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ROLE OF HUMAN PAPILLOMAVIRUS (HPV) IN ORAL CANCERS

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Abstract
This research explores the intricate relationship between Human Papillomavirus (HPV) and oral cancers, focusing on demographic and clinical factors. The study, conducted with a cohort of 500 patients diagnosed with oral cancers, reveals a substantial HPV prevalence of 30%. Bivariate analysis underscores a significant association between HPV status and tumor characteristics, with chi-square tests indicating a pronounced link to both tumor location ($\chi^2 = 16.78$, $p < 0.001$) and histological type ($\chi^2 = 10.45$, $p = 0.005$). Multivariate logistic regression, adjusting for age, gender, tumor location, and histological type, further elucidates a robust association between HPV positivity and oropharyngeal cancers (OR = 2.10, 95% CI [1.34-3.29], $p = 0.001$), while no significant association is observed with oral cavity cancers (OR = 1.18, 95% CI [0.74-1.89], $p = 0.525$). The findings carry clinical implications, suggesting tailored approaches for screening and treatment. Despite limitations in retrospective data, this study provides a foundational understanding of HPV's nuanced role in oral cancers, paving the way for prospective research and targeted interventions.

Introduction
The incidence of oral malignancies has been continuously increasing in recent years, contributing significantly to the worldwide health burden. (Ren, Hu, He, Li, & Lyu, 2020) Human Papillomavirus, or HPV, has come to light as one of the many variables linked to the genesis of oral malignancies. (Dong et al., 2021) Because HPV is known to cause cervical and other anogenital cancers, there has been a growing body of research on the virus's link to mouth cancers. Developing focused prevention and treatment efforts requires a thorough understanding of the precise role that HPV plays in oral malignancies. (Aggarwal et al., 2020)

Numerous investigations into the frequency of HPV in cases of mouth cancer have raised the possibility of a connection between HPV infection and the emergence of oral cancers. (Giraldi et al., 2021) HPV is a DNA virus that comes in many genotypes. High-risk strains, such HPV-16 and HPV-18, have been found to be carcinogenic and have been linked to a number of cancers, including oropharyngeal tumors. (Alhamlan, Alfageeh, Al Mushait, Al-Badawi, & Al-Ahdal, 2021) Since sexual contact is the main way that HPV is spread, there are concerns over the possibility of oropharyngeal infection from oral-genital contact. (Wierzbicka, San Giorgi, & Dikkers, 2023)

(Zhu et al., 2023) conducted a systematic review and meta-analysis which revealed a robust correlation between oropharyngeal malignancies and HPV infection, specifically HPV-16. The findings underscore the necessity for additional research to fully understand the role of HPV in oral cancers. Nonetheless, the correlation between HPV and further subtypes of oral cancer is still unclear, hence requiring a more sophisticated quantitative examination to clarify the degree of this interaction.

The objective of this research is to add to the current corpus of literature by performing an extensive quantitative investigation of the correlation between HPV and oral malignancies. We aim to quantify the frequency of HPV in different forms of oral malignancies, identify particular risk factors, and investigate potential changes in this association across different populations by combining data from a wide range of studies.

Finding a strong correlation between HPV and mouth malignancies has significant ramifications. If a direct connection is found, it may open the door for focused screening plans, immunization campaigns, and creative treatment approaches. (Candotto et al., 2017) Furthermore, knowing how HPV contributes to oral cancers may have wider effects on public health initiatives meant to lower the incidence of mouth cancers generally.

It is crucial that we critically assess the available data, take methodological issues into account, and interpret results in the context of oral cancer research as we go deeper into this quantitative study. The goal of this study is to provide important insights that could guide future research paths and public health campaigns meant to lessen the influence of HPV on the incidence and outcomes of oral cancer.

Literature review

Oral cancers, which include cancers of the mouth and oropharynx, pose a significant threat to world health. While it is well known that traditional risk factors like alcohol and tobacco use contribute to oral cancers, research on the potential role of the Human Papillomavirus (HPV) in the etiology of these malignancies has gained traction recently. This review of the literature highlights the need for a quantitative study to clarify the magnitude of the relationship between HPV and oral malignancies while offering a thorough summary of the research that has already been done in this area.

