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# Cervical Pathologic Findings in Women Infected with Human Papilloma Virus 52

## İnsan Papilloma Virüs Tıp 52 ile Enfekte Kadınların Servikal Patolojik Bulguları

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## ABSTRACT

**Aim:** Human papillomavirus (HPV) type 52 is a high-risk genotype. However, oncogenic potential of HPV 52 remains controversial. This study aimed to evaluate the cervical pathological outcomes associated with HPV 52 infection and to determine whether the risk of high-grade lesions differs between isolated HPV 52 positivity and coinfection with other high risk HPV types.

**Materials and Methods:** A retrospective analysis was conducted on 3546 women who underwent colposcopic evaluation. A total of 102 (2.9%) patients with HPV 52 positivity were included. In the study, isolated HPV 52 positivity was defined as the presence of only HPV 52, while combined HPV 52 positivity was defined as the presence of HPV 52 along with other high risk HPV genotypes.

**Results:** In our cohort, 39.2% had isolated HPV 52 infection. High-grade squamous intraepithelial lesions (HSIL) or cancer were detected in 11.8% of women. In addition, with isolated HPV 52 or combined HPV 52 infection didn't effect final pathological result (p=0.657). One case of stage IB1 cervical squamous cell carcinoma was identified in a patient with isolated HPV 52.

**Conclusion:** The rate of ≥HSIL among HPV 52 positive women was found to be over 10%. Additionally, no significant difference was observed regarding the risk of developing ≥HSIL lesions between patients with isolated HPV 52 and combined HPV 52 infections. Our study underscores the need to include HPV 52 in individualized risk assessment models for cervical cancer screening programme.

**Keywords:** HPV 52, Cervical intraepithelial neoplasia, Colposcopy.

## ÖZ

**Amaç:** İnsan papillomavirüsü (HPV) tip 52 yüksek riskli bir genotiptir. Ancak HPV 52'nin onkojenik potansiyeli hala tartışmalıdır. Bu çalışmanın amacı, HPV 52 enfeksiyonu ile ilişkili servikal patolojik sonuçları değerlendirmek ve yüksek dereceli lezyon riskinin izole HPV 52 pozitifliği ile diğer yüksek riskli HPV tipleriyle birlikte enfeksiyon arasında farklılık gösterip göstermediğini belirlemektir.

**Gereç ve Yöntemler:** Kolposkopik değerlendirmeden geçen 3546 kadın üzerinde retrospektif bir analiz yapıldı. Toplam 102 (%2,9) HPV 52 pozitif hasta dahil edildi. Çalışmada, izole HPV 52 pozitifliği yalnızca HPV 52'nin varlığı olarak tanımlanırken, kombine HPV 52 pozitifliği diğer yüksek riskli HPV genotipleriyle birlikte HPV 52'nin varlığı olarak tanımlanmıştır.

**Bulgular:** Kohortumuzda %39,2'si izole HPV 52 enfeksiyonuna sahipti. Kadınların %11,8'inde yüksek dereceli skuamöz intraepitelyal lezyonlar (HSIL) veya kanser tespit edildi. Ek olarak, izole HPV 52 veya kombine HPV 52 enfeksiyonu nihai patolojik sonucu etkilemedi (p=0.657). İzole HPV 52 taşıyan bir hastada evre IB1 servikal skuamöz hücreli karsinom vakası tespit edildi.

**Sonuç:** HPV 52 pozitif kadınlar arasında ≥HSIL oranı %10'un üzerinde bulunmuştur. Ek olarak, izole HPV 52 ve kombine HPV 52 enfeksiyonu olan hastalar arasında ≥HSIL lezyonları geliştirme riski açısından anlamlı bir fark gözlenmedi. Çalışmamız, rahim ağzı kanseri tarama programları için kişiselleştirilmiş risk değerlendirme modellerine HPV 52'nin dahil edilmesi gerektiğini vurgulamaktadır.

