

## Original Article

## Human Papillomavirus Prevalence and Genotype Distribution in Cervical Swab Samples in Istanbul, Turkey

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**Introduction:** Human papillomavirus (HPV) is the most common sexually transmitted infection agent worldwide and, with high-risk (HR) HPV genotypes, is the main factor for development of cervical cancer. This study aimed to assess the prevalence of HPV and distribution of HR-HPV genotypes in cervical swab samples and compare them with demographic and clinical data.

**Methodology:** Cervical swab samples of 2,285 women between the age of 17 and 76 were assessed between January 2018 and October 2020 in order to obtain the data of Turkey. Fifteen different HR-HPV genotypes were determined using multiplex real-time polymerase chain reaction test.

**Results:** HPV was positive in 36.3% (829/2,285) of DNA samples. Prevalence of multiple HR-HPV infection was 40.7%. Of the women, 30.9% (256/829) were infected with HPV16, 14.6% (121/829) with HPV39, and 14.2% (118/829) with HPV51. The most frequently detected genotypes with HPV16 were HPV31, HPV39 and HPV52, respectively. In women with cervical dysplasia, HPV16, 31, and 39 were the most common, and in women with genital warts, HPV16, 59 and 66 were most common, respectively. The highest HR-HPV prevalence was detected in the 17-34 age group (44.1%) ( $p < 0.001$ ).

**Conclusions:** The prevalence of HR-HPV was 36.3% in this study. High prevalence (44.1%) especially in young women was consistent with findings in literature. The most common HR-HPV genotypes were HPV16, 39 and 51, respectively. Determining the prevalence and genotypes of HR-HPV playing role in the etiology of cervical cancer will be guiding for measures on prevention of cervical cancer and research on preventive vaccines.

**Key words:** Human papillomavirus; genotype; prevalence; real-time PCR.

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**Introduction**

Human papillomavirus (HPV), a member of the *Papillomaviridae* family, is small, icosahedral, non-enveloped virus with circular double-stranded DNA genome. Sexually transmitted HPV, which mainly infects mucosal and keratinized epithelium, has a cytopathic effect on the epithelium. Genital mucosal HPV infection is persistent and multifocal and can be subclinical [1]. More than 200 different HPV genotypes according to genomic sequences have been identified up to now [2,3]. According to their relationships with cancer development, about 60 HPV genotypes that can affect genital mucosa are infect anogenital area [4]. HPV genotypes such as HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 were accepted as high-risk (HR) HPV due to their carcinogenic potentials and roles in neoplastic transformation [5]. HPV16 and 18 have a

role in about 70% of cervical cancer [6]. Some HPV genotypes can also cause genital warts [7]. These are a clinical manifestation of persistent infection with low risk (LR) HPV genotypes [8]. HPV6 and 11 are LR-HPV genotypes and both are associated with 90% of genital warts [7]. HR-HPV genotypes can progress to persistent precancerous lesions and invasive cancer. In addition, it is the main cause of nearly all (99%) of cervical carcinoma cases [4,9]. Cervical cancer ranked the fourth most common cancer among women worldwide, with an estimated 570,000 new cases in 2018. Approximately 90% of 311,000 deaths worldwide in 2018 were in low- and middle-income countries [10]. Most of cervical HPV infections are asymptomatic and 70% of them are naturally eliminated by the immune system within two years. However, symptoms such as atypical vaginal bleedings, vaginal

discharge with an odor, urinary or anorectal symptoms and loss of weight can appear as a result of invasive disease, malignant proliferation and cancer [2,11]. Global prevalence of HPV is 11.7% and differs according to continents. While the highest prevalence is in Africa (2.3%-75.3%) these rates are 3.2%-25% in Europe and 5.7%-38.5% in America. The prevalence in Asia is lower compared to the other continents and generally under 23.5% [4,12]. Understanding that the main cause of cervical cancer was HPV has led to the development of advanced screening techniques. Early diagnosis and treatment of precancerous lesions can prevent progression of cervical cancer. Risk description of cervical (pre)cancerous lesions in women is mainly performed with cytological screening of cells. Molecular diagnostic tests that can distinguish LR-HPV and HR-HPV genotypes, have high sensitivity and specificity, detect HPV DNA, are used as complementary tests to cytology [13]. These tests are also follow-up tests that are used to determine the necessity for colposcopy or referral to the other follow-up proceedings in women with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial neoplasia monitored on Pap smear test results [14]. In addition, molecular tests are used to determine the genotype distribution of HPV, which is necessary in making decisions about public health policies and in vaccine preparations [15]. A large sampling group of women was formed in this study. HR-HPV prevalence and distribution of genotypes in cervical swab samples were examined and compared with demographic and clinical data.

