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Histopathological Outcomes in Women with High-Risk HPV Infections: A Focus on HPV 31

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ABSTRACT

OBJECTIVE: To evaluate the histopathological findings of patients with high-risk human papillomavirus (hr-HPV) positivity.

STUDY DESIGN: This retrospective cohort study included 814 women aged 30–65 years who underwent colposcopic evaluation following a positive hr-HPV DNA result detected using the Hybrid Capture 2 test (Qiagen, Hilden, Germany). HPV genotyping and concurrent cervical cytology were performed for all participants.

RESULTS: Among the cohort, 495 women were positive for HPV 16 and/or 18, while 319 had non-16/18 hr-HPV types with negative cervical cytology. Colposcopic biopsy was performed in 515 cases. The prevalence of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) was significantly higher in women with HPV 16/18 and negative cytology (23.3%) compared to those with non-16/18 hr-HPV and negative cytology (3.8%) (p=0.001). In the subgroup with HPV 16/18 positivity, CIN2+ lesions were detected in 42.6% of women with LSIL and 21.2% of those with ASCUS cytology (p=0.043). Among patients with ASCUS cytology, CIN2+ was identified in 40% of those with HPV 31 and only 6.3% of those infected with other non-16/18/31 hr-HPV types (p=0.021). Among patients with non-16/18 HPV DNA types, regardless of cytology, there was no statistically significant difference in terms of CIN2+ lesions between those with HPV type 31 and those with other high-risk types (excluding HPV 16, 18, and 31).

CONCLUSIONS: HPV 16/18 remains the highest-risk group regardless of cytology. Among non-16/18 HPV patients, no significant difference in CIN2+ risk was found between HPV 31 and other types overall. However, HPV 31 poses a higher risk in patients with ASCUS cytology, indicating the need for closer management in this subgroup. Therefore, a more individualized evaluation is recommended for non-16/18 HPV infections.

Keywords: Human papillomavirus; High-risk HPV types; HPV genotyping; Cervical dysplasia; Cervical intraepithelial neoplasia grade 2 or worse

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Introduction

Human papillomavirus (HPV) is present in 99.9% of patients with cervical cancer (1). Of the more than 200 identified HPV types, 14 (specifically HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered pathogenic or 'high-risk (hr)' for the progression to cervical cancer (2).

Among the hr-HPVs, HPV 16 and 18 are the most carcinogenic types, accounting for 70% of HPV-positive cervical cancer cases. Non-16/18 hr-HPV types are responsible for the remaining 25% to 35% of cervical cancers (3). In patients diagnosed with hr-HPV, the interval from detection to development of cervical intraepithelial neoplasia (CIN) 2/3 is approximately 3 to 5 years, while progression to cancer typically occurs 10 to 20 years later (4). It is estimated that 30-40% of CIN 3 cases progress to cancer (5). Therefore, treating high-risk patients immediately is appropriate. The most commonly used techniques in treating CIN are ablative methods (cryotherapy and laser ablation) and excisional methods (cold conization, laser conization, LEEP). According to controlled studies, all these methods have high success rates of 80-90% in treating CIN (6).

The prevalence of hr-HPVs varies significantly according to the severity of CIN. According to Bao et al., the distribution of high-risk HPV genotypes demonstrates a clear gradient correlating with the severity of CIN (7). In their study, HPV 16/18 was more frequently detected in high-grade lesions and was positive in 52% of CIN2/3 cases. In contrast, the prevalence of HPV 16/18 was considerably lower in CIN1 at 25.4%. Conversely, non-16/18 hr-HPV types were more common in CIN1 (64.3%) than in CIN2/3 (56.6%). The overall prevalence of hr-HPV was 92.2% in CIN2/3 and 78% in CIN1, indicating a significant presence of hr-HPV in all lesion grades (7). This gradient influences how clinicians approach diagnostic and management protocols for HPV-related cervical abnormalities.

This study aimed to evaluate the histopathological findings of patients with hr-HPV positivity.

Material and Method

Our study included women aged 30 to 65 who presented positive for high-risk HPV DNA between January 2014 and August 2017 at the Ministry of Health, University of Health Sciences, Etlik Zubeyde Hanim Women's Diseases Training and Research Hospital. The Medical Specialty Ethics Committee approved this study (Decision date: 20/09/2017, Decision number: 19), and appropriate informed consent was obtained from each patient. The study adhered to the principles outlined in the Declaration of Helsinki.

