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HPV TYPES AND PATHOLOGY RESULTS IN PATIENTS WITH HIGH-RISK HPV

YÜKSEK RİSKLİ HPV POZİTİF OLAN HASTALARDA HPV TİPLERİ VE PATOLOJİ SONUÇLARI

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ÖZ

Amaç: Yüksek riskli HPV pozitif hastalarda yüksek riskli HPV tipi dağılımını ve patoloji sonuçlarını analiz etmeyi amaçladık.

Materyal ve Metot: Araştırma retrospektif olarak yürütülmüş olup veriler üçüncü basamak bir jinekolojik onkoloji kolposkopi polikliniğinden elde edilmiştir. Eylül 2019'dan Aralık 2022'ye kadar HPV testi pozitif çıkan ve kolposkopik muayene yapılan 3546 hastanın verileri analiz edildi. Tüm hastalar kuruma klinik verilerinin kullanılması için açık izin verdi.

Bulgular: Ortanca yaşı 40 (aralık, 18-77 yıl) olan toplam 3546 hasta analiz edildi. Hastanın HPV durumu; Hastaların 1169'u (%33) HPV 16, 343'ü (%9,7) HPV 18 ve 2318 (%65,4) hasta HPV diğerleri pozitif idi. Hastaların ayrıntılı HPV pozitif sonuçları, 888 (%25,4) hastanın yalnızca HPV 16, 197 (%5,6) hastanın yalnızca HPV 18 ve 2097 (%59,9) hastanın yalnızca HPV diğerleri olduğu şeklindeydi. Çalışma grubunda 529 (%14,9) hastada CIN 2+ lezyon vardı. CIN 2+ lezyonlu 529 hastanın 331'inde (%62,5) HPV 16 ve/veya HPV 18 tespit edildi. 507 (%14,3) hastanın nihai patoloji sonucu CIN 2/3, 22 (%0,6) hastanın ise kanser olduğu belirlendi.

Sonuç: Sonuç olarak, HPV'nin diğer tipleri hastaların üçte ikisinde pozitif iken, HPV 16 ve/veya 18'in kanser vakalarının beşte dördünden fazlasında pozitif olduğunu bulduk. Yüksek riskli HPV pozitif hasta grubunda hastayı kolposkopiye yönlendirirken HPV tipi kriter olarak kullanılabilir.

Anahtar Kelimeler: Serviks Uteri, Kolposkopi, İnsan Papilloma Virüsü

ABSTRACT

Aim: We aimed to analyze the high-risk HPV type distribution and pathology results in high-risk HPV positive patients.

Materials and Methods: The research was retrospectively conducted, and data was obtained from a tertiary gynecologic oncology colposcopy outpatient clinic. We analyzed data from 3546 patients who tested positive for HPV and underwent colposcopic examination from September 2019 to December 2022. All patients granted the institution explicit permission to utilize their clinical data.

Results: A total of 3546 patients with a median age of 40 years (range, 18–77 years) were analyzed. The patient's HPV status was: 1169 (33%) patients were HPV 16, 343 (9.7%) patients were HPV 18, and 2318 (65.4%) patients were HPV others. The detailed HPV positive results of patients were that 888 (25.4%) patients were only HPV 16, 197 (5.6%) patients were only HPV 18, and 2097 (59.9%) patients were only HPV others. In the study cohort, 529 (14.9%) patients had CIN 2+ lesions. HPV 16 and/or HPV 18 were detected in 331 (62.5%) of 529 patients with CIN 2+ lesions. The final pathology result of 507 (14.3%) patients was CIN 2/3, and that of 22 (0.6%) patients was cancer.

Conclusion: In conclusion, we found that while HPV other types were positive in two thirds of the patients, HPV 16 and/or 18 were positive in more than four fifths of the cancer cases. In the high-risk HPV positive patient group, HPV type can be used as a criterion when referring the patient to colposcopy.

