



# Prevalence of High-Risk Human Papillomavirus Types and Their Association with Cervical Squamous Cell Carcinoma, and High- and Low-Grade Squamous Intraepithelial Lesions in Turkish Women

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## Abstract

**Background:** This study aimed to investigate human papillomavirus (HPV) type prevalence in our region and the relationship between uterine cervical HPV types and squamous cell carcinoma (SCC)/intraepithelial lesions.

**Methods:** HPV test results were obtained from patient file archives of the Gynecology and Obstetrics Clinic. Pathology report results were obtained from the digital records of the Pathology Laboratory and the patient file archives of the Gynecology and Obstetrics Clinic in 2018.

**Results:** The most frequently detected was HPV16 (29.2%), followed by HPV51 (13.1%), HPV56 (11%), HPV31 (9.2%), HPV52 (8.4%), and HPV68 (8.2%). HPV16 was positive in 50% of patients diagnosed with SCC, 54.9% of patients with HSIL, 27% of patients with LSIL, and 25% of cases diagnosed as benign ( $P<0.001$ ). HPV18 was positive in 25% of patients diagnosed with SCC, 11% of patients with HSIL, 4.7% of patients with LSIL, and 5.2% of cases diagnosed as benign ( $P=0.019$ ).

**Conclusion:** The most frequent hrHPV genotype was HPV16, followed by HPV51, HPV 56, and HPV 31. There is an increase in the frequency of HPV51 and HPV56. HPV51, not included in HPV vaccines and is the second most frequent, should be included in these vaccines. In addition, although the frequency of HPV18 has decreased, HSIL and SCC generation is still high together with HPV16.

**Keywords:** Cervical carcinoma; Cytology; Epithelial abnormality; High-risk human papillomavirus; Type prevalence

## Introduction

Invasive cervical cancer (ICC) is the fourth most common cancer in women worldwide in Glo-

bocan 2020 reports (1). The highest ICC frequency is found in countries with the weakest



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infrastructure for cervical cancer screening and treatment (2). ICC incidence and mortality rates have decreased significantly in developed countries in the last five decades, largely due to screening programs and the detection of human papillomavirus (HPV) (3).

Genital HPV infection is the most common sexually transmitted viral infection worldwide (4). HPV is an epitheliotropic virus that infects human skin and mucosa (5).

More than 100 HPV types can infect the anogenital epithelium, but twenty-two genotypes (HPV16,18,26,31,33,35,39,45,51,52,53,56,58,59,66,67,68,69,70,73,82,85) that produce high-grade squamous intraepithelial lesion (HSIL) are classified as intermediate or high-risk HPV (hrHPV) types (5-9). Two of them (HPV16, HPV18) cause over 70% of all ICC cases (6-8, 10, 11). HPV16,18,31,33, and 35 are associated with cancer and premalignant lesions of the anogenital region (2, 5, 6). They cause low-grade squamous intraepithelial lesion (LSIL), HSIL, or squamous cell carcinoma (SCC) (6). For this reason, they are called oncogenic hrHPVs (5).

Some geographic variations in the distribution of HPV types have been reported, with frequencies ranging from 3% to 30% (10). HPV infection is usually seen in younger women, and the rate of HSIL cases is higher in middle-aged women (6). It is necessary to combine cytology and HPV tests to improve the current cervical screening process (6).

This study aimed to investigate HPV type prevalence in our region and the relationship between HPV types and SCC/intraepithelial lesions.

## Methods

The permission was obtained from the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Decision number: 2011-KAEK-25 2019/05-12).

Our study group consisted of women who underwent PAP smears and HPV tests within the framework of national cervical cancer screening in our region between Jan 1, 2018, and Dec 31, 2018. HPV tests were performed on 559 patients in our hospital within one year. Patients with low risk HPV (lrHPV) positivity (n=49) were excluded from the study. Overall, 510 referred women were included in the study.

