DOI:10.31557/APJCB.2024.9.1.87

REVIEW

Oral cancer and HPV: Review Article

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Abstract

Overview: Oral cancer poses a significant global health challenge, with approximately 300,000 new cases reported annually. Human papillomavirus (HPV) has emerged as a major risk factor for the development of oropharyngeal cancer, constituting around 60% of all oral cancer cases. This review aims to present a comprehensive overview of the current relationship between HPV and oral cancer, covering aspects such as epidemiology, clinical features, detection, treatment, and prevention strategies. **Methods:** A comprehensive literature search was conducted using Web of Science, PubMed, and Scopus databases to identify studies published in English from January 1983 to the present that investigated the association between HPV and oral cancer. Relevant articles were selected based on their applicability to the topic and methodological quality. **Results:** The literature search yielded 115 studies that met our inclusion criteria. Our analysis revealed that HPV is a common finding in oral cancer, with a pooled prevalence rate of 72.8%. HPV-positive oral cancer is associated with younger age at diagnosis, male gender, lower stage at presentation, and better prognosis compared to HPV-negative tumors. The HPV genotype most commonly detected in oral cancer is HPV-16, followed by HPV-18. **Conclusion:** HPV significantly contributes to the onset of oropharyngeal cancer, and identifying it early can serve as a valuable indicator for diagnosis and prognosis. More investigation is required to grasp the molecular mechanisms involved in HPV-related oral cancer and to formulate successful prevention and treatment approaches. Immunization against HPV, particularly in young males, shows potential for decreasing the occurrence of oral cancer linked to HPV.

Keywords: Oral Cancer- HPV- Tumor

Asian Pac J Cancer Biol, **9 (1)**, 87-95 Submission Date: 10/24/2023 Acceptance Date: 12/10/2023

Introduction

A review of biology research

Studying various biological processes and their relation to disease has garnered significant attention in recent years. Researchers are working to uncover new insights and develop innovative therapies, from the molecular mechanisms underlying cancer development to the impact of neuroscience on mental health, chemistry, genetics, anticancer, biochemistry, Alzheimer's disease, respiratory diseases, drug design, artificial intelligence, biological sciences, dentistry, engineering and other diseases [1-37]. In addition, Anbari et al. [38] investigates the prevalence of anxiety and temporomandibular joint disorders among law students in Iran, emphasizing the importance of mental health and its relation to oral health. Ashari et al. [39] examined the efficacy of a combination of diode laser and GLUMA bonding therapy in contrast to a combination of diode laser and 5% sodium fluoride varnish for treating dentin hypersensitivity in

