



Cytology May not be Sufficient for Cervical Screening in Women with HPV Types Other than Type 16-type 18

Tip 16 ve 18 Dışı HPV Taşıyan Kadınlarda Kansere Taraması için Sitoloji Yeterli Olmayabilir

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Abstract

Objective: The aim of this study was to examine the relationship between human papilloma virus (HPV) types 16-18 and other high risk HPV types and final pathology in HPV positive women who underwent colposcopy and loop electroincision procedure (LEEP).

Method: The data of 528 HPV positive women hospitalized at tertiary center between January 2017 and January 2019 were recorded retrospectively. The ages of the patients, smear results, HPV types, pathology results of colposcopic biopsies and pathology results of LEEP material in LEEP patients were evaluated. Women with HPV DNA type 16 and/or 18 named as high risk group (HRG) and women with high risk HPV DNA types other than type 16 and/or 18 (31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 types) named as other high risk group (OHRG). Pregnant women were not included in the study. Women with vaginal infections were included in the study after treatment. Both groups were statistically analyzed according to their colposcopic and pathological findings.

Results: There were 322 women (61%) in the OHRG. While there were benign findings in the colposcopy in approximately 75% of OHRG, cervical cancer was suspected in 3 (1%) of them. Benign colposcopic findings were the most common in the HRG, and CIN1 (30%) was the second most common. CIN3 and cancer were more common in the HRG (6.8% and 2.9%, respectively). 75% of the patients in the OHRG were followed up; 25% had LEEP. CIN1 was found in 18% of the women who underwent LEEP.

Conclusion: In the OHRG, invasive cervical cancer was diagnosed in 2 patients, even if the smear was negative; for this reason, colposcopy may be required regardless of cytology, as in HPV 16 and 18 positivity in these patients.

Keywords: Cervical cancer, colposcopy, cytology, human papilloma virus, smear

Öz

Amaç: Bu çalışmanın amacı, kolposkopi ve loop elektroensizyon prosedürü (LEEP) yapılan human papilloma virüsü (HPV) pozitif kadınlarda HPV tip 16-18 ve diğer yüksek riskli HPV tipleri ile final patolojisi arasındaki ilişkiyi incelemektir.

Yöntem: Ocak 2017-Ocak 2019 tarihleri arasında tersiyer bir merkezde tedavileri yapılan 528 HPV pozitif kadının verileri geriye dönük olarak incelendi. LEEP yapılan hastaların yaşları, smear sonuçları, HPV tipleri, kolposkopik biyopsilerin ve LEEP materyallerinin patoloji sonuçları değerlendirildi. HPV tip 16 ve/veya 18 olan grup yüksek risk grubu (HRG), tip 16 ve/veya 18 dışında olup da genital kanserlere neden olabilen HPV tiplerini (31, 33, 35, 39, 45, 51, 52, 56, 58, 59 ve 68 tipleri) diğer yüksek riskli HPV grubu (OHRG) olarak tanımladık. Gebeler çalışmaya dahil edilmedi. Vajinal enfeksiyonu olan kadınlar tedavi sonrası çalışmaya dahil edilmiştir. Kolposkopi ve patoloji sonuçları mevcut HPV tipine göre istatistiksel olarak değerlendirildi.

Bulgular: OHRG grubunda 322 kadın (%61) vardı. Bu grupta HPV'li kadınların yaklaşık %75'inde kolposkopiye benign bulgular, 3 (%0,9) kadında serviks kanseri tespit edildi. HRG grubunda en yaygın kolposkopik bulgu benign bulgular, CIN1 (%30) ikinci sıklıkta idi. CIN3 ve serviks kanseri yüksek risk grubunda daha yaygındı (sırasıyla %6,8 ve %2,9). OHRG grubunda %75 kadına LEEP yapılmadan takip yapılmıştı, LEEP yapılan (%25) kadınlarda %18 CIN1 tespit edildi.

Sonuç: OHRG'de smear negatif olsa bile 2 hastada kanser görüldü; bu nedenle bu gruptaki hastalarda da HPV 16 ve 18 pozitifliğinde olduğu gibi sitolojiden bağımsız olarak kolposkopi yapılması gerekebilir.

Anahtar kelimeler: İnsan papilloma virüsü, kolposkopi, rahim ağzı kanseri, sitoloji, yayma



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Cite this article as: Okuyan E, Karabay Akgül Ö. Cytology May not be Sufficient for Cervical Screening in Women with HPV Types Other than Type 16-type 18. Bagcilar Med Bull 2023;8(1):78-81

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Bagcilar Medical Bulletin published by Galenos Publishing House.

Introduction

There are more than 200 subtypes of human papilloma virus (HPV) virus that invade through microcracks in the epithelium. In women, the vulva, vagina, cervix, perianal area, and anal canal are affected. The incidence of HPV was 10% worldwide (1). It is most common in Africa. HPV can be seen in patients of all ages. The frequency of HPV decreases after the age of 25, with a small peak in some populations after menopause (2).

