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Cervical human papillomavirus infection and cytologic abnormalities in patients with vulvar squamous cell carcinoma

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ABSTRACT

Aims: To assess the prevalence of cervical human papillomavirus (HPV) infection and related cytologic or histopathologic abnormalities in patients with vulvar squamous cell carcinoma (VSCC), and to explore their association with HPV-related and HPV-independent tumor subtypes.

Methods: This retrospective study included 41 surgically treated VSCC patients at Ankara Bilkent City Hospital (2019-2024). Clinical, cytologic, and pathologic data, including vulvar and cervical HPV status, were analyzed. Cervical HPV testing was performed by polymerase chain reaction (PCR), and cytology was classified according to the Bethesda system.

Results: HPV-associated VSCC was identified in 17.1% of patients, and cervical HPV positivity in 7.1%. Among 34 cytology results, 32.4% showed abnormalities (ASCUS, ASC-H, or HSIL). Cervical biopsy revealed LSIL or HSIL in 6 patients and invasive carcinoma in 1. Preinvasive or invasive cervical lesions were more frequent in HPV-associated VSCC (57.1%) than in HPV-independent cases (28.6%), though not statistically significant (p=0.204).

Conclusion: Cervical HPV infection and cytologic abnormalities were uncommon, likely reflecting the predominance of HPV-independent tumors in this older cohort. Nevertheless, abnormal cytology in a subset of patients supports comprehensive cervical assessment and risk-adapted surveillance, particularly in HPV-associated VSCC.

Keywords: Vulvar squamous cell carcinoma, human papillomavirus, cervical cytology

INTRODUCTION

Vulvar carcinoma is a relatively rare but **clinically significant** malignancy that predominantly affects postmenopausal women. Human papillomavirus (HPV), especially types 16 and 18, has been significantly associated with the development of precancerous lesions and invasive vulvar carcinomas.[1] This framework, formalized in the 2020 World Health Organization (WHO) Classification of Female Genital Tumours, aligns with molecular surrogates (diffuse p16 expression for HPV-related disease and aberrant p53 patterns for HPV-independent disease), and it increasingly informs diagnostic workup and treatment planning.[2,3] In invasive vulvar cancer, squamous cell carcinoma (SCC) accounts for the vast majority of cases (>90%), whereas the remainder is composed of adenocarcinomas (many arising from the Bartholin gland), melanomas, basal cell carcinomas and other rare histologies.[1]

Clinically, multifocal lower genital tract disease involving the vulva, cervix, vagina and perianal/anal epithelium may occur synchronously or metachronously. In patients with HPV-associated vulvar squamous cell carcinoma (VSCC), synchronous or metachronous high-grade cervical intraepithelial neoplasia or invasive cervical carcinoma has been reported in approximately 19% of cases during long-term follow-up. Following treatment for vulvar carcinoma, subsequent surveillance reveals high-grade cervical or vaginal dysplasia in roughly 8% of patients.[2] Although tumor-based meta-analyses indicate HPV involvement in approximately 34-43% of VSCCs overall, comprehensive and standardized data regarding cervical HPV DNA prevalence within these cohorts remain limited.[3]

The present study examines the accompanied of cervical HPV infection with vulvar SCC and correlates it with cervical cytology and pathology, testing its value as a prognostic indicator with potential therapeutic implications. The aim of this study was to determine the prevalence of cervical human papillomavirus infection and cytologic and histopathologic abnormalities in patients with vulvar squamous cell carcinoma and to explore their relationship with HPV-related and HPV-independent tumor subtypes.

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METHODS

This retrospective study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 22.11.2023, Decision No: E2-23-5674) and was conducted in accordance with the principles of the Declaration of Helsinki.

This retrospective, cross-sectional study included patients diagnosed with vulvar cancer at Ankara Bilkent City Hospital from September 2019 to December 2024. A total of 67 patients with VSCC underwent surgical treatment. Inclusion criteria was, patients were eligible if they had a histopathologically confirmed diagnosis of vulvar SCC and available cervical HPV test results or cervical cytology reports. Patients with missing data were not excluded; instead, any unavailable information was documented as "not reported". Ultimately, the study was conducted with 41 patients.