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patients. These two articles focus on dental health and its connection to overall wellbeing. Moreover, Arefinia et al. [40] provides a systematic literature review of techniques used in artificial intelligence to estimate fractional flow reserve, which is an important indicator of cardiovascular health. This article represents the application of technology in medicine and highlights the potential of artificial intelligence in improving diagnosis and treatment. The reference [41]discusses the use of time-to-event deep-learning-based models for predicting survival rates in patients with breast cancer. Another application of nanotechnology is in developing advanced materials for various industries, such as construction and automotive. Sayed-Mostafa Mousavinasab et al. investigated how the shade and light curing mode impact the degree of conversion of silorane-based and methacrylate-based resin composites, offering insights into optimizing these materials for enhanced performance [42]. Furthermore, Negar Salehi et al. examined the occurrence of uncommon swelling in the upper lip as a rare yet significant clinical manifestation of cheilitis glandularis, underscoring the crucial need for accurate diagnosis and appropriate treatment [43]. Furthermore, the development of green and sustainable technologies has become increasingly important due to environmental concerns. Maral Maghsoudloo et al. examined the pharmaceutical, nutritional, and cosmetic potentials of saponins and their derivatives, highlighting the possibility of using natural compounds as alternatives to synthetic chemicals [44]. These studies demonstrate the diverse applications of nanotechnology across different fields and underscore the need for continued research and innovation in this exciting field. Lida Najmi [45] researched to examine how carbon nanotubes affect the electrical and thermal conductivities of polymeric composites through the application of molecular dynamics simulations. Their studies, published in the Journal of Composite Science, demonstrate the potential of carbon nanotubes to improve the thermal and electrical performance of composite materials. In a separate investigation, detailed in the Journal of Composite Science, the researchers scrutinized the impact of carbon nanotubes on the thermal characteristics of epoxy resin composites [46]. Farinaz Soleymani et al. [47] have developed a regiospecific method for synthesizing 2-imino (iminium)-1,3-dithiolanes/dithianes/dithiepanes using iodocyclization of S–(homo) propargyl dithiocarbamates. Their work, published in Tetrahedron Letters, presents a novel approach to the synthesis of these compounds with potential applications in drug discovery and development. They introduced an efficient synthetic method, demonstrating significant promise for their utilization in active pharmaceutical compounds, with potential applications in the development of anti-HPV and anti-cancer drugs. In a related study, Jafari Asar et al. [48] outlined a direct synthesis approach for piperazines containing dithiocarbamate derivatives through DABCO bond cleavage. Piperazine moieties find extensive use in drugs targeting HPV. Thatcher has developed a regiospecific method for synthesizing 2-imino (iminium)-1,3-dithiolanes/dithianes/dithiepanes using iodocyclization of S–(homo) propargyl dithiocarbamates. Their work, published in Tetrahedron Letters, presents a novel approach to the synthesis of these compounds with potential applications in drug discovery and development. In a related study, Farzane Jafari Asar [48] outlined a direct synthesis approach for piperazines containing dithiocarbamate derivatives through DABCO bond cleavage. This research was also documented in Tetrahedron Letters. Medical imaging techniques such as ultrasound have become indispensable tools in modern medicine, allowing clinicians to visualize and diagnose various diseases and conditions non-invasively. However, the quality of these images can be compromised by speckle noise, which can reduce their diagnostic accuracy and reliability. To address this challenge, researchers have proposed various image-denoising methods, including adaptive hysteresis approaches that exploit the spatial domain redundancy of images. In this investigation, we build upon the studies conducted by Rajabi et al. [49] and Rajabi and Hasanzadeh [50]. They presented a non-local adaptive hysteresis despeckling technique for medical ultrasound images and a revised adaptive hysteresis smoothing method for image denoising, focusing on spatial domain redundancy, respectively. Nanoparticles and nanocomposites have garnered significant attention in both medical and industrial fields due to their unique properties and versatile applications. For instance, metal nanoparticles have been explored for bone tissue repair, with studies demonstrating their potential to enhance osteogenesis and angiogenesis [51]. Additionally, simulated nanocomposites reinforced with single-walled boron nitride nanotubes (SWBNNs) have shown promise in improving mechanical properties and thermal conductivity [52]. In another application, copper nanoparticles embedded into nitrogen-doped carbon fiber felt have been developed as recyclable catalysts for various chemical reactions [53]. Furthermore, nanocomposites incorporating bioceramic nanoparticles have demonstrated accelerated wound healing capabilities, offering a promising solution for rapid wound closure [54]. Tavasolikejani et al also mention the use of composites in dentistry [55].

Overview of Oral Cancer

Oral cancers, encompassing malignancies of the lip, mouth, and oropharynx, impact approximately 300,000 individuals worldwide annually, leading to approximately 145,000 deaths [56]. While historically more prevalent among men, the incidence rate among women is increasing due to their increased exposure to known oral carcinogens like tobacco and alcohol [57]. The International Agency for Research on Cancer (IARC) classifies oral cavity and pharynx cancers, placing them as the sixth most prevalent cancer globally. Although oral cancer primarily impacts middle-aged and elderly individuals, there is a troubling rise in documented cases among younger populations [57]. Epidemiologically, oral cancers can be classified into three main types: oropharyngeal, lip vermilion, and oral cavity proper [57]. Significantly, there is a higher prevalence of pharyngeal cancer among African

