

## A retrospective cohort study of human papillomavirus (HPV) genotypes in women with abnormal Pap smear cytology in Turkey

Hayati Beka

Istanbul Arel University, Faculty of Medicine,  
Department of Medical Microbiology, Istanbul,  
Turkey

ORCID ID of the author(s)

HB: 0000-0002-5509-0248

### Corresponding Author

Hayati Beka  
Istanbul Medical Faculty, Faculty of Medicine,  
Department of Medical Microbiology, Istanbul,  
Turkey  
E-mail: hayatibeka@gmail.com  
hayatibeka@arel.edu.tr

### Ethics Committee Approval

The study was approved by the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (reference number: 2018/881/11). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

### Conflict of Interest

No conflict of interest was declared by the authors.

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### Abstract

**Background/Aim:** The most common genotypes of human papillomavirus (HPV) in patients with cervical cancer worldwide are HPV16 and HPV18. The persistence of these genotypes is associated with cervical cancer and detection, and HPV genotyping, particularly in women with abnormal Pap smears, has become a crucial tool for cervical cancer screening, diagnosis and management. We evaluated the overall prevalence of HPV in women with abnormal Pap smear cytology and also investigated age-specific HPV prevalence and HPV genotype distribution.

**Methods:** We analyzed 716 cervical smear specimens in this retrospective cohort study. Cytological diagnoses of typical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSILs), and high-grade squamous intraepithelial lesions (HSILs) were made utilizing the Bethesda System. The Papanicolaou method was used for the staining of the Pap smears. The specimens were pre-screened for HPV DNA positivity using an HC2 assay (Qiagen, USA). After the pre-screening, a Cobas 4800 HPV test system (Roche Diagnostics GmbH, Germany) was used to genotype the HPV-positive samples.

**Results:** Of the 716 cervical smear samples, 520 (72.6%) were found to be HPV-negative. Among the HPV-positive samples, 106 (23.2%), 57 (28.8%) and 33 (53.2%) were identified from 456 ASCUS, 198 LSIL and 62 HSIL cases, respectively. These findings revealed a gradual decrease in HPV prevalence with increased cytological grade ( $P<0.05$ ). For high-risk, low-risk and high-risk/low-risk HPV types, 76 (38.8%), 78 (39.8%) and 42 (21.4) were positive according to the HC2 assay, respectively ( $P<0.05$ ). Only 117 of the 196 HPV-positive samples were found to be HPV-positive with the Cobas 4800 HPV test system. HPV16 was the most prevalent type detected by the Cobas 4800 HPV test: 55 out of 117 HPV-positive smear samples across all age groups (47%). HPV16 was significantly more frequently detected in the HSIL samples than HPV18 ( $P<0.05$ ). The prevalence of HPV was the highest in women with ages between 29 and 38 (71/196, 36.22%) and declined with age.

**Conclusion:** We found that HPV16 and HPV18 were the most prevalent genotypes of HPV in a cohort of Turkish women; HPV16 was most frequently detected in HSIL samples from women with ages between 29 and 38. We conclude that investigating the incidence of HPV16 and HPV18 genotypes will be important for implementing new programs and protocols to reduce the incidence of cervical cancer. These data may contribute to the development of preventive strategies to reduce the cervical cancer burden in Turkey.

**Keywords:** human papillomavirus genotypes, cervical cancer, HPV16, HPV18

## Introduction

Cervical cancer, the fourth most frequent malignancy in women worldwide, is believed to be responsible for more than 342,000 deaths annually in low- and middle-income nations [1]. Ninety percent of human papillomavirus (HPV) infections are typically resolved within two years [2], and the majority of HPV infections are transitory. However, high-grade squamous intraepithelial lesions (HSILs) and cervical cancer development are linked to the persistence of high-risk HPV strains [2]. Human papillomavirus genotyping is a very useful tool for diagnosing, screening, and treating cervical cancers [3,4]. There are currently at least 200 known HPV genotypes [3]. In humans, 25 of these genotypes are known to be carcinogenic, with HPV16 and HPV18 being the most common genotypes in cervical cancer patients globally [5,6]. The average probability of developing cervical cancer increases with a person's age, their number of sexual partners, whether they smoked during young adulthood and whether they engaged in unprotected sexual activity in a young age [7,8]. We evaluated the overall prevalence of HPV, the age-specific prevalence of HPV and HPV genotype distribution in a cohort of Turkish patients with cervical Pap smears indicating atypical cells.

