Multi-site HPV infection in women with cervical intraepithelial neoplasia: an exploratory analysis

Tuğba Akçaoğlu[1-3], Yağmur Soykan[4,5], Neslihan Bayramoğlu Tepe[6], Ozan Doğan[7]

[1]Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America

[2]Department of Obstetrics and Gynecology, İstanbul Medipol University Faculty of Medicine, İstanbul, Türkiye

[3]Clinic of Obstetrics and Gynecology, Cengiz Gökçek Gynecology and Pediatrics Hospital, Gaziantep, Türkiye

[4]Clinic of Gynecologic Oncology, Cengiz Gökçek Gynecology and Pediatrics Hospital, Gaziantep, Türkiye

[5]Department of Medical Biology and Genetics, Gazi University Faculty of Medicine, Ankara, Türkiye

[6]Department of Obstetrics and Gynecology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye

[7]Department of Obstetrics and Gynecology, İstanbul Nisantaşı University Faculty of Medicine, İstanbul, Türkiye

Abstract

Objective: Human papillomavirus (HPV) positivity is associated with cervical, oropharyngeal, and anal cancers. There is insufficient published evidence regarding the effectiveness of obtaining oropharyngeal and anal swabs from patients with cervical HPV positivity to detect potential pathologies. Our aim was to analyze the feasibility of this potential screening protocol in a pilot group.

Material and Methods: In this cross-sectional exploratory analysis, women diagnosed with cervical intraepithelial neoplasia (CIN) grades 1, 2, or 3 were recruited. In order to evaluate HPV infection beyond the cervix, oropharyngeal and anal swab samples from HPV-positive women presenting to the obstetrics and gynecology clinic with histopathologically confirmed CIN were collected.

Results: A total of 30 women who provided informed consent were included in this pilot study. HPV 16 was the predominant cervical HPV type across all CIN grades (46.7% of cases), but HPV genotype did not significantly correlate with the severity of CIN lesions (p=0.786). No statistically significant association was found between cervical and anal HPV infections (p=0.427). Oral HPV positivity was rare (6.7%) and similarly showed no significant correlation with cervical HPV infection (p=0.499).

Conclusion: These findings provide preliminary data on the effectiveness of multi-site HPV screening in this population. Future larger-scale studies are needed to determine whether detecting extra-cervical HPV in women with cervical HPV positivity will influence clinical management decisions. [J Turk Ger Gynecol Assoc. 2025; 26(4): 289-96]

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Address for Correspondence: *Tuğba Akçaoğlu*
e-mail: *takcaog1@jh.edu* ***ORCID:*** *orcid.org/0000-0002-0354-3292*

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Introduction

Human papillomavirus (HPV) is a DNA virus from the Papillomaviridae family virus family, and associated with cervical, oropharyngeal and anal cancers (1). The International Agency for Research on Cancer and World Health Organization classify HPV as a necessary cause of cervical cancer (2-4). Persistent infection with high-risk HPV, particularly HPV-16 and HPV-18, is an almost universal cause of cervical cancer, with studies showing HPV DNA in 99.7% of cases (2,3). In patients with confirmed cervical HPV positivity and pathological findings categorized as cervical intraepithelial neoplasia (CIN) 1, CIN 2, or CIN 3, there is a paucity of data in the current literature regarding the clinical utility of concurrent oropharyngeal and anal sampling for the detection of additional HPV-associated lesions (5).

Although HPV's primary clinical impact is in the cervix, high-risk types like HPV-16 and HPV-18 may also cause malignancies in the oropharynx and anus (6,7). Approximately 5% of all cancers worldwide are attributable to HPV, with women more affected than men (8). Cervical HPV is far more common than oral HPV, but coinfection risk increases substantially in HPV-positive women (9). Notably, women with cervical HPV are up to five times more likely to harbor oral HPV (10). Simultaneous cervical and anal infections occur even more frequently, with studies reporting anal HPV positivity in over 50% of cervical HPV-positive women, often involving oncogenic strains (9,11).