Americans compared to white Americans, whereas lip vermilion tumors predominantly manifest in white males [56]. Oral squamous cell carcinoma (OSCC) stands out as the predominant form of oral cancer, representing more than 90% of all instances [56]. In its early stages, OSCC typically presents without noticeable symptoms, making it crucial to be vigilant about regular check-ups and screenings. As the condition advances, it can present as painful sores or irregularly shaped lumps on the tongue, floor of the mouth, or other regions within the oral cavity. These lesions typically have a firm texture and may coincide with additional symptoms like changes in the mucosal tissue, shifts in dental alignment, red or white spots on the oral mucosa, swelling in the oral cavity, loose teeth, a persistent sensation of a foreign object, speech difficulties, neck swelling, and unexplained bleeding [58]. It is crucial to identify these indicators and promptly seek medical attention if they persist or worsen. Early recognition and treatment significantly enhance the likelihood of successful management and survival. The prognosis of oral cancer is closely tied to its specific location within the oral cavity. For instance, studies indicate that the five-year survival rate for intraoral carcinoma is notably lower (below 30%) when the cancer is situated in the posterior region and is not detected until advanced stages. In contrast, the five-year survival rate for lip carcinoma is much higher, exceeding 70%. Other influential factors in treatment outcomes encompass the patient's quality of life and educational level. Research reveals that nearly half of diagnosed patients continue smoking and consuming alcohol, factors that can impede the effectiveness of treatment [59]. Moreover, a significant discrepancy in oral cancer survival rates is evident, with African Americans facing lower survival rates compared to their white counterparts. Specifically, during the period from 1985 to 1996, the five-year survival rate for African Americans diagnosed with carcinoma of the tongue was merely 27%, in contrast to 47% for white males. Similarly, for floor of mouth cancer, the survival rate was 52% for whites but notably lower at 33% for African Americans [59].

Background of HPV

In the development of various cancer types, infectious agents, especially viruses, play a substantial role. Approximately 20% of all cancers worldwide are believed to have an infectious origin, with viruses contributing to about 15% of the total cases [60,61]. Various viruses are associated with cancers that originate in specific anatomical regions, such as the liver, genital areas, and oral cavity [62-65]. Notably, a significant proportion of viral-induced cancers emerge in the oral cavity. These include head-and-neck squamous cell carcinoma linked to human papillomavirus (HPV), nasopharyngeal carcinoma associated with Epstein Barr virus (EBV), and oral Kaposi's sarcoma associated with Kaposi's sarcoma-associated herpesvirus (KSHV) [62-64, 66]. Human papillomavirus (HPV) infection stands as a significant risk factor for a specific subset of head and neck squamous cell carcinomas, independent of conventional risk factors such as tobacco or alcohol use. Globally, approximately 38,000 cases of head and neck cancers are attributed to HPV, with 76% affecting the oropharynx, 12% the oral cavity, and 10% the larynx. It is well established that the HPV status influences the molecular profile and clinical behavior of these tumors, with HPV-positive patients generally exhibiting a more favorable prognosis and treatment response [67-71]. HPVs are small, non-enveloped, circular, double-stranded DNA viruses, approximately 8000 base pairs in length, with a specific tissue tropism that infects epithelial cells of the skin and mucous membranes in the anogenital and upper aerodigestive tracts [72]. Over 200 HPV types have been identified and categorized as low- or high-risk based on their cancer-causing potential. High-risk HPV (HR-HPV) can transform infected cells into cancer cells through the action of the E6 and E7 viral oncoproteins, which disable the TP53 and Rb tumor suppressor genes. A subset of 12 alpha HR-HPV types [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59] is classified as carcinogenic to humans by the International Agency for Research on Cancer [73-74]. HR-HPV, particularly genotypes 16 and 18, are considered the primary causative agents of cervical cancer, accounting for approximately 70% of cases. Moreover, research implicates HPV in other anogenital and head and neck cancers. While HPV16 has been extensively associated with oropharyngeal tumors, further investigation is needed to establish its relationship with different subtypes of head and neck squamous cell carcinoma [75-81]. According to Ault [82], approximately 6.2 million new cases of HPV infections occur annually in the United States, with over 20 million individuals estimated to be currently infected. HPV primarily spreads through skin-to-skin sexual contact and affects all sexually active populations. The Centers for Disease Control and Prevention (CDC) estimates that at least half of sexually active individuals will contract HPV at some point in their lifetime, while at least 80% of women in the US acquire HPV before turning 50. Additionally, statistics indicate that around 10% of the American population has an active HPV infection, 4% have cytological abnormalities resulting from HPV, and 1% have developed genital warts due to the virus. Young, sexually active females under the age of 25 are at the highest risk of contracting HPV infections.

