ABSTRACT

Background: A higher occurrence of oral cancer is observed in South Asian and Southeast Asian countries when compared with other countries in the world. Cancer, a disease with complex pathophysiology, has been linked to chronic inflammation. Inflammation has been considered an important component of tumor initiation and progression. This is supported by the fact that many cancers arise at the sites of chronic inflammation, but the exact mechanism by which inflammation influences cancer is unknown. Purpose: This review article correlates single nucleotide polymorphisms (SNPs), chronic inflammation, and oral cancer. The article emphasizes the critical role that SNPs play in oral cancer susceptibility, progression, and prognosis. This involves discussing the impact of specific SNPs on oral cancer risk and patient outcomes. Review: Gene polymorphism has been documented in the molecular pathogenesis of various cancers, including oral cancer, and SNPs are the most common form of gene polymorphism. Genetic variation has been documented in the molecular pathogenesis of various cancers, including oral cancer, and SNPs are the most common form of gene polymorphism. SNPs have been documented in inflammatory conditions as well as in various diseases. Conclusion: SNPs have phenotypic consequences and therefore can serve as genetic fingerprints. The upregulation or downregulation of genes is able to drive oral carcinogenesis.

Keywords: chronic inflammation; gene polymorphism; oral cancer; SNP

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INTRODUCTION

The pathophysiology of cancer is very complex, and various contributing factors have been documented, including genetic susceptibilities and a wide variety of environmental exposures leading to chronic inflammation. The interrelationship between cancer and inflammation was documented centuries ago by Rudolf Virchow, and the concept of “cancer-associated inflammation” has been acknowledged recently. Chronic inflammation is one of the important molecular changes that assists in the development and progression of cancer. The significance of chronic infections or inflammation in the development of colorectal, lung, gastric, hepatocellular, pancreatic, and cervical cancers is well established. However, the exact mechanism by which inflammation influences cancer is unknown.1,2

Oropharyngeal cancer includes cancerous growths observed in the lip, oral mucosa, nasopharynx, or oropharynx. Geographical variation is observed in both incidence and prevalence rates of oropharyngeal cancer. A higher burden of oral cancer is observed in South Asian and Southeast Asian countries when compared with other countries in the world. The prevalence of oral cancer in India contributes one-third of the global prevalence, which is due to risk factor exposures. According to the World Health Organization (WHO), “657,000 new cases and more than 330,000 deaths due to oral cancer occur each year across the globe.” One-fourth of the global incidences of new cases and deaths are reported annually in India.3,4
Research studies have documented that chronic inflammation can predispose oral cancer formation by analyzing inflammatory cells in the biopsied specimens from oral cancerous tissue. One study investigated samples of various grades of dysplasia and oral squamous cell carcinoma (OSCC), and their findings show a significant relationship between the inflammatory cellular infiltrate and the severity of dysplasia and OSCC. Another study demonstrated dense inflammatory cell infiltrate in both well- and moderately-differentiated grades of OSCC, whereas there is a sparse amount of inflammatory infiltrate in a poorly differentiated tumor. Hence, immune cell density in the tumor microenvironment may influence tumor growth, progression, and clinical outcome.

Inflammatory molecules found in oral cancer tissue encompass transcription factors and cytokines, each playing distinctive roles in the context of oral cancer initiation and progression. Transcription factors such as nuclear factor kappa B (NFκB) and signal transducer activator of transcription-3 (STAT3) contribute to the early stages of oral cancer development. Within the tumor microenvironment, pro-inflammatory cytokines, including interleukin 1β (IL-1β), interleukin 23 (IL-23), interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α), exert their influence. Furthermore, a range of additional factors, including TNF-α, prostaglandins, p53, nitric oxide (NO), reactive oxygen species (ROS), nitrogen species, and specific microRNAs (miRNAs), have been identified within this complex milieu. Despite this wealth of information, the precise functions of these inflammatory molecules within the cancer microenvironment remain incompletely understood. Recent research has shed light on the potential role of inflammation, particularly through TNF-α, in influencing cancer invasion, adding to our evolving comprehension of this intricate interplay.