Genital HPV is mainly transmitted by sexual contact. However, intravaginal cleaning also causes HPV positivity in young girls without a history of sexual contact (8%) (3).

There are more than 40 types of HPV that infect anogenital skin and mucous membranes. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are high risk HPV types for the development of malignancy. Condyloma acuminata (types 6 and 11 being the most common), squamous intraepithelial lesions and cancer (types 16 and 18 being the most common) are associated with HPV.

With a cervical smear, it is possible to diagnose and follow-up lesions due to HPV. Colposcopy is performed for the diagnosis and follow-up of precancerous lesions and cancer following an abnormal cervical screening test or in cases of clinical suspicion. If there are suspicious findings in colposcopy, the pathological examination should be detailed by performing the loop electrosurgical excision procedure (LEEP). LEEP describes a conical excision of the cervix, including the transformation zone and areas that appear suspicious on colposcopy. Moreover, LEEP is also a treatment method.

In routine practice, post-smear colposcopy and LEEP follow-up are recommended for women with high risk HPV. However, if there are abnormal examination findings and clinical complaints for patients with non-16/18 HPV, colposcopy and LEEP follow-up are recommended. Moreover, malignancy can also develop with other high risk group HPV (4).

Other than HPV types 16 and 18, we planned this study to investigate the frequency of precancerous and malignant lesions developing with high risk HPV types and to compare them with patients with high risk types of HPV.

Materials and Methods

Our study was conducted retrospectively in a secondary center after obtaining the permission of the Local Ethics Committee of Batman State Hospital (no: 2020/232). Data

were collected in the pilot province where mobile HPV screening was performed. In the study, a retrospective evaluation of the data of 528 female patients aged between 27 and 65 whose cervical smears were taken and HPV DNA examined. The US Food and Drug Administration approved ThinPrep Imaging System was used for primary screening.

The cervix was first visualized by applying saline, then 3-5% acetic acid was applied to the cervix and upper vagina, waited for 30-60 seconds, and the squamocolumnar junction and ectocervix were examined. Finally, Schiller's test was done with 5% Lugol solution. Cervical biopsy was taken under local anesthesia from the abnormal epithelium. A Kevorkian cervical biopsy instrument was used for the cervical biopsy. Monsel's solution (ferric subsulfate) was applied to the biopsy site, and if the bleeding did not stop, bleeding site was sutured with 2/0 polyglactin, absorbable, synthetic, monofilament material.

Endocervical curettage was performed all women with a pathological appearance in colposcopy, and in women with ASCH, HSIL, AGC, LSIL or ASCUS smear results without lesions in colposcopy.

Statistical Analysis

All analyses were performed using the SPSS v21 program (SPSS Inc., Chicago, IL, USA). The compliance of the quantitative data with the normal distribution was checked with the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables with the normal distribution are the mean \pm standard deviation, and the median (smallest value-maximum value) of the other variables given in the form. Frequency and percentage values were preferred in the presentation of categorical data. The chi-square test was used in the analysis of the categorical data. The Fisher's Exact test was used for the HPV subtype and different category comparisons. A p-value less than 0.05 was considered significant.

Results

Five hundred twenty-eight HPV positive women were included in the study. The mean age of the HPV detected patients is 42 years. Considering HPV positive patients; it is positive in 38% at 35 years of age, in approximately 48% at 40 years of age, and in approximately 22% at 50 years of age. Considering each demographic characteristics, no similarity was found between the two groups in terms of age, body mass index, literacy and smoking rates (Table 1).

Non-16/18 HPV was detected in 322 women (61%). While there were benign findings in the colposcopic evaluation in approximately 75% of the women with OHRG, cervical cancer was detected in three women (0.9%). In the OHRG and HRG groups, there was a difference between the patients with and without LEEP ($p=0.027 < 0.05$). Benign colposcopic findings were the most common finding in the HRG, and cervical intraepithelial neoplasia-1 (CIN1) (30%) was the second most common pathological diagnosis of colposcopic biopsy materials. CIN2 was seen at the same rate in both groups. CIN3 and cervical cancer (6.8% and 2.9%, respectively) were more common in the HRG (Table 2). Seventy-five percent of the patients in the OHRG were followed up; 25% had LEEP. CIN1 were found in 18% of the women who underwent LEEP (Table 3).