## Materials and methods

### Study population

We analyzed retrospectively 716 cervical smear specimens with atypical cells indicated on a Pap test. The specimens were collected from the Gynecology and Obstetrics Clinics of Istanbul Faculty of Medicine between 2008 and 2018. All of the eligible specimens derived from women who had a history of sexual activity, either current or previous, with were not pregnant at the time of the sample collection. All patients gave their consent to undergo HPV genotyping and cervical histopathology evaluation. Patients with acute genital inflammation, clinically suspected immunodeficiency, cervical or total uterus resection, or a previous cervical, vulval, or vaginal cancer diagnosis or treatment were excluded from the study. Atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) were the three cytological diagnoses that were made utilizing the Bethesda System [9]. The Istanbul University, Istanbul Faculty of Medicine Ethics Committee approved this study (reference number: 2018/881/11).

### HPV DNA analysis

The Hybrid Capture Cervical Sampler Qiagen GmbH, Hilden, Germany) and the Hybrid Capture 2 (HC2) DNA Collection Device (Qiagen GmbH, Hilden, Germany) were used to collect the smear specimens. The modified Papanicolaou procedure was used to stain Pap smears. The residual material was stored at -80°C until the specimens were pre-screened for HPV DNA positivity with a HC2 assay (Qiagen, Maryland, USA). The HC2 assay (*in-vitro* nucleic acid hybridization assay) was used to identify DNA from five low-risk genotypes (HPV6, 11, 42, 43 and 44) and 13 high-risk HPV genotypes (genotypes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [10]. After pre-screening the Pap smear samples with the HC2 assay,

the HPV-positive samples were genotyped using a Cobas 4800 HPV system (Roche Diagnostics GmbH, Germany). The Cobas 4800 HPV test is a qualitative multiplex assay that detects 12 high-risk HPV types (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) while providing specific genotyping information for HPV16 and HPV18. The results were interpreted automatically by the Cobas 4800 HPV system software (Roche Diagnostics GmbH, Germany) as "Target Not Detected," "HPV16," "HPV18," "other high-risk HPV" or any combination of the latter three. Samples that yielded invalid results were retested.

### Statistical analysis

We used SPSS software (version 21) (IBM, New York, USA) to analyze the data. Categorical data were presented as numbers and percentages. To evaluate the categorical data, we used the chi-square method. The chi-square test was also used to assess HPV prevalence with cytological grade and HPV infection prevalence predictions with age to evaluate trends. A *P*-value less than 0.05 was considered to indicate statistical significance.

## Results

Of the 716 cervical smear samples, 520 (72.6%) were found to be HPV-negative via pre-screening with the HC2 assay. Among the HPV-positive samples, 106 (23.2%), 57 (28.8%) and 33 (53.2%) were identified from 456 ASCUS, 198 LSIL and 62 HSIL cases, respectively. These numbers indicate a gradual decrease in HPV prevalence with increasing cytological grade ( $P<0.05$ ). The proportion of HPV positivity was highest in the HSIL group (Table 1).

For high-risk, low-risk and high-risk/low-risk HPV types, 76 (38.8%), 78 (39.8%) and 42 (21.4) were positive according to the HC2 assay, respectively ( $P<0.05$ ) (Table 2).

After pre-screening the atypical Pap smear samples with the HC2 assay, only 117 of the 196 HPV-positive samples were detected to be HPV-positive according to the Cobas 4800 HPV test. The most common genotype discovered by the Cobas 4800 HPV test was HPV16: 55 out of 117 HPV-positive smear samples across all age groups (47%). HPV16 was significantly more frequently detected in the HSIL samples than HPV18; 13 versus 3 samples were HPV DNA positive. The next most prevalent genotype was HPV18, which was detected in 20 of the samples (17.1%) (Table 3).

HPV16 was most commonly detected in smears from women with ages between 29 and 38 (54.8%). However, the detection frequency of HPV16 was slightly higher in women aged 18–28 than in those aged 29–38 (17.5% versus 16.6%). Other high-risk HPV genotypes (HPV31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66 and 68) were detected in 27.4% of HPV-positive samples across all age groups (Table 4). However, a type-specific genotype was not available.

Table 1: HPV prevalence in pap smears.

Cytology	ASCUS n=456 n (% , 95 CI)	LSIL n=198 n (% , 95 CI)	HSIL n=62 n (% , 95 CI)	Total
HPV DNA-	350 (76.8, 72.38-81.22)	141 (71.2, 63.73-78.67)	29 (46.8, 28.64-64.96)	520 (72.6, 68.77-76.43)
HPV DNA+	106 (23.2, 15.16-31.24)	57 (28.8, 17.04-40.56)	33 (53.2, 36.18-70.22)	196 (27.4, 21.16-33.64)

ASCUS: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, CI: confidence interval

Table 2. HPV positivity prevalence distribution in different age groups.