Demographic, clinical, and histopathological data were extracted from the hospital electronic database and medical records. Collected variables included age, tumor size, International Federation of Gynecology and Obstetrics (FIGO) 2021 stage, and vulvar cancer HPV status (positive, negative, or not reported). The results of the cervical HPV test and cytology findings were documented, encompassing normal cytology, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), and high-grade squamous intraepithelial lesion (HSIL), with missing values classified as "not reported". Furthermore, colposcopy and cervical biopsy results were obtained from pathology reports.

Etiologic classification of vulvar squamous cell carcinoma as HPV-related or HPV-independent was abstracted from the original pathology reports. During the study period, systematic p16 and p53 immunohistochemistry was not applied to all vulvar tumors; therefore, HPV status largely reflected documented HPV DNA testing and the descriptive histopathologic diagnosis.

HPV testing was conducted by the polymerase chain reaction (PCR) method, and cervical cytological evaluations were classified according to the Bethesda system. According to cytological findings and HPV test results, a cervical biopsy was indicated in 11% of cases.

The colposcopy and biopsy results were evaluated according to the histopathology reports.

Statistical Analysis

All data analyses were performed utilizing IBM SPSS Statistics version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were represented as mean±standard deviation and median (min-max), while categorical variables were given as frequencies and percentages. The correlation between HPV status of vulvar SCC and cervical smear results was assessed using the chi-square test or Fisher's exact test, while cervical biopsy outcomes were examined by cross-tabulations. Missing data were classified as a separate group and evaluated to evaluate their distribution and possible impact on the findings. A p-value below 0.05 was considered statistically significant.

RESULTS

General characteristics are detailed in Table. A total of 41 patients diagnosed with vulvar cancer were included in the study. The mean age at diagnosis was 65.2±10.76 years and the 22 (53.7%) patients were in geriatric age (65 years or older). The mean tumor size was 43.9±29.91 mm. The majority were classified as stage IB (41.5%), followed by stage IIIC (22%).

Table. Patients' characteristics

Features		Mean±SD	Median (min-max)
Age at initial diagnosis		65.2±10.76	66 (40-87)
Tumor size (mm)		43.9±29.91	40 (4-130)
		n	**%**
Geriatric age	<65 years	19	46.3
	≥65 years	22	53.7
Stage	IA	4	9.8
	IB	17	41.5
	II	4	9.8
	IIIA	4	9.8
	IIIB	3	7.3
	IIIC	9	22
HPV-related vulvar SCC	Negative	18	43.9
	Positive	7	17.1
	Not reported	16	39
Cervical HPV testing	Negative	26	63.4
	Positive	2	4.8
	Not reported	13	31.7
Cervical smear	Normal cytology	23	56.1
	ASCUS	7	17.1
	ASC-H	2	4.9
	HSIL	2	4.9
	Not reported	7	17.1

The "not reported" category represents cases with incomplete clinical records; these patients were retained as a separate analytic group rather than being excluded from the analyses.
SD: Standard deviation, Min: Minimum, Max: Maximum, SCC: Squamous cell carcinoma, HPV: Human papillomavirus, ASCUS: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells-cannot exclude high-grade lesion, HSIL: High-grade squamous intraepithelial lesion

HPV-dependent vulvar cancer was present in 7 patients (17.1%), while 18 (43.9%) patients showed no evidence of HPV involvement. HPV association was not documented in 16 patients. Cervical HPV testing was conducted in 28 patients, of whom 2 were positive and 26 were negative. Among the 34 patients with available cervical cytology, normal findings were reported in 23 cases, ASCUS in 7, ASC-H in 2, and HSIL in 2. Colposcopic cervical biopsy was performed in 11 (26.8%) patients due to the presence of cervical pathology or abnormal cytological findings. LSIL was identified in 3 patients, HSIL in 3 patients, and cervical SCC in 1 patient (Table).

Among patients with HPV-dependent vulvar cancer, 42.9% had benign cervical cytology, whereas 57.1% showed preinvasive or invasive abnormalities. In comparison, 71.4% of those with HPV-independent vulvar carcinoma had benign cytology, and 28.6% had preinvasive or invasive findings. However, the association between HPV status and cervical cytology results was not statistically significant (p=0.204). Similarly, no significant association was found between HPV status and age group (p=0.409).