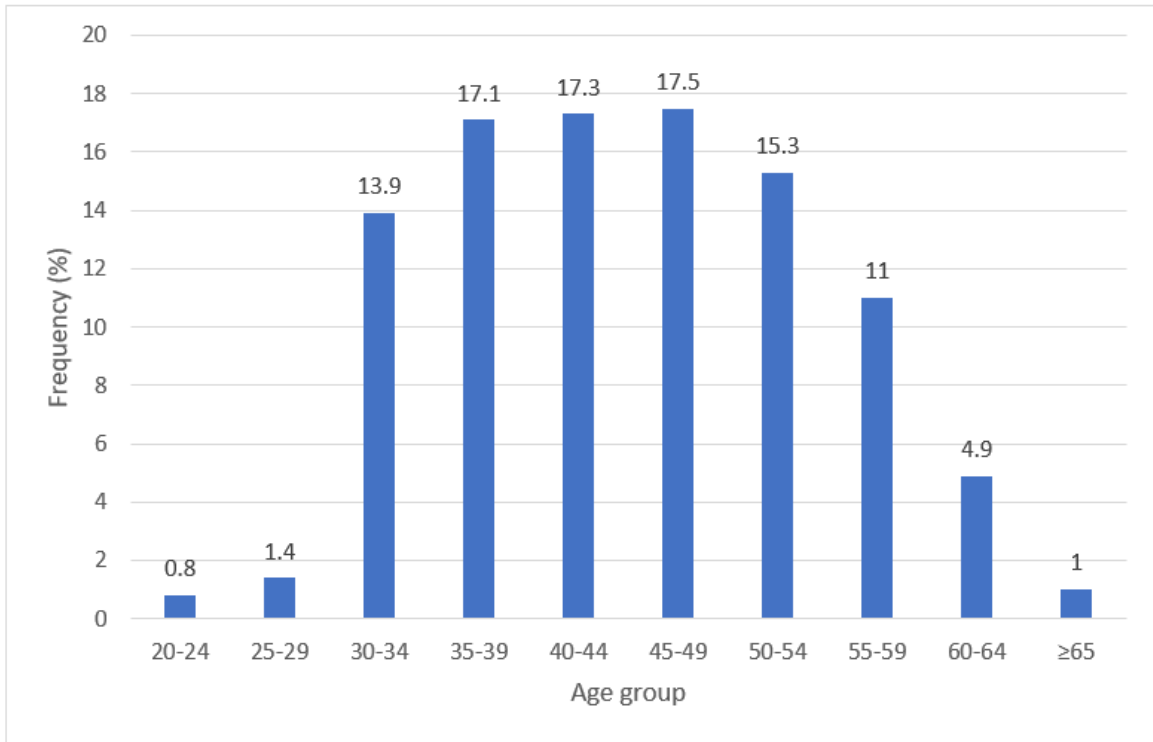
National cervical cancer screening institution used the QIAGEN Digene HC2 HPV DNA Test kits. Both low and high-risk HPV probes were used.

HPV test results were obtained retrospectively from patient file archives of the Gynecology and Obstetrics Clinic. PAP smears, colposcopy-guided cervical biopsies, and conization results were obtained from the digital records of the Pathology Laboratory of our hospital and the patient file archives of the Gynecology and Obstetrics Clinic.

The SPSS 15.0 for Windows program (Chicago, IL, USA) was used for statistical analysis. Descriptive statistics of the evaluation results are given as numbers and percentages for categorical variables, and mean, standard deviation, minimum and maximum for numerical variables. Proportions in independent groups were tested using Chi-square analysis. The statistical significance level of alpha was accepted as  $P < 0.05$ .

