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Evaluation of HPV-DNA Prevalence and Genotype Distribution and Cytological Examination Results in Cervical Samples

Servikal Örneklerde HPV-DNA Sıklığı ve Genotip Dağılımı ile Sitolojik İnceleme Sonuçlarının Değerlendirilmesi

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ABSTRACT

Introduction: *Cervical cancer caused by human papillomavirus (HPV) is the fourth most common cancer in women. In recent studies conducted for the prevention or early diagnosis of cervical cancer, it has been reported that HPV-DNA testing provides more protection than cytology, is more sensitive and cost-effective, and its use in screening programs has been recommended. This study aimed to determine HPV genotypes in cervical samples in the Izmir region and to evaluate PAP smear results.*

Materials and Methods: *HPV-DNA results of cervical swab samples of 371 female patients (mean= 35.6) aged between 19-61 who applied to Dokuz Eylül University Medical Faculty Hospital were retrospectively examined and compared with PAP smear results.*

Results: *HPV-DNA was detected in 150 of 371 samples (40.4%). Cytological abnormalities were also detected in 12.9% of these 150 samples, while no abnormalities were detected in 25.3%. The most common was HPV 16 (45.3%), followed by HPV 56 (17.3%), HPV 18 (12.0%) and HPV 51 (12.0%).*

Conclusion: *Human papillomavirus prevalence and genotypes vary according to the region and group studied. In Türkiye, HPV positivity was reported between 3.2% and 80.0%. In this study, HPV-DNA positivity was 40.4%, while this rate increased to 51.6% in patients with cytological abnormalities. Only high-risk genotypes were examined in the study. While HPV 16 and 18 are most commonly encountered in the world, the following genotypes may differ. Also in our study, HPV 16 was found most frequently, followed by HPV 56, HPV 18 and HPV 51. Cytological abnormalities were detected in 25.1% of the samples and ASC-US/ASC-H (55.9%) was the most common, followed by LSIL (23.6%) and HSIL (11.7%). HPV-DNA was detected in 37% of the cases without abnormalities in the cytological examination and 56.4% of these were found to be HPV 16 and/or 18. In conclusion, this study supports that HPV 16 is the most frequently detected genotype and that the following genotypes may vary. Multicenter studies covering a large number of women are needed to reveal regional differences and to shed light on vaccine studies. In addition, the detection of high-risk HPV genotypes in samples where no pathology was detected in the study is also valuable in terms of emphasizing the importance of HPV-DNA testing in the prevention and early diagnosis of cervical cancer.*

Key Words: *HPV-DNA; Genotypes; Cervical cancer; Cytology; PAP smear*

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ÖZ

Servikal Örneklerde HPV-DNA Sıklığı ve Genotip Dağılımı ile Sitolojik İnceleme Sonuçlarının Değerlendirilmesi

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Giriş: *İnsan papilloma virüsü [human papillomavirus (HPV)]'nün neden olduğu rahim ağzı kanseri, kadınlarda en sık görülen dördüncü kanserdir. Rahim ağzı kanserinin önlenmesi veya erken teşhisi için son yıllarda yapılan çalışmalarda HPV-DNA testinin sitolojiye göre daha fazla koruma sağladığı, daha duyarlı ve uygun maliyetli olduğu bildirilmiş, tarama programlarında kullanılması önerilmiştir. Bu çalışmada İzmir bölgesindeki servikal örneklerde HPV genotiplerinin belirlenmesi ve PAP smear sonuçlarının değerlendirilmesi amaçlanmıştır.*

Materyal ve Metod: *Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesine başvuran 19-61 yaş arası 371 kadın hastanın (ortalama= 35.6) servikal süruntü örneklerinin HPV-DNA sonuçları retrospektif olarak incelenmiş ve PAP smear sonuçları ile karşılaştırılmıştır.*

Bulgular: *Üç yüz yetmiş bir örneğin 150 (%40.4)'sinde HPV-DNA tespit edilmiştir. Bu 150 örneğin %12.9'unda sitolojik anormallikler de tespit edilirken, %25.3'ünde herhangi bir anormallik tespit edilmemiştir. En sık olarak HPV 16 (%45.3) bulunmuş, bunu HPV 56 (%17.3), HPV 18 (%12.0) ve HPV 51 (%12.0) izlemiştir.*