Evidence suggests that cervical HPV positivity could serve as a predictive marker for extra-cervical infection risk, particularly for the anal region (12). Collaborative pooled analysis show HIV-negative women with cervical HPV-16 positivity have a 41% prevalence of anal HPV-16, versus 2% in HPV-16-negative counterparts (13,14). While anal HPV screening (via cytology and anoscopy) is cautiously being considered for high-risk groups in recent international guidelines, there is still no standardized screening recommendation for oropharyngeal HPV (15). Current global and national cervical screening programs, including in Türkiye, do not include oropharyngeal or anal sampling, largely due to insufficient data.

Despite growing awareness of the potential for multisite impact of HPV, clinical guidelines do not currently support routine extra-cervical HPV screening (16). Key barriers include a lack of validated screening protocols for the oropharynx and uncertainty about how to manage subclinical findings in the anal region. Existing studies are often small and geographically limited (17,18). Nonetheless, theoretical benefits, such as early detection of premalignant lesions, refined individual risk profiling, and improved prevention strategies, support the need for further large-scale studies (17).

This study sought to evaluate the diagnostic value of adding oropharyngeal and anal swabs in women with cervical HPV positivity. We aimed to assess whether concurrent oropharyngeal and anal HPV screening would detect otherwise unrecognized HPV-related lesions in patients with established cervical HPV infection. The clinical utility of such screening, including its potential to inform patient management decisions, was the primary objective.

Material and Methods

This prospective cross-sectional pilot study was conducted at the department of obstetrics and gynecology to evaluate the prevalence of extra-cervical HPV infections in women with histopathologically confirmed CIN. Women who presented to the outpatient gynecology clinic and had cervical HPV DNA positivity along with histologic findings consistent with CIN 1, CIN 2, or CIN 3 were invited to participate between April 2023 and June 2024. A total of 30 women were recruited, and written informed consent was obtained from all participants prior to enrollment.

Ethics

Ethics committee approval

The study protocol was reviewed and approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 362, date: 14.04.2023).

Clinical trial registration

This trial was registered at ClinicalTrials.gov under the identifier NCT06906913.

Sample collection and laboratory methods

All patients were previously diagnosed by the gynecologic oncology specialist (YS), and pathological evaluations were used to stratify the study groups. Patient management, including follow-up and treatment decisions, was conducted in accordance with the guidelines of the American Society for Colposcopy and Cervical Pathology (19), with surgical intervention offered when indicated by colposcopic and histopathologic findings.

Oropharyngeal and anal swab samples were collected from each participant under sterile conditions by a gynecologic oncology specialist (YS) using standardized sampling techniques. All samples were labeled with unique, anonymized patient identifiers and stored in validated transport media under temperature-controlled conditions until processing. HPV DNA detection was performed using PCR-based assays incorporating both consensus and type-specific primers. Internal human DNA controls, as well as positive and negative controls, were used in each run to ensure assay accuracy and sensitivity. All laboratory procedures were carried out under the supervision of faculty of the department of medical microbiology from the sponsor institution.

Samples were collected from the patients using Digene® HC2 DNA Collection Device (Qiagen, Hilden, Germany) swabs. Each sample was vortexed separately to ensure homogeneous mixing. Then 800 µL of the samples were removed and extracted in an automated QIAsymphony SP/AS (Qiagen, Hilden, Germany). The extraction products were amplified in Rotor Gene Q 5Plex Real Time PCR (Qiagen, Hilden, Germany) using NLM HPV Genotypes 14 Real-TM Quant kit (Nuclear Laser Medicine, Italy). For each patient, 14 different HPV DNA types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) were analyzed. Negative and K2 positive controls were used as controls.

To ensure methodological integrity, quality control measures included complete documentation of sample collection and processing steps, random repeat testing for a subset of samples, and strict adherence to data handling and reporting protocols (20). These procedures were followed to ensure the reproducibility, validity, and reliability of the data.