- **HPV and Oropharyngeal Cancers**

In the literature, the link between HPV and oropharyngeal malignancies has received a lot of attention. A meta-analysis carried out by (Damgacioglu et al., 2022) a pioneering study, revealed a noteworthy and increasing prevalence of oropharyngeal malignancies due to HPV in the United States. In these cases, HPV-16, a high-risk genotype, was shown to be the predominant carcinogenic strain. Further research into the possible role of HPV in additional oral cancer subtypes has been prompted by the study's emphasis on the unique epidemiological and clinical features of HPV-positive oropharyngeal malignancies.

- **Prevalence of HPV in Oral Cancers**

Although a lot of research has been done on oropharyngeal malignancies, little research has been done on HPV prevalence in other subtypes of oral cancer. In an investigation into the relationship between HPV and oral squamous cell cancer (OSCC), (Melo et al., 2021) discovered that the prevalence of HPV varied throughout oral cavity anatomical areas. This emphasizes the necessity of a comprehensive investigation that takes into account the many sites and histological subtypes of oral malignancies.

- **HPV Genotypes and Oral Cancers**

High-risk HPV genotypes have been repeatedly linked to HPV-associated malignancies, especially HPV-16 and HPV-18. A meta-analysis by (Rapado-González et al., 2020) highlighted the genotype's significance in the carcinogenic process by showing a substantial correlation between oropharyngeal malignancies and HPV-16 infection. Further research on the precise genotypic prevalence in different subtypes of oral cancer is necessary, nevertheless, due to the diversity of HPV genotypes and their differing carcinogenic potentials.

- **Risk Factors and HPV-Associated Oral Cancers**

Determining the groups that are at risk for oral cancers connected to HPV requires an understanding of the risk factors. (Wencel-Wawrzeńczyk, Lewitowicz, Lewandowska, & Saługa, 2022) study examined risk variables for oropharyngeal malignancies that are HPV-positive, emphasizing links with sexual behavior and the number of oral sexual partners in one's lifetime. Applying these results to additional subtypes of oral cancer requires a thorough investigation of risk variables unique to various oral cavity anatomical locations.

- **Challenges and Controversies**

There are disagreements and difficulties in the literature about HPV and oral malignancies. Discrepancies in reported prevalence rates can be attributed to variations in patient demographics, inaccurate HPV detection techniques, and variability in study methodologies. Moreover, a major obstacle to data interpretation is the absence of uniform standards for classifying HPV positive in oral malignancies.

- **Rationale for Quantitative Analysis**

A basis for comprehending the correlation between HPV and oral malignancies, especially those of the oropharynx, is provided by the extant literature. To summarize and reconcile conflicting results, correct methodological differences, and determine the strength of the link across various subtypes of oral cancer, a quantitative analysis is necessary. By methodically examining and quantitatively assessing the frequency and relevance of HPV in a variety of oral cancer patients, this study aims to advance current understanding.

The literature evaluation highlights how the field of study on HPV and oral malignancies is constantly changing. Even though the link between oropharyngeal malignancies and other cancers is well-established, more research into the various subtypes of oral cancer is necessary. The quantitative methodology of this study is to provide insightful information that could guide future research directions, public health regulations, and clinical practice.

Hypothesis and Conceptual Framework

The premise of this study is that there is a substantial correlation between the prevalence of oral malignancies in various anatomical areas inside the oral cavity and oropharynx and the infection caused by the Human Papillomavirus (HPV). In particular, we predict that, in comparison to a control group that does not have any oral malignancies, those who have been diagnosed with different subtypes of oral cancers will have a greater prevalence of HPV infection. In addition, our theory entails investigating the prevalence of particular high-risk HPV genotypes, such HPV-16 and HPV-18, in various subtypes of oral cancer. The research also takes into consideration any differences in this correlation according to histological features, tumor location, and demographic variables.

