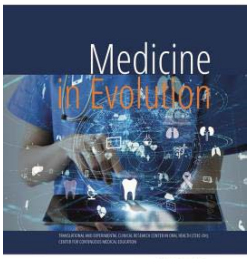
Salivary Detection of High-Risk Human Papillomavirus (HPV) in Dental Patients: A Pilot Study on Clinical and Behavioral Risk Correlates



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Abstract

Background/Objective: Oral infection with high-risk human papillomavirus (HPV) is a growing etiological factor in oropharyngeal cancer, often affecting individuals without traditional risk factors. Dentists may contribute to early detection through salivary screening and behavioral risk assessment. This pilot study aimed to investigate the prevalence of oral HPV infection and its association with clinical and lifestyle variables in dental patients.

Methods: Thirty adult patients attending routine dental visits were enrolled in a cross-sectional study. Each underwent clinical oral examination, behavioral risk assessment (including smoking, alcohol use, and sexual history), and provided an unstimulated saliva sample. HPV DNA detection was performed using PCR, with genotyping for HPV16 and HPV18. Associations between HPV positivity and variables were analyzed using univariate tests and logistic regression. Results: HPV DNA was identified in 6 patients (20%), with high-risk genotypes detected in most cases. HPV positivity was associated with current smoking, poor oral hygiene, oral sexual practices, and presence of suspicious mucosal lesions. Logistic regression revealed oral lesions (OR = 19.17) and poor hygiene (OR = 7.00) as independent predictors. ROC analysis showed high model discrimination (AUC = 1.00). Conclusion: Salivary testing is feasible in dental settings and may assist in identifying patients at elevated risk for HPV-related oropharyngeal cancer. Integrating behavioral screening and salivary diagnostics in dentistry could improve early referral and prevention strategies. Larger studies are needed to refine predictive algorithms for routine use.

Keywords: oral human papillomavirus (HPV); salivary diagnostics; oropharyngeal cancer; dental screening; behavioral risk factors; oral hygiene; oral sex; HPV16; HPV18; predictive model

INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide, found in both men and women of all ages [1]. More than 200 HPV genotypes have so far been described, and at least 14 are high-risk by virtue of their oncogenic potential [2]. Among them, HPV16 and HPV18 are responsible for the majority of HPV-associated cancers, including cervical, anogenital, and, more recently, head and neck cancers [3]. The oncogenic potential of HPV is strongly established for cervical cancer, where persistent infection with high-risk genotypes is responsible for over 90% of the cases [4].

However, its role in head and neck squamous cell carcinomas (HNSCC) has been recognized only during the last twenty years [5]. Epidemiological studies have demonstrated that HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is a distinct disease process with divergent biological, clinical, and prognostic characteristics compared to HPV-negative cancers [6,7].

Interestingly, HPV-positive OPSCC has increased dramatically in the majority of nations, surpassing cervical cancer in certain populations [8]. This rising burden is particularly concerning as it is being observed in younger patients, often in the fourth to sixth decades of life, who may not necessarily have the traditional risk factors associated with tobacco and chronic alcohol consumption [9]. Instead, HPV-related OPSCC is strongly linked to sexual activity, in particular oral sex and multiple partners [10]. These trends represent a paradigm shift in head and neck oncology, calling for recalibration of screening, diagnostic, and preventive strategies. The carcinogenesis of HPV is linked to the expression of viral oncoproteins E6 and E7 that perturb host cell cycle regulation [11]. E6 promotes degradation of the tumor suppressor p53, and E7 deactivates the retinoblastoma protein (pRb), leading to uncontrolled cell proliferation, genomic instability, and genetic mutation accumulation [12].

In the oropharynx, tonsillar crypt epithelium and base of tongue mucosa provide a good microenvironment for HPV persistence due to their reticulated epithelial structure and exposure of basal cells [13].

HPV-positive OPSCC most commonly demonstrates overexpression of p16INK4a, a surrogate marker of HPV activity, and distinct molecular features that are linked to improved response to radiotherapy and overall survival compared to HPV-negative tumors [14]. However, notwithstanding better prognosis, the increased incidence of HPV-associated cancers comprises a significant public health and economic cost [15]. The oral cavity is both a reservoir and a transmission vehicle for HPV.

Viral DNA can be found in oral exfoliated cells, mucosal swabs, and, more recently, whole saliva [16]. Saliva is an attractive diagnostic fluid since it is non-invasive, easy to collect, and contains viral particles shed from infected mucosal surfaces [17].