Age, age at first sexual intercourse, educational status, marital status, history of abnormal or postcoital bleeding, parity, menopausal status, smoking history, HPV test results, cervical cytology results, and colposcopic histopathology findings of the patients were evaluated retrospectively. Pregnant patients, patients under follow-up for cervical dysplasia, patients with a history of gynecologic malignancy, patients with a history of previous total hysterectomy, and patients with a history of HPV positivity were excluded from the study. HPV test results were obtained from patients referred to Cancer Early Diagnosis, Screening, and Education Centers (CEDSECs), family health centers, and private health institutions. The HPV DNA was analyzed using the Hybrid Capture 2 HPV DNA test, which detects 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) (HC2; Qiagen, Hilden, Germany). Genotyping was performed. Conventional cytology was applied and evaluated based on the Bethesda system (8).

HPV 16 and 18 positivity is a significant indication for referral to colposcopy. In the presence of non-16/18 hr-HPV types with any cytology abnormality (≥ atypical squamous cells of undetermined significance (ASCUS)), patients were referred to colposcopy. In the presence of non-16/18 hr- HPV types along with negative cervical cytology results, patients underwent colposcopy at the specialist's discretion based on physical examination and clinical suspicion. Surgeons specialized in gynecologic oncology performed colposcopy in our institution. Specialized gynecologic pathologists evaluated the pathologic specimens. Among 909 patients who presented with HPV positivity, patients with indeterminate HPV type were excluded from the study. The physicians used a binocular Leica MS5 colposcope with ×20 magnification and a green filter. During the colposcopy procedure, the cervix was washed with saline as standard, and 3% acetic acid was applied to the cervix. After the application of acetic acid, the cervix was observed. Following this period, Lugol's solution was used according to the physician's preference. The cervix was examined under small and large magnifications. Biopsies were taken from areas with aceto-white, mosaic, punctation, erosion, ulcer, leukoplakia, atypical vascularization, and Lugol-negative features, using Tischler and Kevorkian cervical biopsy forceps. Biopsy specimens were sent to the laboratory in formalin. Colposcopy-guided biopsies were classified according to the lower anogenital squamous terminology (LAST) criteria as either high-grade squamous intraepithelial lesion (HSIL) or low-grade squamous intraepithelial lesion (LSIL) (9). HSIL includes cervical intraepithelial neoplasia (CIN) 2-3 lesions, whereas LSIL includes CIN 1. This study classified biopsy results as benign, CIN 1, and CIN 2+ lesions. CIN 2+ lesions included CIN 2, CIN 3, and squamous cell carcinoma (SCC).

A total of 814 patients who underwent colposcopy because of HPV DNA positivity were evaluated.

Statistical analysis

The SPSS 22.0 program was used for the analysis. Mean ± standard deviation, median (minimum-maximum), frequency, and percentage values were used in descriptive statistics of the data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Student's t-test was used to determine whether there was a statistically significant difference between numerical (continuous) variables (or groups).

Results

The number of patients with HPV 16 and/or 18 positive and non-16/18 hr-HPV who underwent colposcopy was 495 and 319 cases, respectively. The median age was 43 years and 44 years for patients with HPV16/18 and those with non-16/18 hr-HPV, respectively (range: 30-65 years). There was no statistically significant difference in clinical and demographic characteristics between the two groups, as detailed in Table I. The rates of the HPV 16 and HPV 18 were 47.3% (n=387) and 9.3% (n=76), respectively. The most common types among non-16/18 hr-HPV types were HPV 31 and HPV 51, with rates of 4.9% and 4.7%, respectively. The other types are shown in Table II.

***Table I:** Demographic characteristics of women with HPV types 16 and 18 and non- HPV 16/18 oncogenic types*

	HPV 16-18 (n=495)	non 16/18 hr-HPV types∞ (n=319)	p
Age			0.011
≤45	319	177	
>45	176	142	
Menopausal Status			0,095
Premenopausal	358	213	
Postmenopausal	120	94	
Unknown	17	12	
Age at First Sexual Intercourse	20 ± 4.6	20 ± 4.2	0.594
Marital Status			
Married	393	248	
Single	11	9	0.921
Divorced	1	1	
Live together	73	49	
Unknown	17	12	
Postcoital Bleeding			
Yes	24	24	0.111
No	454	283	
Unknown	17	12	
Abnormal Uterine Bleeding			
Yes	39	23	0.735
No	439	284	
Unknown	17	12	
Smoking Status			
Smoker	205	112	
Non-smoker	237	172	0.235
Ex-smoker	37	23	
Unknown	16	12	
Education Status			
None	23	8	
Literate	9	5	
Primary	203	130	0.613
Middle	57	34	
High	120	74	
University	52	44	
Master's degree	14	9	
Unknown	17	15	

∞ Types other than HPV 16/18

Colposcopic biopsy was performed in 515 cases. Biopsies were collected from 339 (65.8%) patients with HPV types 16/18 and 176 (34.2%) patients with non-16/18 hr-HPV types. Regardless of cytology results, rates of CIN 2+ lesions were 26.8% and 11.4% for patients with HPV 16/18 and non-16/18 hr-HPV types, respectively (p<0.001, Table III). SCC was found in 3 (0.8%) patients with HPV DNA 16/18, whereas it was detected in a patient with non-16/18 hr-HPV types (Table IV).