## Methodology

In this retrospective, descriptive and cross-sectional study, between the ages of 17 and 76, a total of 2,285 women, whose cervical swab samples were examined at the virology laboratory of our hospital between January 2018 and October 2020, were included. HPV genotype PCR results of cervical swab samples of these patients were analyzed. The study was approved by the ethics committee of Istanbul Education Research Hospital (Reference number: 2020/12/2618).

### *Molecular analysis*

After samples in PreservCyt (Hologic Corp.) for cervical samples arrived at the laboratory they were kept at 2–8°C (maximum two weeks) until DNA extraction. Viral DNA extraction in cervical swab samples was performed with in the QIAamp MinElute Media Kits (Qiagen, Venlo, Netherlands) or QIASymphony DSP Virus/Pathogen Kits (Qiagen,

Venlo, Netherlands) according to extraction instructions of the manufacturer. Magnetic beads were used for isolation and purification processes. Viral nucleic acid products obtained were amplified with Rotor-Gene Q MDx device (Qiagen, Germany) by distributing 15 µl of QIAscreen master mix into tube strips as 5 µl for each and using QIAscreen HPV PCR Test kit (Qiagen, Netherlands). In addition, a positive control (β-globin) and a negative control were used to measure experimental process and minimize sampling and device errors. QIAscreen HPV PCR Test kit is a multiplex and real-time PCR-based analysis which targets a preserved region in E7 gene of HR-HPV type and uses florescent probes to detect one or more than one accumulated PCR product. The results were qualitatively assessed with a software program and 15 most common and oncogenic HR-HPV genotypes including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, and 68 were investigated.

### *Interpretation of Results*

HPV positive: When  $C_T$  values are  $< 36$  for HPV16 and/or HPV18 and/or  $< 33.5$  for the other HPV types (regardless of β-globin  $C_T$  value) the detection channel shows the available types.

HPV negative: When  $C_T$  value is  $\leq 30$  for β-globin and  $C_T$  values are  $\geq 36$  for HPV16 and HPV18 or when there is no signal and when they are  $\geq 33.5$  for the other HR-HPV types or when there is no signal.

Invalid: When  $C_T$  value is  $> 30$  for β-globin and  $C_T$  values are  $\geq 36$  for HPV16 and HPV18 or when there is no signal and when  $C_T$  values are  $\geq 33.5$  for the other HR-HPV types or when there is no signal.

### *Statistical Analysis*

General and type-specific prevalence of HPV was calculated with SPSS version 22 (IBM Corp.) and general prevalence was presented with 95% confidence interval. Normal distribution of variables was assessed with visual methods (histogram and probability plots) and Kolmogorov-Smirnov test. While Independent sample t test was used in comparison of normally distributed groups non-normally distributed parameters were compared with Mann-Whitney U test. All genotypes for single and multiple infections were separately calculated. Data were classified according to age (17-34, 35-44,  $\geq 45$  years). Pearson's chi-square test or Fisher's exact test was used for comparing the prevalence among categorical variables. P values of  $< 0.05$  were accepted to reveal a statistically significant difference.

**Results**

*HPV prevalence*

A total of 2,285 women were included in the study. Ages of women ranged from 17 to 76 (Median age was 39.4 years) and 58 (2.5%) of them were foreign nationals. Out of 2,285 cases, 829 women (36.3%, 95%CI: 34.31-38.29) were HPV DNA positive (Table 1). HPV DNA positivity rates were determined as 36.1% (803/2,226) for Turkish citizens and 44.8% (26/58) for foreign national women (p = 0.17).

