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ORIGINAL ARTICLE

Hpv-Specific Risk Management in Cervical Pathology Screening and Comparison of Pathological Results

Servikal Patoloji Taramasında Hpv'ye Özgü Risk Yönetimi ve Patoloji Sonuçlarının Karşılaştırılması

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ABSTRACT

Background: In the process of detecting cervical cancer, cytology and HPV genotype screening both play a significant part. More researches are required to determine whether or not multiple HPV genotyping can accurately predict cytological abnormalities.
Methods: A total of 696 female individuals were subjected to analysis for cytology and HPV genotype testing. HPV-DNA, smear and final pathology results of these patients and the relationship between them were investigated using statistical methods.
Results: Cytological data indicating abnormalities were seen in a total of 110 subjects. HPV-16 was determined to be the most prevalent variety among the patients, and HPV-16-positive females were found to have an elevated risk of cervical lesions. HPV 16 infection rates were substantially increased in patients with HSIL and higher lesions.
Conclusion: An infection caused by HPV-16 is a major risk factor for cervical lesions. A test that examines many HPV genotypes may be able to predict cytological problems.

Keywords: HPV, Smear, Cervical Screening, Cervical Preinvasive Lesions, Cervical Cancer.

ÖZ

Arka plan: Serviks kanserinin saptanması sürecinde sitoloji ve HPV genotip taramasının her ikisi de önemli bir rol oynamaktadır. Çoklu HPV genotiplemesinin sitolojik anormallikleri doğru bir şekilde tahmin edip edemeyeceğini belirlemek için daha fazla araştırma yapılması gerekmektedir.
Yöntemler: Toplam 696 kadın birey sitoloji ve HPV genotip testi için analize tabi tutulmuştur. Bu hastaların HPV-DNA, smear ve nihai patoloji sonuçları ve aralarındaki ilişki istatistiksel yöntemler kullanılarak araştırılmıştır.
Bulgular: Toplam 110 olguda anormallik gösteren sitolojik veriler görüldü. HPV-16'nın hastalar arasında en yaygın çeşit olduğu ve HPV-16-pozitif kadınlarda servikal lezyon riskinin yüksek olduğu bulunmuştur. HPV 16 enfeksiyon oranları HSIL ve daha yüksek lezyonlu hastalarda önemli ölçüde artmıştır.
Sonuç: HPV-16'nın neden olduğu bir enfeksiyon servikal lezyonlar için önemli bir risk faktörüdür. Birçok HPV genotipine bakan bir test sitolojik sorunları öngörebilir.

Anahtar Kelimeler: HPV, Smear, Servikal Tarama, Servikal Preinaziv Lezyonlar, Serviks Kanseri

Introduction

The burden of cervical cancer is disproportionately high in several low- and middle-income countries despite the fact that the disease affects people all over the world. Thanks to the efficacy of some preventative treatments, such as vaccination against the most carcinogenic strains of the human papillomavirus (HPV), which is the primary factor in the development of cervical cancer, and screening, in particular, using HPV-based diagnostic techniques, cervical cancer is a disease that may be avoided to a considerable extent (1, 2). The World Health Organization (WHO) issued a request for a worldwide effort to be created with the goal of eradicating cervical cancer as a public health issue in May 2018. In order to accomplish this objective, it will be necessary to expand, on a worldwide scale, the administration of an effective vaccine against HPV, as well as to screen and treat cervical cancer. Cervical cancer is the second most frequent malignancy in women of reproductive age and the second leading cause of cancer-related mortality among women globally (3). It is possible to successfully limit the incidence and progression of cervical cancer by the early diagnosis and management of cervical lesions, which results in a better prognosis (4). Screening, triage of individuals with positive findings on screening, confirmation on biopsy and treatment of patients with precancerous lesions are often required for the prevention of cervical cancer and mortality by screening. Population-based screening, nonpopulation-based screening, and opportunistic screening are all common methods of providing this service, and settings with limited resources may opt for a screen-and-treat strategy (immediate testing followed by treatment, without confirmation on biopsy) to get the job done. Coverage and participation rates vary significantly across regions and institutions (5)

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The 2019 ASCCP (American Society of Colposcopy and Cervical Pathologies) Risk-Based Management Consensus Guidelines indicate a paradigm change away from the use of predominantly results-based algorithms and towards the use of risk-based management based on a mix of current screening test results and historical screening data. Previously, results-based algorithms were used. When compared to cytology by itself, screening that includes either HPV testing or co-testing that includes HPV testing gives improved risk categorization. As a consequence, the incorporation of HPV testing into risk stratification and the provision of advice for monitoring in the event of aberrant findings were critical components of the 2019 guidelines (6).

