Review Article

Biomarkers in Head-and-neck Cancer: A Scoping Review

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Abstract

Head-and-neck cancers (HNCs) refer to a diverse group of cancers that originate in the soft tissues of the head-and-neck area. This category includes all tumors that start in areas such as the oral cavity, pharynx, larynx, thyroid gland, and cervical esophagus. The application of biomarkers in managing HNCs has grown significantly due to advances in genomics, proteomics, transcriptomics, and related technologies. These biomarkers are valuable for the early diagnosis of head-and-neck squamous cell carcinoma (HNSCC) and play a crucial role in enhancing patient outcomes. HNSCC develops through a series of stages marked by the accumulation of phenotypic and genetic alterations. Identifying particular biomarkers is crucial for specifying the various stages of cancer, making it essential for managing HNSCC. The absence of appropriate biomarkers for monitoring disease progression can result in a poor prognosis due to late-stage diagnosis. The objective of this review is to highlight emerging biomarkers relevant to HNSCC, covering primary locations such as the oral cavity, oropharynx, hypopharynx, larynx, and thyroid.

Keywords: Biomarker, head-and-neck cancer, laryngeal carcinoma, nasopharyngeal carcinoma, thyroid carcinoma

Introduction

Head-and-neck squamous cell carcinomas (HNSCC) are cancers that arise from the squamous cell layer lining the oral cavity, pharynx, larynx, and the upper part of the esophagus.[1] The important risk factors for HNSCC include smoking, and alcohol consumption, which are responsible for causing malignancy at the oral cavity, pharynx, and larynx.[2] Another risk factor for oropharyngeal cancer is human papillomavirus (HPV). Smoking and/or alcohol-induced HNSCC and HPV-related oropharyngeal cancer are two different entities with different clinical and molecular features.[3] Gaining a more profound understanding of the molecular biology behind HNSCC provides important insights into how malignant disease develops and advances. This knowledge also introduces different biomarkers that could be used for screening head-and-neck cancer (HNC) and for monitoring treatment responses.[4] In addition to tissue biopsies, body fluids such as blood, serum, urine, and saliva play a crucial role in recent testing methods for HNC. Measuring protein levels in these fluids has been extensively studied and is regarded as a crucial diagnostic technique for detecting the disease.[5] A biomarker is a specific cellular, biochemical, molecular, or genetic alteration that is linked to a biological or pathological process.[6] These changes can be identified and are typically measurable in tissues, cells, or body fluids.[6]

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Methods of Literature Search

The search was done for recent research articles on the biomarkers in HNC. First, we conducted a search of the PubMed, Scopus, Medline, and Google Scholar databases online. We developed our search strategy based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The published works' abstracts were identified by our search method, although more research publications had to be manually located from the citations. A variety of study designs were looked at, such as case reports, case series, comparative studies, observational studies, and randomized controlled trials. There were 11 case reports, 18 case series, and 34 research papers in all [Figure 1]. The aim of this review article is to focus only on the biomarkers in HNC. A better knowledge of the biomarkers in HNC is provided by this review analysis. It will also catalyze further study and better awareness about the biomarkers in HNC which is helpful for early detection and treatment of HNC.

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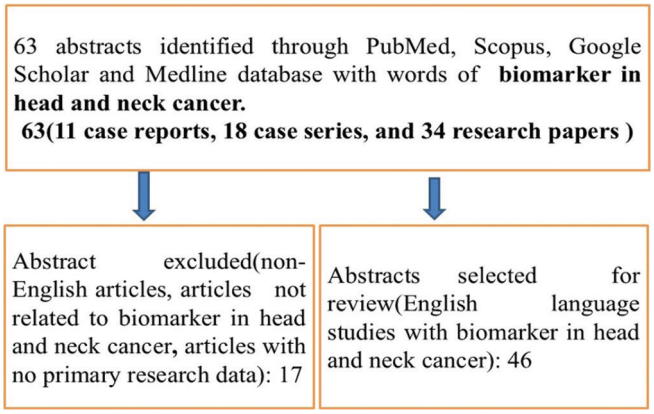