*Distribution of HPV genotypes*

Of the women infected with HR-HPV, 30.9% (256/829) were infected with HPV16, 14.6% (121/829) with HPV39 and 14.2% (118/829) with HPV51. HPV18 was detected in 9.9% (82/829) of women. The most common HR-HPV genotypes detected in Turkish women are HPV16 (30.8%, 247/803), HPV39 (14.7%, 118/803), HPV31 (13.9%, 112/803) and HPV51 (13.9%, 112/803) and in foreign women were HPV16 (34.9%, 9/26), HPV51 (23.1%, 6/26), HPV56 (19.2%, 5/26) and HPV39 (11.5%, 3/26), respectively. Of the women, 21% were diagnosed with cervical dysplasia, 2% with genital wart and 0.2% with cervical neoplasm. While 45% of the patients were admitted for general examination 20.4% had the diagnosis of vaginitis, 4.1% had abnormal uterine or vaginal bleeding, 5.4% had irregular menstruation, and 1.8% had urinary system infection. In women with cervical dysplasia, the most common HR-HPV genotypes were HPV16, 31, and 39, while in women with genital warts, HPV16, 59, and 66

were detected most frequently. Only one out of four women diagnosed with cervical neoplasia was infected with three HR-HPV genotypes (HPV39, 52 and 56). The distribution of common HR-HPV genotypes according to clinical diagnoses independent from the presence of multiple genotypes were showed in Table 2.

*Distribution of multiple HPV infections*

Out of 829 women, 492 (59.3%, 95% CI: 55.92-62.71) had single HR-HPV infection and 337 (40.7%, 95% CI: 37.29-44.08) had multiple HR-HPV infection. The distribution rates of single and multiple HR-HPV genotypes were showed in Table 1. There was no significant difference between the rates of single (59.3%, 476/803 and 61.5%, 16/26 respectively) and multiple (40.7%, 327/803 and 38.5%, 10/26 respectively) infection in Turkish citizens and foreign nationals (p = 0.82).

Of the 256 women infected with HPV 16, the most common genotypes causing multiple infections in 146 (57%) were HPV31 and HPV39. Out of 82 women infected with HPV18, 52 (63.4%) were found to be concomitantly infected with HPV31 and HPV39 most frequently.

*Prevalence of HPV infection according to age*

The patients were examined in three groups according to their age (17-34, 35-44 and ≥ 45). The highest prevalence of HPV infection according to age was in the group of 17-34 with 44.1% (p < 0.001) (Table

**Table 1.** Distribution of HPV type infections according to age groups.

Age groups	Total n (%)	17-34 n (%)	35-44 n (%)	≥ 45 n (%)	p-value
HPV -	1456 (63.7)	449 (55.9)	505 (65.7)	502 (70.4)	<b>&lt; 0.001</b>
HPV +	829 (36.3)	354 (44.1)	264 (34.3)	211 (29.6)	
Single infection	492 (59.3)	185 (52.3)	173 (65.5)	134 (63.5)	<b>0.001</b>
Multiple infection	337 (40.7)	169 (47.7)	91 (34.5)	77 (36.5)	
<b>HPV type (n = 829)</b>					
16	256 (30.9)	111 (31.4)	75 (28.4)	70 (33.2)	0.52
18	82 (9.9)	40 (11.3)	26 (9.8)	16 (7.6)	0.36
31	114 (13.8)	54 (15.3)	34 (12.9)	26 (12.3)	0.55
33	26 (3.1)	9 (2.5)	6 (2.3)	11(5.2)	0.13
35	62 (7.5)	33 (9.3)	18 (6.8)	11(5.2)	0.18
38	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	0.23
39	121 (14.6)	61 (17.2)	39 (14.8)	21(10.0)	0.06
45	42 (5.1)	19 (5.4)	11(4.2)	12 (5.7)	0.71
51	118 (14.2)	65 (18.4)	29 (11.0)	24 (11.4)	<b>0.01</b>
52	91 (11.0)	52 (14.7)	26 (9.8)	13 (6.2)	<b>0.006</b>
56	92 (11.1)	33 (9.3)	31(11.7)	28 (13.3)	0.32
58	42 (5.1)	17 (4.8)	12 (4.5)	13 (6.2)	0.70
59	68 (8.2)	32 (9.0)	20 (7.6)	16 (7.6)	0.75
66	106 (12.8)	57 (16.1)	26 (9.8)	23 (10.9)	<b>0.04</b>
68	99 (11.9)	37 (10.5)	34 (12.9)	28 (13.3)	0.52

n: number of patients.