Statistical analysis

All statistical analyses were conducted using SPSS, version 27 (IBM Inc., Armonk, NY, USA). Descriptive statistics were calculated to summarize the demographic and clinical characteristics of the study population. Categorical variables were analyzed using pearson's chi-square (χ^2) test to evaluate associations between cervical HPV status and concurrent oropharyngeal and anal HPV positivity. A p-value of <0.05 was considered statistically significant.

Results

The patient dataset comprised 30 valid observations. The mean age across all cases was 45.07±8.71, and ranged from 29 to 65 years. Of the 30 women, 11 (36.7%) had experienced menopause, while 19 (63.3%) had not. In terms of obstetric history, the mean number of pregnancies (gravida) was 4.1, with a range from 0 to 8. The mean number of live births (parity) was 3.37, with a range from 0 to 7.

Cervical HPV infection in relation to dysplasia severity

Among 30 women with cervical dysplasia, HPV-16 was the most frequently detected cervical HPV type (46.7%), followed by other high-risk HPV types and mixed infections. One patient (3.3%) was positive for HPV 18, and two patients (6.7%) tested positive for both HPV-16 and HPV-18. Furthermore, three patients (10%) were positive for HPV-16 along with other HPV types, and one patient (3.3%) was positive for HPV-16, HPV-18, and non-HPV-16/18 oncogenic type. Nine patients (30%) tested positive for other types of HPV (Table 1).

In the study dataset, HPV-16 was the most common type across all CIN grades. Moreover, the presence of specific HPV types (16, 18, or others) did not differ between CIN 1, 2, or 3 ($p=0.786$) (Table 1).

Anal HPV detection in patients with cervical dysplasia

Among women without anal HPV positivity, all were positive for HPV-16 in cervical samples. Meanwhile, among those with anal HPV positivity, cervical HPV infection was more diverse (HPV-16, 18, and other types detected). Despite this trend, the difference was not significant, likely because of small sample size (Table 2).

Regarding the anal swab results, six (20%) tested positive for HPV-16, one (3.3%) tested positive for HPV-18, and six others (20%) were positive for other HPV types. Additionally, 6 patients (20%) were positive for both HPV-16 and another HPV type, while 1 patient (3.3%) tested positive for HPV-16, HPV-18, and another HPV type. No HPV types were detected in the anal swabs of 10 patients (33.3%). No statistically significant association between anal and cervical HPV positivity was found ($p=0.427$, $p>0.05$) (Table 2).

Oral HPV detection in patients with cervical dysplasia

Oropharyngeal HPV infection was rare, being present in only two of the patients (6.7%), both of them with a type of HPV other than those specified. No correlation was observed between cervical and oropharyngeal HPV infection ($p=0.499$) (Table 3).

Discussion

HPV is a common, sexually-transmitted virus associated with significant health risks (7). Infections at one anatomical site may increase susceptibility at others, particularly with cervical high-risk HPV, which elevates the likelihood of concurrent anal and possibly oral infections (21). Though oral transmission from the anogenital area is less common, isolated oral HPV cases without simultaneous genital or anal involvement are rare (21). Our study supports these observations (Tables 1-3).

HPV-related cancer risks vary across populations, including transgender and gender-diverse individuals assigned female at birth (TGD AFAB), who may face similar or even greater risks than cisgender women. This highlights the need for accessible screening tools, such as self-sampling (22,23).

In the present study of HPV-positive women with CIN 1-3, 66.7% had HPV DNA in anal swabs, while only 6.7% had it in oral swabs (Table 1). This suggests that the anal canal is a far more frequent site of concurrent infection than the oropharynx. Our findings are consistent with prior studies, including one by Nasioutziki et al. (5), which found anal high-risk HPV in 54.2% of women referred for colposcopy.