Figure 1: Method of literature search

Epidemiology

About 90% of HNCs are squamous cell carcinomas, which originate from the epithelial cells lining the mucosal surfaces of the upper aerodigestive tract. This type of cancer is commonly referred to as HNSCC.[7] Globally, HNSCC represents 6% of all cancer cases and is the 6th leading cause of cancer-related deaths.[8] HNSCCs are mostly found between 6th and 7th decade of life.[6] While HNSCCs are more common in males, the incidence of this disease is increasing among both young people and females, largely due to changing lifestyles.[9] The 5-year survival rate for HNSCC is around 50%, primarily influenced by the stage of the tumor at diagnosis.[9]

Etiopathogenesis

The primary risk factors responsible for developing HNSCC include addiction to smoking or using chewing tobacco, consuming alcohol, using smokeless tobacco products, and having a genetic tendency.[9] Chronic smoking and alcohol consumption have a synergistic effect, which means that their combined influence on risk is greater than the total of their separate effects.[10] HPV is considered a major contributor to HNSCC. In the United States, roughly 40%–80% of oropharyngeal tumors are associated with HPV infection. In European countries, the occurrence of HPV-related cancers reveals a significant variation, with around 90% in Sweden and approximately 20% in nations with high tobacco consumption.[11] Furthermore, HPV-positive HNSCC can be sexually transmitted, with a significant link identified between HPV-16-positive HNSCC and oral sex.[12] HPV-related HNSCCs are mainly found in the lingual and palatine tonsils, as HPV specifically targets the specialized reticulated epithelium of the tonsillar crypts.[13] In comparison, Epstein–Barr virus (EBV) is recognized as a causative factor for nasopharyngeal carcinoma (NPC).[14] Some inherited disorders, such as Fanconi anemia, can increase the risk of developing HNSCC.[15]

Biomarkers

Tumor biomarkers can be represented by a variety of substances, including messenger RNAs (mRNAs), DNA, and proteins, as well as carbohydrates, small molecules such as metabolites, and other cellular molecules.[16] Biomarkers can include individual molecules, combinations of several molecules, or distinct molecular profiles. In the early detection of HNSCC, certain biomarkers such as p53 mutations, loss of heterozygosity on chromosomes 3p, 9p, 17p, and 18q, as well as promoter hypermethylation identified in saliva, can be especially valuable.[16] The detection of telomerase activity in saliva can serve as a molecular biomarker for the early detection of HNSCC in individuals at high risk.[17] Salivary interleukin-8 (IL-8) and melanoma-associated antigens show strong sensitivity and specificity for early identification of HNSCC.[18] Numerous protein biomarkers [Table 1] have been identified in tissue, serum, and saliva samples from patients with HNSCC.[19] The secreted tumor proteins can trigger the production of autoantibodies, which may be detectable from the patient's serum.

Oral Cancer

Developments in molecular technology are making it possible to use nucleic acid molecules as potential noninvasive diagnostic biomarkers. These genetic materials can be amplified from minimal quantities, allowing for precise detection through the pairing of complementary nucleotides.[20] Diagnosis is based on genetic materials and is considered the gold standard for many diseases.[21] RNA biomarkers, including microRNAs (miRs), are believed to play oncogenic or tumor-suppressive roles by targeting specific genes. For instance, miR-345 and miR-31-5p are found to be upregulated in patients with oral cancers.[22] Both circulating-free DNA in plasma and circulating tumor DNA in saliva are considered effective DNA biomarkers for detecting HPV-positive oral squamous cell carcinoma.[23] DNA biomarkers are crucial for detecting oral squamous cell carcinoma and can be used to identify both HPV-positive and HPV-negative cases. One study identified elevated levels of fibronectin alpha and beta chains, fibronectin-1, and serum amyloid A-1 in patients with oral squamous cell carcinoma.[24]