Table 1. Demographic characteristics of patients

	HRG (Mean + SD)	OHRG (Mean + SD)	p-value
Age	44+0.9	39+0.8	0.120
Gravida	4+0.3	3.8+0.8	0.08
Parity	3+0.4	2.67+0.7	0.62
Abortus	1+0.5	1+0.7	0.65

HRG: High risk group, OHRG: Other high risk group, SD: Standard deviation

Table 2. Comparison of histopathologic findings in colposcopically directed biopsies of patients in HRG and OHRG

Cervical biopsy	OHRG	HRG	p-value
Benign	241	123	0.039
CIN1	63	61	0.125
CIN2	3	2	0.143
CIN3	12	14	0.134
Cervical cancer	3	6	0.04
Total	322	206	-

HRG: High risk group, OHRG: Other high risk group, CIN: Cervical intraepithelial neoplasia

Table 3. Comparison of histopathologic findings of LEEP materials in HRG and OHRG

LEEP results	OHRG	HRG	p-value
CIN1	57	51	0.157
CIN2	15	11	0.190
CIN3	7	12	0.034
Cervical cancer	1	1	-
Total	80	75	

HRG: High risk group, OHRG: Other high risk group, CIN: Cervical intraepithelial neoplasia, LEEP: Loop electroincision procedure

Discussion

In our study, we found out that the women with the HRG had a higher rate of cervical pathologies than OHRG. The frequency of benign lesions was approximately 75% in the women with OHRG and approximately 60% in patients with HRG. We found that performing a colposcopy and LEEP in addition to smear tests in women with carcinogenic HPV has a higher diagnostic value for the diagnosis of precancerous lesions and cancer.

ThinPrep, which we used for cervical evaluation, uses programmed algorithms. If abnormalities are found, the entire slide is reviewed by a cytopathologist. With the use of this device, HSIL and LSIL diagnoses are detected at a higher rate than in traditional pathological examinations (5). However, the clinical efficacy of automated systems and their role in cervical cancer screening are still unclear.

In our study group, non-16/18 HPV types were detected in 133 and high risk HPV types in 85 of 218 patients with normal smear results. In the colposcopy results of these patients with normal smear results in OHRG; CIN1, 2 and 3 was detected in 17%, 0.7% and 5.2%, respectively. The CIN1, CIN2, and CIN3 rates of the patients in HRG detected and normal smear results were analyzed as 21%, 1.2%, and 5.9%, respectively. High risk HPV was detected in 22 of 68 patients whose smear results were ASCUS, and cervical cancer was detected in one patient as a result of colposcopic biopsy. One of the reasons for the inconsistency of the smear results and colposcopy results may be that the person performing the examination is not a gynecologic pathologist.

Not every infection with HPV type 16 or 18 will necessarily progress to cervical, vaginal, or vulvar cancer. In several studies in women, the presence of anti-HPV antibodies, which are indicative of prior infection, has been associated with a reduced risk of subsequent HPV infection, particularly for types 16 and 18, suggesting the potential for protective immunity following natural infection (6). In cervical cancer prevention guidelines, age is also important in HPV follow-up along with HPV16/18 typing to determine the risk of CIN3 and cancer in terms of cytology and cervical cancer risk. According to ASCCP recommendations, if HPV type 16/18 or HPV positive and genotype is uncertain, the management of these patients is colposcopy or repeat cytology 2-4 months later (4). In our study, CIN2 was observed as the same rate in both groups and it was found to differ from the literature.

LEEP is a treatment method that can provide remission in persistent HPV infections in the treatment of SIL (7).

In fact, it is not HPV that is treated, but lesions caused by HPV. According to the data of 141 women who underwent LEEP for CIN and had clean surgical margins, LEEP can effectively eliminate HPV infections. Most HPV positive women had HPV eradicated at six months. While the HPV persistence rate is 45% in the 3rd month, it decreased to 2.1% by the 12th month. The most common persistence rate is in HPV type 16. In women with high risk HPV, recurrence and residual disease are more common after LEEP (8). In our study, we found a higher rate of CIN3 in HRG. (5.8%, 2.1%) ($p < 0.05$) (Table 3).

Study Limitations

In our study, we considered the absence of previous HPV anamnesis a limitation. Moreover, the tests were performed by different physicians at different institutions.

Conclusion

According to the results of our study, we believe that the presence of HPV types other than HPV 16 and 18 is a risk of precancerous and cancerous lesions and should be evaluated further with colposcopy.

Ethics

Ethics Committee Approval: Our study was conducted retrospectively in a secondary center after obtaining the permission of the Local Ethics Committee of Batman State Hospital (no: 2020/232).

Informed Consent: Written and verbal consent was obtained from all patients before starting the study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.O., Ö.K.A., Design: E.O., Ö.K.A., Data Collection or Processing: E.O., Ö.K.A., Analysis or Interpretation: E.O.,

Ö.K.A., Critical Revision of Manuscript: E.O., Ö.K.A., Final Approval and Accountability: E.O., Ö.K.A., Technical or Material Support: E.O., Supervision: Ö.K.A., Writing: E.O., Ö.K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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