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RESEARCH ARTICLE

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The prevalence and distribution of human papillomavirus in 4267 Turkish women with or without cervical lesions: A hospital-based study

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Abstract

In the present study, it was aimed to screen the genotypes of human papillomavirus (HPV) retrospectively in women with gynecological symptoms who were admitted to a tertiary care university hospital in Ankara, Turkey. A total of 4267 cervical swab samples of women aged 18–79 years were sent to Medical Virology Laboratory from January 2017 to November 2020. Nucleic acid extraction and amplification of samples were done by an automated system. The test can detect 14 high-risk HPV (HR-HPV) types in a single analysis that performs a real-time polymerase chain reaction, by providing individual results on the highest-risk genotypes HPV 16 and HPV 18 and pooled results on other high-risk genotypes (OHR-HPV) (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). HPV DNA positivity was detected in 14.2% (605/4267) of the samples. HPV type 16 and type 18 were detected in 2.4% and 0.7% of the samples, respectively. OHR-HPV types were found in 8.8% of the samples. Of the 1.9% and 0.4% samples had mixed types with type 16+ OHR-HPV and type 18+ OHR-HPV, respectively. The results of this study presented the rates of HR-HPV genotypes of a university hospital in Ankara, over a 4-year period. It was observed that the positivity rate of type 18 is decreasing and some OHR-HPV types are increasing. HPV vaccination is not in the national immunization program in Turkey yet, however, HPV vaccines are available and the vaccination rates for women are increasing.

KEYWORDS

high-risk HPV, human papillomavirus, real-time PCR, screening

1 | INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and the fourth most common cause of death from cancer in women.[1] Incidence data from the Global Burden of Cancer (GLOBOCAN) database indicate that a total of 570 000 new cervical cancer cases were diagnosed and 311 000 deaths were determined in 2018, and approximately 84.3% of these occurred in developing countries.[1] In 2014 database of the Turkish Statistics Institute (National Cancer Registry Report), reported that the incidence of cervical cancer is 4/100 000 females and the mortality rate of cervical cancer is 2/100 000. Each year 1800 new diagnoses have been made and cervical cancer is the ninth most common cancer in Turkey.[2] There is a great difference between developing and developed countries in mortality and morbidity rates of cervical cancer because the implementation of effective screening programs significantly reduced cervical cancer in developed countries.[3] Cervical cancer is a preventable disease because it has a comparatively long progression time from a precancerous lesion to an invasive disease. Thanks to the implementation of effective screening programs, the

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disease can be diagnosed before it progresses to advanced stages, and it can be considered almost curable.[4] Cervical cancer is unique among common cancers in that it can be almost totally eradicated.

It has been established that human papillomavirus (HPV) is the main etiological agent for cervical carcinogenesis.[5] HPV is the most common cause of sexually transmitted disease in women and results in various clinical conditions from asymptomatic infections to malignant genital diseases. Accordingly, HPV sequences have also been identified in the chorionic villi of healthy pregnant females.[6] More than 200 types of HPV have been identified to date on the basis of DNA sequence, which can be categorized into either cutaneous and mucosal types and approximately 40 HPV types infect firstly the cervix, vagina, vulva, and anus.[7–9] HPV types can also be classified as high and low-risk groups.[10] The high-risk group includes HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82, infection with these types may potentially progress into invasive cervical cancer.[11] The overall prevalence of HPV infection worldwide is estimated to be nearly 10% (<3%–26%).[12] In patients with cervical cancer the prevalence of high-risk HPV DNA is more than 95%.[13] Thus, the detection of high-risk HPV (HR-HPV) has become increasingly attractive as a primary screening tool for cervical cancer due to its sensitivity and cost-effectiveness.[14] In addition, the prevalence and distribution of HPV types differ around the world and the importance of different HPV types varies by region. In the United States and Europe, four types are most often found in patients with cervical cancer, with type 16 accounting for nearly 50% of cases, followed by types 18, 31, and 45.[15] According to the results of population-based cervical cancer screening program using HPV testing in four million Turkish women, the most common HPV genotypes were 16, followed by 51, 31, 52, 56, and 18.[16] HPV infection is preventable via vaccination. Currently, there are three HPV vaccines, Cervarix (bivalent; HPV types 16 and 18), Gardasil-4 (quadrivalent; HPV types: 6, 11, 16, and 18), and Gardasil-9 (nonavalent; HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58). Knowledge of geographic variation in the prevalence of carcinogenic types and HPV genotype distribution is fundamental to estimate the impact of HPV prophylactic vaccines.[11] Currently there is no national HPV vaccination program in Turkey, however, quadrivalent HPV vaccines are available. In addition, a nationwide HPV DNA screening program is ongoing since 2014.[16]