## Results

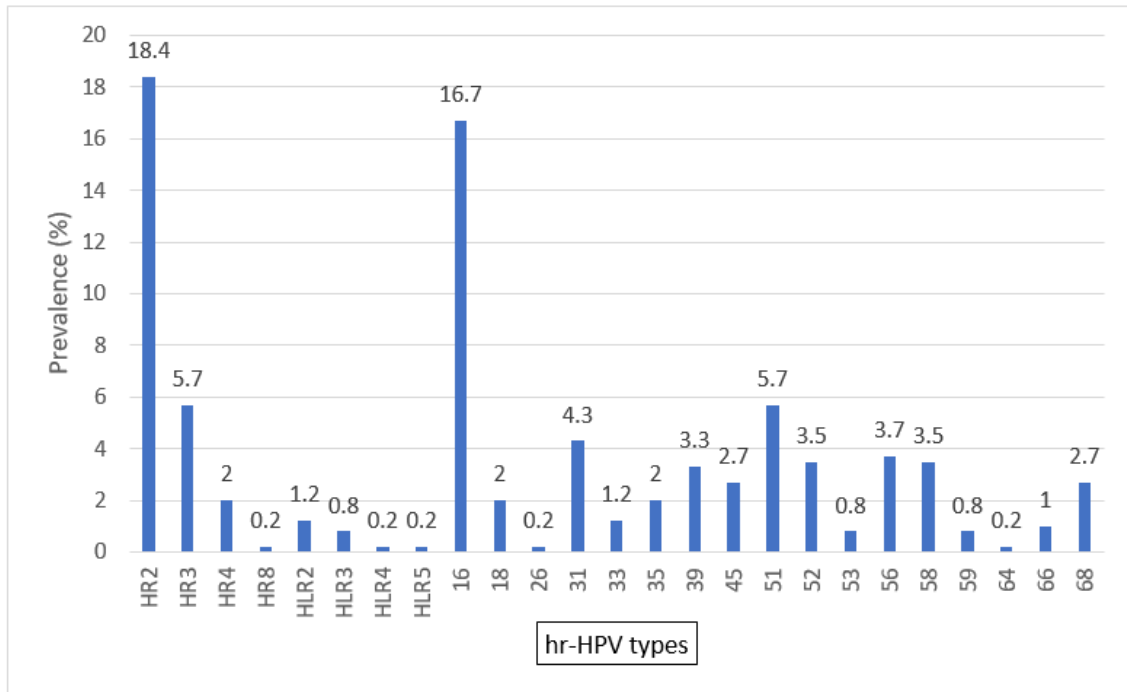
The ages of the 510 women were between 22 and 69 yr and the mean age was  $44.7 \pm 9.3$  yr. Most of these patients (92.1%) were in the 30-59 yr age range. There were 4 (0.8%) patients in the 20-24 yr age group, 5 (1.0%) patients in the 65 yr and over and 7 (1.4%) patients in the 25-29 yr age groups. There were 25 (4.9%) patients in the 60-64 yr age group (Fig. 1).



**Fig. 1:** Age group distribution of the patients. Patients of having suspected epithelial abnormality and/or hrHPV infection were mostly aged 30-59 yr