The presence of a persistent infection with high-risk HPV (HR-HPV) has been linked to the development of cervical cancer. HPV-16 and HPV-18 are the most prevalent genotypes found in invasive cervical cancer cases (7).

The risk that a certain HPV subtype poses for developing cervical cancer varies depending on the subtype. Is it possible to utilize more than one subtype of HPV to predict cervical cytology. In this study, we analyzed the HPV infection based on the various cytological findings in order to identify the particular HPV genotype that is more likely to induce cervical lesions. Additionally, we investigated the feasibility of predicting cervical cytological lesions based on combinations of HPV genotypes.

Materials and Methods

Patients who were admitted to Necmettin Erbakan University Faculty of Medicine, Department of Obstetrics and Gynecology, gynecology outpatient clinic between January 2017- July 2022 and who were with positive HPV DNA test were included in the study. In these patients, smear test was performed along with the HPV-DNA test.

The smear test results of the patients with positive HPV DNA test were evaluated. However, the pathologist who evaluated the smear test did not know the patient's current HPV status. The final pathology reports obtained as a result of colposcopic biopsies and surgical procedures (cervical excisional treatment methods, hysterectomy) performed on the patients according to the results of the smear test and HPV DNA tests were examined. The relationship between the type of HPV that the patient was infected with and the detected cervical pathology and the degree of this pathology were determined using statistical methods. Thus, it was investigated whether it is possible to predict the cervical pathology, if any, with the HPV type of a patient with a positive HPV-DNA test.

Statistical analysis of the data was performed using SPSS version 26 software. The chi-square test was used to compare the frequencies of HPV genotypes, smear positivity and CIN severity among HPV-positive cases. The odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate the association between HPV genotypes and smear positivity or CIN severity. A p-value less than 0.05 was considered statistically significant.

All procedures performed in the current study were approved by the institutional review board (Reference number: 3870 and Year: 2022) following the 1964 Helsinki Declaration and its later amendments.

Results

A total of 696 females with positive HPV-DNA test were included this study. The ages of the participants ranged between 25 and 65, with a mean age of 39.52 years and a standard deviation of 9.876 years. The median age was 38 years.

The distribution of HPV types according to cytological diagnosis is shown in Table 1. The most common HPV type detected was HPV 16, followed by HPV other than 16-18 and HPV 68. HPV 16 was found in 78.35% of the cases with a negative malignancy diagnosis, 4.12% of the cases with Low Grade Squamos Intraepithelial Lesion (LSIL), 5.15% of the cases with High Grade Squamos Intraepithelial Lesion (HSIL), and 1.03% of the cases with cervical adenocarcinoma. HPV types other than 16-18 were found in 78.81% of the cases with a negative malignancy diagnosis, 3.31% of the cases with LSIL, and 1.32% of the cases with HSIL. HPV type 68 was found in 84% of the cases with a negative malignancy diagnosis, 2% of the cases with LSIL, and 2% of the cases with HSIL. The other HPV types had lower frequencies and were mostly associated with a negative malignancy diagnosis or Atypical Squamos Cells of Undetermined Significance (ASCUS). No HPV type was detected in any case with Atypical Glandular Cells of Undetermined Significance (AGUS).

The association between HPV genotypes and smear positivity is shown in Table 2. The results indicated that there was no significant difference in the frequency of smear positivity among the different HPV genotypes. The only exception was HPV 16+18 Plus, which had a significantly lower frequency of smear positivity than the other genotypes (p=0.032). However, this result should be interpreted with caution, as the sample size for this genotype was very small (n=14). The other HPV genotypes had similar frequencies of smear positivity, ranging from 0% to 22.7%. The overall frequency of smear positivity was 10.8% among the HPV-positive cases.