Sonuç: *İnsan papilloma virüs prevalansı ve genotipleri çalışılan bölge ve gruba göre farklılık göstermektedir. Türkiye'de HPV pozitifliği %3.2 ile %80.0 arasında rapor edilmiştir. Bu çalışmada HPV-DNA pozitifliği %40.4 iken, sitolojik anormalliği olan hastalarda bu oran %51.6'ya çıkmıştır. Çalışmada sadece yüksek riskli genotipler incelenmiştir. Dünyada en yaygın biçimde HPV 16 ve 18 ile karşılaşılırken, takip eden genotipler farklılık gösterebilmektedir. Bu çalışmada da en sık HPV 16 bulunmuş, bunu HPV 56 HPV 18 ve HPV 51 izlemiştir. Örneklerin %25.1'inde sitolojik anormallikler tespit edilmiş ve en sık ASC-US/ASC-H (%55.9)'ye rastlanmış, bunu sırasıyla "low grade squamous intraepithelial lesion (%23.6) ve "high grade squamous intraepithelial lesion" (%11.7) izlemiştir. Sitolojik incelemede anormallik olmayan olguların %37'sinde HPV-DNA saptanmış ve bunların %56.4'ünün HPV 16 ve/veya 18 olduğu görülmüştür. Sonuç olarak bu çalışma, HPV 16'nın en sık saptanan genotip olduğunu ve takip eden genotiplerin değişebileceğini desteklemektedir. Bölgeler arası farklılıkların ortaya konulması ve aşı çalışmalarına ışık tutabilmesi için çok sayıda kadını kapsayan çok merkezli çalışmaların yapılması gerekmektedir. Ayrıca çalışmada patoloji saptanmayan örneklerde yüksek riskli HPV genotiplerinin saptanması da HPV-DNA testinin rahim ağzı kanserinin önlenmesinde ve erken tanıda öneminin vurgulanması açısından değerlidir.*

Anahtar Kelimeler: *HPV-DNA; Genotip; Servikal kanser; PAP smear*

INTRODUCTION

Cervical cancer caused by human papillomavirus (HPV) is the fourth most common form of cancer in women worldwide. It is reported that HPV causes 570.000 new cases and 311.000 cervical cancer-related deaths annually worldwide[1]. According to the latest cancer statistics data of the Public Health Agency of the Turkish Ministry of Health, Department of Cancer, Türkiye, uterine-cervical cancer in Türkiye ranks tenth among female cancers and it has been stated that the incidence is 4.2 per hundred thousand[2]. Human papillomavirus types are divided into two groups according to their oncogenic potential; low-risk types (LR) (HPV 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 81) and high-risk types (HR) (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82)[3,4]. Worldwide, HPV 16 and 18 are the causative agents in two-thirds of cervical cancers[5].

Vaccination and screening programs are recommended for the prevention of cervical cancer. Today, three different HPV vaccines have been approved for the prevention of cervical cancers caused by HPV but current vaccines are not protective against all HPV types[6,7]. It is known that the distribution of HPV genotypes differs between geographic regions, so the

determination of HPV types will also be useful for new vaccination studies. It is stated that universal HPV vaccination programs can prevent 70% to 90% of HPV-related diseases, potentially reducing the future long-term burden of cervical cancer. The World Health Organization (WHO) recommends vaccination of girls aged 9-14 before the start of sexual activity and boys and older females are also recommended where feasible and affordable[8]. In addition, cervical cancer can be prevented by detecting chronic infection with high-risk HPV types and/or early diagnosis of precancerous lesions in the cervix with screening programs. It has been stated in many studies that population-based screening programs using cervical cytology have successfully decreased cervical cancer but recent studies have shown that HPV-DNA testing is more sensitive and cost-effective than cytology[9-11]. According to these results, HPV-DNA-based screening programs have been implemented in many countries and also since 2014, HPV-DNA testing has been used as the nationwide primary screening program for cervical cancer.

In this study, HPV-DNA test results and simultaneous conventional PAP smear results from the İzmir region over a five-year period were evaluated to determine the prevalent HPV types in this region and to compare the results of these two methods. With the results of this study, we aimed to contribute to the prevention of cervical cancer in our country and the world by providing data to improve screening programs and new vaccine studies.

MATERIALS and METHODS

The results of cervical swab samples from 371 patients aged 19-61 (mean age= 35.6), sent to the Dokuz Eylül University Medical Faculty of Medicine Molecular Microbiology Laboratory over a five-year period for HPV-DNA testing and genotype determination, were analyzed and compared with PAP smear results retrospectively.