**Anahtar Kelimeler:** HPV 52, Servikal intraepitelyal neoplazi, Kolposkopi.

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## INTRODUCTION

Cervical cancer is the fourth most common malignancy in women and continues to be a significant public health issue worldwide (1). High-risk human papillomavirus (HR-HPV) infections have fundamental role in the development of cervical cancer (2). HPV is a virus that contains double-stranded DNA, and over 200 different types have been identified today. These types are classified into 2 groups based on their oncogenic potential; low-risk and high-risk. Especially HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are in the high-risk group and are directly associated with cervical cancer (3). The development of HPV-related lesions is not limited to the virus's genotype. Host factors (e.g., immune system, genetic predisposition, smoking, reproductive history, and patterns of sexual behavior) can be decisive in viral persistence and the transformation process (4). Current guideline of American Society for Colposcopy and Cervical Pathology (ASCCP) mostly evaluate HR-HPV types collectively, excluding HPV 16/18, while such subtype-focused data may enable the development of more customized algorithms in the future (5).

HPV infections are the precursor to the development of cervical intraepithelial neoplasia (CIN). HPV 16 and 18 are responsible for approximately 70% of all cervical cancers, while other high-risk types, including HPV 52, constitute the remaining cases (6). Studies have shown that approximately 5% of HR-HPV infections progress to CIN3, and one-third of these lesions eventually transform into invasive cancer over time (7).

The geographical distribution of HPV types varies. It has been reported that HPV types 52 and 58 are more frequently isolated in invasive cervical cancers, particularly in East Asian populations (8). For example, in a large-scale epidemiological study conducted in China, HPV 52 was identified as the fourth most commonly type in women with cervical cancer (9). Therefore, the regional prevalence of HPV 52 is an important factor to consider for screening and vaccination.

HPV 52 is phylogenetically a member of the alpha papillomavirus 9 (Alpha 9) family and is in the same phylogenetic group as HPV 16 (10). The oncogenic effects are primarily based on the inhibition of p53 and pRb tumour suppressor proteins by the E6 and E7 oncoproteins. The E6 protein suppresses apoptosis and DNA repair pathways by targeting p53 for degradation, while the E7 protein triggers cellular proliferation by inactivating pRb, which regulates the cell cycle (11, 12). Genetic variations in the E6/E7 sequences specific to HPV 52 increase the oncogenicity and persistence of the virus, thereby raising the risk of malignant transformation (13). It is believed that the current knowledge regarding the clinical significance of HPV 52 is still insufficient.

The aim of this study is to evaluate the final cervical pathology findings observed in women infected with HPV 52 and to investigate the effect of the presence of HPV 52 alone or in combination with other HR-HPV types on the development of precancerous lesions and cervical cancer.

## MATERIALS AND METHODS

This retrospective study was conducted by scanning the files and patient information in the system of a group of 3546 patients examined in the colposcopy unit between December 2019 and December 2023. The study included 102 patients (2.9%) who tested positive for HPV 52. The exclusion criteria were pregnancy, being under immunosuppressive treatment, negativity for HPV 52, or lack of information on HPV subtypes (14). All patients were managed in accordance with the guidelines of the ASCCP. In the study, HPV 52 was classified in two groups; "isolated HPV 52 positivity" was defined as the presence of only HPV 52, while "combined HPV 52 positivity" was defined as the presence of HPV 52 along with other HR-HPV strains. This study was approved by the Ethics Committee of Ankara Bilkent City Hospital with number 487 on 18/09/2024. Detailed informed consent forms were obtained from all patients.

In our country, the cervical cancer screening programme is conducted with the HPV-based programme. The Max-prep (TM) cytology system (Corebiotec Ltd.o. Ltd., Korea) was used for HPV DNA isolation, and the liquid-based cytology preparation.