In this study, it was aimed to provide high-risk HPV frequency and distribution related to age-specific features of HPV infection, cervical lesions, and single or multiple type HPV infections that can be useful for efficient management of cervical lesions and provides epidemiological data on a large number of Turkish women.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective study included 4267 women (mean age 43.17 years [min–max: 18–79]) in whom both were examined because of several gynecologic complaints between January 2017 and November 2020 at Gynecologic Oncology Department of Gazi University, Turkey. Each participant had a gynecologic examination including liquid-based cytology and a cervical sample for HPV detection. We investigated multiple data fields on demographic, clinical, and laboratory variables of patients.

Patients with intact uterus with suffer from gynecologic complaints involving postcoital bleeding, dyspareunia, groin pain, and malodorous discharge with no past history of gynecologic malignancy were included in the present study. Current pregnancy, history of cervical conization, and hysterectomy were the exclusion criteria in this study.

2.2 | Liquid-based cytology

A cervix brush was used to collect samples from the cervix. The brush was immediately rinsed in a vial of preservative solution and was placed in this vial. Sure path preservative fluid is an alcohol-based, preservation solution that serves as a transport, preservative, and antibacterial medium for gynecologic specimens (Roche Diagnostics). Abnormal cytology was reported using the 2014 Bethesda system as an atypical squamous cell of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot exclude HSIL (ASC-H), atypical glandular cells not otherwise specified, and squamous cell carcinoma (SCC).[17] Noncancerous conditions can also be found in Pap test including infections and inflammation.

2.3 | HPV DNA testing

Nucleic acid extraction and amplification of cervical smear samples were done by an automated system (Cobas®4800; Roche Diagnostics). Primers are used to identify a sequence of approximately 200 nucleotides in the polymorphic L1 region of the HPV genome. The test can detect 14 high-risk HPV (HR-HPV) types in a single analysis by providing individual results on the highest-risk genotypes, HPV 16 and HPV 18, and pooled results on other high-risk genotypes (OHR-HPV) (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).[18]

2.4 | The colposcopy examination

Colposcopy is a medical diagnostic procedure to examine the lower genital tract and cervix using magnification from a colposcope with a good light source. Colposcope is a lighted binocular microscope connected to a video monitor which magnifies the area of interest 6–40 times its normal size.[19] The squamocolumnar junction and transformation zone should be identified; this assesses whether the examination is acceptable or not. Acetic acid is then used to determine the size, shape, margin, and location of any neoplastic lesion. These findings can then be described according to the new terminology of the International Federation for Cervical Pathology and Colposcopy.[19]

2.5 | Histology

Women with abnormal cytology and/or HR-HPV positivity were referred to colposcopic examination. If abnormal colposcopic findings such as atypical transformation zone, keratosis, acetowhite epithelium, punctation, mosaicism, atypical vessels, and unsatisfactory colposcopic findings were determined, patients were referred to cervical biopsy. All biopsy specimens were examined histologically. Histologic findings were gradated by the standard grades of CIN1, CIN2, CIN3.[20]

2.6 | Statistical analysis

Statistical analysis was performed with SPPS version 22 software. Data are presented as the mean ± SD, as percentages of the mean, or as the distribution of the frequency. Pearson χ^2 and continuity correction χ^2 tests were used to compare categorical measurements between the groups. When two groups were compared, differences in continuous variables were analyzed using the Student's *t*-test. When two groups were compared, the distribution of normal variables was analyzed using the Student's *t*-test, and if three groups were compared, using one-way analysis of variance test. Values of $p < 0.05$ were considered to indicate a statistically significant result.[21]

3 | RESULTS

Totally 4267 female patients with gynecologic symptoms were included in the study. Among all, 605 patients (14.2%) were HR-HPV positive. Other high-risk HPV types were the most frequent types among all types (8.8%) and the lowest rate belonged to mix types with type 18 and OHR-HPV types (0.4%). The patients with ASCUS cytology results comprised the highest number of patients (Table 1).

The mean age of patients was 43.17 (min–max: 18–79). The patients were divided into three age groups (<30, 30–55, >55). The frequency of HPV infection was the highest in the 30–55 age group (13.6%) among all age groups. That was followed by the >55 age group (9%) and the lowest HPV rate belonged to the <30 age group (2%). The distribution of HPV positivity in different age groups was statistically significant ($p = 0.03$). The distribution of HPV genotypes according to age groups was given in Figure 1.