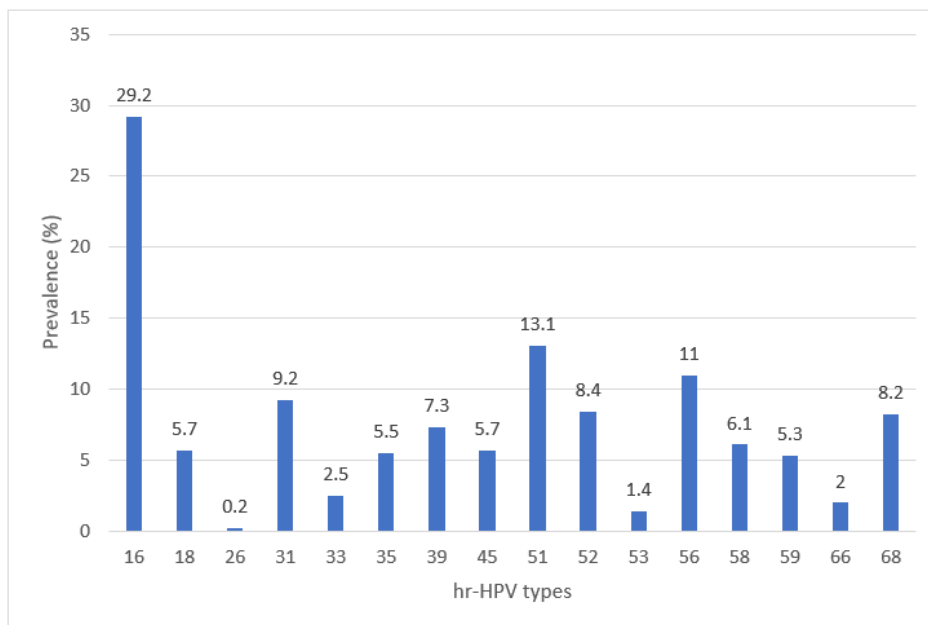
When we examined the distribution of hrHPV on a case-by-case basis, hrHPV was detected in 423 of 510 patients tested for HPV; the remaining 87 patients were negative for HPV. Among the HPV-positive females, 146 (34.5%) of these 423 hrHPV test-positive cases were multiple hrHPV (mhrHPV) and 277 (65.5%) were single hrHPV. Among multiple hrHPV infections, the rate of all hrHPV mhrHPV (mhhrHPV) infections was 26.3%, and the rate of mixed with lrHPV mhrHPV (mhlrHPV) infections was 2.4%. The most common HPV infection was dual HPV (HR2) infection. Among the dual HPV infections, the most common (7.5% of all dual HPV infections) with a clear difference is the HPV16-HPV51 coexistence. HPV16-HPV18, HPV16-

HPV31, HPV16-HPV56, HPV51-HPV56, HPV56-HPV68 couples come second, each with 2.7% of dual HPV infections. Among the dual HPV infections, the most common HPV types were 16, 51, 56 and 31, respectively (Fig. 2). When we looked at the distribution of hrHPV types based on type, among the total of 616 hrHPV types detected in 423 cases. The distribution of hrHPV types in patients suspected of having epithelial abnormalities is shown in Fig. 3. The most common hrHPV type was HPV16, followed by HPV51, HPV56, HPV31, HPV52, and HPV68, respectively. The least common hrHPV infection was HPV26, followed by HPV53, HPV66, and HPV33, respectively.



**Fig. 2:** Distribution of case-based hrHPV types

HR2: Multiple 2 high-risk HPV strains, HR3: Multiple 3 high-risk HPV strains, HR4: Multiple 4 high-risk HPV strains, HR8: Multiple 8 high-risk HPV strains, HLR2: Multiple 1 high-risk and 1 low-risk total 2 HPV strains, HLR3: Multiple at least 1 high and 1 low-risk total 3 HPV strains, HLR4: Multiple at least 1 high and 1 low-risk total 4 HPV strains, HLR5: Multiple at least 1 high and 1 low-risk total 5 HPV strains



**Fig. 3:** Distribution of hrHPV types in patients suspected of having epithelial abnormalities

Colposcopy-guided cervical biopsy or conization was performed for histopathologic examination

and treatment in 455 of 510 patients tested for HPV (Table 1).

