The significance of non-coding RNA networks in metabolic reprogramming and tumor growth was clarified by this study.[6] Tian et al. looked into the role of lncRNA LINC00974 in OSCC and showed that it promotes tumor progression by acting as a molecular sponge for miR-122 which results in the upregulation of RhoA, a small GTPase involved in cytoskeletal rearrangement and metastasis. It has been demonstrated that long non-coding RNAs (lncRNAs), or transcripts longer than 200 nucleotides, control gene expression in a number of ways. This finding highlights the significance of the

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lncRNA-miRNA-mRNA axis in promoting OSCC invasiveness.[7]

Additionally, Jia et al. investigated miR-148a's tumor suppressor role in OSCC. According to their findings, miR-148a targets IGF-IR, a receptor implicated in the ERK/MAPK signaling cascade, was markedly downregulated in OSCC tissues. OSCC cell migration and proliferation were suppressed when miR-148a levels were restored, indicating that it may have therapeutic potential. The contribution of dysregulated miRNA expression to aberrant signaling cascades that facilitate carcinogenesis was highlighted in this work.[8] Chamorro Petronacci et al. assessed the expression of specific miRNAs in tumor and normal samples in an attempt to verify miRNA biomarkers in OSCC. Their results demonstrated that particular miRNAs were regularly dysregulated in OSCC, suggesting that they could be used as prognostic and diagnostic biomarkers. These kinds of investigations are essential for turning molecular discoveries into instruments that may be used in clinical settings.[9]

Conversely, DNA hypermethylation contributes to cancer development by inactivating tumor suppressor genes and hindering DNA repair mechanisms. This occurs through the addition of methyl groups to CpG islands within gene promoter regions[16]. In the context of oral cancer, studies have documented the hypermethylation-induced silencing of over 40 tumor suppressor genes, affecting key cellular processes such as cell cycle regulation, programmed cell death (apoptosis), and intercellular adhesion.[17,18] In contrast, frequently observed histone modifications in HNSCCs and Oral Potentially Malignant Disorders include acetylation, methylation, phosphorylation, parylation, and ubiquitination.[19] Unlike DNA methylation, which typically silences gene expression, these histone alterations can also enhance gene transcription.[19] Studies on cancer cells have shown that reduced levels of histone modifications are often associated with more aggressive tumor behavior.[20]

DNA demethylation processes are crucial for preserving epigenomic stability in addition to RNA-based epigenetic changes. The depletion of the enzyme TET2 and 5-hydroxymethylcytosine (5hmC) in OSCC tissues was documented by Jäwert et al. A crucial stage of DNA demethylation, the conversion of 5-methylcytosine to 5hmC, is carried out by TET2. The decrease in 5hmC levels and TET2 expression indicate extensive epigenetic dysregulation in OSCC, which may be a factor in the development of malignant transformation.[10] The epigenetic regulation of tumor suppressor genes is also linked to genetic signaling networks. Pramanik et al. showed that glycogen synthase kinase 3 (GSK3) signaling controls the expression of RECK, a recognized metastasis suppressor gene. Increased OSCC cell invasion and angiogenesis resulted from the downregulation of RECK brought on by abnormal GSK3 activity. The findings opened up new therapeutic targeting possibilities by highlighting the relationship between epigenetic control and genetic signaling pathways.[11]

Overexpression of specific genes, such as IFIT1 and IFIT3, has been linked to metastasis in OSCC patients, according to a number of studies, including those by Pidugu et al. Pidugu notes that both in vitro and in vivo, increased expression of IFIT1 or IFIT3 contributes to tumor growth and distant and regional metastatic activities.[13] Through the epigenetic control of the MMP2 gene, Yamamoto et al.[14] showed that BRD4 cell line levels were increased in OSCC patients and were often linked to metastasis. Sakata et al.[15] showed how HMGA2 regulates genes linked to angiogenesis in OSCC and influences clinical outcomes. According to Sakata data, increased HMGA2 expression might also be a unique potential biomarker for OSCC that might be utilized to forecast prognosis and distant metastases.

This systematic review was conducted in order to fill a major knowledge gap on the molecular pathways underlying the advancement of OSCC. Due in large part to late-stage diagnosis and high recurrence rates, the prognosis for OSCC is still dismal despite improvements in surgical and therapeutic approaches. Recent data i
dysregulation and genetic
DNA methylation, miRNA, lncRNA, and circRNA changes, are important factors in the development and spread of OSCC. These results, however, are dispersed throughout many studies with different

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approaches and findings. In order to help identify possible diagnostic, prognostic and therapeutic targets, this review attempted to provide a consolidated picture of important genetic and epigenetic biomarkers linked to OSCC by synthesizing this review.

It is important to recognize a number of limitations even if this systematic study offers insightful information about the molecular landscape of OSCC. The review is noticeably unbalanced, with a disproportionately greater number of research concentrating on epigenetic modifications as opposed to genetic ones. A thorough assessment of genetic variants' contribution to OSCC progression is hampered by the paucity of available data. Direct comparisons and meta-analysis were hampered by methodological heterogeneity, which included differences in sample types (tissue, blood, saliva), detection methods (PCR, IHC, arrays), and study design. It is limited to 10 selected studies focusing on genetic and epigenetic alterations in OSCC, potentially narrowing the scope of conclusions. In this most studies analyzed tissue samples, with limited exploration of non-invasive sources such as saliva or blood, which are crucial for clinical applicability.

The review emphasizes how crucial genetic and epigenetic biomarkers are becoming for OSCC early identification, prognosis, and treatment targeting. The available information is still developing, though, and further research is necessary in a few crucial areas. Standardizing procedures should be the goal of future research, especially with regard to biomarker detection methods, sample sources (such as tissue, blood, and saliva), and outcome reporting. Better comparisons and possible meta-analyses between research would be made easier as a result. Large-scale, multicentric, and longitudinal studies are necessary to validate the diagnostic and prognostic utility of promising biomarkers such as miR-148a, LINC00974 and circ_0072387. Integration of multi-omics data (genomic, epigenomic, transcriptomic) in OSCC research could also enhance our understanding of tumor heterogeneity and lead to personalized treatment strategies.

Clinically, OSCC diagnosis in high-risk populations may be transformed by the conversion of epigenetic markers into non-invasive screening instruments, such as those obtained from saliva or mouth brushings. Furthermore, although their safety and effectiveness in OSCC have not yet been thoroughly assessed, the possibility of reversing epigenetic modifications using small-molecule inhibitors presents intriguing therapeutic opportunities.

Conclusion

This systematic study emphasizes how genetic and epigenetic changes are important to the onset and spread of oral squamous cell cancer. Tumor suppressor genes, oncogenes, and important signaling pathways are modulated by DNA methylation, miRNAs, lncRNAs, circRNAs, and genetic polymorphisms, according to evidence from the chosen research. Tumor initiation, progression, metastasis, and resistance to treatment are all influenced by these molecular changes.

Interestingly, more number of studies have been done on epigenetic indicators than on genetic ones, indicating a research gap that needs to be filled. Despite limitations such as variations among study designs, sample kinds, and analytical methods, the results highlight the molecular markers' capacity for diagnosis and prognosis. Prospective pathways for early identification, risk assessment, and tailored therapy in OSCC may be provided by future advances in high-throughput and non-invasive biomarker technologies, which would eventually enhance clinical results and patient care.

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