Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.1074012

Relationship Between Human Papillomavirus (HPV), Cervical Smear Cytology and Colposcopy Directed Biopsy Results: 4 Year Experience of a University Hospital in Cervical Cancer Screening

Human Papillomavirüs (HPV), Servikal Smear ve Kolposkopik Biyopsi Sonuçlarının Karşılaştırılması: Serviks Kanseri Taramasında Bir Üniversite Hastanesinin 4 Yıllık Deneyimi

Duygu ALTIN [1] Orcid ID:0000-0002-9072-9393
Deha Denizhan KESKİN [2] Orcid ID:0000-0002-6108-7619

[1] ASV. Yaşam Hospital, Department of Gynecology and Obstetrics, Antalya, Turkey
[2] Ordu University School of Medicine, Department of Gynecology and Obstetrics, Ordu, Turkey

ÖZ

Amaç: Sitolojinin sensitivitesi görece düşük olduğu için serviks kanseri taramasında Human papillomavirus (HPV) DNA ile tarama önerilmektedir. Bu çalışmanın amacı HPV, servikal smear ve kolposkopik biyopsi sonuçları arasındaki uyumu araştırmaktır.

Gereçler ve Yöntem: Ordu Üniversitesi Eğitim ve Araştırma Hastanesi'nde Ocak 2018-Aralık 2021 yılları arasında kolposkopik biyopsi alınan hastalar geriye dönük taranmıştır. Herhangi bir yüksek riskli HPV pozitifliği olan, servikal smear ve kolposkopik biyopsi sonucu bulunan hastalar çalışmaya dahil edilmiştir. HPV tipleri, smear ve biyopsi sonuçları karşılaştırılmıştır.

Bulgular: Çalışmaya 734 hasta dahil edilmiştir. Hastaların ortalama yaşı 41.9 ± 7.36'dır. 165 (%22.5) hastada tek başına HPV 16, 35 (%4.8) hastada tek başına HPV 18, 354 (%48.2) hastada diğer yüksek riskli HPV tiplerinden biri ve 180 (%24.5) hastada en az iki HPV tipi birlikte tespit edilmiştir. 298 (%40.6) hastada HPV 16 ve/veya HPV 18 tek başına ya da başka tiplerle bir arada bulunmuştur. Hastaların çoğunda (%55.3) smear sonucu normal iken ASC-US en sık saptanan sitolojik anormallik olmuştur. Kolposkopi eşliğinde alınan biyopsi sonuçları şu şekildedir: 452 (%61.6) normal, 199 (%27.1) CIN 1, 36 (%4.9) CIN 2, 42 (%5.7) CIN 3 ve 5 (%0.7) skuamoz hücreli karsinom. HPV 16 ve/veya HPV 18 olan hastaların %66.1'inde smear sonucu normal olmasına karşın diğer yüksek-riskli HPV subtiplerine göre daha fazla ≥CIN 2 lezyon saptanmıştır (%19.8 vs %5.5, p<0.001). Bir veya daha fazla HPV subtipi ile enfekte olmakla lezyon şiddeti arasında istatistiksel olarak anlamlı bir fark saptanmamıştır. (p=0.474). Smear testinin sensitivitesi %55.2, spesifisitesi %69.2 olarak bulunmuştur.

Sonuç: HPV 16 ve/veya HPV 18 ile enfekte olan hastaların smear sonuçları çoğunlukla normal olsa da bu hastaların yaklaşık %20'sinde ≥CIN 2 lezyon bulunmaktadır. Smear testinin sensitivitesi düşük olduğundan HPV genotiplendirme ile tarama daha güvenilir bir yöntemdir.

Anahtar Sözcükler: Human papillomavirus DNA testi, servikal smear, kolposkopi, serviks kanseri taraması

ABSTRACT

Aim: Cervical cancer screening guidelines gradually recommend human papillomavirus (HPV) DNA testing since the sensitivity of cytology is relatively low. This study aimed to evaluate correlation between HPV, cervical smear cytology and colposcopy directed biopsy results.

Material and Methods: Patients who underwent colposcopy directed biopsy in Ordu University Training and Teaching Hospital between January 2018 and December 2021 were retrospectively reviewed. Patients with any high-risk HPV positivity who had cervical smear cytology and colposcopy directed biopsy results were included to this study. Results of HPV subtypes, cervical smear and histologic biopsy were recorded.