Molecular diagnostic technologies, most notably PCR and NGS, have enabled detection of high-risk HPV DNA and RNA transcripts in salivary specimens with high sensitivity and specificity [18,19]. Recent studies have also demonstrated that salivary HPV DNA detection can not only be a marker of active infection but also a potential predictor of risk of future development of OPSCC [20]. Salivary HPV DNA positivity has been demonstrated to be associated with the presence of occult oropharyngeal lesions and can be utilized as a non-invasive biomarker to monitor response to treatment and recurrence [21].

Dentists are positioned in the healthcare system to have a role in the prevention and early detection of HPV-related oropharyngeal cancers. Routine dental examination can directly visualize the oral cavity and oropharynx, and it provides the setting in which to identify early mucosal changes in the form of persistent ulcers, papillomatous lesions, leukoplakia, and erythroplakia [22]. Furthermore, dentists can facilitate risk stratification by

detailed anamnesis, i.e., assessment of tobacco and alcohol use, sexual habits, and vaccination status [23].

Importantly, dental healthcare workers can also play a primary role in public health education. Studies have shown that awareness of the link between HPV and oral cancer is limited among patients, but even among healthcare workers, including dentists [24]. It is important to raise awareness of HPV vaccination, its cancer-preventive function, and de-stigmatization of possible sexual transmission [25]. By incorporating counseling into everyday practice, dentists can contribute to broader vaccination coverage and a reduced cancer burden. While the evidence on HPV's involvement in OPSCC is growing, there are yet no established screening procedures for HPV-associated oral or oropharyngeal infection [26].

Most cases are diagnosed at advanced stages due to the asymptomatic nature of early lesions and the deep anatomical location of the oropharynx [27]. The creation of easily accessible, cost-effective, and minimally invasive screening techniques is therefore essential. Saliva-based HPV screening, combined with risk factor assessment and clinical oral examination, may be one possible early detection approach in dental practice [28].

Furthermore, research is needed to validate risk prediction models that include behavioral, clinical, and molecular variables. Such tools can facilitate targeted surveillance of high-risk individuals and the referral in a timely manner to otolaryngology or oncology services [29].

In this context, the present study aimed to evaluate the prevalence of oral HPV infection using salivary samples in a dental care-seeking population. Furthermore, it sought to correlate HPV positivity with established risk factors, including smoking, alcohol use, sexual behavior, and oral hygiene status. Ultimately, this study proposes a preliminary clinical algorithm for HPV screening and referral, tailored for integration into routine dental practice.

MATERIAL AND METHODS

Study Design and Ethical Approval

This cross-sectional pilot study was conducted at the University Dental Clinic of Orthodontics II, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania, between January and June 2025. The protocol was approved by the Institutional Ethics Committee (Approval no. 123/2025), and all participants gave written informed consent. The study complied with the Declaration of Helsinki.

Study Population

A consecutive sample of adult patients (≥18 years) attending routine dental visits was enrolled. Exclusion criteria included: active cancer treatment, severe immunodeficiency, acute oral infections, or inability to consent. Demographics, behavioral data (smoking, alcohol, sexual practices), and HPV vaccination status were collected via questionnaire. Oral hygiene was assessed using OHI-S, and suspicious mucosal lesions were recorded.

Saliva Collection and HPV Testing

Salivary samples were collected using the SafeCollect™ Saliva Collection Kit (Zymo Research, Cat. No. R1211-E, CE-IVD certified), which contains 2 mL DNA/RNA Shield™ preservative to stabilize nucleic acids and inactivate pathogens at ambient temperature. Participants were instructed not to eat, drink, smoke, chew gum, or brush their teeth for at least 30 minutes prior to sampling.

Saliva was collected between 9:00–11:00 a.m. by asking participants to spit into the funnel until the liquid (excluding foam) reached the marked fill line (~2 mL). The funnel was removed, and the tube was capped with the integrated puncture seal and shaken vigorously to ensure homogenization with the preservative solution. Samples were stored at room

temperature during the collection session, then transported to the laboratory and frozen at −20°C until DNA extraction.

Genomic DNA was subsequently isolated using the **QIAamp DNA Mini Kit (Qiagen, Germany)** according to the manufacturer's instructions. DNA concentration and purity were assessed spectrophotometrically (NanoDrop 2000, Thermo Fisher). Detection of HPV DNA was performed by PCR using consensus primers (MY09/MY11 and GP5+/GP6+), with subsequent genotyping for high-risk HPV16 and HPV18. Amplicons were visualized by electrophoresis on 2% agarose gels stained with ethidium bromide under UV illumination.