Age	*HR HPV n=76 (%, 95% CI)	*LR HPV n=78 (%, 95% CI)	HR/LR HPV n=42 (%, 95% CI)	HPV (-) n=520 (%, 95% CI)
18-28	25 (32.9%, 14.4-51.3)	24 (30.8%, 12.3-49.2)	15 (35.7%, 11.4-59.9)	114 (22%, 14.4-29.6)
29-38	27 (35.5%, 17.4-53.5)	28 (35.9%, 18.1-53.6)	16 (38%, 14.2-61.7)	186 (35.8%, 28.9-42.6)
39-48	16 (21%, 1-40.9)	17 (21.8%, 2.1-41.4)	9 (21.4%, 5.3-48.1)	143 (27.5%, 20.1-34.8)
49<	8 (10.5%, 10.7-31.7)	9 (11.5%, 9.3-32.3)	2 (4.7, 3.9-13.3)	77 (14.8%, 6.8-22.7)

HR: high risk, LR: low risk, CI: confidence interval

Table 3: HPV status versus cervical cytology.

Cytology	ASCUS n=58 (%, 95% CI)	LSIL n=34 (%, 95% CI)	HSIL n=25 (%, 95% CI)	Total n=117 (%, 95% CI)
HPV16	31 (53.4%, 35.8-70.9)	11 (32.3%, 4.6-59.9)	13 (52%, 24.8-79.1)	55 (47%, 33.8-60.1)
HPV18	10 (17.2%, 6.1-40.5)	7 (20.6%, 9.3-50.5)	3 (12%, 24.7-48.7)	20 (17.1%, 0.6-33.6)
OHR types*	14 (24.1%, 1.7-46.5)	13 (38.2%, 11.7-64.6)	5 (20%, 15-55)	32 (27.4%, 11.9-42.8)
HPV16/ OHR types	1 (1.7%, 23.6-27)	2 (5.9%, 26.7-38.56)	3 (12%, 24.7-48.7)	6 (5.1%, 12.5-22.7)
HPV18/ OHR types	2 (3.4%, 21.7-28.5)	1 (2.9%, 29.9-35.7)	1 (4%, 34.4-42.4)	4 (3.4%, 14.3-21.6)

ASCUS: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, CI: confidence interval, \*Other high-risk (OHR) HPV types: 31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66, 68

Table 4: The age distribution of patients by HPV type.

Age range	HPV 16 n, (% , 95% CI)	HPV 18 n, (% , 95% CI)	Other High Risk HPV* (OHR) n, (% , 95% CI)	HPV16/OHR n, (% , 95% CI)	HPV 18/OHR n, (% , 95% CI)
18-28 (n=40)	18 (45%, 22.02-67.9)	7 (17.5%, 10.6-45.6)	12 (28%, 30.4-55.9)	2 (5%, 25.1-35.2)	1 (2.5%, 28.1-33.1)
29-38 (n=42)	23 (54.8%, 41.4-68.2)	7 (16.6%, 10.9-44.1)	10 (23.8%, 2.5-50.1)	1 (2.4%, 27.6-32.4)	1 (2.4%, 27.6-32.4)
39-48 (n=25)	10 (40%, 9.6-70.3)	2 (8%, 29.6-45.6)	10 (40%, 9.6-70.3)	2 (8%, 29.6-45.6)	1 (4%, 4.4-42.4)
49< (n=10)	4 (40%, 8-88)	4 (40%, 8-88)	0	1 (10% , 48.8-68.8)	1 (10%, 48.8-68.8)
Total (n=117)	55 (47%, 33.8-60.1)	20 (17%, 0.5-33.4)	32 (27.4%, 11.9-42.8)	6 (5.1%, 12.5-22.7)	4 (3.4%, 14.3-21.1)

\* Other high-risk (OHR) HPV types: 31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66, 68; CI: confidence interval

Table 5: Prevalence rates of HPV in women with abnormal cytology tested in Istanbul and Ankara (included are studies with more than 400 tested samples).