The rate of the CIN 2+ lesions was 23.3% for patients with HPV 16/18 and negative cytology, whereas that was 3.8% for those with non-16/18 hr- HPV types and negative cytology (p=0.001). Among patients with HPV 16/18, CIN 2+ lesions were 42.6% and 21.2% of those with LSIL and ASCUS, respectively (p=0.043). Among patients with ASCUS cytology, the rate of the CIN 2+ was 40% and 6.3% for patients with HPV DNA 31 and types other than HPV DNA 16/18/31 (p=0.021). Among patients with non-16/18 HPV DNA types, regardless of cytology, there was no statistically significant difference in terms of CIN 2+ lesions between those with HPV type 31 and those with other high-risk types (excluding HPV 16, 18, and 31). (Table III).

***Table II:** Distribution of HPV types of patients, and cytology distribution of patients with HPV 16-18 vs. types other than HPV 16/18*

Distribution of HPV types in patients		
HPV Types	**n**	**%**
HPV 16	387	47.3
HPV 18	76	9.3
HPV 31	40	4.9
HPV 51	38	4.7
HPV 16 and 18	32	3.9
HPV 52	25	3.1
HPV 39	23	2.8
HPV 56	22	2.7
Other types	173	21.2
Cytology distribution of patients with HPV 16-18 vs. types other than HPV 16/18		
Cytology result	**HPV 16-18**	**non-16/18 hr-HPV types∞**
NILM	321 (%64.8)	135 (%42.3)
ASC-US	50 (%10.1)	62 (%19.4)
LSIL	57 (%11.5)	67 (%21)
HSIL	7 (%1.4)	6 (%1.9)
ASC-H	7 (%1.4)	2 (%0.6)
AGC	6 (%1.2)	4 (%1.3)
Unsatisfactory	41 (%8.3)	34 (%10.7)
SCC	-	1 (%0.3)
Unknown	6 (%1.2)	8 (%2.5)
Total	495 (%100)	319 (%100)

HPV: Human papilloma virus; NILM: Negative for Intraepithelial Lesion or Malignancy; ASCUS: Atypical Squamous Cells of undetermined significance; ASC-H: Atypical squamous cells, cannot exclude a high-grade lesion; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; AGC: Atypical glandular cells; SCC: Squamous cell carcinoma.
∞ Types other than HPV 16/18

Discussion

The most critical risk factor for cervical cancer is the HPV virus. HPV disrupts the cell cycle in host cells and causes their immortalization by inhibiting tumor suppressor genes such as p53 and Rb, which can lead to cancer (10). CIN 2 and CIN 3 are considered precursor lesions with the potential to develop into invasive cervical cancer over time. The risk of progression between CIN grades varies depending on the types of HPV, the immune system, age, and smoking (11). Therefore,

Table III: *Association between combinations of cytology + HPV type results and biopsy results*

	Benign / CIN1 % (n)	CIN 2+ lesion % (n)	p
HPV type, regardless of cytology			
HPV 16/18	73.1% (248)	26.8% (91)	**<0.0001**
Types other than HPV 16/18	88.6% (156)	11.4% (20)	
Cytology normal			
HPV 16/18 and cytology normal	76.7% (158)	23.3% (48)	**0,001**
Types other than HPV 16/18 and cytology normal	96.2% (51)	3.8% (2)	
HPV 16/18			
with ASCUS	78.8% (26)	21.2% (7)	**0.043**
with LSIL	57.4 (27)	42.6 (20)	
Types other than HPV 16/18			
with normal cytology	96.2% (51)	3.8% (2)	**0.024**
with ASCUS cytology	82.7 (62)	17.3% (13)	
Cytology is normal, and types other than HPV16/18			
HPV 31 and cytology normal	90% (9)	10% (1)	0.345
other HPV * types and cytology normal	97.7% (42)	2.3% (1)	
ASCUS			
with HPV 31	60% (6)	40% (4)	**0.021**
With other HPV* types	93.8% (30)	6.3% (2)	
HPV 31			
HPV 31 and CVS normal	90% (9)	10% (1)	0,204
HPV 31 and CVS ASCUS or LSIL	64.7% (11)	35.3% (6)	
LSIL			
with HPV 31	75% (6)	25% (2)	0,68
with other HPV * types	97.5% (39)	2.5% (1)	

