Zeynep Kamil Med J 2024;55(1):34–38
DOI: 10.14744/zkmj.2023.77698

ORIGINAL ARTICLE

The relationship between cervical lesions and human papillomavirus subtypes: A retrospective third stage single-center study

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ABSTRACT

Objective: Cervical cancer is a preventable disease. Oncogenic HPV subtypes play a very important role in the development of many cancers, especially cervical cancer. In this study, we aimed to investigate the importance of HPV subtypes in cervical lesions.

Material and Methods: Two hundred seventeen women who were examined in the gynecological oncology outpatient clinic of the hospital, had a positive HPV test, and underwent colposcopic biopsy were retrospectively analyzed. The clinical and examination information of the patients were obtained from the hospital system and files.

Results: Among the HPV subtypes in the patients, HPV subtype 16 was the most common. HPV subtype 16 was found most frequently in H-SIL and L-SIL lesions. In addition, cervical premalignant or malignant lesions were detected in 79 of 217 patients who underwent colposcopic cervical biopsy.

Conclusion: Cervical cancer screening methods are one of the few screening methods that have been proven to reduce the mortality and incidence of invasive cancer. The most important risk factor in the etiology of cervical cancer is the HPV virus. As a result, we found that HPV subtype 16 was the most common, and HPV positivity decreased with age.

Keywords: Cervical cancer, colposcopy, HPV.

Cite this article as: Bayramoğlu D. The relationship between cervical lesions and human papillomavirus subtypes: A retrospective third stage single-center study. Zeynep Kamil Med J 2024;55(1):34–38.

Received: February 08, 2023 **Revised:** July 21, 2023 **Accepted:** August 22, 2023 **Online:** February 27, 2024
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INTRODUCTION

The most common sexually transmitted viral infection in the world is Human papillomavirus (HPV). HPV is associated with cervical, vulvar, vaginal, penile, oropharyngeal, and anal cancers, as well as respiratory papillomatosis and anogenital warts.[1] Almost all cases of cervical cancer are associated with high-risk HPV infection.[2] High-risk HPV subtypes are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Low-risk HPV subtypes are 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81. In vaccine studies aimed at preventing HPV subtypes, the bivalent vaccine includes HPV subtypes 16 and 18, and the quadrivalent vaccine includes HPV subtypes 6, 11, 16, and 18. As the latest vaccine, the nonavalent vaccine includes HPV subtypes 6, 11, 16, 18, 31, 33, 45, 52, and 58.[3,4]

The fourth most common type of cancer is cervical cancer. In 2018, approximately 570,000 women worldwide were diagnosed with cervical cancer, and approximately 311,000 women died from cervical cancer. The incidence of cervical cancer is 6.9 cases per 100,000 in Western European countries and 14.9 cases per 100,000 in Central and Eastern European countries.[3] According to these results, cervical cancer is more common in Central and Eastern European countries than in Western European countries. The incidence of cervical cancer in Türkiye is 4.3 per 100,000, and the death rate is 1.7 per 100,000. In addition, when we look at the HPV subtypes, HPV16 and HPV18 are responsible for 75.4% of HPV-positive invasive cervical cancer cases in Türkiye.

Screening programs are very important because cervical cancer is preventable and treatable when detected early. Therefore, the World Health Organization (WHO) decided to eradicate cervical cancer. In line with this decision, WHO emphasized that vaccination against HPV will reduce deaths from cervical cancer. In addition, the importance of cervical cancer screening tests was emphasized again. In Türkiye, it was decided that every woman between the ages of 30–65 should be screened with HPV DNA and Pap smear test every five years.

In this study, we wanted to investigate the pathogenicity and the effects of HPV subtypes observed in intraepithelial lesions and malignancies observed in the cervix.