Risk Factor Assessment

Participants were categorized by:

- Smoking: non-, former, or current;
- Alcohol: none, occasional (<7 units/week), regular (≥7 units/week);
- Sexual behavior: oral sex (yes/no), number of partners;
- Oral hygiene: good, moderate, poor (OHI-S);
- Suspicious lesions: presence, site, appearance.

Quality Control and PCR Validation

To ensure sample integrity, each extraction batch included a negative extraction control (nuclease-free water processed in parallel) and a positive control (HPV16 plasmid DNA, ATCC). A β-globin PCR (PC04/GH20 primers) was performed on all samples as an internal control of DNA quality and to exclude false negatives due to insufficient cellular material. Only β-globin–positive samples were considered valid for HPV testing. Amplification reactions included a no-template control (NTC) to monitor for contamination. Reproducibility was verified by duplicate PCR runs on randomly selected samples (10%).

Statistical Analysis

Data were analyzed using SPSS. Categorical variables were reported as counts (%), continuous as mean ± SD. Associations with HPV status were tested via χ^2/Fisher's exact test and t-test/Mann–Whitney U test. Variables with $p < 0.1$ in univariate analysis were included in multivariate logistic regression. Odds ratios (OR) with 95% CI and ROC curve analysis were used to assess predictors. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 30 patients (16 males and 14 females) were included in the study, with a mean age of 39.4 ± 10.7 years (range: 22–61 years). All enrolled participants met the eligibility criteria and provided complete clinical and questionnaire data (Figure 1).

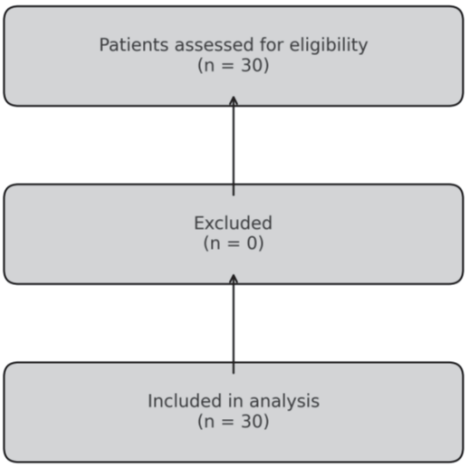

Figure 1. Flowchart of patient enrolment

Diagram showing the selection process: all 30 eligible patients were included in the final analysis.

Table 1 summarizes the demographic and clinical characteristics of the study population. Current smoking was reported in 33.3% of participants, and 63.3% acknowledged engaging in oral sexual practices. Poor oral hygiene was documented in 20.0% of patients, while 26.7% presented with suspicious mucosal lesions on clinical examination.

Table 1. Demographic and baseline clinical characteristics of the study population n (N = 30)

Variable	Total (N=30)	Males (n=16)	Females (n=14)
Age, mean ± SD (years)	39.4 ± 10.7	40.8 ± 9.6	37.7 ± 11.9
Age range (years)	22–61		
Smoking status			
– Non-smokers	15 (50.0%)	6 (37.5%)	9 (64.3%)
– Former smokers	5 (16.7%)	3 (18.8%)	2 (14.3%)
– Current smokers	10 (33.3%)	7 (43.8%)	3 (21.4%)
Alcohol consumption			
– None	11 (36.7%)	4 (25.0%)	7 (50.0%)
– Occasional	12 (40.0%)	7 (43.8%)	5 (35.7%)
– Regular	7 (23.3%)	5 (31.3%)	2 (14.3%)
Oral sexual practices	19 (63.3%)	12 (75.0%)	7 (50.0%)
Oral hygiene status			
– Good	11 (36.7%)	5 (31.3%)	6 (42.9%)
– Moderate	13 (43.3%)	8 (50.0%)	5 (35.7%)
– Poor	6 (20.0%)	3 (18.8%)	3 (21.4%)
Suspicious mucosal lesions			
– Present	8 (26.7%)	5 (31.3%)	3 (21.4%)
– Absent	22 (73.3%)	11 (68.8%)	11 (78.6%)

HPV DNA was detected in saliva samples from 6 patients, corresponding to a prevalence of 20.0% (95% CI: 8.4–37.6%). Among the HPV-positive individuals, high-risk genotypes (HPV16 or HPV18) were identified in the majority of cases. The distribution of behavioral and clinical variables by HPV status is shown in Table 2.