Keywords: Cervix Uteri, Colposcopy, Human Papillomavirus

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INTRODUCTION

Cervical cancer ranks as the fourth most prevalent cancer in women worldwide, with nearly 570.000 cases of invasive cervical carcinoma detected and 311.000 deaths caused by cervical cancer each year (1). Cervical cancer screening involves the use of cervical cytology, commonly known as the Pap test, and/or the detection of oncogenic subtypes of the human papillomavirus (HPV) (2). The results from these tests, in conjunction with a patient's previous results (if available), are utilized to direct subsequent evaluation, such as repeating cervical cytology, conducting colposcopy with cervical biopsies, or, less frequently, performing an excisional procedure (2). Treatment decisions are subsequently determined based on diagnostic findings obtained from the histologic examination (3).

The evidence establishing a connection between HPV and cervical carcinoma is substantial (4, 5). HPV types are categorized into distinct groups according to their respective levels of risk for causing cervical cancer. High-risk types were: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. A worldwide study investigates HPV distribution. HPV types 16 and 18 were detected in 71% of invasive cervical patients. The other five high-risk HPV types (HPV 31/33/45/52/58) had additional incidences of 18.5% (6, 7).

The development of cervical cancer involves a prolonged period of precancerous lesions formation, specifically the cervical intraepithelial neoplasia 1 (CIN 1), CIN 2, and CIN 3 stages(8).

The likelihood of developing invasive cervical cancer is four times greater for CIN 1, 14.5 times greater for CIN 2, and 46.5 times greater for CIN 3, compared to individuals without CIN (9).

In our study, we aimed to analyses the high-risk HPV type distribution and pathology results in high-risk HPV positive patients.

METHOD

The research was retrospectively conducted, and data was obtained from a tertiary gynecologic oncology colposcopy outpatient clinic. We analyzed data from 3546 patients who tested positive for HPV and underwent colposcopic examination from September 2019 to December 2022. All patients granted the institution explicit permission to utilize their clinical data. The institutional review board of Ankara Bilkent City Hospital approved the study (approval: E2-23-4127). In our country's screening program, we use HPV testing and co-testing (with both cytology and HPV) for cervical cancer screening. The liquid-based cytology preparation utilized the NOVAprep® system from Novaprep Inc., Russia, and the Max-prep® system from Corebiotech Co., Ltd., Korea. We examined the pathologic reports of the colposcopic biopsy, the age, and the HPV test results. HPV DNA was extracted using the QIAsymphony® DSP Virus/pathogen Midi kit and subsequently identified and classified using the QIAscreen HPV PCR kit (Qiagen Inc., Germany). Patients who presented with HSIL, microinvasive cancer, adenocarcinoma in situ (AIS) as detected by colposcopic biopsy, and a discrepancy between the biopsy results and clinical evaluation underwent conization. Among the pathology results of smear, cervical biopsy, conization, and hysterectomy, the result containing the highest-grade lesion was defined as the final pathology result. The CIN 2+ lesions were defined as CIN 2/CIN 3, adenocarcinoma in situ, microinvasive cancer, and cervical cancer. Gynecologic oncologists performed all colposcopic examinations and conization procedures. The surgical specimens were evaluated by specialized gynecologic pathologists.

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL) version 20.0. Descriptive values are expressed as the arithmetic mean ± standard deviation, median, and percent.

RESULTS

A total of 3546 patients with a median age of 40 years (range, 18–77 years) were analyzed. The patient's HPV status was: 1169 (33%) patients were HPV 16, 343 (9.7%) patients were HPV 18, and 2318 (65.4%) patients were HPV others. The detailed HPV positive results of patients were that 888 (25.4%) patients were only HPV 16, 197 (5.6%) patients were only HPV 18, and 2097 (59.9%) patients were only HPV others. The HPV status of the study cohort is shown in detail in Table 1.

Table-1 HPV status of the study cohort

Characteristics			Mean±SD	Median (range)
Age (year)			41.0±10.83	40 (18-77)
			n	%
HPV	HPV 16 [1]		1169	33
	HPV 18 [2]		343	9.7
	HPV others [3]		2318	65.4
	HPV positive but type not reported		43	1.2
Detailed HPV positive result [4]	Only HPV 16		888	25.4
	Only HPV 18		197	5.6
	HPV 16 + 18		100	2.9
	HPV 16 + others		175	5
	HPV 18 + others		40	1.1
	HPV 16 + 18 + others		6	0.2
	Only HPV others		2097	59.9
Detailed HPV others type positive result [5]	HPV 31	Only HPV 31	68	1.9
		HPV 31 + other types [6]	130	3.7
	HPV 33	Only HPV 33	18	0.5
		HPV 33 + other types [6]	26	0.7
	HPV 35	Only HPV 35	17	0.5
		HPV 35 + other types [6]	48	1.4
	HPV 52	Only HPV 52	40	1.1
		HPV 52 + other types [6]	101	2.9
	HPV 58	Only HPV 58	15	0.4
		HPV 58 + other types [6]	37	1.1