Behavioral risk factors and anatomical proximity likely explain the frequent detection of identical HPV types in

Table 1. Analysis of the association between colposcopic biopsy findings and cervical HPV

Variable	CIN 1 n=17 (56.7%)		CIN 2 n=5 (16.7%)		CIN 3 n=8 (26.7%)		p**
	n	%	n	%	n	%	
Cervical HPV							
HPV 16	7	41.2	3	60.0	4	50.0	
HPV 18	-	-	-	-	1	12.5	
Other HPV types	6	35.3	1	20.0	2	25.0	χ^2=6.336
HPV 16 and 18	1	5.9	-	-	1	12.5	p=0.786
HPV 16 and other	2	11.7	1	20.0	-	-	
HPV 16 and 18 and other	1	5.9	-	-	-	-	

**There was no statistically significant relationship between colposcopic biopsy and cervical HPV (p>0.05). The groups were found to be independent and homogeneous in terms of the specified characteristics
HPV: Human papillomavirus, CIN: Cervical intraepithelial neoplasia

Table 2. Analysis of the association between anal and cervical HPV infections

Variable	Anal HPV (-) n=10 (33.3%)		Anal HPV (+) n=20 (66.7%)		p*
	n	%	n	%	
Cervical HPV					
HPV 16	5	100.0	9	45.0	
HPV 18	-	-	1	5.0	
Other HPV types	-	-	4	20.0	χ^2=4.911
HPV 16 and 18	-	-	2	10.0	p=0.427**
HPV 16 and other	-	-	3	15.0	
HPV 16 and 18 and other	-	-	1	5.0	

*The association between two categorical variables was analyzed using pearson chi-square cross-tabulations
**There is no statistically significant association between anal HPV and cervical HPV (p>0.05). The groups were found to be independent and homogeneous with respect to the specified characteristics
HPV: Human papillomavirus

Table 3. Analysis of the association between oral and cervical HPV infections

Variable	Oral HPV (-) n=28 (93.3%)		Oral HPV (+) n=2 (6.7%)		p**
	n	%	n	%	
Cervical HPV					
HPV 16	13	46.4	1	50.0	
HPV 18	1	3.6	-	-	
Other HPV types	9	32.1	-	-	χ^2=4.362
HPV 16 and18	2	7.1	-	-	p=0.499
HPV 16 and other	2	7.1	1	50.0	
HPV 16 and 18 and other	1	3.7	-	-	

**There is no statistically significant association between oral HPV and cervical HPV (p>0.05). The groups were found to be independent and homogeneous with respect to the specified characteristics
In summary, no significant associations were found between cervical lesion grade (CIN 1-3) and HPV type, between cervical and anal HPV infection, and between cervical and oral HPV infection (Tables 1-3)
HPV: Human papillomavirus

cervical and anal sites. This co-infection supports the theory of autoinoculation and highlights the clinical significance that the women with cervical neoplasia are at increased risk for anal lesions. Histologic high-grade intraepithelial lesions of the anus have been reported in up to 9% of women with cervical or vaginal dysplasia (24,25), and anal cancer incidence is several times higher in women with a history of cervical high-grade lesions (26).

While there are no established screening guidelines for anal cancer in immunocompetent women, some experts advocate targeted screening for high-risk subgroups (27). Similar to cervical pap testing, anal cytology and HPV testing, followed by high-resolution anoscopy for abnormal results, have been studied, but mostly in HIV-positive individuals and men who have sex with men (28). For women with cervical HPV, it remains unclear whether detecting and treating anal lesions improves outcomes. Our findings support further research into this area (Table 2). Until definitive evidence emerges, individualized evaluation and clinical vigilance are recommended, particularly for patients with persistent HPV-16 infection, immunosuppression, or prior anogenital warts.