The relationship between HPV genotypes and the severity of cervical intraepithelial neoplasia (CIN) is shown in Table 3. The results indicated a significant difference in the frequency of CIN> 2 among the different HPV genotypes (p=0.006). The only genotype that had a significantly higher frequency of CIN> 2 was HPV 16, which was found in 24.6% of the cases with CIN> 2, compared to 16% of the cases with CIN

Table 1. Distribution of HPV types by cytological diagnosis in HPV-positive cases

HPV Type	No Test	Normal Cytology	Chronic Cervicitis	ASCUS	LSIL	HSIL	AGUS	Adeno carcinoma	Total
HPV other than 16-18	7(4.64%)	119(78.81%)	3(1.99%)	14(9.27%)	5(3.31%)	2(1.32%)	1(0.66%)	0(0%)	151
16 Plus	0(0%)	66(86.84%)	1(1.32%)	5(6.58%)	1(1.32%)	3(3.95%)	0(0%)	0(0%)	76
16+18 Plus	1(7.14%)	13(92.86%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	14
16+18	0(0%)	34(80.95%)	2(4.76%)	3(7.14%)	1(2.38%)	2(4.76%)	0(0%)	0(0%)	42
18 Plus	1(3.33%)	21(70%)	0(0%)	5(16.67%)	3(10%)	0(0%)	0(0%)	0(0%)	30
16	3(3.09%)	76(78.35%)	1(1.03%)	7(7.22%)	4(4.12%)	5(5.15%)	0(0%)	1(1.03%)	97
18	1(6.25%)	13(81.25%)	0(0%)	2(12.5%)	0(0%)	0(0%)	0(0%)	0(0%)	16
31	2(5.41%)	26(70.27%)	2(5.41%)	3(8.11%)	3(8.11%)	1(2.70%)	0(0%)	0(0%)	37
33	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1
35	0(0%)	8(72.73%)	0(0%)	2(18.18%)	1(9.09%)	0(0%)	0(0%)	0(0%)	11
39	1(2.94%)	29(85.29%)	0(0%)	4(11.76%)	0(0%)	0(0%)	0(0%)	0(0%)	34
45	1(4.35%)	19(82.61%)	0(0%)	2(8.70%)	0(0%)	1(4.35%)	0(0%)	0(0%)	23
51	0(0%)	35(83.33%)	1(2.38%)	5(11.90%)	1(2.38%)	0(0%)	0(0%)	0(0%)	42
52	1(7.14%)	12(85.71%)	0(0%)	0(0%)	1(7.14%)	0(0%)	0(0%)	0(0%)	14
56	0(0%)	20(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	20
58	1(11.11%)	8(88.89%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
59	1(9.09%)	7(63.64%)	0(0%)	2(18.18%)	1(9.09%)	0(0%)	0(0%)	0(0%)	11
66	1(5.56%)	14(77.78%)	0(0%)	3(16.67%)	0(0%)	0(0%)	0(0%)	0(0%)	18
68	2(4%)	42(84%)	2(4%)	2(4%)	1(2%)	1(2%)	0(0%)	0(0%)	50

ASCUS: Atypic Squamous Cells Undetermined Significance, LSIL: Low Grade Squmous Intraepithelial Lesion, HSIL: High Grade Intraepithelial Squmous Lesion, AGUS: Atypic Glandular Cells Undetermined Significance

Table 2. Association between HPV genotypes and smear positivity in HPV-positive cases

Genotypes (HPV)	Smear negativity	Smear positivity	p-value	OR (for Smear positivity)	95 % CI
HPV other than 16-18	126(21.5%)	25(22.7%)	.077	1.07	0.65 to 1.74
16 Plus	66(11.3%)	10(9.1%)	.503	0.78	0.39 to 1.58
16+18 Plus	14(2.4%)	0(0.0%)	.032	0.17	0.01 to 3.01
16+18	34(5.8%)	8(7.3%)	.565	1.26	0.56 to 2.80
18 Plus	22(3.8%)	8(7.3%)	.101	2.01	0.87 to 4.64
16	79(13.5%)	18(16.4%)	.423	1.25	0.71 to 2.19
18	14(2.4%)	2(1.8 %)	.714	0.75	0.16 to 3.37
31	28(4.8%)	9(8.2%)	.149	1.77	0.81 to 3.87
33	1(0.2%)	0(0.0%)	.728	1.76	0.07 to 43.63
35	8(1.4%)	3(2.7%)	.302	2.02	0.52 to 7.75
39	30(5.1%)	4(3.6%)	.510	0.69	0.24 to 2.02
45	20(3.4%)	3(2.7%)	.712	0.79	0.23 to 2.71
51	35(6.0%)	7(6.4%)	.874	1.06	0.46 to 2.47
52	13(1.9%)	1(0.1%)	.385	0.40	0.05 to 3.12
56	20(3.4%)	0(0.0%)	.147	0.12	0.00 to 2.08
58	9(1.3%)	0(0.0%)	.374	0.27	0.01 to 4.76
59	8(1.4%)	3(2.7%)	.302	2.02	0.52 to 7.75
66	15(2.2%)	3(2.7%)	.919	1.06	0.30 to 3.75
68	44(7.5%)	6(5.5%)	.446	0.71	0.29 to 1.71

OR: Odds Ratio, CI: Confidence Interval.