[1]: HPV 16 ± others HPV types
[2]: HPV 18 ± others HPV types
[3]: HPV others ± HPV 16-18
[4]: n=3503 (43 patients with HPV positive but type not reported excluded)
[5]: n=2318 (Patient with HPV others type positive ± HPV 16-18 type positive)
[6]: Other types: HPV 16 and/or HPV 18 and /or HPV others

Table-2 Smear results of the study cohort

Smear results	n	%
Negative cytology	1366	38.5
Unsatisfactory for evaluation	61	1.7
Atypical squamous cells of undetermined significance (ASCUS)	1457	41.1
Low-grade squamous intraepithelial lesion (LSIL)	480	13.5
Atypical squamous cells cannot exclude HSIL (ASC-H)	92	2.6
High-grade squamous intraepithelial lesion (HSIL)	63	1.8
Atypical glandular cells not otherwise specified (AGC-NOS)	11	0.3
Adenocarcinoma in situ (AIS)	1	0.03
Not reported	15	0.4

In the study cohort, 529 (14.9%) patients had CIN 2+ lesions. HPV 16 and/or HPV 18 were detected in 331 (62.5%) of 529 patients with CIN 2+ lesions. The final pathology result of 507 (14.3%) patients was CIN 2/3, and that of 22 (0.6%) patients was cancer. A total of 27.6% of only HPV 16 positive patients and 7.6% of only HPV 18 positive patients had CIN 2+ lesions. Furthermore, 9.2% of only HPV others positive patients had CIN 2+ lesions. Final pathological result of the study cohort is shown in detail in Table 3.

Table-3 Final pathological result of the study cohort

HPV type	Final pathological result		Total
	Benign or CIN 1	CIN 2/3 or cancer	
	n (%)	n (%)	
Only HPV 16 positive	643 (72.4)	245 (27.6)	888
Only HPV 18 positive	182 (92.4)	15 (7.6)	197
HPV 16 + HPV 18 positive	82 (82.0)	18 (18.0)	100
HPV 16 + HPV 18 + HPV others positive	6 (100.0)	0 (0)	6
HPV 16 + HPV others positive	131 (74.9)	44 (25.1)	175
HPV 18 + HPV others positive	31 (77.5)	9 (22.5)	40
HPV others positive	1904 (90.8)	193 (9.2)	2097
HPV positive but type not reported	38 (88.4)	5 (11.6)	43

The final pathology revealed the presence of squamous cell carcinoma in 14 out of the 22 cancer-diagnosed patients, and detected adenocarcinoma in 8. Patients had cancer as a result of the final pathology in 1.1% of those with only HPV 16 positive, in 1.5% of those with only HPV 18 positive, and in 0.1% of those with HPV others. HPV 16 and/or HPV 18 were positive in 18 (81.8%) of 22 patients with cancer. HPV types of patients with cancer as a result of the final pathology are shown in detail in Table 4.

Table-4: HPV types of patients with cancer as a result of the final pathology

HPV type	No cancer	Cancer (squamous cell cancer or adenocancer)	Total
	n (%)	n (%)	
Only HPV 16 positive	878 (98.9)	10 (1.1)	888
Only HPV 18 positive	194 (98.5)	3 (1.5)	197
HPV 16 + HPV 18 positive	99 (99.0)	1 (1.0)	100
HPV 16 + HPV 18 + HPV others positive	6 (100.0)	0 (0)	6
HPV 16 + HPV others positive	172 (98.3)	3 (1.7)	175
HPV 18 + HPV others positive	39 (97.5)	1 (2.5)	40
HPV others positive	2094 (99.9)	3 (0.1)	2097
HPV positive but type not reported	42 (97.7)	1 (2.3)	43

DISCUSSION

Our study cohort's smear results revealed abnormal cytology in 61.5% of patients. There were 14.9% of patients with CIN 2+ lesions. Cancer was the final pathology result for 0.6% of the entire cohort. HPV 16 and/or HPV 18 were detected in 81.8% of cancer patients. Cancer was diagnosed in 1.1% of patients with only HPV 16 positive, 1.5% of those with only HPV 18 positive, and 0.1% of those with HPV others.