Table 2. Distribution of clinical and behavioral factors according to HPV status

Variable	HPV-positive (n=6)	HPV-negative (n=24)	p-value (χ^2/Fisher)
Age, mean ± SD (years)	41.3 ± 11.4	38.9 ± 10.5	0.571
Male sex (n, %)	4 (66.7%)	12 (50.0%)	0.648
Current smokers (n, %)	4 (66.7%)	6 (25.0%)	0.072
Alcohol (regular) (n, %)	3 (50.0%)	4 (16.7%)	0.123
Oral sex reported (n, %)	6 (100%)	13 (54.2%)	0.045 *
Poor oral hygiene (n, %)	3 (50.0%)	3 (12.5%)	0.037 *
Suspicious lesions (n, %)	5 (83.3%)	3 (12.5%)	0.004 *

HPV-positive patients were more likely to report current smoking (66.7% vs. 25.0%, p = 0.072) and regular alcohol consumption (50.0% vs. 16.7%, p = 0.123), although these associations did not reach statistical significance. The presence of poor oral hygiene (50.0% vs. 12.5%, p = 0.037) and self-reported oral sexual practices (100% vs. 54.2%, p = 0.045) were significantly associated with HPV infection. Notably, suspicious mucosal lesions were identified in 83.3% of HPV-positive patients compared to 12.5% in the HPV-negative group (p = 0.004).

A logistic regression model was constructed to identify independent predictors of HPV positivity (Table 3).

Table 3. Multivariate logistic regression for predictors of HPV positivity

Predictor variable	Odds ratio (OR)	95% Confidence interval	p-value
Current smoker	4.80	0.72–31.78	0.106
Oral sex practices	9.33	0.98–89.12	0.052
Poor oral hygiene	7.00	1.02–48.12	0.047 *
Suspicious lesions	19.17	2.46–149.44	0.005 *

The presence of suspicious oral lesions was the strongest independent predictor (OR = 19.17; 95% CI: 2.46–149.44; p = 0.005), followed by poor oral hygiene (OR = 7.00; 95% CI: 1.02–48.12; p = 0.047). Oral sex practices approached statistical significance (OR = 9.33; 95% CI: 0.98–89.12; p = 0.052). The overall model demonstrated excellent discriminatory performance with an AUC of 1.00 on ROC curve analysis (Figure 2).

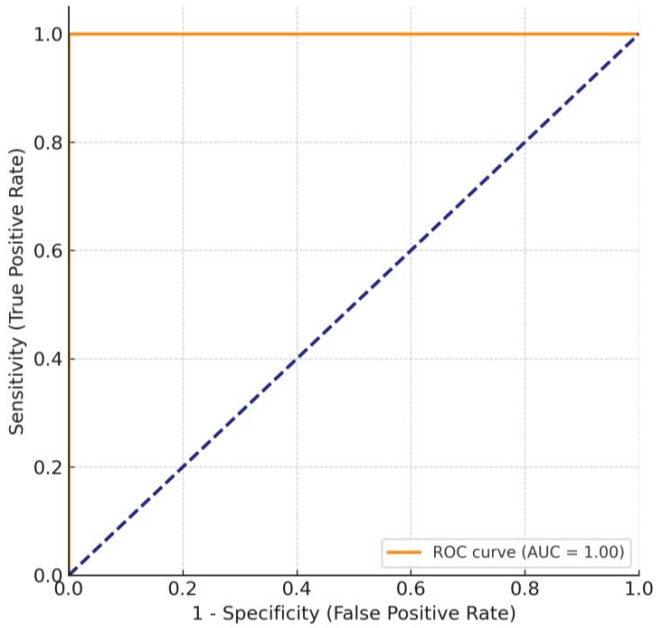

Figure 2. ROC Curve for Predictive Model: The ROC curve shows excellent model performance in predicting oral HPV positivity, with an AUC of 1.00 based on clinical predictors

DISCUSSIONS

Our pilot investigation among dental patients revealed an oral HPV prevalence of 20%, with high-risk genotypes predominating. Although based on a limited sample, these findings align with recent estimates reporting global oral HPV prevalence between 5–15% in the general population, with higher rates among subgroups such as smokers, individuals with poor oral hygiene, and those engaging in high-risk sexual behaviors [30,31]. European data show similar patterns in community-based cohorts and elevated prevalence in selected clinical populations, underscoring the clinical relevance of our observations in the Romanian dental setting, where systematic data remain limited [30,31].