**Table 1:** Histopathologic diagnosis distribution of HPV test cases.

<i>Histopathologic diagnosis of HPV test cases</i>	<i>n</i>	<i>%</i>
BENIGN	212	46.6
LSIL	148	32.5
HSIL	91	20.0
SCC	4	0.9
Total	455	100

LSIL: Low-grade Squamous Intraepithelial Lesion, HSIL: High-grade Squamous Intraepithelial Lesion, SCC: Squamous Cell Carcinoma

HPV tests were performed on 510 suspected cases within one year in our hospital. Of these, 423 were HPV positive, and 87 were HPV negative. Of the 423 HPV positive cases, 146 were multiple HPV positive and 277 were single HPV positive. Histopathologic diagnosis was made

using biopsy in 137 of 146 multiple HPV-positive cases; biopsy was not performed in the remaining 9 cases. The histopathologic diagnosis distribution of patients with multiple hrHPV was similar to the histopathologic diagnosis distribution of all patients with HPV testing (Table 2).

**Table 2:** Histopathological diagnosis of patients with multiple HPV

<i>Histopathological diagnosis of cases with multiple HPV</i>	<i>n</i>	<i>%</i>
BENIGN	67	48.9
LSIL	43	31.4
HSIL	26	19.0
SCC	1	0.7
Total	137	100

LSIL: Low-grade Squamous Intraepithelial Lesion, HSIL: High-grade Squamous Intraepithelial Lesion, SCC: Squamous Cell Carcinoma

HPV16 was cytogenetically positive in 50% of patients histopathologically diagnosed as having SCC, 54.9% diagnosed as having HSIL, 27% of patients diagnosed as having LSIL, and 25% of patients diagnosed as being negative for epithelial abnormalities ( $P<0.001$ ). HPV18 was cytogenetically positive in 25% of patients histopathologically diagnosed as having SCC, 11% of patients diagnosed as having HSIL, 4.7% of patients diagnosed as having LSIL, and 5.2% of patients diagnosed as being negative for epithelial abnor-

malities ( $P=0.019$ ). HPV51 was cytogenetically positive in 11% of patients histopathologically diagnosed as having HSIL, in 23% of patients diagnosed as having LSIL, and in 9.9% of patients diagnosed as being negative for epithelial abnormalities ( $P<0.001$ ). HPV 68 was cytogenetically positive in 2.2% of patients histopathologically diagnosed as having HSIL, in 10.1% of patients diagnosed as having LSIL, and in 10.8% of patients diagnosed as being negative for epithelial abnormalities ( $P=0.049$ ) (Table 3).

**Table 3:** hrHPV rates in histopathologic diagnosis groups

	<i>NO HISTOLOGICAL EXAMINATION</i>		<i>BENIGN</i>		<i>LSIL</i>		<i>HSIL</i>		<i>SCC</i>		p
	n	%	n	%	n	%	n	%	n	%	
HPV16	4	7.3	53	25.0	40	27.0	50	54.9	2	50.0	<0.001
HPV18	0	0.0	11	5.2	7	4.7	10	11.0	1	25.0	0.019
HPV26	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0	0.585
HPV31	4	7.3	23	10.8	13	8.8	6	6.6	1	25.0	0.478
HPV33	0	0.0	6	2.8	2	1.4	5	5.5	0	0.0	0.262
HPV35	2	3.6	13	6.1	6	4.1	7	7.7	0	0.0	0.685
HPV39	4	7.3	22	10.4	7	4.7	3	3.3	1	25.0	0.058
HPV45	2	3.6	12	5.7	9	6.1	6	6.6	0	0.0	0.950
HPV51	2	3.6	21	9.9	34	23.0	10	11.0	0	0.0	<0.0011
HPV52	3	5.5	20	9.4	14	9.5	6	6.6	0	0.0	0.823
HPV53	0	0.0	4	1.9	3	2.0	0	0.0	0	0.0	0.538
HPV56	3	5.5	26	12.3	20	13.5	7	7.7	0	0.0	0.387
HPV58	1	1.8	13	6.1	12	8.1	4	4.4	1	25.0	0.194
HPV59	4	7.3	16	7.5	5	3.4	2	2.2	0	0.0	0.221
HPV66	2	3.6	2	0.9	5	3.4	1	1.1	0	0.0	0.253
HPV68	2	3.6	23	10.8	15	10.1	2	2.2	0	0.0	0.049

LSIL: Low-grade Squamous Intraepithelial Lesion, HSIL: High-grade Squamous Intraepithelial Lesion, SCC: Squamous Cell Carcinoma

## Discussion

Overall, the prevalence of hrHPV in the entire group (n=510) was 82.9% (423 out of 510) (Fig.2). Although this result is somewhat at the upper limit, it is consistent with similarly structured studies in other countries reporting HPV prevalence ranging from 35.3% to 88.9% in women with cytologic abnormalities (4, 12-19).