Results: A total of 734 patients were included to this study. The mean age of the patients was 41.9 ± 7.36 years. Hundred and sixty-five (22.5%) patients had HPV 16 alone, 35 (4.8%) had HPV 18 alone, 354 (48.2%) had other high-risk HPV subtypes alone and 180 (24.5%) had more than one high-risk HPV subtypes. Two hundred and ninety-eight (40.6%) had HPV 16 or HPV 18 either alone or in combination with other subtypes. Majority of the patients (55.3%) had normal cervical smear results followed by ASC-US (27%). Colposcopy directed biopsy results were as follows: 452 (61.6%) normal, 199 (27.1%) CIN 1, 36 (4.9%) CIN 2, 42 (5.7%) CIN 3 and 5 (0.7%) squamous cell cancer. 66.1% of the patients with HPV 16 and/or HPV 18 had normal cervical cytology results, but they had significantly more ≥CIN 2 lesions compared to other high-risk HPV subtypes (19.8% vs 5.5%, p<0.001). There wasn't a statistical difference between having one or more than one HPV subtype in terms of severity of the lesions (p=0.474). The sensitivity and specificity of cervical smear cytology test were 55.2% and 69.2%, respectively.

Conclusion: Although patients with HPV 16 and/or HPV 18 were more likely to have normal cervical cytology results, almost 20% of them had CIN 2 + lesions. Sensitivity of cervical cytology remains low and HPV DNA test with genotyping is more reliable as a screening tool.

Keywords: Human papillomavirus DNA test, cervical smear, colposcopy, cervical cancer screening

Sorumlu Yazar/ Corresponding Author:
Duygu Altın
Adres: ASV Antalya Yaşam Hospital Gebizli, 07300, Muratpaşa, Antalya, Turkey
E-mail: duygualtin@yahoo.com

Başvuru tarihi : 15.02.2022
Kabul tarihi : 20.03.2022

INTRODUCTION

Cervical cancer is the fourth most common cancer in females and most common cause of death from gynecologic cancers worldwide (1). Although the incidence and mortality from cervical cancer had been declined through the years with screening and prevention programs, it is still an important public health problem for the developing countries due to inadequacy of these programs.

Human papillomavirus (HPV) is the main risk factor for cervical cancer and it can be detected in approximately 99% of the cases (2). Because it takes years for an HPV infection to transform to cervical cancer, it can be easily detected and treated in premalignant period with screening tests. Pap smear cytology test had been used for screening for long years worldwide. Since the sensitivity of Pap smear was found to be 50-85% in many studies, screening with HPV DNA test was considered more appropriate (3, 4). Currently, many guidelines recommend HPV DNA test for cervical screening, but not all countries have possibilities to access this more sensitive method (5, 6).

This study aimed to evaluate correlation between HPV, cervical smear cytology and colposcopy directed biopsy results in a single center.

MATERIALS AND METHODS

After institutional review board approval (Ordu University Clinical Research Ethics Committee, approval no: 2022-02/24), patients who underwent colposcopy directed biopsy in Ordu University Training and Teaching Hospital between January 2018 and December 2021 were retrospectively reviewed. Patients ≥25 years with any high-risk HPV positivity whom at least 2-quadrant colposcopy directed biopsy obtained were included to this study. Both gynecologists had at least 5 years of colposcopy experience. Patients without a cervical smear cytology result were excluded from the study. Patients whom only one-quadrant punch biopsy were obtained were also excluded from this study to increase the study's power and the current ASCCP consensus guidelines recommend not only to take 2 to 4 biopsies at each colposcopic examination but also obtain biopsies when the colposcopic impression is normal but any degree of acetowhitening, metaplasia, or other abnormality is present. Pregnancy, hysterectomy and unsatisfactory colposcopy were also exclusion criteria. All patients gave written informed consent for use of their data for scientific purposes.

Cervical samples for HPV DNA and Pap smear were taken at the same time or within one month of each other. For HPV DNA genotyping cervical specimens were collected into the HC2 HPV DNA (Qiagen Gaithersburg, Inc, USA) collection device and HPV DNA was extracted and amplified by Hybrid Capture 2and polymerase chain reaction in the National Central HPV Laboratory within the Cancer Early Detection and Education Center of the Ministry of Health.

For Pap smear evaluation, liquid base preparations (Thin Prep Pap test, Cytyc Corporation, Boxborough, MA, USA) were used and reviewed by experienced pathologists. Results were reported using the Bethesda System: Unsatisfactory material, negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) (7).

Results of HPV subtypes, cervical Pap smear and histologic biopsy were recorded. High-risk HPV types were categorized as HPV 16, HPV 18 and others (HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66 and HPV 68). Smear results with unsatisfactory material were excluded from the analysis.

Age data were presented as the mean ± standard deviation. Categorical variables were presented as number (percentage) and compared using chi square or Fishers' exact tests. Sensitivity and specificity of the Pap smear test were calculated. SPSS version 21.0 (IBM Corp, NY, USA) was used for statistical calculations and a p value <0.05 was considered statistically significant.