Region	Study	Number of samples tested	HPV DNA (+)(%)	HPV16 (+)(%)	HPV18 (+)(%)	OHR (+)(%)
Turkey, multicenter	[ref #17]	6170	25.0	32.0	8.0	23.4
Istanbul	This study	716	27.4	47	17	27.1
Istanbul	[ref #18]	500	16.5	34.0	n.d.	n.d.
Istanbul	[ref #19]	420	20.2	n.d.	n.d.	n.d.
Ankara	[ref #16]	403	23.0	36.0	13.0	8.8
Ankara	[ref #20]	1797	22.4	25.5	2.5	41.8
Ankara	[ref #21]	530	17.9	3.6	0.4	5.8
Ankara	[ref #22]	501	4.2 (hr)	n.d.	n.d.	n.d.
Ankara	[ref #23]	890	25.7	46.3	4.4	61.9

n.d.: not determined, hr: high-risk

## Discussion

In Turkey, cervical cancer is the eighth most common malignancy overall among women and the 12th most common among women aged 15–44 [1]. According to estimates, 4.2% of women in the general Turkish population have a cervical HPV16/18 infection at any given time, and invasive cervical malignancies caused by HPV16 or HPV18 account for 67.6% of cases [11]. Because more than 96% of cervical malignancies test positive for high-risk HPV types, it is well-documented that HPV16 and HPV18 are the primary causes of cervical cancer [12]. It has been shown that there are significant regional and global differences in the prevalence of HPV and the distribution of HPV genotypes [13]. The prevalence of HPV has been

reported to be higher in the United States and Africa for women with ages between 35 and 50 but lower in European, Asian and Middle Eastern countries [4,14-15]. Dursun et al. [16] retrospectively evaluated data from 6388 patients from Turkey collected between 2006 and 2010 and found that 25% of cervical samples were positive for HPV DNA. Other studies from Turkey have reported HPV prevalence rates varying from 17–25% (Table 5) [16-22].

The slightly lower prevalence of HPV in Turkey in the Dursun et al. [16] results may be explained by the inclusion of HPV genotypes detected in women who had negative cytology results. In our study, on the other hand, we included only women who had abnormal cytology results. The HPV DNA positivity

prevalence in our study on cervical smear samples with atypical Pap smear test results is similar to the numbers reported worldwide.

The most common genotype that we detected across all age groups was HPV16. This genotype is also the most prevalent genotype worldwide regardless of cytological status [18,23-25]. Another commonly found genotype was HPV18 (17%); however, other HPV genotypes that indicated a high risk of cancer were not differentiated the Cobas 4800 HPV test. Therefore, we suggest that the HPV18 genotype was the second most commonly detected genotype in this study. The high prevalence of HPV18, unlike that noted in other limited studies in Turkey, is consistent with the findings of other studies [13,14,24,26].

HPV16- and HPV18-related cancer cases have been reported to be the highest in Africa (94.2%) [26]. The prevalence of such cases has been noted to be 89.2% and 68.0% in North America and Asia, respectively [26]. Dursun et al. [17] identified HPV16 and HPV18 as the most common HPV genotypes (32% and 8%, respectively). However, those authors found a slightly lower prevalence than we did (47% and 17%, respectively). High-grade squamous intraepithelial lesions were significantly associated with HPV16 across all age groups in our investigation. Interestingly, higher rates of HPV16 and HPV18 infections were found in women older than. We note, however, that the sample size of that older cohort (10) was too small to draw robust conclusions.

A review of the literature published about HPV screening in cervical samples with abnormal cytology from Istanbul and Ankara revealed no significant difference in HPV prevalence in those two cities [11]. Turkey is the first Islamic country to recently implement a centralized national cervical cancer screening program. Preliminary results of this centralized HPV testing revealed a prevalence rate of 3.8% for high-risk HPV, which is low compared to European and Western countries [27]. Vaccinations can help prevent HPV infections. However, because the HPV vaccination is not included in Turkey's immunization program, it is administered solely based on a medical recommendation [28]. Given that Turkey has not yet introduced a publicly funded national HPV vaccination program [12,29], we expect that our work will inform decisions about the development of such a program.

### Limitations

We considered data from a relatively small cohort of women, and our results were restricted to a single center. Therefore, it is difficult to draw comprehensive conclusions from our investigation. Another limitation is the retrospective nature of this study; we did not include prognostic variables. An incorrect diagnosis could result from an HPV DNA test administered without a colposcopic examination. To more accurately estimate the prevalence and distribution of the HPV genotypes with aberrant and normal cytology, more population-based research is required.

### Conclusions

The HPV genotypes that are most frequently observed in women with abnormal Pap smears are HPV16 and HPV18. In our work, the HPV16 genotype was more frequently detected in HSIL samples of women with ages between 29 and 38. The HPV

DNA positivity rates that we found are similar to those reported in other studies worldwide. Moreover, the high prevalence of HPV18 that we noted is consistent with other investigations but higher than that reported by other Turkish studies. We suggest that investigating the incidence of HPV16 and HPV18 genotypes will be important for implementing new programs to curb the incidence of cervical cancer. These data may contribute to the development of preventive strategies to reduce the cervical cancer burden in Turkey.

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