Nasopharyngeal Cancer

Biomarkers associated with NPC progression and neck node metastasis enhance our understanding of the disease, individual susceptibility, and the prediction of a patient's response to treatment.[25] Molecular biomarkers related to the risk factors for NPC include EBV, ethnic background, and the intake of foods containing volatile nitrosamines.[26] The genetic variation in the nitrosamine-metabolizing gene CYP2A6 may be crucial in determining susceptibility to NPC and could serve as a risk marker for the disease.[27] Numerous potential molecular biomarkers for NPC have been identified, including DNA (genomic), mRNA (transcriptomic), protein (proteomic), and metabolite (metabolomic) markers. Abnormal expression of miRNAs is linked to NPC development due to their impact on the regulation of various genetic pathways, thereby affecting cell cycles.[28] The tumor produced oncogenic proteins that can provide real-time insights into the disease's state and aid in

Table 1: Biomarkers of head-and-neck squamous cell carcinoma and their use

Biomarkers	Purpose	Use/application
BCL-2, GST-pi, p53, bax expression	HNSCC	Detect pathological response and prognosis
Alpha-1-antichymotrypsin and factor XIIIa	Oral cavity-giant cell lesion	Diagnostic
Cytokeratin-CK19, CK8	Oral SCC	Premalignant lesion
Beta 2-microglobulin	Oral submucous fibrosis, oral cancer	Diagnostic
CD44	Oral SCC	Low CD44=Reduced survival
CD80	Adenoid cystic salivary tumors	Low CD80=High tumorigenicity
CD105	Adenoid cystic salivary tumors	CD105 in vessel=Metastatic risk
Cathepsin-d	Metastatic neck node in HNSCC	Prognostic
CEA, CA19-9, CA125, SCC-Ag	CEA in adenoid cystic carcinoma CA125 in oral SCC Cyfra 21-1 in oral SCC	Diagnostic
TGF-alpha	HNSCC	Increased relapse and adverse survival
C-erb2	Oral SCC	Progression-free survival and overall survival reduced in recurrent HNSCC
Cyclin D1, Ki6758, MIB	Ora SCC, precancerous lesion	Surrogate biomarkers in chemoprevention trial, prognosis
Carbohydrate associated antigens	Biomarkers of salivary glandular differentiation	Diagnostic

SCC: Squamous cell carcinoma, SCC-Ag: SCC antigen, HNSCC: Head-and-neck SCC, TGF: Transforming growth factor, CEA: Carcinoembryonic antigen, MIB: Minimally invasive biomarker

NPC biomarker research. Measuring EBV DNA levels along with BARF1 mRNA detection in nasopharyngeal brushings enables noninvasive diagnosis of NPC.[29] It indicates that EBV involvement specific to carcinoma is localized to the tumor's origin, reducing the necessity for invasive biopsies. This approach is beneficial for confirming diagnoses in extensive serological screening programs for NPC.[30] The nasopharyngeal swab, when combined with polymerase chain reaction (PCR)-based detection of EBV *LMP-1* and *EBNA*, can be a valuable complement to the pathological diagnosis of NPC.[31]

Oropharyngeal Cancer

Malignancies of the oropharynx develop in the palatine tonsils, tongue base, soft palate, and posterior wall of the pharynx. Most of these cancers originate from squamous cells in the mucosal lining of the epithelium and are referred to as oropharyngeal squamous cell carcinoma.[32] Cancers of the oropharynx caused by HPV typically have a positive prognosis. However, 20%–25% of patients may experience recurrence within 5 years of treatment, and most of these individuals eventually succumb to their disease.[33] The presence of HPV DNA or its surrogate marker, the p16 protein, is linked to a more favorable prognosis for oropharyngeal squamous cell carcinoma.[33]