HR-HPV positivities were 41% and 20.9% in patients with abnormal and normal cytology, respectively. The distribution of cervical cytology results according to HPV genotypes was given in Table 2. The highest rate belonged to other high-risk (OHR) HPV types (22.6%) in cytology positive cases and it was followed by type 16 (9.5%). A statistically significant difference was detected between HPV genotypes and cytology results ($p < 0.001$).

The patients with normal cytology results comprised 88.7% of the patients and 9.6% had HR-HPV positivity with normal cytology results. The highest number of patients with cervical lesions belonged to ASCUS (7.2%) and 2.1% were HR-HPV positive. Patients with ASCUS were followed by patients with LSIL (2.2%) and 1.4% were HR-HPV positive (Table 3).

TABLE 1 Demographic and clinical data of patients

	Average (*n*)	Min–max (%)
Age (total)	43.17	18–79
HPV positive	40.28	19–76
HPV negative	43.64	18–79
	n	**%**
Cervical cytology results		
SCC/AC	2/1	0.1
AGUS	24	0.6
ASC-H	24	0.6
HSIL	29	0.7
LSIL	95	2.2
ASCUS	308	7.2
Normal	3784	88.7
Colposcopy results	431	10.1
Normal	214	5.01
Atypical finding	217	5.08
Biopsy results		
SCC/AIS	3/1	0.1
HSIL/CIN3	33	0.8
HSIL/CIN2	17	0.4
LSIL + HSIL	5	0.1
LSIL/CIN1	53	1.2
Chronic cervicitis	104	2.4
Total	4267	100

Abbreviations: AGUS, atypical glandular cells of undetermined significance; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exclude HSIL; ASCUS, atypical squamous cell of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OHR, other high risk; SCC/AC, squamous cell carcinoma/adenocarcinoma.

4 | DISCUSSION

In the present study, the presence of HPV infection among 4267 women who underwent a gynecological examination in a university hospital in Ankara Province was tested employing a commercially available HR-HPV DNA kit. The overall HR-HPV frequency is 14.2% in patients with (11.3%) or without (88.7%) cervical lesions. Previously, many studies have been conducted on HPV frequency and genotype distribution in Turkey. A multi central study of Dursun

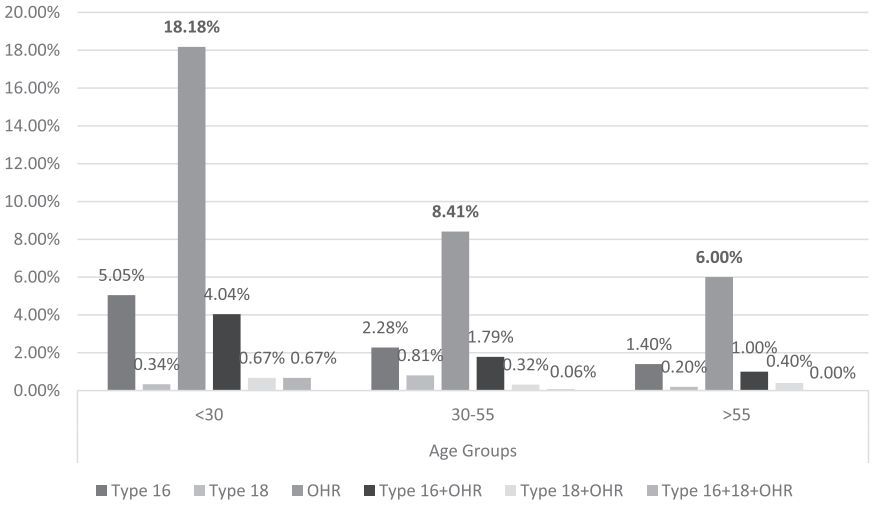


FIGURE 1 Age distribution of patients according to human papillomavirus genotypes. OHR, other high risk

TABLE 2 The distribution of cervical cytology results according to HPV genotypes

HPV types	Abnormal cytology *n* (%)	Normal cytology *n* (%)	*p* value
Type 16	46 (9.5)	55 (1.3)	
Type 18	8 (1.6)	22 (0.5)	
OHR-HPV types	109 (22.6)	267 (6.3)	<0.001[a]
Multiple HPV types	35 (7.2)	63 (1.5)	
Total HR-HPV positive	198 (41)	890 (20.9)	

Abbreviations: HPV, human papillomavirus; OHR-HPV, other high-risk genotypes.
[a]Pearson's χ^2 test.