≤ 2 (p=0.026). The other HPV genotypes had lower frequencies of CIN> 2, ranging from 0% to 33.3%. The overall frequency of CIN> 2 was 10.8% among the HPV-positive cases. These results suggest that HPV 16 is a more oncogenic genotype than the other HPV types detected in this study.

Table 3. Relationship between HPV genotypes and the severity of cervical intraepithelial neoplasia in HPV-positive cases

Genotypes (HPV)	≤ CIN 2	> CIN 2	p-value	OR (for cervical pathology positivity)	95 % CI
Other than 16-18	111(91.7%)	10(8.3%)	0.006	0.35	0.16 to 0.75
16+plus	36(83.7%)	7(16.3%)	0.321	1.58	0.63 to 3.96
16+18+plus	6(66.7%)	3(33.3%)	0.134	2.97	0.71 to 12.40
16+18	13(72.2%)	5(27.8%)	0.126	2.33	0.78 to 6.95
18+plus	14(87.5%)	2(12.5%)	0.771	0.79	0.17 to 3.65
16	43(16.0%)	14(24.6%)	0.026	2.27	1.10 to 4.70
18	9(18.0%)	0(0.0%)	0.388	0.28	0.01 to 4.96

OR: Odds Ratio, CI: Confidence Interval, CIN: Cervical İntraepithelial Neoplasia

Discussion

This research analyzed the risk of various cervical lesions in the case of HPV infection as well as the risk of different cervical lesions in the event that HPV infection was present.

In our study smear test results were reported as negative in 90.2% of the patients. This indicates that not all HPV-positive cases may have abnormal cytology results and emphasizes the importance of HPV testing in addition to cytology for cervical cancer screening (8). It should be noted that the study population consisted of women with positive HPV-DNA tests, which may have affected the frequency of smear positivity.

This result was higher than in a study in which 4337 patients with a positive HPV-DNA test were evaluated and 74.7% of the smear test results were negative (9). During the evaluation of the smear test, it is known that knowing the current HPV status provides a more accurate pathological diagnosis (10). This may be the reason for the high number of negative smear tests. In a study conducted in a very large population in which patients with positive HPV-DNA test results were analyzed, 14.2% of the patients had smear test results of ASCUS or more (11). This result is partially compatible with the result of our study.

The study results showed that HPV 16 was the most common HPV type detected in the study population, followed by HPV types other than 16-18 and HPV 68. According to the findings of our research, the HPV-16 genotype (32.9%) is the one that is identified the most often overall which is similar to a previous study from Türkiye (12). The incidence of HPV-18 was 6.6%, which was similar to the rate of 8% in the same study (12).

Persistent infection with HPV 16 has been reported to be an important cause of cervical precancerous lesions and cervical cancer (13). HPV 16 positivity was observed in 66.6% of patients whose smear results were reported as HSIL. This rate is consistent with the result obtained in the same study (12). HPV-18 DNA positivity was detected in 13.3% of the patients whose smear results were reported as HSIL. This rate is not compatible with the HPV-18 positivity rate of 4% in the same study (12).

Only HPV-16 DNA positivity statistically significantly increased the risk of cervical lesion formation above CIN 2. Only HPV-16 DNA positivity in lesions above CIN2 was found as 24.6% in our study. This value is lower than the same result in a very large-scale study conducted throughout Türkiye (11).

Conclusion

It was concluded that HPV-16 DNA positivity is an important risk factor for the development of cervical pathologies. It would be appropriate to conduct further studies in order to predict cervical pathologies that may occur with HPV DNA positivity.

Conflict Of Interest

The authors declare no conflicts of interest.

Funding

None.

Data Availability Statement

Upon a reasonable request, the corresponding author can provide access to the data supporting the conclusions of this research.

Author Contributions

Idea/Conception: S.Ö., Supervision: A.A., Data Collection and/or Processing: Ş.Ç., T.Ş., Analysis and/or Interpretation: F.A., Writer: S.Ö., Critical Review: E.T.D.

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