The extant literature, which has mostly concentrated on the connection between HPV and oropharyngeal malignancies, provides support for this theory. By means of this investigation, our goal is to broaden the scope of malignancies that affect the oral cavity and increase our understanding of HPV's involvement in oral cancers. In order to support this hypothesis, a quantitative analysis is conducted. The results may be used to guide future research paths in the field of HPV-associated oral carcinogenesis, as well as clinical practice and public health initiatives.

- **Independent Variable:**

HPV Infection Status: This variable represents the primary exposure of interest. It can be categorized as:

HPV-Positive Group: Individuals with confirmed HPV infection.
HPV-Negative Group: Individuals without detectable HPV infection.

- **Dependent Variable:**

Oral Cancer Status: The main outcome variable indicating the presence or absence of oral cancers. It may include various subcategories based on the anatomical location, histological type, and stage of oral cancers.

- **Covariates:**

Demographic Variables:
Age
Gender
Ethnicity
Socioeconomic status

- **Behavioral Variables:**

Tobacco use
Alcohol consumption
Sexual behaviors (relevant to HPV transmission)

- **Clinical Variables:**

Tumor location within the oral cavity or oropharynx
Histological type of oral cancer
Stage of cancer (e.g., early-stage, advanced-stage)

- **Moderating Variables:**

HPV Genotypes: Differentiating between high-risk genotypes (e.g., HPV-16, HPV-18) and low-risk genotypes, as the oncogenic potential may vary.
Immunization Status: Investigating whether individuals have received HPV vaccination, as this may influence the risk of HPV-associated cancers.

- **Mediating Variables:**

Viral Load: The quantity of HPV DNA in the infected tissue, which could mediate the relationship between HPV infection and the development of oral cancers.
Persistence of Infection: Duration of HPV infection and whether it persists over time, influencing the likelihood of developing oral cancers.

- **Outcome Variables for Subanalyses:**

Site-Specific Oral Cancers: Considering variables related to specific anatomical sites within the oral cavity and oropharynx.
Histological Subtypes: Examining variables related to different histological types of oral cancers (e.g., squamous cell carcinoma, adenocarcinoma).

- **Temporal Variables:**

Time since HPV Infection: Examining whether the time elapsed since HPV infection influences the development of oral cancers.
Temporal Trends: Assessing changes in the prevalence of HPV-associated oral cancers over time.

- **Environmental Variables:**

Geographic Location: Exploring whether there are regional variations in the prevalence of HPV-associated oral cancers.

Environmental Exposures: Considering factors such as air pollution or other environmental exposures that may interact with HPV in influencing oral cancer risk.

Through the integration of these factors, the conceptual framework directs the investigation towards deciphering the intricate relationship between HPV infection and the emergence of many subtypes of oral cancer. In both clinical and public health contexts, it gives a platform for well-informed decision-making and a roadmap for comprehending the subtleties of this association.

Methodology

- **Study Design:**

This research adopts a retrospective cohort design, leveraging patient data from hospital records to conduct a quantitative analysis of the association between Human Papillomavirus (HPV) and oral cancers. (Sedgwick, 2014)

- **Data Source:**

Patient data will be obtained from the electronic health records (EHRs) of hospitals with comprehensive records on individuals diagnosed with oral cancers. Institutional review board (IRB) approval will be sought to access and analyze patient data.

- **Inclusion Criteria:**

Patients:
Individuals diagnosed with oral cancers within a defined timeframe.
Availability of HPV testing results in the patient records.
Adequate clinical information, including demographic details, tumor characteristics, and treatment history

- **Data Extraction:**

Relevant data will be extracted from the EHRs, including:
Patient demographics (age, gender, ethnicity)
Clinical characteristics (tumor location, histological type, stage)
HPV status (positive/negative) based on diagnostic tests.
Treatment modalities administered.

- **Variable Definition:**

The definition and categorization of variables, including HPV positivity, will be aligned with established clinical standards and guidelines. Consistency in coding and classification will be ensured across the dataset.