TABLE 3 The distribution of cervical lesions for HPV genotypes

HPV types	ASCUS *n*, (%)	LSIL *n*, (%)	HSIL *n*, (%)	ASC-H *n*, (%)	AGUS *n*, (%)	SCC/AC *n*, (%)	Normal cytology *n*, (%)	Total *n*, (%)
Type 16	18 (0.4)	10 (0.2)	13 (0.3)	3 (0.1)	1 (0.02)	1/- (0.02/-)	55 (1.3)	101 (2.4)
Type 18	4 (0.1)	3 (0.1)	1 (0.02)	-	-	-	22 (0.5)	30 (0.7)
OHR-HPV types	56 (1.3)	32 (0.7)	11 (0.3)	8 (0.2)	1 (0.02)	1/- (0.02/-)	267 (6.3)	376 (8.8)
Multiple HPV types	12 (0.3)	19 (0.4)	2 (0.04)	1 (0.02)	1 (0.02)	-	63 (1.5)	98 (2.3)
Negative	218 (5.1)	31 (0.7)	2 (0.04)	12 (0.3)	21 (0.6)	0/1 (0.0/0.02)	3377 (79.1)	3662 (85.8)
Total	308 (7.2)	95 (2.2)	29 (0.7)	24 (0.6)	24 (0.6)	2/1 (0.1/0.02)	3787 (88.7)	4267 (100)

Abbreviations: ASC-H, atypical squamous cells cannot exclude; ASCUS, atypical squamous cell of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OHR-HPV, other high-risk genotypes; SCC/AC, squamous cell carcinoma/adenocarcinoma.

et al. showed that HPV frequency in 6388 patients who applied for regular gynecological examination at 12 healthcare centers in Turkey was 25% between 2006 and 2010.[22] Yuce et al. reported in their study that the prevalence of any HPV type was 25.7% while HR-HPV was positive in 23% of women who admitted either for routine gynecologic examination or due to gynecologic complaints.[23] In the study of Kaleli et al. total HPV frequency was 37.2% in patients who applied for regular gynecologic examination or due to several gynecologic complaints, while the HR-HPV rate was found as 21.2%. The highest HPV rate belonged to HPV type 16 (8.9%).[24] Seneldir et al. detected 34.7% HR-HPV in their hospital-based study. Among HR-HPV positive samples, 25.3% were HPV type 16, 3.9% were type 18% and 71.3% were OHR-HPV.[25] Alan et al. detected 34.2% HR-HPV in their hospital-based study.[21] The studies attributed their high HPV prevalence to a high rate of abnormal cytology, hospital-based patients, higher educational status of their patient population, and use of more sensitive HPV detection methods.[22–26] The results of Turkey's HPV screening program, which contains four

million women, reported that 4.39% of screened women in the community were HPV DNA positive.[16] This rate is lower than other studies because this result represents community and not only HR-HPV types, but also other HPV types. The ATHENA trial evaluated the prevalence of HR-HPV genotypes in a routine cervical screening program in 40 901 women aged ≥25 years in the United States. It was reported that the overall HR-HPV prevalence was 10.3% between 2008 and 2009.[27]

The highest rate of HR-HPV positivity was found in the 30–55 years of age (13.6%) group in the present study. It was followed by the >55 years of age group (9%) and the <30 years of age group (2%). There was a statistically significant difference in HPV positivity among age groups ($p = 0.03$). In the initial results of Turkey's HPV screening program, the HPV positivity rate by age group was 4.3% (30–34), 4.0% (35–39), 3.6% (40–44), 3.2% (45–59), and 2.8% (60–65), respectively. According to these data, HPV infection rates were slightly higher in younger patients.[16] In contrast to our study, in the study of Kaleli et al., HPV positivity is the most common between the ages of 51–60 (28%), followed by the ages of 17–30 (25.8%).[24] The age-specific prevalence of HPV infection is significantly different among age groups in the world. However, most of the studies showed that HPV prevalence decreases with increasing age with a peak prevalence in younger women.[28] Carozzi et al. reported in their study from Italy, that HR-HPV positivity was higher in patients younger than 35 years of age (62.9%) than patients older than 35 (54.7%).[29] In the study of Hashim et al., HR-HPV positivity rates in two age groups (34–43, 44–69) were close, however, the older age group had a slightly higher number.[30] A population-based study from China, reported that regarding participant age, the overall rate of HPV was distributed in a U-shaped manner, with the highest peak in the younger than a 20-year-old cohort.[31] In the ATHENA trial in the United State, HR-HPV prevalence (10.3%) was decreased with age, with a range from 17.8% in women aged 25–29 years to 6.5% in women aged ≥50 years.[27] In the present study, OHR-HPV types were the highest (18.18%) in the <30 age group in genotype distribution according to age groups. It was followed by 30–55 age group with a rate of 8.41% and the lowest rate belonged to the>55 age group (6%). OHR-HPV types were followed by type 16 and type 16+ OHR types in all age groups. Besides, type 18 had the lowest rate of all age groups.