1). It was found that the positivity rates of HPV infections decreased as the age of the women increased.

**Discussion**

Epidemiological studies on the distribution of HR-HPV and determination of HR-HPV prevalence in different geographical regions can considerably help for preventive strategies against HPV-associated cancer especially in a vaccine-friendly era [16,17]. This study helped us predict the prevalence of HR-HPV and distribution of HR-HPV types in Istanbul, Turkey.

The prevalence of HR-HPV was 36.3% in our study. These data were similar to the rates found for global general female population [18]. When compared with global rates, the prevalence in this study was higher than those reported in America, Europe, Asia and Australia and lower than those in Africa.

Previous studies on Turkish population revealed that the lowest HPV rate was 10.7% while the highest HPV rate was 47.7% based on the population assessed and detection method [19,20]. These rates were 10.8% and 79.7% in different studies performed in our region [21,22]. This high rate may be because Istanbul is a city where an important part of Turkish population lives and which has a high socioeconomic and cultural diversity.

HPV negative women (63.7%) are under the risk for HPV infection. They should be encouraged to make use of preventive measures in order to decrease infection

risk and prevent development of HPV-associated cervical cancer [23]. For that purpose, prophylactic HPV vaccines and early diagnosis with screening tests are quite important in prevention of precancerous lesions and cervical cancer [24].

In Turkey, the prevalence of HPV in a multicenter study comprising 12 different regions were found to be 25%. In this comprehensive study, the rate of HPV positivity was found to be significantly higher in women under the age of 30 [25]. HPV prevalence rates have been reported to be lower in previous studies [26,27,28]. This discrepancy can be explained by the effects of technological advances in the methods used for HPV diagnosis on the results, the educational status of the patients admitted to the hospital, and their awareness for HPV infection.

The highest HPV prevalence according to age was reported in women under the age of 25 globally [29,30]. The prevalence of HPV was 58.1% among women in a study in South Africa and the highest prevalence was 74% among women between the ages of 18 and 25 [31]. Contrary to these studies, there are studies reporting that HPV infection is more common among older women [32]. Therefore, in our study, we examined the HPV prevalence in three different age groups. In this study, the highest prevalence of HPV infection was 44.1% in women in the age group of 17-34 and HPV prevalence was strongly associated with age. According

**Table 2.** Distribution of HPV genotypes in different clinical conditions (n=829).

HPV infection	Genital wart n = 46	Cervical dysplasia n = 484	Cervical neoplasm n = 4	Other* n = 1751	p-value
<b>Age groups (year)</b>	n (%)	n (%)	n (%)	n (%)	
17-34	20 (71.4)	91 (40.6)	0 (0)	243 (42.2)	
35-44	5 (17.9)	77 (34.4)	1 (100)	181 (31.4)	<b>0.04</b>
≥ 45	3 (10.7)	56 (25.0)	0 (0)	152 (26.4)	
All ages (Total)	28 (60.9)	224 (46.3)	1(25)	576 (32.9)	<b>&lt; 0.001</b>
<b>Single infection</b>	10 (35.7)	130 (58)	0 (0)	352 (61.1)	
<b>Multiple infection</b>	18 (64.3)	94 (42)	1 (100)	224 (38.9)	<b>0.03</b>
<b>HPV genotypes</b>					
16	11/28	67/224	0/1	178/576	
18	2/28	27/224	0/1	53/576	
31	4/28	41/224	0/1	69/576	
33	0/28	7/224	0/1	19/576	
35	3/28	15/224	0/1	44/576	
38	0/28	0/224	0/1	1/576	
39	3/28	30/224	1/1	87/576	
45	4/28	13/224	0/1	25/576	
51	1/28	27/224	0/1	90/576	
52	7/28	24/224	1/1	59/576	
56	3/28	26/224	1/1	62/576	
58	5/28	14/224	0/1	23/576	
59	6/28	23/224	0/1	39/576	
66	6/28	27/224	0/1	73/576	
68	4/28	27/224	0/1	68/576	