**except HPV 16/18/31, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, Chi-square test, Fisher's exact test, CIN 2+ lesions included CIN 2, CIN 3, and squamous cell carcinoma*

Table IV: *Biopsy results of patients positive for HPV 16/18 and non-16/18 hr-HPV oncogenic*

	HPV 16 and/or 18 n (%)	non-16/18 hr-HPV types∞ n (%)	p
Benign	189 (55.8%)	110 (62.6%)	
LSIL	59 (17.4%)	46 (26.1%)	
HSIL	88 (26%)	19 (10,8%)	0.001
SCC	3 (0.8%)	1 (0.5%)	
TOTAL	339	176	

∞ Types other than HPV 16/18, LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; SCC: Squamous cell carcinoma

monitoring and treating lesions at these stages is crucial when needed. Early diagnosis and intervention play a critical role in preventing cancer development. In the presence of HPV types 16 and 18, most national screening programs are similar in recommending immediate colposcopy (12-14). According to the American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines, patients must be referred to colposcopy in the presence of non-16/18 hr-HPV types with ASCUS cytology in the first presentation (14). A co-test, which includes both cervical cytology and HPV DNA test, is recommended one year after detecting non-16/18 hr-HPV types, along with negative cervical cytology results (14). However, while guidelines (14-16) generally do not differentiate management based on non-16/18 hr-HPV types, studies indicate varying degrees of risk for cervical intraepithelial neoplasia among these other types. An Icelandic study examined the distribution of oncogenic HPV types in CIN 2-3, recurrent CIN 2-3, and cervical cancer. HPV 16 was the most frequent type in CIN 2-3, followed by HPV 33, 31, 52, and 35 (17). According to a study by Zhang et al., the most common HPV type found in CIN 2/3 lesions was HPV16 (45.69%), with the prevalence of other types decreasing in the following order: HPV 58 (15.50%), HPV 52 (11.74%), HPV 33 (9.35%), and HPV 31 (4.34%) (18). The ongoing research into HPV type distribution and its correlation with CIN development highlights the need for a more nuanced approach to HPV screening and management, particularly for non-16/18 hr-HPV types. Karaca et al. found that 1.1% of patients with non-16/18 hr-HPV types and negative cytology had CIN 2+ lesions (19). Consequently, the authors concluded that there is a risk of missing the diagnosis of CIN 2+ lesions in 1.1% of patients when following the algorithm recommended by the guidelines (19). In a study by Zhao et al. involving 1,274 women, hr-HPV DNA was detected in 194. They reported that primarily HPV 16, along with types 33, 51, 52, and 58, collectively accounted for 87.5% of all CIN2+ lesions (20). Similarly, in a recent study conducted by Tokalioglu et al., focusing on 333 patients with single non-16/18 hr-HPV infections, found an overall ≥CIN2 lesion rate of 7.8%, with HPV 33 (21.1%), HPV 39 (16.7%), and HPV 58 (13.3%) showing the highest prevalence of ≥CIN 2, although no overall statistically significant correlation between specific HPV type and ≥CIN 2 was observed (21). In our study, the rates of HPV DNA types 16 and 18 were 47.3% and 9.3%, respectively. Among non-16/18 hr-HPV types, the most prevalent were HPV DNA types 31 (4.9%) and 51 (4.7%), followed by types 52 (3.1%), 39 (2.8%), and 56 (2.7%). Among the 339 patients with biopsies, 163 were in the HPV DNA 16 and/or 18 groups, while 176 were in the group for non-HPV 16 and 18 oncogenic types. Of the biopsies that resulted in benign or LSIL, 88.6% were from patients with non-16/18 hr-HPV types, whereas 73.1% were from patients with HPV 16 and/or 18. When examining biopsy results for CIN 2+ lesions, 11.4% of benign or LSIL biopsies were associated with other HPV types. Meanwhile, 26.8% of the biopsy results for CIN 2+ lesions were from patients who tested positive for HPV 16 and/or 18. The observed results demonstrate significant variations in the prevalence of high-risk HPV (hr-HPV) and the distribution of specific HPV genotypes across different populations.