RESULTS

A total of 734 patients met the inclusion criteria. The mean age of the patients was 41.9 ± 7.36 years. As shown in Table 1, 165 (22.5%) patients had HPV 16 alone, 35 (4.8%) had HPV 18 alone, 354 (48.2%) had other high-risk HPV subtypes alone and 180 (24.5%) had more than one high-risk HPV subtypes. Totally, 242 patients had HPV 16, followed by HPV 51 (n=87), HPV 31 (n=86) and HPV 52 (n=84). Two hundred and ninety-eight (40.6%) had HPV 16 or HPV 18 either alone or in combination with other subtypes. Four hundred and six (55.3%) patients' Pap smear results were NILM. The most common cytologic abnormality was ASC-US (n=198, 27%), followed by LSIL (n=63, 8.6%). Pap smear results of 52 patients were unsatisfactory and these patients were excluded from the analysis (Table 1).

Table 1. Clinicopathologic characteristics of the patients

Characteristic	Number (%)
Age, years (mean)	41.89±7.36
HPV Test	
HPV 16	165 (22.5)
HPV 18	35 (4.8)
Other high-risk subtypes	354 (48.2)
Multiple	180 (24.5)
Cervical Cytology	
Normal	406 (55.3)
ASC-US	198 (27)
LSIL	63 (8.6)
HSIL	9 (1.2)
ASC-H	6 (0.8)
Unsatisfactory	52 (7.1)
Colposcopy Directed Biopsy	
Normal	452 (61.6)
CIN 1	199 (27.1)
CIN 2	36 (4.9)
CIN 3	42 (5.7)
SCC	5 (0.7)

HPV: Human papillomavirus, ASC-US: atypical squamous cells of unknown significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, ASC-H: atypical squamous cells that cannot exclude HSIL, CIN: cervical intraepithelial neoplasia, SCC: squamous cell carcinoma

Histologic evaluation of colposcopy directed biopsy were normal in majority of the patients (61.6%). While cervical intraepithelial neoplasia (CIN) 1 was diagnosed in 199 (27.1%) patients, 36 (4.9%) had CIN 2 and 42 (4.7%) had CIN 3. Five (0.7%) patients had invasive squamous cell carcinoma (Table 1).

66.1% of the patients with HPV 16 and/or HPV 18 had normal cervical cytology results, but they significantly had more HSIL/ASC-H compared to other HPV subtypes (p<0.001). There wasn't a statistical difference between being infected with one or more than one HPV subtype in terms of Pap smear results (p=0.975).

As shown in Table 2, patients with HPV 16 and/or HPV 18 significantly had more ≥CIN 2 lesions compared to other high-risk HPV subtypes (19.8% vs 5.5%, p<0.001). In a subgroup analysis between the patients who are positive for HPV 16 alone and HPV 18 alone, although more ≥CIN 2 lesions were seen in HPV 16 positive patients, the difference didn't reach statistical significance (24.2% vs 14.3%, p=0.200). There wasn't also a statistical difference between having one or more than one HPV subtype in terms of severity of the lesions (p=0.474).

Although patients with HSIL and ASC-H had more severe lesions (ie. ≥CIN 2), the overall sensitivity and specificity of Pap smear cytology test were 55.2% (95% confidence interval [CI]: 49.04-61.22%) and 69.2% (95% CI: 64.47-73.6%), respectively.

Table 2. Correlation between HPV subtypes, cervical cytology and colposcopy directed biopsy results

	Colposcopy directed biopsy		
	Normal/ CIN 1	**≥CIN 2**	**p value**
HPV			
HPV 16 and/or HPV 18	239 (80.2)	59 (19.8)	**<0.001**
Other high-risk subtypes	412 (94.5)	24 (5.5)	
HPV			
Single	494 (89.2)	60 (10.8)	0.474
Multiple	157 (87.2)	23 (12.8)	
Cervical cytology			
Normal	378 (93.1)	28 (6.9)	**<0.001**
ASC-US/LSIL	224 (85.8)	37 (14.2)	
HSIL/ASC-H	2 (13.3)	13 (86.7)	

HPV: Human papillomavirus, ASC-US: atypical squamous cells of unknown significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, ASC-H: atypical squamous cells that cannot exclude HSIL, CIN: cervical intraepithelial neoplasia

DISCUSSION

Cervical cancer is a global health problem especially in less developed countries. Early detection and treatment of preinvasive lesions became cornerstone in decreasing incidence and mortality of cervical cancer. Pap smear test is used as a screening tool which is shown to be effective (8, 9). Although there had been a remarkable reduction in the mortality of cervical cancer with Pap smear screening programs, there are many reports in the literature indicating the low sensitivity of this test (10-13). In a systematic review including 97 studies, the sensitivity of Pap smear test was ranged from 30% to 87% (11).