Hypopharyngeal Carcinoma

Hypopharyngeal squamous cell carcinoma is the predominant type of malignancy in the hypopharynx, representing approximately 5% of HNSCC.[34] Due to its unique anatomical location, hypopharyngeal squamous cell carcinoma is often not detected in its early stages, leading most patients to be diagnosed only at advanced stages.[35] The biomarker such as circRNA is an ideal molecular marker for cancer of the aerodigestive tract including the hypopharynx.[36] The demonstration of circMORC3 expression levels is significantly lower in hypopharyngeal in comparison to normal tissues.[37] CircMORC3 expression levels in the plasma from hypopharyngeal carcinoma patients are usually detected by quantitative reverse transcription PCR.[37]

Salivary Protein Biomarkers

Saliva of human beings is a complex biofluid containing various molecules such as DNA, RNA/miRNA, proteins, and metabolites, along with alterations in microbiota. These elements may act as potential biomarkers for identifying HNCs. Among these, IL-6 is the most thoroughly studied protein in the saliva of patients with HNC. IL-6 cytokines play a crucial role in inflammation and are involved in regulating processes such as differentiation, proliferation, migration, and apoptosis of target cells.[38] The levels of IL-6 in saliva are higher in older patients compared to younger individuals with HNSCC.[39] In addition, smokers exhibit higher levels of IL-6 in their saliva than nonsmokers.[40] Patients with oral squamous cell carcinoma have higher levels of IL-1β in their saliva compared to those with potentially malignant lesions such as leukoplakia and erythroplakia.[41] IL-10 is a cytokine found at elevated levels in the saliva of patients with HNSCC. It plays a role in regulating the immunosuppressive and anti-inflammatory properties of cells.[42] Matrix metalloproteinase 9 (MMP-9) is present at higher levels in the saliva of patients with oral squamous cell carcinoma compared to those with leukoplakia or healthy individuals.[43] MMP-9 is associated with cancer pathology, including processes such as invasion, metastasis, and angiogenesis.[43]

Second Primary Tumors

Patients with HNSCC face a heightened chance of developing a second primary cancer, which is often linked to poor prognosis

and early mortality. The presence of these second primary tumors significantly contributes to reduced life expectancy in HNSCC patients. On average, there is about a 4% annual risk for these patients to develop a second primary tumor.[44] These second primary tumors are believed to arise due to a phenomenon known as "field cancerization," where the entire area of the mucosa is exposed to carcinogenic factors, leading to multiple areas of precancerous changes and tumor development.[45] Identifying biomarkers associated with field cancerization and developing targeted strategies to prevent disease recurrence or the emergence of second primary tumors is crucial. The combination of the genes ITPR3 and DSG3 is frequently linked to the development of second primary malignancies. DSG3, a component of cell–cell junctions, is overexpressed in HNSCC, and its inhibition has been shown to suppress tumor growth.[46] DSG3 is also suggested as a potential predictive biomarker for neck node micrometastasis in oral cavity malignancies.[46]

Conclusion

The absence of suitable biomarkers and late presentations of HNSCC are features of poor prognosis. Biomarkers play a crucial role in the early detection of HNSCC and are essential for improving patient outcomes. Serum, plasma, and saliva contain various stable biomarkers with differential expressions that appear specific to certain HNCs. Molecular profiling is highly valuable for predicting tumor behavior and assessing responsiveness to therapy. Identifying specific biomarkers is crucial for characterizing each type of HNSCC. However, more research is needed to validate the sensitivity and specificity of these biomarkers for early detection of HNSCC.

Author's statement

This review was conducted in accordance with the principles of the Declaration of Helsinki. We ensured that all included studies adhered to ethical standards, including obtaining appropriate ethical approval and informed consent, and the ethical conduct of the cited studies was evaluated.

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Conflicts of interest

There are no conflicts of interest.

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