Siegler et al. screened 226 patients. In the group with CIN 2+ lesions, HPV DNA 16 was identified at a rate of 42%, ranking first, while HPV DNA 31 ranked second, followed by HPV DNA 18 at 8.8% (22). Research studies have indicated that HPV DNA 16 possesses the highest positive predictive value for CIN 2 and CIN 3 (23-25). Similarly, in our study, among the 111 patients with CIN 2+ lesions, regardless of cytology results, 91 (81.9%) tested positive for HPV 16 and/or 18, while 20 (18.0%) had non-16/18 hr-HPV types. This supports the well-established strong association between HPV 16 and CIN 2+ lesions, but also suggests that other high-risk types can play a significant role.

In a study that examined 49 women, CIN 2+ lesions were identified in 6.5% of patients with non-16/18 hr-HPV types who had negative cytology (25). CIN 3+ lesions were detected in 20 women (2.7%). Additionally, one patient with HPV 39 and negative cytology was diagnosed with invasive cervical cancer (0.1%) (26). In our study, the rates of CIN 2+ lesions were 23.3% for patients with HPV DNA types 16/18 and negative cytology, whereas it was 3.8% for those with non-16/18 hr-HPV types and negative cytology. SCC was found in 3 patients (0.8%) with HPV DNA types 16/18, whereas it was identified in a patient with non-16/18 hr-HPV types. The existing literature suggests that HPV DNA types 31 and 33 possess higher positive predictive values than HPV DNA type 18 for CIN 2+ (27), highlighting their significance in cervical cancer screening. Our study's findings support this notion, further illustrating the complex interplay among HPV type, cytology, and the risk of CIN 2+. Specifically, the CIN 2+ rates among patients who are HPV 16/18 positive varied significantly based on cytology (42.6% with LSIL, 21.2% with ASCUS, p=0.043), emphasizing the ongoing importance of cytology in risk stratification. Among patients with ASCUS cytology, HPV DNA type 31 was associated with a significantly higher CIN 2+ rate (40%) compared to other non-16/18/31 types (6.3%, p=0.021). According to data from another study, women aged 25-29 showed that HPV 31 presents a higher risk for ≥CIN3 compared to HPV18 (8.0% vs 2.7%, respectively) (28). Another study similarly highlights that HPV 33 and HPV 31 are implicated to a greater extent in the development of cervical precancerous lesions than is HPV18 (28). Analysis of CIN 2 lesion detection rates by HPV type reveals that HPV 33 (7.7%, CI: 0.0- 17.9) and HPV 31 (16.9%, CI: 10.3-23.5) have notably higher rates than HPV 18 (1.7%, CI: 0.0-5.0). Although the confidence interval for HPV 33 is vast, the non-overlapping confidence interval for HPV 31 compared to HPV 18 strongly suggests a greater risk of CIN 2 development. This suggests HPV 31 infection should be more closely monitored for CIN 2 development (29). This suggests that HPV type 31 in the context of ASCUS cytology may warrant particularly close monitoring or a lower threshold for intervention. However, when examining the non-HPV 16/18 group, no statistically significant difference was observed between HPV 31 and other types. This indicates that the increased risk associated with HPV 31 may depend on or be influenced by cytology results.

Limitations and strengths: This study's limitations include its retrospective design and the absence of follow-up data. However, its strengths lie in acceptable sample size, the involvement of experienced colposcopists and pathologists, and the consistency of diagnostic protocols applied within a single institution, all of which contribute to ensuring reliable and homogeneous data.

Conclusion

HPV 16/18 remains the highest-risk group regardless of cytology. This study observed a significantly lower rate of CIN2+ lesions in patients infected with non-16/18 hr-HPV types who had negative cytology results. Of particular importance is the strong association between HPV 31 and the development of CIN2+ in individuals with ASCUS cytology, indicating a need for closer monitoring in this group. Therefore, genotyping remains essential for patients with hr-HPV types other than HPV 16 and HPV 18. Furthermore, our study findings suggest that in ASCUS cases with non-16/18 hr-HPV types, incorporating HPV 31 into at least the partial genotyping step during triage could aid in improved detection of high-grade lesions. Further research is needed to fully clarify the specific risk profiles of different HPV types related to varying cytology findings, aiming to enhance personalized cervical cancer screening strategies.

Declarations:

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the Medical Specialty Ethics Committee, Etlik Zubeyde Hanim Women's Diseases Training and Research Hospital (Decision date: 20/09/2017, Decision number: 19). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study are available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SO and SK: Raised the presented idea. SO, YS, and DB: Designed the study. YS: Conducted the analyses. SO, YS, and EK: Developed the first draft of the manuscript. All authors contributed to the writing of the paper and have read and approved the final manuscript.

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