In this study, overall, the most frequent hrHPV genotype was HPV16 (29.2%), followed by HPV51 (13.1%), HPV56 (11%), and HPV31 (9.2%). Both globally and in Turkey, HPV16 was

the most common type of hr-HPV in all (18/20) studies except for two studies (20, 21). In studies performed in China and Turkey, HPV52 and HPV51 were the most frequent hr-HPV types, respectively (20, 21).

In this study, HPV51 was the 2nd most frequent type. In Turkey, HPV51 was the most frequent (21). In Italy, Greece, and Turkey, HPV51 was the 2nd most frequent, in parallel with our study (4, 6, 22). The predominant genotypes HPV16 and HPV31 found in European, Mexican, Turkish, and Chinese Uyghur women with cervical cytologic abnormalities did not parallel the find-



ings of other studies. In these studies, HPV31 was the 2nd most frequent (12, 19, 20, 23-27). In studies in the United States of America (USA) and Turkey, HPV18 was the 2nd most frequent, but it was followed by HPV51, HPV31 and HPV45 as the 3rd most frequent (8, 28-30). In studies in Europe, and two in Turkey, HPV51 was the 4th most frequent (26, 28, 29). In studies in China and Turkey, HPV51 was the 5th most frequent (23, 31). In Korea, HPV51 was the 6th most frequent (9). In six other studies, HPV51 was not included in the first seven. These data also support the increase of HPV51 in women with cytologic abnormalities.

In this study, HPV56 was the 3rd most frequent type. Demirci et al. determined the prevalence of HPV56 as the 3rd most frequent in Turkey, in parallel with this study (32). In Greece, Korea, and three Turkish studies HPV56 was 4th (6, 9, 22, 30, 33). In studies in China and Turkey, HPV56 was the 5th most frequent HPV type (20, 24). In studies in South Italy and Turkey, HPV56 was placed 6th and 7th, respectively (21, 34). However, in another eight studies, HPV56 was not included in the first seven.

The present study found that HPV31 was the 4th most frequent. HPV31 was the 2nd most frequent in studies in China, Italy, Turkey, Europe, and Mexico (23, 24, 26, 27, 34). HPV31 was the 3rd most frequent in two studies in Turkey (28, 29). In parallel with this study, HPV31 was the 4th most frequent in studies in Italy and Turkey (4, 31, 32). In addition, HPV31 was the 5th most frequent in studies in Greece and Turkey (6, 22). In four other studies, HPV31 was not included in the first seven.

In this study, HPV52 was the 5th most frequent. Similarly, HPV52 was the 4th most frequent in studies in China, the USA, and Mexico (8, 23, 27). In addition, it was the 6th most frequent in studies in Turkey (21, 29, 30). In studies in Italy, Korea and Turkey, HPV52 was 7th (4, 9, 28). In contrast to our study, studies in China, Turkey, and Europe, HPV52 was the 1st, 2nd, 2nd, and 3rd most frequent, respectively (20, 26, 32, 33). In five other studies, HPV52 did not make the first seven.

HPV68 was the 6th most frequent type in the present study. In two studies in China and Korea, unlike this study, HPV68 was the 3rd most common type (9, 23). In addition, HPV68 was the 5th most common type in studies in Turkey and 7th in another study in Turkey, in parallel with this study (24, 30, 32). HPV68 was not included in the first seven frequencies in 13 other studies.