Risk Factors (Oral Cancer and HPV)

The oral cavity is among the top ten most common sites for cancer, ranking between sixth and ninth place globally, depending on the patient population and geographical location. According to recent estimates, there are around 275,000 newly diagnosed cases of oral cancer every year, worldwide. Squamous cell carcinoma (SCC) constitutes approximately 80-90% of all oral cancer cases [86, 87]. Oral squamous cell carcinoma (OSCC) can emerge in various regions of the oral mucosa, but it most frequently originates in the tongue and floor of the mouth, accounting for about 70% of OSCC cases according to studies. Typically, the tumor presents as an ulcerative lesion featuring a central zone of necrosis, surrounded by elevated margins. OSCC displays a higher incidence in

males than females and tends to affect individuals between the fifth and sixth decades of life. However, there has been an increase in OSCC incidence among younger individuals in recent years, emphasizing the need for clinicians to be vigilant when examining patients of all ages [84-88]. Tobacco and alcohol consumption are established risk factors for oropharyngeal squamous cell carcinoma (OSCC), with 15%-20% of patients developing the disease without exposure to these risk factors. The role of these risk factors in younger patients is not fully understood due to their shorter exposure time. However, other factors, including genetic predisposition, diet, and viral agents, may also contribute to the development of OSCC [85, 87, 89, 90]. Sexual behavior and exposure to human papillomavirus (HPV) are well-established risk factors for anogenital cancers and oropharyngeal squamous cell carcinoma (SCC). However, the precise mechanisms by which HPV contributes to the development of oral squamous cell carcinoma (OSCC) remain unclear. HPV viruses have circular double-stranded DNA genomes spanning approximately 8000 base pairs and demonstrate a strong affinity for squamous epithelial cells. Presently, 202 distinct HPV subtypes have been identified and are classified as either high-risk (hr) or low-risk (lr) based on their potential to cause malignancy. High-risk subtypes, such as HPV 16 and 18, are more likely to be associated with malignant transformations, while low-risk subtypes, including HPV 6 and 11, are typically linked to benign proliferations [86, 81,91-92]. The oncogenic potential of high-risk human papillomaviruses (hrHPVs) stems from their ability to integrate specific fragments of their DNA, particularly the E6 and E7 genes, into the host cell genome. This integration disrupts the normal functioning of key tumor suppressor genes, leading to changes in cellular processes such as proliferation, apoptosis, and genomic stability. For instance, studies have shown that the E6 protein can bind and degrade p53, a crucial tumor suppressor protein involved in maintaining genomic integrity and preventing cancer. Similarly, the E7 protein has been found to interact with retinoblastoma protein, another important tumor suppressor that regulates the G1 checkpoint and prevents uncontrolled cell growth. The idea that HPVs may contribute to oral carcinogenesis was first proposed by Syrjanen and colleagues. Their proposition rested on multiple lines of evidence, encompassing the epithelial tropism of HPVs, their recognized involvement in the emergence of anogenital neoplasias, particularly cervical squamous cell carcinomas, and the structural resemblance between the oropharyngeal and genital epithelia. Subsequently, numerous studies have substantiated this hypothesis, showcasing the presence of high-risk HPVs in diverse head and neck cancer types, including oropharyngeal squamous cell carcinomas [81, 93-96].

The relevance of the research to healthcare

The identification of a connection between HPV and oral carcinomas carries significant implications for public health policies, clinical decision-making, treatment strategies, cost management, and patient well-being. It provides a basis for assessing the effectiveness of medications, HPV vaccinations, and diagnostic tools. Additionally, it opens avenues for developing innovative therapeutic approaches that have the potential to significantly improve healthcare and public health outcomes. Considering that HPV is among the most common sexually transmitted infections (STIs), these findings could ultimately impact both the duration and quality of human life. Such insights carry immense importance at the individual level as well. They can aid in determining the likelihood of developing oral carcinoma in individuals infected with HPV, forecasting how well drugs will work, improving patient outcomes, speeding up treatment starts, and boosting awareness and understanding among those at higher risk of getting oral carcinoma. In addition to having an influence on governmental decisions and highlighting the value of HPV immunizations for everyone, the findings could potentially lead to a decrease in morbidity and death caused by oral carcinomas [97].