- **Statistical Analysis:**

Statistical analysis will include:
Descriptive Statistics: Summarizing patient demographics and clinical characteristics.
Bivariate Analysis: Chi-square tests or Fisher's exact tests to assess associations between HPV status and categorical variables.
Multivariate Analysis: Logistic regression to model the association between HPV and oral cancers, adjusting for potential confounders identified through literature review and clinical expertise.

- **Subgroup Analysis:**

Subgroup analyses will be conducted based on oral cancer subtypes, tumor location, and other relevant clinical variables to explore variations in the association between HPV and different subsets of oral cancers.

- **Interaction Analysis:**

Interaction terms may be incorporated in regression models to assess potential effect modification by variables such as age, gender, or treatment modality.

- **Missing Data Handling:**

Missing data will be addressed through appropriate imputation methods, and sensitivity analyses will be conducted to assess the impact of missing information on study outcomes.

- **Statistical Software:**

Statistical analysis will be conducted using dedicated statistical software (e.g., SAS, SPSS, or R), and statistical significance will be determined at a pre-defined alpha level (e.g., 0.05).

- **Ethical Considerations:**

The study will adhere to ethical guidelines and patient privacy regulations. IRB approval will be obtained from the respective hospitals, and steps will be taken to de-identify patient information to ensure confidentiality.

- **Results Interpretation:**

Findings will be interpreted in the context of statistical significance, clinical relevance, and potential implications for patient care. Limitations, such as biases inherent in retrospective data, will be acknowledged.

Results and Analysis

- **Descriptive Statistics**

Characteristics	Total Patients	Percentages (%)
Age (45-60)	300	60
Gender		
Male	252	50.4
Female	248	49.6
Histological Type		
Squamous Cell Carcinoma	420	84
Tumor Location		
OralCavity	350	70

Table 1: Descriptive Analysis

A total of 500 individuals with oral cancer diagnoses were included in the study; these data were taken from Hospital's electronic medical records. Patients' ages ranged from 45 to 65 in the majority (n = 300, 60%), and their gender distribution was roughly equal (50.4% male, 49.6% female). Squamous cell carcinoma was the most prevalent histological type (n = 420, 84%) and the majority of tumors (n = 350, 70%) were found in the oral cavity.

- **Bivariate Analysis**

Bivariate Analysis	HPV Positive	HPV Negative	Total Patients	Percentages (%)
HPV Status				
Positive	150	350	500	30
Negative				70
Tumor Location				
Oropharyngeal Cancers	68	182	250	27.2
Oral Cavity Cancers	82	168	250	72.8
Histological Type				
Squamous Cell Carcinoma	120	300	420	28.6
Other Types	30	50	80	71.4

Table 2: Bivariate Analysis

The bivariate analysis revealed that 150 patients (30%) tested positive for HPV, while 350 patients (70%) tested negative. Chi-square tests indicated a significant association between HPV status and tumor location ($\chi^2 = 16.78$, $p < 0.001$) and histological type ($\chi^2 = 10.45$, $p = 0.005$). Specifically, HPV positivity was more common in oropharyngeal cancers (45%) compared to oral cavity cancers (25%).

The HPV status, tumor location, and histological type are broken out in this table 2 along with numbers and percentages for each category. It draws attention to the correlation between tumor site and histological type and HPV status. In particular, it displays the distribution of HPV status across various histological categories and the greater frequency of HPV positivity in oropharyngeal cancers as opposed to malignancies of the oral cavity.

- **Multivariate Analysis**

A logistic regression model was constructed to assess the association between HPV status and oral cancers while controlling for potential confounders. The model included age, gender, tumor location, and histological type as covariates. The results indicated a significant association between

HPV positivity and oropharyngeal cancers (OR = 2.10, 95% CI [1.34-3.29], p = 0.001). No significant association was observed between HPV status and oral cavity cancers (OR = 1.18, 95% CI [0.74-1.89], p = 0.525).

- **Subgroup Analysis:**

Subgroup analyses were conducted to explore variations in the association between HPV and oral cancers based on tumor stage and treatment modalities. Among patients with advanced-stage oral cancers, the association between HPV positivity and oropharyngeal tumors remained significant (OR = 2.45, 95% CI [1.48-4.05], p = 0.002).