MATERIAL AND METHOD

Two hundred seventeen patients who applied to our clinic between 2020 and 2022 were included in our study. Our study is retrospective. Patients who were HPV positive and underwent colposcopic cervical biopsy were included in our study. Colposcopic biopsy and HPV subtype results of all patients were recorded. Biopsies were taken from suspicious areas by colposcopic analysis from all patients. Colposcopic examinations were performed with a green filter and 4.5–30 magnification binocular Welch Allyn brand colposcopy device. In the colposcopic examination, the cervix was scanned with small magnification after washing with saline, then 3% acetic acid was applied and waited for 3 minutes. Aceto-white areas were scanned at small and high magnifications, and abnormal vascularities were evaluated with a green filter. Lugol's solution was applied in cases that could not be seen adequately and clinical suspicion continued, and the presence of iodine-free areas was screened. Biopsies were taken with cervical biopsy forceps from the areas that were considered abnormal by colposcopic analysis. Biopsy materials were fixed in formaldehyde and sent to the pathology laboratory for histopathological examination. More than 100 subtypes of HPV have been identified. Diagene® HC2 HPV DNA test kits were used for HPV screening tests (Qiagen GmbH, Hilden, Germany). HPV DNA was performed with PCR, LCD Array HPV 3.5 kit (Chipron GmbH, Germany).

Ethics Committee

Mardin Training and Research Hospital Local Ethics Committee approval was obtained (date: 2022/09/29, decision number: E-37201737-602.99).

Statistical Analysis

All data of our patients were analyzed using the SPSS-21 program (Statistical Packages for the Social Sciences, software, edition 21, SPSS Inc., Chicago, USA). Descriptive statistical analyses were performed.

RESULTS

The mean age of the 217 female patients included in the study was 42±9.2, and the mean number of colposcopic biopsy quadrants from the patients was 3.3. Histopathologically, cervical premalignant or malignant lesions were detected in 79 of 217 patients. Our most common HPV subtypes are HPV 16, HPV 18, HPV 31, HPV 45, and HPV 33, respectively. In general, HPV subtype 16 and/or HPV subtype 18 were observed in 60 of our 79 patients with premalignant and malignant lesions. LSIL was detected in 22 (29.3%), HSIL in 5 (6.6%), and squamous cell carcinoma in 2 (2.6%) of our HPV subtype 16-positive patients. LSIL was detected in 8 (26.6%), HSIL in 2 (6.6%), and squamous cell carcinoma in 1 (3.3%) of our HPV subtype 18-positive patients. LSIL was detected in 1 (16.6%), squamous cell carcinoma in 1 (16.6%), and cervical adenocarcinoma in 1 (16.6%) of our HPV subtypes 16 and 18-positive patients. LSIL was detected in 6 (21.4%), and HSIL in 2 (7.1%) of our HPV subtype 16 and other HPV subtypes-positive patients. LSIL was detected in 5 (23.8%) and HSIL in 1 (12.5%) of our HPV subtype 18 and other HPV subtypes-positive patients. LSIL was detected in 2 (25%) and HSIL in 1 (12.5%) of our HPV subtypes 16, 18, and other HPV subtypes-positive patients. LSIL was detected in 17 (34.6%) and HSIL in 2 (4.08%) of our other HPV subtypes-positive patients. The distribution of cervical premalignant and malignant lesions according to HPV subtypes in our HPV-positive patients is presented in Table 1. More than one HPV positivity was observed in some of our patients, and the diagram of multiple HPV positivity is presented in Figure 1.

Considering the positivity of HPV subtypes according to age, HPV 16 positivity was seen most frequently in all age groups. The second most common HPV subtype 18 was observed in the 30–39 age group. Most frequently, the other HPV subtypes were observed in the 40–49 age group. The second most common HPV subtype in the 50–59 age group was HPV subtype 18. In the 60–69 age group, the most frequently seen HPV subtypes were HPV subtype 18 and other HPV subtypes. The distribution of HPV subtypes by age groups is presented in Table 2.