The rising incidence of anal squamous cell carcinoma (SCC) justifies a shift in focus toward prevention through detection of precancerous lesions. Asymptomatic individuals, as well as those with proctological symptoms, should undergo appropriate evaluation (27,29). The nonavalent HPV vaccine, which protects against nine major types (6, 11, 16, 18, 31, 33, 45, 52, 58), offers a first line of defense not only against cervical cancer but also oropharyngeal and anal cancers (30).

Oral HPV infections were much less common in our cohort. Only 2 of 30 women (6.7%) had detectable oral HPV, both involving HPV-16 (Table 3). HPV-16 is the genotype most strongly associated with oropharyngeal SCCs. Nonetheless, our detection rate was low, consistent with studies like that of Nasioutziki et al. (25), who found a 2.5% prevalence in similar populations, although others have reported higher rates (31-33). These discrepancies may reflect differences in sampling methods and population characteristics. Our use of oropharyngeal swabs rather than oral rinse may have contributed to lower sensitivity, and many oral infections may be transient and undetectable by single sampling. Moreover, prior research has shown that oral HPV infections are often independent of cervical types, even when both sites are infected (34). While we did not assess concordance between oral and cervical genotypes, both oral-positive cases involved HPV-16, suggesting possible overlap. The low prevalence of oral HPV compared to anal HPV suggests differences in susceptibility, exposure, or immune clearance between these sites.

Given the limited yield, routine oral HPV screening is not currently recommended in asymptomatic women. No clinical guidelines support testing the oropharynx for HPV, especially since the most affected areas which are the tonsils and base of tongue, are not easily accessible for swabbing. In addition, no proven treatment exists for asymptomatic oral infections, making screening less actionable. Since recent increases in incidence and survival of oropharyngeal cancers in the United States (US) have been attributed to HPV infection, researchers from the National Cancer Institute of the National Institutes of Health estimated trends in HPV prevalence and concluded that the increases in the population-level incidence and improved survival of oropharyngeal cancers in the US since 1984 are caused by HPV infection (35). Patients with detected oral HPV can be counseled about signs and risks of oropharyngeal cancer, but referral for invasive evaluation is not generally indicated without lesions.

A meta-analysis of HPV biomarkers in head and neck cancer found that combining HPV DNA, E6/E7 mRNA, and p16INK4a was most effective in identifying HPV-driven tumors, with E6/E7 mRNA being the most biologically relevant (36). More work is needed to validate screening strategies and biomarkers for HPV-associated oral and anal pathologies.

Our findings support the hypothesis that HPV positivity across anatomical sites is often interconnected. Behavioral factors, such as non-coital sex and autoerotic practices, may contribute to viral transmission across sites (37-40). However, no routine otolaryngologic or surgical consultations were performed in our cohort to investigate potential subclinical oral or anal disease.

Public health efforts focused on education, HPV vaccination, and regular screening are essential to reduce the HPV-related cancer burden (41). These strategies are especially important in high-risk populations, such as incarcerated individuals. HPV-related cancers, including anal SCC, are on the rise, reinforcing the need for preventive screening (42).

Although infections may vary by site, the natural history of HPV likely differs anatomically. Prospective studies should assess multi-site infection patterns to inform effective screening and vaccination protocols (11). As Darragh and Winkler (43) note, while both anal and cervical cancers share an HPV etiology, especially HPV-16, screening methods differ. Anal cytology has lower sensitivity and specificity than cervical cytology, and standardized anal screening guidelines are still under development (43). A widespread lack of awareness about HPV and other sexually transmitted infections (STI) persists (44). Frisch et al. (45) found that anal cancer, like cervical cancer, is strongly associated with sexual behavior, including multiple partners, positive STI history, receptive anal intercourse, and immunosuppression.

Surveys among students revealed that many are unaware HPV causes cancers beyond the cervix (46). This highlights the need for public health campaigns focused on safe sex, early STI diagnosis, self-sampling, and HPV vaccination, especially among vulnerable groups (47,48).