%; column percentage; other: acute cystitis, acute/chronic vaginitis, amenorrhea, abnormal uterus and vaginal bleeding, irregular menstruation, pregnancy, general examination, infertility, menopause, myoma uteri.

to our results, the prevalence of HR-HPV considerably increased and peaked in the ages between 17 and 34. We also found that this rate decreased by age. The observed age distribution suggests that the first HPV infection was acquired shortly after the woman became sexually active, and epidemiological evidence supports this [29,33]. These may be the development of clearance within time, changes in sexual activity and immunity acquired by the previous infection [34]. Contrary to this, Jing *et al.* [35] found two HPV infection peaks in women aged < 25 years (8.2%) and women aged > 50 years (9.6%) in their study involving women aged 18-75, and reported that HPV positivity showed a bimodal age distribution. The increase in HPV prevalence in advanced age can be explained by the reactivation of a latent infection [23,29]. Thus, cervical screening programs for HPV are of particular importance for perimenopausal women [36,37].

HPV16 is the most common HR-HPV genotype among women in the world. Genotypes such as HPV18, 52, 31, 58, 39, 56 and 51 are the most common genotypes after HPV16, but their prevalence differs according to regions [18]. The three most common HR-HPV genotypes in this study were HPV16, 39, and 51. In our population, HPV16 was the most common genotype in single or multiple infections. The results were consistent with previous studies [38,39]. HR-HPV16 and 18 were associated with cervical carcinoma, and LR-HPV6 and 11 were associated with genital warts in 90%. However, HR-HPV genotypes have also been frequently detected in patients with genital warts [7,40]. In this study consistent with the literature, HR-HPV was detected in 60.9% of 46 women with genital warts, and the most common HR-HPV types were HPV16, 59 and 66, respectively.

The most common HR-HPV genotype was HPV16 in Turkish citizens and foreign nationals in this study. While the other most common genotypes were HPV39, 31 and 51 in Turkish population they were HPV51, 56 and 68 in foreign nationals. Increasing these epidemiological studies is important in developing preventive strategies, especially for cosmopolitan cities with large populations such as Istanbul. In this study, the HPV prevalence rate was higher than previous studies in our country. This reveals the necessity of vaccination to protect especially young girls against HPV infection. HPV vaccine is not included in the vaccine schedule in our country. The high cost of HPV vaccines, the thought that the vaccines do not provide sufficient protection against HPV, and the parents' opposition to vaccination due to the concerns that they may encourage sexual activity at an earlier age limit the

use of vaccines in our country. Therefore, it is important for healthcare professionals to recommend the HPV vaccines and to inform parents about the vaccines [41]. In addition, the heterogeneity in the distribution of HPV genotypes among women from different populations should be taken into account when developing HPV screening tests and predicting the effect of vaccines on the incidence of HPV infection [25].

This study has some limitations. Turkey's most populous city, this study conducted in Istanbul, despite having a large number of samples does not reflect the HPV prevalence estimates of populations in other regions of Turkey. Also, the data were based solely on the detection of DNA in cervical swab samples, and cervical cytology data could not be included. Although the study provided information about HPV prevalence, since it was a retrospective study, risk factors of HPV infection such as sexually active age, number of sexual partners, and use of oral contraceptives could not be evaluated.

## Conclusions

In this study, the prevalence of HR-HPV was 36.3%. This rate was similar to those reported in studies in our country. High prevalence (44.1%) especially in young women was consistent with findings in literature. The most common HR-HPV genotypes were HPV16, 39 and 51 respectively. Determining the prevalence and genotypes of HPV playing a role in the etiology of cervical cancer will be guiding for research on preventive vaccines.

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