Genetic variability plays a significant role in the molecular pathogenesis of various cancers, including oral cancer, with single nucleotide polymorphisms (SNPs) representing the most prevalent form of gene polymorphism. In particular, inflammatory gene polymorphisms have garnered attention in the context of human tumors. A recent study, for instance, conducted an analysis of polymorphisms in 11 inflammation-related genes (interferon γ, IL-10, IL-1α, IL-1β, IL-2, IL-4R, IL-4, IL-6, PTGS2 (COX-2), TGF-β1, and TNFα) and found that IL-1β promoter polymorphisms may influence the development of lung cancer. Likewise, another study indicates that genetic variations within the inflammation pathway could impact the development of prostate cancer. These investigations underscore the potential significance of inflammatory gene polymorphisms in the initiation and progression of various cancers, a concept that may also hold relevance in the context of oral cancer development. The knowledge gap in this topic, is an incomplete understanding of the precise mechanisms of SNPs and their influence on oral cancer, and how this understanding can be leveraged for more effective prevention, diagnosis, and treatment strategies.

METHODS

The study primarily utilized three widely recognized academic databases for our literature search: PubMed/MEDLINE, Web of Science, and Scopus. These databases were selected due to their comprehensive coverage of biomedical and life science literature, which makes them suitable sources for our research topic. To ensure a rigorous and focused selection of articles, we established specific eligibility criteria that articles had to meet to be included in our review: (1) Relevance to SNPs and oral/oropharyngeal cancer: Articles needed to be directly related to SNPs and their association with oral or oropharyngeal cancer. Irrelevant articles were excluded. (2) Peer-reviewed: We exclusively considered peer-reviewed articles to maintain the quality and reliability of the sources. (3) Publication date: Our search was limited to articles published within the last 10 years to ensure that we included the most recent research in this rapidly evolving field. Our search strategy was designed to be comprehensive while capturing all potentially relevant articles. The search terms we used included variations and combinations of “SNP,” “single nucleotide polymorphism,” “oral cancer,” and “oropharyngeal cancer.” These terms were employed in Boolean searches to identify articles containing these keywords in their titles, abstracts, or keywords. Given the limited number of publications meeting these criteria, we proceeded with the review and analysis of four articles to provide the most accurate and reliable information available within the scope of our research. While we acknowledge that this number may appear limited, it reflects the current state of the literature in this specialized field, and our paper aims to present a concise and focused analysis of these studies.

DISCUSSION

Significance of SNPs

DNA constitutes genomic information and serves as a blueprint of human tissue. DNA can be identified in the nucleus of a cell and also in the mitochondria and chloroplast as membrane-bounded organelles. The function of DNA is to store and transfer genetic information and serve as a regulator of proteins synthesized from a cell. DNA content in the nucleus is termed as genomes, whereas extra-nuclear DNA material is termed extra-chromosomal DNA. This DNA is made up of molecular structures called nucleotides, which consist of a phosphate group, sugar group, and nitrogen base. Genomes of any two individuals demonstrate a variation of approximately 0.1%, and these variations are termed polymorphisms. The variations of nucleotides lead to a change in genotype called mutations. These mutations result from addition, deletion, duplication, inversion, or translocation in a DNA sequence. A genetic mutation with the addition or deletion of a single nucleotide base in DNA is termed a single
nucleotide polymorphism (SNP) (Figure 1). SNP variations are prevalently observed in human DNA with at least 1% variation in any given population, and they are called human DNA polymorphisms.\textsuperscript{16}

SNP variation can be identified in intronic or exonic regions of the genome. SNPs in intronic or noncoding regions have no influence on protein products. Exonic SNPs in coding or exonic regions can alter amino acids or protein length.\textsuperscript{17} Based on the sites where SNPs occur, the alteration of gene products, protein structures, protein quantity, gene splicing, transcription factor binding, or the sequence of non-coding RNA is observed. SNPs cannot directly influence the causation of a disease but significantly influence disease by increasing genetic susceptibility or altering disease progression. They can be used to predict drug interactions, environmental vulnerability, and disease inheritance within families.\textsuperscript{18}

SNPs are classified based on the site of occurrence as rSNP, miR-rSNAm, and srSNP. SNPs observed in protein-coding areas of the genome are termed regulatory SNPs (rSNPs), whereas SNPs in non-coding gene locations are called microRNA regulatory SNPs (miR-rSNPs). SNPs seen in both precursor and mature mRNA structures are called RNA SNPs (srSNPs), whereas microRNA are termed miR-srSNPs. SrSNPs regulate the translation, structure, stability, protein maturation, and function of mRNA. MiR-srSNPs affect splicing and transcript processing by binding miRNA and mRNA to achieve their function roles. SNPs are further classified into two types, namely nonsense nsSNPs and missense nsSNPs. The function of nonsense nsSNPs is to generate stop codons and protein premature termination, whereas missense nsSNPs assist in generating amino acid changes.\textsuperscript{19}

**Methodologies for SNP analysis**

Understanding the role of SNPs in oral cancer requires a multifaceted approach that combines laboratory techniques and bioinformatics tools. This section explores the methodologies used for SNP identification and analysis in the context of oral cancer research.