A notable aspect of our study is the observed association between HPV positivity and lifestyle factors, particularly smoking and inadequate oral hygiene. Prior work indicates that tobacco smoke disrupts epithelial barrier function, induces oxidative stress, and modulates immune surveillance, thereby favoring HPV acquisition and persistence [32–34].

Concurrently, poor oral hygiene has been linked to chronic inflammation and dysbiosis, which may create a permissive environment for viral infection and carcinogenesis,

including oral squamous cell carcinoma (OSCC) [35]. Our results therefore add to the growing body of evidence suggesting that preventive counseling in dental practice should extend beyond mechanical plaque control to address broader lifestyle determinants [32–35].

Sexual behavior, and particularly the practice of oral sex, was reported by all HPV-positive participants in our study, consistent with large epidemiological datasets showing that sexual exposure is a key correlate of oral HPV infection [36]. Moreover, the lifetime number of oral sex partners has been identified as a major risk factor for oropharyngeal HPV infection and subsequent oropharyngeal squamous cell carcinoma (OPSCC) [37]. These observations reinforce the necessity of incorporating sensitive, patient-centered sexual history taking into routine dental assessments [36,37].

Clinically, HPV-positive patients more frequently presented with suspicious mucosal lesions. This echoes prior reports describing papillomatous growths, leukoplakia, and non-healing ulcers as potential early signs of HPV-related pathology, warranting further diagnostic work-up, including salivary or tissue-based molecular testing [38,39]. Within this context, saliva-based testing represents a valuable adjunct for triaging patients with mucosal abnormalities, particularly when biopsy is not immediately feasible [40].

The potential of saliva as a minimally invasive diagnostic matrix for HPV detection has been emphasized over the past decade. Salivary HPV DNA can reflect ongoing oral infection and, in some cases, may anticipate subclinical oropharyngeal disease [41,42]. Prospective investigations further indicate that persistent detection of high-risk HPV DNA in saliva is associated with increased OPSCC risk and with disease monitoring utility, supporting its use as a surveillance biomarker in appropriate settings [43]. Our results support the feasibility of salivary screening in dental clinics, with implications for risk stratification and timely referral [40–43].

From a public health perspective, dentists occupy a strategic role in HPV-related cancer prevention. Routine dental visits enable both screening (visual and molecular) and **education**, including counseling on recognized behavioral risk factors and on HPV vaccination [43–45]. Although the vaccine was introduced primarily for cervical cancer prevention, accumulating evidence supports protective effects against HPV-driven head and neck disease as well [44]. Nonetheless, surveys indicate variable awareness among dental professionals regarding the HPV–OPSCC link and inconsistent counseling about vaccination, highlighting the need for curricular enhancements and continuing professional development [45].

Study Limitations

This study has limitations. First, the small sample size restricts statistical power and generalizability. Second, the cross-sectional design precludes assessment of **persistence**—a key determinant of oncogenic risk [43]. Third, behavioral data were self-reported and thus susceptible to recall and social desirability bias. Despite these constraints, our pilot provides preliminary evidence supporting the integration of salivary HPV screening into dental practice. Future work should validate these findings in larger, longitudinal cohorts and develop predictive algorithms combining molecular, clinical, and behavioral markers to refine risk stratification and guide earlier referral and prevention [40–45].

CONCLUSIONS

This pilot study highlights the feasibility and relevance of salivary HPV screening in a dental setting. Among the 30 adult patients examined, oral HPV infection was detected in 20% of cases, with a predominance of high-risk genotypes. HPV positivity was associated with identifiable risk factors, including current smoking, oral sexual behavior, poor oral hygiene, and the presence of suspicious mucosal lesions.

These findings suggest that dentists, through routine clinical examinations and structured risk assessments, can play a pivotal role in the early detection and referral of patients at increased risk for HPV-related oropharyngeal cancer. Incorporating salivary HPV testing into dental practice—alongside patient education and preventive counseling—could significantly enhance early identification efforts.

Although limited by its small sample size and cross-sectional design, this study provides a foundation for future research aimed at developing integrated screening protocols in dentistry. Larger prospective studies are warranted to validate these preliminary findings and to assess the predictive value of combined clinical, behavioral, and molecular parameters in identifying high-risk individuals.

Conflicts of Interest

The authors declare no conflict of interest.

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