In a Turkish study between August 2013 and December 2018, cytology results for more than 4 million women were evaluated on a population-based screening program. In this patient group, 163.411 HPV positives were detected. HPV positive women's smear results were classified as normal in 69.2% of cases and as unsatisfactory cytology in 16.6% of cases.

The remaining patients with abnormal cytology reports had cytology results classified as ASC-US in 6.5%, ASC-H in 0.6%, LSIL in 6.4%, HSIL in 0.3%, AGC in 0.4%, and other (adenocarcinoma in situ) in 0.002% of patients (10). In our study, the cohort's smear results were as follows: normal cytology 38.5%, unsatisfactory cytology 1.7%, ASCUS 41.1%, LSIL 13.5%, ASC-H 2.6%, HSIL 1.8%, AGC-NOS 0.3%, and AIS 0.03%. The difference is that the study cohort we present consists of patients admitted to the hospital. Additionally, our study does not cover Türkiye in general. It includes patients in the cross-sectional period between 2019 and 2022. The other study was a population-based screening study.

A study presented by Aydın et al. between June 2015 and October 2019 in Istanbul province included patients with high-risk HPV positives who underwent coloscopy. In their study population, 23.3% of women tested positive for HPV 16, 4.9% for HPV 18, and 7.1% for both HPV 16 and 18 (11). In our study, 33% of women were HPV 16 positive, and 9.7% were HPV 18 positive.

The prevalence of CIN 2/3 in high-risk HPV-positive patients varies across different studies. Meyer et al. investigated 809 patients' distribution of HPV types in different grades of dysplasia. Prevalences of HPV types in different grades of dysplasia were HPV 16 and 18 (19.7%), HPV 31 (4.7%), HPV 33 (3.5%), HPV 35 (1.1%), HPV 52 (2.1%), and HPV 58 (0.6%) (12). In our study, the prevalences of HPV types were HPV 31 (5.6%), HPV 33 (1.2%), HPV 35 (1.9%), HPV 52 (4%), and HPV 58 (1.5%). According to a Korean study, 27% of women who tested positive for HPV 31 had CIN 2/3 (13). A study conducted in the Netherlands found that women with HPV others positive had a 3.5% risk of developing CIN 2 and a 7.9% risk of developing CIN 3 (14). In our study, 9.2% of HPV others type positive patients with CIN 2+ lesions.

In the study presented by Meyer et al., HPV 16 and 18 were found in 30.8% of cancer patients (12). Spinillo et al. included 3601 patients' colposcopy results to determine the high-risk HPV-type incidences in cervical cancer. They found 58.2% of cancer patients were HPV 16 and/or HPV 18 positive (15). In our study, HPV 16 and/or HPV 18 were positive in 81.8% of patients with cancer. Three patients were HPV others positive, and one patient was HPV positive but type not reported.

The 2019 American Society of Colposcopy and Cervical Pathology (ASCCP) guideline for HPV primary screening states that if an HPV test is positive for HPV 16 or 18, it should be referred directly to colposcopy; if the test is positive for another high-risk HPV type (not HPV-16/18), cytology should be performed. Unless there is enough evidence to support using the assay in a different way, HPV assays should be used for management in accordance with their regulatory approval for screening (16).

The retrospective study design is our study's most significant limitation. Another limitation is that the results we present are not population-based screening results, so they cannot reflect the country as a whole. The advantages of our study were that colposcopy and excisional procedures were all performed by gynecological oncology specialists. The same clinic provided follow-up for the patients. Pathology samples from the patients were examined by pathologists specializing in gynecological pathology.

In conclusion, from the study we presented, we found that while HPV other types were positive in two-thirds of the patients, HPV 16 and/or 18 were positive in more than four fifths of the cancer cases. In the high-risk HPV positive patient group, HPV type can be used as a criterion when referring the patient to colposcopy. However, community-based studies with large participation are necessary to clarify this situation.

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