**Laboratory techniques for SNP analysis**

Genomic DNA extraction: SNP analysis typically begins with the extraction of high-quality genomic DNA from biological samples, such as blood, saliva, or tissue. This DNA serves as the template for subsequent analyses.\textsuperscript{20}

Polymerase chain reaction (PCR): PCR is a fundamental technique used to amplify specific DNA regions containing SNPs. Researchers design primers flanking the SNP of interest, allowing for the selective amplification of the targeted DNA sequence.\textsuperscript{20}

DNA sequencing: Once amplified, DNA fragments can be subjected to Sanger sequencing or next-generation sequencing (NGS) technologies. Sanger sequencing is suitable for analyzing a single SNP or a few SNPs in a small number of samples. NGS, on the other hand, enables high-throughput sequencing of entire genomes or targeted SNP panels in large cohorts.\textsuperscript{21}

Mass spectrometry: Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and other mass spectrometry techniques are employed

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**Figure 1.** The variations of SNPs can be deletion, addition, duplication, inversion, or translocation of the nucleotide.
for genotyping SNPs. These methods can accurately detect and quantify allele-specific signals.20

Restriction fragment length polymorphism (RFLP) analysis: RFLP exploits the fact that SNPs may create or abolish restriction enzyme recognition sites. By digesting DNA with specific enzymes, researchers can identify SNP-related changes in fragment lengths.22

Bioinformatics tools for SNP analysis

Genome databases: Comprehensive genomic databases like the Single Nucleotide Polymorphism database (dbSNP) and the 1000 Genomes Project provide extensive catalogs of known SNPs, including their genomic locations and allele frequencies. Researchers use these resources for reference and comparison.21

SNP annotation tools: Bioinformatics tools like ANNOVAR and SnpEff are used to annotate SNPs. They predict the functional consequences of SNPs, such as whether they are synonymous or nonsynonymous mutations, which affects protein structure and function.21

Linkage disequilibrium (LD) analysis: LD analysis helps identify SNPs that are in close genetic proximity and tend to be inherited together. Haploview and PLINK are commonly used tools for LD analysis.21

Statistical software: Specialized statistical software packages like PLINK and SNPStats are employed to perform association analyses. Researchers use these tools to identify significant associations between specific SNPs and oral cancer risk, prognosis, or treatment response.21

Genome-wide association studies (GWAS) and candidate gene studies

GWAS are a powerful approach to identify SNPs associated with oral cancer susceptibility. In GWAS, researchers analyze hundreds of thousands to millions of SNPs across the entire genome in large cohorts of oral cancer patients and controls. Statistical analyses reveal SNP-disease associations, which can highlight novel genetic markers for oral cancer risk.23

Candidate gene studies, in contrast, focus on specific genes that are known or hypothesized to play a role in oral cancer development. Researchers select candidate genes based on biological relevance and prior evidence. They then genotype SNPs within these candidate genes to assess their association with oral cancer risk or other clinical parameters.24

Both GWAS and candidate gene studies have contributed significantly to our understanding of SNPs in oral cancer. While GWAS can uncover novel susceptibility loci, candidate gene studies offer a more targeted approach to investigating specific genetic pathways implicated in oral carcinogenesis.23,24

Clinical implications of SNPs in oral cancer

The insights gained from investigating SNPs in oral cancer extend beyond the realms of research. Specifically, we discuss the potential for SNP-based risk assessment, early detection strategies, and the development of personalized treatment approaches. These clinical applications represent a promising avenue for improving oral cancer diagnosis, prognosis, and therapeutic interventions.