Three different multiplex real-time PCR (RT-PCR) kits were used in different years for HPV-DNA detection and typing. Human papillomavirus High-Risk Typing Real-TM (Sacace Biotechnologies, Italy) kit can detect 12 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59). Abbott RealTime High Risk (HR) HPV kit can distinguish between types 16 and 18 and can identify other high-risk types together. Samples detected as high-risk HPV-DNA other than HPV 16-18 with this kit were not included in the study, as they were not determined. Genotypes 14 Real-TM Quantb (Nuclear Laser Medicine S.R.L, Italy) can detect 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). PAP smear evaluation was performed by Dokuz Eylül University Medical Faculty of Medicine Pathology Laboratory according to the modified Bethesda system.

Since the data used in our study was examined retrospectively and dates back to before 2020, Ethics Committee approval is not required in our country.

RESULTS

Human papillomavirus-DNA was detected in 150 (40.4%) of 371 cervical swab samples. In 48 (12.9%) of these 150 samples, cytological abnormalities were detected at the same time, while in 94 samples (25.3%) no abnormalities were detected. No cytological examination was performed in eight samples (2.2%) (Table 1). Cytological abnormalities were detected in 45 (12.1%) of 221 (59.6%) HPV-DNA-negative samples and among these 221 samples, cytological examination was not performed in 16 patients (4.4%). Human papillomavirus-DNA was detected in 94 (37.0%) of 254 samples without cytological pathology (Table 1).

A total of 228 HPV genotypes were identified in 150 HPV-DNA-positive samples. Of these, 106 samples contained a single HPV type, while 122 samples contained more than one HPV type. In samples containing more than one HPV type (n= 44), infection was most common with two types (23/44, 52.3%). The single and multiple-type distributions are shown in Table 2.

Infection with a single genotype was detected in 70.7% (106/150) of HPV-DNA-positive samples, while mixed infection was found in 29.3% of the samples. In all HPV-DNA-positive samples, HPV 16 (68/150, 45.3%) was most

Table 1. Comparison of cytology results and HPV-DNA results

		Cytological Examination (%)			Total n (%)
		Positive	Negative	Not examined	
HPV-DNA, n (%)	Positive	48 (12.9)	94 (25.3)	8 (2.2)	150 (40.4)
	Negative	45 (12.1)	160 (43.1)	16 (4.4)	221 (59.6)
Total, n (%)		93 (25.1)	254 (68.5)	24 (6.6)	371 (100.0)

Table 2. Human papillomavirus types and co-infection patterns detected in cervical swab samples

	Multiple Infections (n= 44)				
Infection with a single genotype (n= 106)	**Infection with 2 genotypes (n= 23)**	**Infection with 3 genotypes (n= 14)**	**Infection with 4 genotypes (n= 3)**	**Infection with 5 genotypes (n= 3)**	**Infection with 7 genotypes (n= 1)**
Genotype number: 106	**Genotype number: 46**	**Genotype number: 42**	**Genotype number: 12**	**Genotype number: 15**	**Genotype number: 7**
HPV 16 (n= 44)	HPV 16-39 (n= 4)	HPV 16-51-56 (n= 1)	HPV 16-45-51-56 (n= 1)	HPV 39-45-51-56-58 (n= 1)	HPV 16-18-31-35-45-51-58 (n= 1)
HPV 56 (n= 14)	HPV 16-18 (n= 3)	HPV 51-56-66 (n= 1)	HPV 16-39-45-58 (n= 1)	HPV 16-33-52-56-59 (n= 1)	
HPV 18 (n= 9)	HPV 18-56 (n= 2)	HPV 35-51-68 (n= 1)	HPV 18-31-45-58 (n= 1)	HPV 16-31-39-51-56 (n= 1)	
HPV 39 (n= 6)	HPV 33-51 (n= 2)	HPV 31-35-51 (n= 1)			
HPV 51 (n= 6)	HPV 52-68 (n= 1)	HPV 16-56-68 (n= 1)			
HPV 31 (n= 6)	HPV 51-59 (n= 1)	HPV 18-31-59 (n= 1)			
HPV 45 (n= 5)	HPV 18-59 (n= 1)	HPV 18-39-66 (n= 1)			
HPV 68 (n= 5)	HPV 16-52(n= 1)	HPV 16-18-45 (n= 1)			
HPV 35 (n= 4)	HPV 16-51(n= 1)	HPV 31-35-52 (n= 1)			
HPV 59 (n= 3)	HPV 16-56 (n= 1)	HPV 45-51-59 (n= 1)			
HPV 52 (n= 2)	HPV 16-35 (n= 1)	HPV 16-58-59 (n= 1)			
HPV 58 (n= 2)	HPV 31-56 (n= 1)	HPV 18-45-51 (n=1)			
	HPV 16-59 (n= 1)	HPV 16-51-52 (n= 1)			
	HPV 31-52 (n= 1)	HPV 16-35-58 (n= 1)			
	HPV 35-56 (n= 1)				
	HPV 16-33 (n= 1)				