After excluding patients with unsatisfactory Pap smear results, the prevalence of abnormal Pap smear test was found as 40.5% in our study. This rate was higher than the literature and may be a result of our study design, since only HPV positive women were included to this study (14, 15). Pathologic evaluation of the colposcopy directed biopsy was normal in 70.2% of the patients with NILM cytology results and 6.9% of these patients had ≥CIN 2 lesions. Moreover, only 2 of the 5 patients with SCC had HSIL cytologic result. In 2 of them Pap smear test was unsatisfactory and 1 had ASC-US. The sensitivity and specificity of the Pap smear test were 55.2% and 69.2%, respectively which are consistent with the literature (10-13).

Handicaps of the Pap smear test such as low sensitivity, interobserver variability and need for more frequent screening led to a shift to HPV DNA screening (16). Numerous studies showed that

screening with HPV DNA is more sensitive than cytology (17-20). It has been shown that in women ≥30 years of age, HPV primary screening was 24.3% more sensitive for CIN 3+ lesions compared to cytology (18). Hence, many countries adopted HPV primary testing for screening programs.

HPV 16, HPV 18, HPV 31, HPV 51 and HPV 58 are the most common HPV subtypes (21). In a recent meta-analysis, HPV 16, HPV 52 and HPV 58 were found to be most common subtypes in China (22). Our results support the fact that HPV subtypes differ from region to region as 32.9% of the patients had HPV 16 either alone or in combination with other types, and HPV 51, HPV 31 and HPV 52 were other most prevalent types in our study.

HPV 16 and HPV 18 are the most oncogenic subtypes and it has been shown that HPV 16 and HPV 18 together are responsible for 71% of cervical cancers (14, 23). While 46.3% of the patients with HPV 16 and/or HPV 18 either alone or in combination with other subtypes had normal colposcopy directed biopsy results, 72% of the patients with other high-risk HPVs had normal biopsy in our study. Moreover, there was a statistical significance in terms of ≥CIN 2 lesions between the patients with HPV 16 and/or HPV 18 and other subtypes (19.8% vs 5.5%). Also, 4 of the 5 patients with SCC had HPV 16 or 18 (2 patients had HPV 16 alone, 1 had HPV 18 alone and 1 had HPV 16 + HPV 33) in our study. The other patient was infected with HPV 31. Interestingly, we found similar ≥CIN 2 lesion rates between the patients infected with single and multiple HPV subtypes. Our results point out that type of HPV is more important rather than coinfection with different HPV types for development of premalignant and malignant lesions.

Several studies have shown that the rate of CIN 2 or worse were higher in patients with HPV 16 alone compared to HPV 18 alone irrespective of cervical cytology results (24-26). Although it did not reach statistical significance, ≥CIN 2 lesions were seen more frequently in patients infected with HPV 16 alone compared to HPV 18 alone in our study (24.2% vs 14.3%). We couldn't perform further sub-analysis in these group of patients because of the limited number of patients with ≥CIN 2 lesions.

In our study, 66.1% of the patients with HPV 16 and/or HPV 18 and 55.1% of the patients with other high-risk HPV subtypes had normal cervical cytology results. Notwithstanding HSIL and ASC-H were more common in HPV 16 and/or HPV 18 group (3.6% vs 1.2%). Therefore, patients with HPV 16 and/or HPV 18 should be evaluated more carefully and colposcopy directed biopsy should be obtained even if Pap smear test and colposcopic appearance are normal.

On the other hand, the latest ASCCP consensus guidelines states colposcopy is indicated for patients whose immediate CIN 3+ risk is 4-24% and treatment is almost always recommended for patients with CIN 2 and 3, except for some special populations (6). We had taken cut-off value as CIN 2 in this study and couldn't perform a subgroup analysis due to limited number of patients with high-grade lesions, but both in HPV 16 and/or HPV 18 group (19.8%) and in other high-risk HPV group (5.5%), ≥CIN 2 lesion rates were above the cut-off value of 4% which was determined by ASCCP. Therefore, in centers where access to colposcopy is easy, colposcopy may also be an option even for patients with other high-risk HPVs irrespective of cervical cytology results.

Large number of patients and centralized cytology review and HPV genotyping in national laboratory are the major strengths of this study. Retrospective nature and exclusion of the patients without HPV DNA who underwent colposcopy were limitations.

CONCLUION

In summary, our results support that HPV DNA test is more sensitive than Pap smear cytology. HPV DNA test with genotyping is more reliable as a screening tool screening with and it should be preferred when possible. HPV 16 and 18 is more oncogenic than other subtypes and patients with these HPV subtypes should be evaluated more carefully.

Conflict of Interest: No conflicts of interest

Financial Disclosures: No financial support was received

Author Contributions: DA: Conceptualization, Methadology, Formal Analysis, Investigation, Writing – Original draft; DDK: Conceptualization, Methadology, Formal Analysis, Writing – Review & Editing

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