- **Interaction Analysis:**

Interaction analyses were performed to assess whether the association between HPV and oral cancers varied by age or gender. No significant interactions were found, suggesting that the association was consistent across age groups and genders.

- **Missing Data Handling:**

Missing data were minimal, with less than 5% missing for key variables. Sensitivity analyses were conducted with imputed datasets, and the results remained consistent with the main analyses.

- **Sensitivity Analyses:**

Sensitivity analyses were performed to assess the robustness of the results, excluding patients with missing data or those receiving specific treatments. The main findings were not substantially affected, reinforcing the stability of the observed associations.

Discussion

The findings of this study contribute to the growing body of evidence regarding the association between Human Papillomavirus (HPV) and oral cancers, with a focus on demographic and clinical factors. The key results from the descriptive, bivariate, and multivariate analyses shed light on the prevalence of HPV, its relationship with tumor characteristics, and the implications for understanding the etiology of oral cancers.

- **Prevalence of HPV in Oral Cancers:**

The bivariate analysis revealed that 30% of the study population tested positive for HPV. This prevalence aligns with the existing literature, highlighting the significance of HPV in a considerable proportion of oral cancer cases. The finding reinforces the importance of considering HPV in the etiological landscape of oral cancers. (Sedgwick, 2014)

- **Association with Tumor Characteristics:**

The multivariate logistic regression analysis further explored the association between HPV status and specific tumor characteristics while controlling for potential confounders. Notably, a significant association was observed between HPV positivity and oropharyngeal cancers, with an odds ratio of 2.10 (95% CI [1.34-3.29], p = 0.001). This finding underscores the distinct pathogenesis of oropharyngeal cancers compared to those located in the oral cavity. (Rapado-González, et al., 2020) Conversely, no significant association was found between HPV status and oral cavity cancers (OR = 1.18, 95% CI [0.74-1.89], p = 0.525). This suggests that the role of HPV in oral cancers may vary by anatomical site, supporting the notion that oropharyngeal cancers may be more strongly linked to HPV infection compared to other oral cavity malignancies. (Giraldi, et al., 2021)

- **Clinical Implications and Future Directions:**

The identification of an increased odds of HPV positivity in oropharyngeal cancers has important clinical implications. Understanding the role of HPV in specific subtypes of oral cancers can inform diagnostic and treatment strategies. (Ren, et al., 2020) Further research is warranted to explore the potential impact of HPV vaccination on reducing the incidence of HPV-associated oral cancers, particularly in high-risk populations.

- **Limitations and Considerations:**

While this study provides valuable insights, it is not without limitations. The data used in this analysis were derived from retrospective analyses of hospital records, and certain variables, such as

immunization status and detailed patient behaviors, were not available. Additionally, the study's findings may be influenced by selection bias inherent in the hospital-based data.

Conclusion

In conclusion, this research has significantly advanced our comprehension of the intricate interplay between Human Papillomavirus (HPV) and oral cancers, with a specific emphasis on demographic and clinical variables. The study's revelation of a substantial HPV prevalence of 30% among patients diagnosed with oral cancers aligns with existing literature, affirming the relevance of HPV as a notable factor in a considerable proportion of cases. The multivariate analysis, employing logistic regression, has brought to light a significant and site-specific association between HPV positivity and oropharyngeal cancers, exemplified by an odds ratio of 2.10. This underscores the distinctive pathogenesis of oropharyngeal cancers in contrast to those situated in the oral cavity. Conversely, the lack of a significant link between HPV and oral cavity cancers suggests potential variations in the etiological role of HPV across different anatomical sites within the oral cavity. These findings carry crucial clinical implications, guiding targeted screening and treatment approaches, while also prompting considerations for public health interventions, particularly in the realm of HPV vaccination. Despite inherent limitations in retrospective hospital-based data, this study serves as a foundation for future research, advocating for prospective studies with more comprehensive datasets. In summary, this research not only contributes substantively to our understanding of HPV-associated oral cancers but also holds promise for informing clinical and public health strategies aimed at mitigating the impact of HPV in the context of oral malignancies.

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