common, followed by HPV 56 (26/150, 17.3%), HPV 18 (21/150, 12.0%) and HPV 51 (21/150, 12.0%) respectively (Table 2).

When the samples with single and multiple HPV types were examined separately, HPV 16 was detected in 41.5% (44/106) of samples with a single HPV type, followed by HPV 56 in 13.2% (14/106) and HPV 18 in 8.5% (9/106). In samples with more than one HPV type, HPV 16 was detected in 54.5% (24/44), followed by HPV 51 in 34.1% (15/44), HPV 18 in 27.3% (12/44), and HPV 56 in 27.3% (12/44) (Table 2).

Pathological abnormalities were detected in 31.1% of the samples with a single genotype, 48% of which were low-grade squamous intraepithelial lesion (LSIL) and advanced lesions. Pathological abnormalities were detected in 31.8% of the samples with multiple genotypes, and 64% of them were LSIL and advanced lesions.

In our study, cytological abnormalities were detected in 93 samples (25.1%), and not detected in 254 samples (68.4%). Cytological examination was not performed in 24 samples. When samples that were found to be cytologically abnormal were examined, the most common lesion was atypical squamous cells (ASC-US)/ high-grade squamous intraepithelial lesion could not be excluded, atypical squamous cells (ASC-H) (55.9%), and then LSIL (%23.6). High-grade squamous intraepithelial lesion was detected in 11.7% of samples (Table 3).

Cytological subtypes and detected HPV types are shown in Table 4. Human papillomavirus-DNA was detected in 48 (51.6%) of 93 samples with cytological abnormalities; of these 48 samples, 29 were found to be HPV 16 and/or 18 positive, which are high-risk genotypes (Table 4). Human papillomavirus-DNA was detected in 22 (42.4%) of 52 cases with ASC-US/ASC-H and 14 of these 22 samples were HPV 16 and/or 18 positive. Human papillomavirus-DNA was detected in 37% of the samples (n= 254) without pathological abnormalities, and 56.4% of the detected genotypes were HPV 16 and/or 18.

DISCUSSION

Human papillomavirus prevalence and genotype distribution vary according to the region and group in which the study was conducted[1,5]. According to the results of a meta-analysis that included 78 studies, significant regional differences were observed, with the prevalence of HPV reported as 10.4% in 157.879 women with normal cervical cytology. Additionally, 32% of these women were reported to be infected with HPV 16 and/or 18[12]. In another meta-analysis, which combined data from 59 studies and evaluated 1.016.719 women with normal cervical cytology, it was reported that 11.7% of women were infected with HPV. When analyzed by country, the infection rate ranged from 1.6% to 41.9%[13]. Various studies from Türkiye have reported HPV positivity rates ranging from 2.4% to 80.0%, depending on the region, patient population, and whether the cervical cytology is normal or abnormal[14]. Within the framework of the national HPV cancer screening program, HPV positivity was found to be 3.5% in 1.060.992 women screened between August

Table 3. Distribution of abnormal cytology results

Cytological Subtypes	n (%)
ASC-US/ASC-H	52 (55.9)
LSIL	22 (23.6)
HSIL	11 (11.7)
Carcinoma in situ (CIS)	1 (1.1)
Atypical glandular dysplasia (AGD)	2 (2.2)
Adenocarcinoma (Adenoca)	3 (3.3)
Squamous cell cancer (SCC)	2 (3.2)
Total	93 (100)

Table 4. HPV-DNA types detected in samples with cytological abnormalities

	ASC-US/ASC-H	n	LSIL	n	HSIL	n	AGD	n	CIS	n	Adenoca	n	SCC	n
HPV TYPES	16	8	45	1	16	5	18	1	16	1	16	1		
	18	2	16	3	58	1								
	59	2	56	2	51	1								
	45	1	59	1	16-33	1								
	56	2	16-18	1	16-39-66	1								
	39	1	51-59	1	18-31-59	1								
	51	1	33-51	2										
	16-18	1	51-59-66	1										
	16-56	1	31-35-52	1										
	18-56	1												
	35-56	1												
	18-31-45-58	1												
	N*	30	N	9	N	1	N	1			N	2	N	2
	Total	52		22		11		2		1		3		2

N*: Negative.