Table 1: Cervical lesion distribution by HPV subtypes

	Normal		LSIL		HSIL		SCC		Ade.		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
HPV 16	46	61.3	22	29.3	5	6.6	2	2.6	0	0	75	34.5
HPV 18	19	63.3	8	26.6	2	6.6	1	3.3	0	0	30	13.8
HPV 16, 18	3	50	1	16.6	0	0	1	16.6	1	16.6	6	2.7
HPV 16, others	20	71.4	6	21.4	2	7.1	0	0	0	0	28	12.9
HPV 18, others	15	71.4	5	23.8	1	4.7	0	0	0	0	21	9.6
HPV 16, HPV18, others	5	62.5	2	25	1	12.5	0	0	0	0	8	3.6
HPV 31	6	54.5	4	36.3	1	9.09	0	0	0	0	11	5.06
HPV 33	5	62.5	3	37.5	0	0	0	0	0	0	8	3.06
HPV 45	5	55.5	3	33.3	1	11.1	0	0	0	0	9	4.14
HPV 39	3	60	2	40	0	0	0	0	0	0	5	2.03
HPV 51	2	66.6	1	33.3	0	0	0	0	0	0	3	1.38
HPV 52	2	66.6	1	33.3	0	0	0	0	0	0	3	1.38
HPV 56	3	75	1	25	0	0	0	0	0	0	4	1.84
HPV59	2	66.6	1	33.3	0	0	0	0	0	0	3	1.38
HPV 66	1	50	1	50	0	0	0	0	0	0	2	0.92
HPV 68	1	100	0	0	0	0	0	0	0	0	1	0.46
Total	138	63.5	61	28.1	13	5.9	4	1.8	1	0.4	217	100

HPV: Human papillomavirus; Ade: Adenocarcinoma; LSIL:Low-grade squamous intraepithelial lesion; HSIL:High-grade squamous intraepithelial lesion; SCC: Squamous cell cancer.

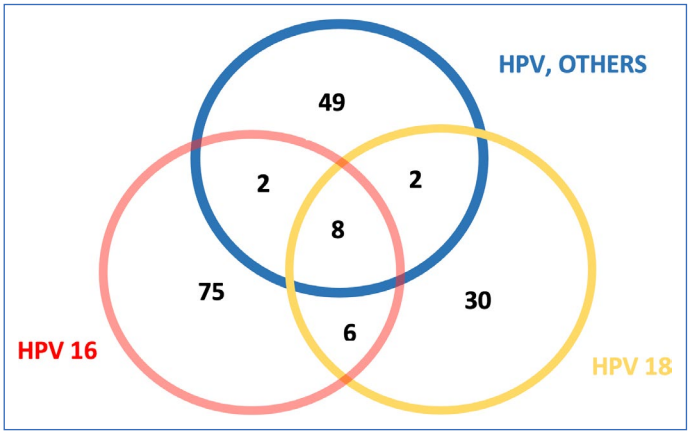

Figure 1: The distribution of HPV subtypes.

DISCUSSION

Cervical cancer caused by HPV is an important health problem among women.[5] Cervical cancer screening methods are one of the few screening methods proven to reduce the incidence of invasive cancer and mortality. Sexual life is very important in HPV infection. Studies have shown that sexual behaviors such as polygamy and unprotected sex increase the risk of HPV transmission. It has been reported that approximately 70–80% of sexually active women become infected with HPV shortly after sexual activity begins.[6] Based on the results of these studies, it was decided to screen sexually active women over the age of 30 for premalignant and malignant lesions.

Within the scope of the HPV screening program launched in Türkiye in 2014, there was an increase in the number of women participating in the screening program. This shows that the importance of the cervical cancer screening program is increasingly understood. In a study showing the first results of the cervical cancer screening program in our country, the HPV positivity rate was found to be 3.5%. In cervical screenings performed in Australia, HPV positivity was found to be 8.1%. Looking at the data from the Asian continent, HPV positivity was found to be 9.9% in the general population. It is evident that there are differences in the geographical distribution of HPV positivity. These differences can be associated with many factors, such as sociocultural differences in societies, perceptions towards risky behaviors, and sexual practices.[7]

In our country, cervical cancer screening is performed with a cervical smear for patients under 30 years old, and with a cervical smear and HPV test for patients over 30 years old. In many countries, such as Sweden, Norway, the United States, Australia, Italy, and the Netherlands, HPV testing has begun to be used for screening purposes.