DISCUSSION

The association between cervical HPV infection, cytology, and pathology results and vulvar cancer was examined in the present study. In our cohort, HPV-associated vulvar SCC was identified in 17.1% of patients, and cervical HPV positivity was detected in only 4.8% of patients. Although not statistically significant, cervical smear abnormalities (preinvasive or invasive cytological findings) were more frequently observed in patients with HPV-associated vulvar SCC compared to those with HPV-independent disease.

In our study, cervical preinvasive and invasive lesions were identified in 57.1% of patients with HPV-associated vulvar SCC, whereas this rate was 28.6% in the HPV-independent group. Although the difference was not statistically significant, the higher prevalence in the HPV-dependent group may indicate a tendency towards multicentric HPV-driven carcinogenesis involving the lower genital tract. This observation is consistent with the findings of de Bie et al.,[2] who reported cervical HSIL in 35% of patients with HPV-associated vulvar SCC, compared to only 2% in those with HPV-independent disease. These results underscore the importance of considering synchronous or metachronous HPV-related lesions across the lower anogenital tract in patients with HPV-associated vulvar malignancies.

The etiologic dichotomy formalized in the 2020 WHO classification-HPV-associated tumors (diffuse p16 overexpression) versus HPV-independent tumors (frequently p53-aberrant)-has improved risk stratification beyond anatomic metrics and is increasingly used to anchor treatment algorithms. Population-based studies indicate that overall trends in vulvar cancer reflect both etiologic routes: modest contributions from HPV-associated disease in some settings against a backdrop of aging populations in whom HPV-independent tumors remain prevalent.[4]

Classic and modern series demonstrate that HPV-associated disease across the lower genital tract may occur synchronously or metachronously, sometimes with clonal relationships across vulvar and cervical compartments, consistent with field oncogenesis and/or seeding from a cervical progenitor lesion.[5,6] These data justify comprehensive evaluation of the cervix, vagina and, where appropriate, the perianal/anal epithelium at baseline and during surveillance.

Historic and contemporary data show enriched rates of cervical abnormalities (HSIL) and/or HPV positivity among women with usual-type Vulvar intraepithelial neoplasia (VIN)-related vulvar SCC, and measurable risks of cervical/vaginal dysplasia after vulvar surgery.[7] Our cohort's low point-prevalence of cervical high-risk HPV likely reflects its older age structure and predominance of HPV-independent disease; nonetheless, the presence of abnormal cytology in a minority of patients underscores the importance of guideline-concordant evaluation and risk-adapted follow-up.

Baseline and longitudinal assessment of the cervix (cytology±HPV testing, colposcopy as indicated) should be integrated into care pathways, with shorter surveillance intervals considered in patients with p16-positive/HPV-positive VSCC or prior cervical disease.[8] Standardized pathology reporting that captures p16/p53 on the index vulvar tumor-and hrHPV status when relevant-enables risk-aligned counseling and adjuvant planning.[9] Evolving guideline recommendations regarding surgical margins, sentinel lymph node (SLN) strategies, and adjuvant therapy in VSCC can be contextualized by etiologic subtype as prospective evidence accrues.

Limitations

Strengths of our study are; a focus on the cervical compartment in a vulvar SCC cohort and alignment with contemporary etiologic taxonomy. Prospective, protocolized testing (p16/p53 for all primaries; extended cervical genotyping) and multi-institutional collaboration are needed to refine estimates and test risk-adapted surveillance. A key limitation of this study is the lack of uniform p16 and p53 immunohistochemical evaluation for all primary vulvar tumors, which restricted strict application of the WHO 2020 etiologic classification and may have led to misclassification of some cases.

CONCLUSION

As a result, our findings reinforce the clinical relevance of integrating cervical assessment into the management of vulvar squamous cell carcinoma, particularly in cases of HPV-associated disease. In this study, we observed low cervical hrHPV positivity and infrequent high-grade cytology yet sufficient abnormalities to support guideline-concordant cervical assessment and risk-adapted surveillance. Consequently, all patients with vulvar squamous cell carcinoma should undergo baseline cervical cytology and, when indicated, colposcopic assessment, and shorter surveillance intervals may be considered in HPV-associated VSCC in line with contemporary guideline-based, risk-adapted follow-up strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 22.11.2023, Decision No: E2-23-5674).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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