HPV18 was not included in the first seven types in this study. By contrast, in studies in the USA and Turkey, it was the 2nd most frequently found type. In two studies in Turkey, HPV18 was discovered to be the 3rd most common type, but it was 4th in another study in Turkey. In three studies in Mexico, Europe, and Turkey, HPV18 was 5th, and in studies in Italy and Turkey, it was the 6th and 7th most commonly found type, respectively (4, 21, 26, 27, 32, 34). HPV18 also was not included in the first seven frequencies in five other studies.

HPV18 prevalence has been reported in other studies to range from 1.8% to 27.9% (12-15, 19, 21-24, 28-32). Although close to the lower limit, the prevalence of HPV18 in the present study was 5.7%, in accordance with the studies mentioned above.

Other studies have reported a prevalence of multiple infections from 11% to 50% of cases (4,12-15,23,25,35). Studies in Italy, South Cyprus, and China found rates of multiple HPV infection at 30.9%, 28.7%, and 17.6% in HPV-positive cases, respectively (4,12,23). In this study, parallel to the literature, we found the rate of multiple HPV infection as 28.7% among HPV-positive cases.

Most multiple HPV infections (91.6%) consisted of mhrHPV infections. The mhrHPV infection rate was 8.4%. In the present study, among the 146 individuals infected with multiple HPV types, 100 had dual infections (100/146, 68.5%), 33 had triple infections (33/146, 22.6%) and 13 were infected with four or more types of HPV (13/146, 8.9%). In a study in China (Xinjiang province), among 200 individuals infected with multiple HPV types, Overall, 169 had dual infections (169/200,84.50%), 26 had triple infections (26/200,13.00%), and five were infected with

four or more types of HPV (5/200, 2.50%) (23). In the present study, among women in Turkey (Bursa Province), the rate of triple infections and infections with four or more types of HPV were about 2 and 5 times, respectively, more than among the Uyghur women in China. Accordingly, dual infections in Turkey (Bursa Province) were fewer than in China.

HPV16 and HPV18 are more likely to progress to cervical cancer than other HPV genotypes (8). Therefore, patients with SIL infected with HPV16 and/or HPV18 should be distinguished from those infected with other hrHPV types for closer monitoring and surveillance. In this study, HPV18 was detected with a low prevalence in all three classes of cytologic abnormalities.

Gardasil 9 is effective against 7 hr-HPV types (HPV16,18,31,33,45,52,58), which is today the broadest spectrum vaccine available (36). Looking at the various studies in the literature, the most common 7 hr-HPV types are HPV16,31,51,52,18,56,58, respectively. Five of these first seven (HPV16,18,31,52,58) are present in the Gardasil 9 vaccine, but the remaining two (HPV51,56) are not. HPV33 and 45 in the Gardasil 9 vaccine were 12th and 13th most frequent, respectively; HPV68,39,53, and 66 were the 8th, 9th, 10th, and 11th most frequent, respectively.

## Conclusion

In women with epithelial abnormalities, the frequency of HPV18 has decreased or tends to decrease to a much greater level when compared with the past. Recently, there has been an increase in the frequency of HPV51 (marked), HPV56, HPV68, HPV39, HPV53, and HPV66 in the world. Although the frequency of HPV18 has decreased, HSIL and SCC generation capacity is still high together with HPV16. HPV51 and HPV68 are significantly associated with LSIL. HPV types may vary according to geographic location. This may cause differences in the effectiveness of HPV vaccines depending on the country. First, we think that HPV51, not included in HPV vaccines but is the 2nd most frequent-

ly found according to current studies, should be included in these vaccines. Even HPV56, 68, 39, 53, and 66, which are 6th, 8th, 9th, 10th, and 11th in terms of frequencies, may be recommended to be included in HPV vaccines.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Conflict of interest

The authors declare that there is no conflict of interests.

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