Since HPV infection and subtype distribution vary regionally, it is practically important to correlate high-risk HPV infection with premalignant and malignant lesions. In many studies conducted

Table 2: The relationship between HPV subtypes and age groups

	Age groups									
	30–39 years old		40–49 years old		50–59 years old		60–69 years old		Total	
	n	%	n	%	n	%	n	%	n	%
HPV 16	35	46.6	27	36	10	13.3	3	4	75	34.5
HPV 18	13	43.3	10	33.3	5	16.6	2	6.4	30	13.8
HPV 16, 18	3	50	2	33.3	1	16.6	0	0	6	2.7
HPV 16, others	12	42.8	10	35.7	4	14.2	2	7.1	28	12.9
HPV 18, others	8	38.09	9	42.8	3	14.2	1	4.7	21	9.6
HPV 16, HPV 18, others	3	37.5	3	37.5	1	12.5	1	12.5	8	3.6
Others	25	51.02	18	36.73	4	8.1	2	4.08	49	22.5
Total	99	45.6	79	36.4	28	12.9	11	5.06	217	100

HPV: Human papillomavirus.

around the world, the most frequently observed HPV subtypes show regional differences.[8–11] In our study, across all age groups, the most common HPV subtype was HPV 16. The second most common HPV subtype was other HPV subtypes in the 30–39 and 40–49 age groups. In the worldwide study by Bruni et al.,[12] the most common HPV subtype was HPV subtype 16, and the second most common subtypes were HPV subtype 18 in Western countries, and HPV subtype 58 in Asia. In studies conducted in Türkiye, HPV subtype 16 was found to be the most common, as in our study.[13–15] Only one study reported the most common HPV subtype as HPV subtype 18.[16] As the latest vaccine, the nonavalent vaccine includes HPV subtypes 6, 11, 16, 18, 31, 33, 45, 52, and 58. In our study, the most common HPV subtypes were HPV 16, HPV 18, HPV 31, HPV 45, and HPV 33, respectively. The results of our study suggest that the nonavalent vaccine would provide significant benefits to our region.

In the current study, 45.6% of our HPV-positive patients were between the ages of 30 and 39, 36.4% were between the ages of 40 and 49, and 12.5% were between the ages of 50 and 59. HPV positivity decreased with age, similar to other studies.

In the study by Dursun et al.,[17] the data of 12 centers were evaluated, and it was determined that 25% of 6388 women were HPV positive. The most common HPV types in their studies were HPV 16, HPV 6, HPV 11, HPV 18, HPV 31, HPV 51, and HPV 33. In a study conducted by Alaçam and Bakır in Istanbul, HPV positivity was found to be 36.3%. The most common HPV types in their study were HPV 16, HPV 39, and HPV 51.[18] In the study by Kaleli et al.[19] in the Aegean region, HPV positivity was found to be 37.2%. Kaleli et al.[19] determined the highest HPV prevalence as HPV 16 with 8.9%, followed by 6, 53, and 52/53/35/58. Yuce et al.[20] found that the most common type was HPV 16, followed by HPV 31 and HPV 51. In the study conducted by Şahiner et al.,[21] it was determined that HPV 52, HPV 58, HPV 31, and HPV 68 were also seen at high rates in addition to HPV 16.

As a result, HPV subtype 16 is the most common HPV subtype in Türkiye. HPV subtypes 16 and/or HPV subtype 18 positivity was detected in 75.9% of the patients with premalignant and malignant lesions. In the current study, the most common HPV subtypes were HPV 16, HPV 18, HPV 31, HPV 45, and HPV 33, respectively. This is an important finding because knowledge of the most common and pathogenic HPV subtypes is essential for prophylactic vaccination.

Our study also has some limitations. Firstly, our data was limited to the population admitted only to a tertiary hospital. Secondly, we evaluated only HPV-positive patients, since our aim in our study was to determine the most common HPV subtypes and the cervical dysplasia caused by these subtypes. Therefore, our HPV-negative patients with cervical dysplasia were not included in the study. The strength of our study is including the HPV subtypes and cervical dysplasias individually, as well as all data. With all these limitations and strengths, the results reported in our study provide up-to-date and strong data on the epidemiology of HPV in the Mardin population. However, stronger surveillance systems, standardized data collection methods, and continuous reports are needed to follow the latest trends in HPV epidemiology in Türkiye.

Statement

Ethics Committee Approval: The Mardin Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 29.09.2022, number: 37201737-602.99).

Conflict of Interest: The author have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The author declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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