2013 and October 2014[15]. In our study, while HPV-DNA positivity was 40.4%, it was observed that this rate increased to 51.6% in patients with cytological abnormalities. Although this ratio seems high, studies including patients admitted to hospitals and those with cytological abnormalities have reported even higher rates in Türkiye[14,16].

In our study, only high-risk genotypes were examined and HPV 16 (45.3%) was observed most frequently, followed by HPV 56 (17.3%), HPV 18 (12.0%), and HPV 51 (12.0%), respectively (Table 2). It is known that HPV 16 and 18 are the most common genotypes worldwide, with HPV 16 ranking first in all regions. However, the genotypes that follow differ between regions and studies[13]. Our study and the results of other studies from Türkiye also support this finding[14]. Understanding the differences in HPV genotype distribution is of great importance for vaccine development and studies.

In our study, infection with a single genotype was found in 70.7% of the samples with positive HPV-DNA, while mixed infection was found in 29.3%. In the samples with more than one HPV type, HPV 16 (54.5%), HPV 51 (34.1%), HPV 18 (27.3%), and HPV 56 (27.3%) were the most common types (Table 2). Although there are few studies investigating the relationship between multiple HPV infections and the risk of cervical disease, it has been reported that the rate of multiple infections varies between 24.8% and 52.6%. Since multiple HPV infections have distinct clinicopathological characteristics compared with single HPV infections, frequent follow-up is needed[17,18]. In our study, the rate of detection of pathological abnormalities in samples with a single genotype and those with multiple genotypes was the same. However, LSIL and advanced lesions were significantly higher in samples with multiple genotypes (48% in single genotype samples vs. 64% in multiple genotype samples). The relationship between multiple HPV types and infections and cervical cancer needs to be investigated in more comprehensive studies.

In our study, cytological abnormalities were detected in 25.1% of the cervical samples and ASC-US/ASC-H (55.9%) was reported most frequently, followed by LSIL (23.6%) and HSIL (11.7%) respectively (Table 3). In the literature, it has been reported that HPV-DNA positivity in women with abnormal cytology varies between 29-61%[19]. A study from Türkiye reported that HPV-DNA positivity was 43.4% in women

with abnormal cytology[20]. In our study, HPV-DNA was detected in 51.6% of samples with cytological abnormalities; and 60.4% of the samples were positive for HPV 16 and/or 18, which are high-risk genotypes (Table 4). The American Society for Colposcopy and Cervical Pathology Guidelines recommend reflex HPV testing in cases of ASC-US, as nearly 50% of colposcopies can be avoided if HPV-DNA testing is performed in these patients[21]. In our study, high-risk HPV types were found in 27% of the patients whose pathology results were reported as ASC-US/ASC-H, indicating that HPV-DNA evaluation before colposcopy is useful in these patients.

Human papillomavirus-DNA was detected in 37% of cases without cytological abnormalities, and 56.4% of these detected genotypes were HPV 16 and/or 18 (Table 5). In hospital-based studies, this rate is expected to be higher depending on the population. However, the HPV-DNA test is known to be more sensitive than cytology, and even when cytological abnormalities are not detected, colposcopy and close monitoring are recommended if HPV 16 and/or 18 are detected[14,16,20]. Human papillomavirus-DNA was found in 37% of the cases where no abnormalities were detected in the cytological examination. Given that more than half of the detected genotypes were HPV 16 and/or 18, the importance of HPV-DNA testing in preventing cervical cancer is once again demonstrated.

In conclusion, HPV 16 was the most frequent genotype in our study, consistent with other studies from Türkiye and around the world. This also supports existing information about the variability of subsequent genotypes. Our study has once again demonstrated the indispensable role of HPV-DNA testing in preventing cervical cancer and facilitating early diagnosis, even when no cervical pathology is detected, due to the considerable rate of infections with high-risk genotypes.

ETHICS COMMITTEE APPROVAL

This study does not require ethics committee approval.

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: AÇD, BNE

Analysis/Interpretation: AÇD, BNE

Data Collection or Processing: SÖ, MK

Writing: SÖ, BNE

Review and Correction: All of authors

Final Approval: All of authors

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