We found the HR-HPV positivity rate in patients with normal and abnormal cytology as 20.9% and 41%, respectively. Our results were comparable to other studies reported from Turkey. A study by Kaleli et al. showed that HR-HPV rates in patients with normal and abnormal cytology were 17.4% and 40.6%, respectively.[24] In other studies, similar results were reported from Turkey. For example, Dursun et al. detected the presence of HPV DNA among patients with abnormal and normal cytology at 52% and 27%, respectively.[22] In another study, HR-HPV was found in 79.7% of patients with abnormal cytology and in 18.7% of patients with normal cytology.[25] The results of Turkey's nationwide HPV DNA screening program on the basis of the first 4 million screened women reported that in patients with HPV positivity, cytology results (163 411) were reported as "normal" in 69.2% and "abnormal (≥ASC-US)" in 14.2% of them.[16] Also other studies from different regions of the world suggest these data.[30,31] A meta-analysis which includes 427 studies from all over the world reported that among women with normal cytology, HPV prevalence varied substantially by region, ranging from 8% to 9% in Western/Central Asia and Europe to more than 20% in Africa, North America, South/Central America, and Oceania.[32]

Evaluation of HPV genotyping showed that the highest positivity belonged to OHR-HPV types (8.8%) in the present study and it was followed by type 16 (2.4%). In addition, the patients with abnormal cytology had OHR-HPV types most commonly (22.6%). This result showed a statistically significant difference among HPV types and cytology results ($p < 0.001$). Two HPV genotypes (16 and 18) cause 70% of cervical cancers and precancerous cervical lesions.[13] HPV type 16 is known as the most common oncogenic genotype in Turkey and also in the world.[16] HPV 18 used to be known as the second most common genotype worldwide.[22] However, in the last few years, many studies reported that other high-risk HPV genotypes such as 31, 33, 35, 45, 51, 52, and 58 are increasing and in some studies, these genotypes have higher rates than type 18.[16,24,33,34] We also found a higher rate of OHR HPV types which include 12 types other than type 18, moreover the lowest rate belonged to type 18. As a limitation of our study, we were not able to do type-specific detection of 12 OHR types, therefore we do not know which type/types are dominant. Another limitation was that we did not have HPV vaccination information of the patients.

It was reported that cytology is more useful for the diagnosis of precancerous lesions when it is evaluated with the HPV result.[35] The number of patients with cytological abnormalities decreased with progress to cancer. Patients with ASCUS comprised a great majority of abnormal cytology in HPV positive cases, especially in multiple type HPV-positive cases. There were only two patients with cancer who have type 16 and OHR-HPV positivity, respectively. These data demonstrate that early diagnosis with HPV testing has been beneficial when patients are still in the ASCUS stage. This finding is also supported by the results of the National Cervical Cancer Screening Program in Turkey.[16]

5 | CONCLUSION

As we know, this study is the latest about hospital-based HPV epidemiology which has a very large number of patients from Turkey. The study evaluates the HPV distribution with clinical findings of patients. It showed that the frequency of genotype 18 is decreasing and some OHR-HPV genotypes are taking their place. In addition, the results demonstrated the significance of the early diagnosis of precancerous lesions with HPV DNA testing.

AUTHOR CONTRIBUTIONS

Aylin Altay-Kocak performed laboratory studies, analyzed data, and wrote the manuscript. Ferah Kazanci collected clinical specimens, analyzed data, and wrote the manuscript. Canan Dogu-Tok

performed laboratory studies. Anil Onan collected clinical specimens. Ozlem Erdem performed the pathological analysis of patients. Secil Ozkan performed the statistical analysis. Gulendam Bozdayi is the administrator of the study, she supervised the study, and reviewed and edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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