Risk Assessment

Personalized risk profiles: Identifying SNPs associated with oral cancer risk allows clinicians to create personalized risk profiles for patients. By analyzing an individual’s genetic makeup, healthcare providers can identify if that person is at higher risk of developing oral cancer. This knowledge enables targeted prevention strategies, such as more frequent screenings and lifestyle modifications.24

Gene–environment interactions: Understanding how specific SNPs interact with environmental factors, such as tobacco and alcohol exposure, provides insights into gene–environment interactions. This knowledge can inform counseling and interventions to mitigate risk factors for susceptible individuals.24

Early detection

Biomarker development: SNPs associated with oral cancer risk can serve as potential biomarkers for early detection. Researchers are exploring the use of specific SNPs as part of saliva-based or blood-based tests that could complement traditional screening methods. Early detection through SNP-based tests may enhance the chances of successful treatment and improved survival rates.25

Targeted surveillance: Individuals identified as high-risk based on their SNP profiles can benefit from more frequent and vigilant surveillance. This targeted approach can lead to the earlier detection of precancerous lesions or early-stage oral cancers when treatment options are less invasive and more effective.26

Personalized treatment strategies

Treatment selection: SNPs can influence how tumors respond to specific therapies. For example, certain SNPs may predict an individual’s response to chemotherapy or radiation therapy. Tailoring treatment plans based on an individual’s genetic profile can maximize treatment efficacy while minimizing adverse effects.27

Drug development: Knowledge of SNPs associated with oral cancer can guide the development of targeted therapies. Researchers are exploring SNP-specific drugs that can inhibit pathways influenced by genetic variations, leading to more precise and effective treatments.27

Prognostic markers: SNPs can also serve as prognostic markers, helping clinicians predict disease progression and patient outcomes. This information is invaluable for making informed decisions about treatment aggressiveness and post-treatment monitoring.28

SNP and cancer susceptibility

Cancer formation results from genomic variations attributed to both genetic and epigenetic modifications. Genetic modifications occur within the DNA framework, whereas
<table>
<thead>
<tr>
<th>Study aims</th>
<th>Genotyping method</th>
<th>Study location</th>
<th>Diagnosis of oral condition</th>
<th>Control population</th>
<th>Study interpretation</th>
<th>Reference</th>
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<tr>
<td>The study aimed to investigate the association of MMP gene polymorphisms and clinical behavior of aggressive ameloblastomas, odontogenic keratocysts, and dentigerous cysts.</td>
<td>PCR restriction fragment length polymorphism and sequencing.</td>
<td>Kerala, India.</td>
<td>15 cases of ameloblastoma. 11 cases of odontogenic keratocysts. 13 dentigerous cysts.</td>
<td>145 healthy individuals</td>
<td>Ameloblastoma samples demonstrated mutant allele T of MMP 9. The study concluded MMP 9 is associated with aggressive behavior of ameloblastomas.</td>
<td>Aloka et al. 2019.</td>
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epigenetic modifications refer to external modifications of DNA that either turn genes on or off. The association of SNPs with cancer can be broadly considered under cancer susceptibility and outcome. Specific types of SNP changes can determine the susceptibility to cancer, whereas the link between outcome and SNPs speaks to the prognosis, survival rate, and possible complications of cancer and cancer treatment. Some studies mention the direct association between SNP variation and cancer susceptibility. SNP changes were researched in various cancerous tissues, including lung, prostate, breast, and colorectal, potentially malignan lesions of the oral cavity, and oral cancer. The research studies on SNPs also focus on the treatment outcomes by identifying the location of the SNP change in the cancer genome to understand the efficacy of treatment. Table 1 presents information on SNPs and the most important oral disease conditions like OSCC, odontogenic keratocysts, and ameloblastomas.

**Conclusion**

Our review has highlighted that SNPs, being hereditary genetic variations, contribute significantly to the intricate landscape of oral diseases. They are not mere genetic markers but play a central role in shaping an individual’s risk profile. These minute genetic variations are like individualized genetic fingerprints, revealing unique susceptibilities and traits that can influence disease development. Moreover, the utility of SNP arrays, particularly the SNP cluster ID method, emerges as an indispensable tool in the study of oral diseases. These arrays enable us to pinpoint the upregulation or downregulation of specific genes, thereby providing crucial insights into the molecular mechanisms underlying oral conditions. Furthermore, our exploration has revealed that SNPs have notable implications in the context of immunity-related genes and the presence of immune cell infiltrations within various tumors, including those of the oral cavity. This has significant clinical implications, as the understanding of these genetic nuances could serve as a pivotal biomarker for stratifying different malignant conditions and even distinguishing aggressive benign tumors. Thus, by understanding genetic insights into disease susceptibility, molecular mechanisms, and immune responses, SNPs offer a promising avenue for both early detection and development of novel therapeutic strategies. SNPs represent an invaluable resource for researchers and clinicians seeking to unravel the complexities of oral diseases and improve patient outcomes.

**REFERENCES**


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