A major preventive opportunity lies in prophylactic HPV vaccination, especially since most of the common strains in cervico-anal co-infections are vaccine-preventable. Many participants in our study were likely unvaccinated or vaccinated later in life. We suggest that future cohorts may benefit from

reduced multi-site HPV prevalence as vaccine coverage improves.

Our findings reinforce the importance of considering HPV as a multi-site infection. For women with cervical HPV positivity and CIN, concurrent anal infection was common, while oral infection remained infrequent (Tables 2, 3). This supports a growing recognition that a subset of women may harbor synchronous HPV infections, especially across the anogenital tract, which may influence future cancer screening practices.

Study limitations

We acknowledge that the inclusion of only 30 patients in this pilot study was a significant limitation, particularly within subgroups, which restricts the statistical power of our findings. Stratification by CIN grade was not performed, nor was genotype concordance between infection sites assessed. Furthermore, the cross-sectional design of the study limits our ability to draw conclusions regarding HPV persistence. Potential confounding variables, such as sexual behavior, HPV vaccination status, and smoking history, which are known to influence HPV transmission and persistence, were not addressed.

The collection of samples from the oral cavity may have resulted in underestimation of infection, as these samples might not fully capture the extent of HPV presence. In addition, variations in pH and local acidity could further affect sample accuracy. Consultation with infectious disease specialists could provide a more comprehensive understanding of these factors.

We also acknowledge that we have not yet consulted with an otolaryngologist or general surgeon in the management of this case, which could offer additional clinical insights. Anal cytology and anoscopy were not performed, potentially leading to missed subclinical lesions. Finally, the lack of robust data explaining the simultaneous presence of different HPV types in multiple anatomical regions underscores the need for further investigation of this topic. We also wish to emphasize that our cohort consisted exclusively of female patients. However, HPV affects individuals of all genders, and comprehensive preventive strategies must address the needs of both men and women and patients in the LGBTQ community (49,50).

Oral and anal pathologies related to cervical HPV positivity are an often-underestimated conundrum (51,52). Our exploratory analysis highlights the multifactorial nature of HPV-related disease progression and suggests that HPV genotyping alone may not be sufficient for risk stratification in cervical dysplasia. Alongside this, would like to note that we have not collected any data regarding the vaccination status of the patients in our cohort, which could potentially be a preventive strategy against the development of multi-site infections (53).

Conclusion

Incorporating oral and anal swab screening in patients with cervical HPV positivity and CIN may aid in the early detection of related pathologies beyond the cervix. However the prevalence of oral positivity in our cohort of women was low, suggesting that oral screening is not as feasible or necessary as anal screening, which may be justified as concurrent CIN and anal HPV infection was present in two-thirds of our cohort. Other populations are likely to be even more at risk of anal HPV positivity.

The swab test emerges as a promising novel strategy and heralds a new era in HPV-related screening protocols. It has the potential to be a valuable addition to STI testing, particularly in the realm of early detection. Clinicians, encountering physical manifestations, such as condyloma acuminatum, might find merit in incorporating this screening tool to avert diagnoses at advanced stages. In doing so, it could contribute to more effective prevention measures, such as vaccination strategies. Nonetheless, the exact data for this population is scarce. Larger studies are warranted to evaluate the feasibility of implementing this sampling method as a routine screening tool.

Ethic

Ethics Committee Approval: *The study protocol was reviewed and approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 362, date: 14.04.2023). This trial was registered at ClinicalTrials.gov under the identifier NCT06906913.*

Informed Consent: *A total of 30 women were recruited, and written informed consent was obtained from all participants prior to enrollment.*

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Footnotes

Author Contributions: *Surgical and Medical Practices: T.A., Y.S., N.B.T., O.D., Concept: T.A., O.D., Design: T.A., O.D., Data Collection or Processing: T.A., Y.S., N.B.T., Analysis or Interpretation: T.A., Y.S., N.B.T., O.D., Literature Search: T.A., Y.S., N.B.T., Writing: T.A., Y.S., N.B.T., O.D.*

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