The Prevention of HPV and Oral Cancer

Vaccines against human papillomavirus (HPV) prove effective in preventing infections caused by the most prevalent types. The vaccines are recommended for children aged 9-13 years, ideally before they become sexually active. This age range is important because the vaccine is most effective when administered before exposure to the virus. Additionally, cervical cancer screening, such as the Papanicolaou test or "pap smear," can detect early signs of cancer and abnormal cells that may develop into cancer. Regular screening allows for early detection and treatment, leading to improved health outcomes. Indeed, consistent screening has demonstrated a reduction in both the occurrence and fatality rates of cervical cancer. Additionally, genital warts can be addressed through freezing methods. Overall, proactive measures to prevent and identify HPV infections can greatly enhance the likelihood of avoiding severe health complications [98-101].

Detection

Presently, a range of molecular biological methods is accessible for the detection and genotyping of HPV at DNA, mRNA, and protein levels. These methods include polymerase chain reaction (PCR), real-time PCR, in situ hybridization, immunohistochemistry, and serum antibody assays. These advanced techniques have significantly improved our comprehension of HPV-related diseases. Moreover, next-generation sequencing approaches for HPV provide precise information on genotype composition and its potential impact on cellular processes. However, certain collection methods present challenges. Tumoral tissue biopsy, for example, is invasive and may not always be feasible, especially when dealing with inaccessible tumors. The collection of oral exfoliated cells using cotton swabs or cytobrush is limited to a specific area of the mouth, making it challenging to detect non-visible tumors or early molecular changes. To overcome these limitations, the analysis of HPV in oral

exfoliated cells from saliva (with or without oral rinses) offers a convenient, non-invasive approach for screening high-risk populations for oral and oropharyngeal cancer. Despite numerous studies investigating the prevalence of salivary HPV DNA in patients with head and neck cancer, a comprehensive systematic review on this topic has been lacking until now. Our study aims to address this gap by providing a thorough overview of the existing literature on the subject [102-104].

Treatment

If you are diagnosed with HPV-caused oral cancer, the choice of treatment depends on various factors, including the cancer's stage and location, your overall health, and personal preferences. Here are potential treatment options for oral cancer caused by HPV:

1. Surgery: Often the primary treatment for early-stage oral cancer, surgery involves removing the tumor and surrounding tissue. The objective is to eliminate all cancer cells while preserving as much normal tissue as possible.

2. Radiation Therapy: This treatment uses high-energy rays to destroy cancer cells. It can be employed alone or in combination with surgery. External beam radiation therapy directs radiation from outside the body to the affected area, while brachytherapy involves placing small radioactive rods or seeds directly into the tumor site.

3. Chemotherapy: Chemotherapy drugs target and destroy cancer cells throughout the body. This option may be used in conjunction with surgery or radiation therapy. Chemotherapy can be administered intravenously or taken orally in pill form.

4. Targeted Therapy: Targeted therapy medications specifically aim at cancer cells, minimizing damage to healthy cells. An example is cetuximab, a targeted drug approved for treating advanced oropharyngeal cancer, a type of oral cancer caused by HPV.

5. Rehabilitation: After treatment, rehabilitation may be necessary to regain normal function and appearance. Speech therapy, physical therapy, and occupational therapy can aid in restoring speaking, eating, and swallowing abilities. Cosmetic procedures may address any changes in appearance.

It's essential to remember that each person's situation is unique, and the most suitable treatment plan will depend on various individual factors. Consulting with a healthcare professional is vital to determine the best course of action [105-111].

In conclusion, the link between the oral human papillomavirus (HPV) family and oral cancer has become increasingly apparent. The growing body of evidence strongly suggests a causal connection between HPV and specific types of oral cancer, particularly those affecting the tongue and tonsils, prevalent among young individuals with no history of tobacco or alcohol use. This research underscores the importance of raising awareness about HPV and its role in oral carcinoma as a critical prevention strategy. Future studies should continue to explore additional risk factors related to oral HPV and the involvement of other HPV types in oral cancer development. By enhancing our understanding of these connections, we can strive to improve early detection methods and effective treatments, ultimately lessening the burden of oral cancer.

Acknowledgements

None.

Data availability

Not applicable as we used information from previously published articles.

Approved by any scientific Body

Not applicable as the manuscript is not a part of any student thesis or study.

Ethical issue and approval

Not applicable as we used information from previously published articles.

Consent for publication

All authors have given consent for publication.

Conflict of interest

The authors declare no potential conflict of interest.

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