According to the guidelines published by ASCCP, conization was performed on patients with high-grade squamous intraepithelial lesions (HSIL), microinvasive cancer, adenocarcinoma in situ (AIS) diagnosed by colposcopic biopsy, or those with no correlation between biopsy and clinical evaluation (14). The highest-grade lesion obtained from smear, cervical biopsy, conization, and hysterectomy was the final pathology (Table 1). The patients' examinations, tests, and colposcopic procedures were performed by gynecologic oncology specialists. Experienced gyneco-pathologists evaluated the specimens. Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Chicago, IL; version 20.0). Descriptive values are represented by arithmetic mean, standard deviation, median range, and percentage.

## RESULTS

A total of 102 patients with mean age of 42.2±8.91 years were evaluated. Isolated HPV 52 positivity was found in 40 (39.2%) patients, while combined HPV 52 positivity was found in 62

**Table 1.** Final pathology decision

| Cervicovaginal smear | ECC pathology | Colposcopic biopsy pathology | Conization pathology | Final pathology |
|---|---|---|---|---|
| **Benign/LSIL/ASCUS** | Benign/LSIL | Benign/LSIL | Benign/LSIL | Benign/LSIL |
| **HSIL** | Benign/LSIL | Benign/LSIL | Benign/LSIL | HSIL |
| **Any result** | HSIL | Benign/LSIL | Benign/LSIL | HSIL |
| **Any result** | Benign/LSIL | HSIL | Benign/LSIL | HSIL |
| **Any result** | Benign/LSIL | Benign/LSIL | HSIL | HSIL |
| **Any result** | Benign/LSIL | HSIL | HSIL | HSIL |
| **Any result** | HSIL | Benign/LSIL | HSIL | HSIL |
| **Any result** | HSIL | HSIL | Benign/LSIL | HSIL |
| **Any result** | HSIL | HSIL | HSIL | HSIL |
| **Any result** | If any of the result is squamous cell cancer or adenocancer | | | Cancer |

**ECC:** Endocervical curettage; **ASCUS:** Atypical squamous cells undetermined significance; **LSIL:** Low-grade squamous intraepithelial lesion (CIN 1); **HSIL:** High-grade squamous intraepithelial lesion (CIN 2 or CIN 3)

(60.8%) patients. The distribution of HR-HPV strains in patients with combined HPV 52 positivity was as follows; HPV 16 in 17 (16.7%), HPV 18 in 3 (%), HPV 31 in 8 (%), HPV 33 in 4 (3.9%), HPV 35 in 8 (7.8%), HPV 39 in 8 (7.8%), HPV 45 in 7 (6.9%), HPV 51 in 14 (13.7%); HPV 56 in 5 (4.9%); HPV 58 in 6 (5.9 %); HPV 59 in 7 (6.9 %) and HPV 68 in 1 (1 %) patient (Table 2). The pathological results were benign or low-grade squamous intraepithelial lesion (LSIL) in 90 (88.2%) patients, HSIL (CIN 2) in 5 (4.9%) patients, HSIL (CIN 3) in 5 (4.9%) patients and undetermined HSIL in 1 (1%) patient, and cancer in 1 (1%) patient (Table 2).

**Table 2.** Features of cohort

| Features | | Mean±SD | Median (range) |
|---|---|---|---|
| **Age (year)** | | 42.2±8.91 | 41 (22-65) |
| | | **n** | **%** |
| **HPV 52 infection** | Isolated HPV 52 infection | 40 | 39.2 |
| | Combined HPV 52 infection | 62 | 60.8 |
| **Other high risk HPV types combined to HPV 52 infection** | HPV 16 | 17 | 16.7 |
| | HPV 18 | 3 | 2.9 |
| | HPV 31 | 8 | 7.8 |
| | HPV 33 | 4 | 3.9 |
| | HPV 35 | 8 | 7.8 |
| | HPV 39 | 8 | 7.8 |
| | HPV 45 | 7 | 6.9 |
| | HPV 51 | 14 | 13.7 |
| | HPV 56 | 5 | 4.9 |
| | HPV 58 | 6 | 5.9 |
| | HPV 59 | 7 | 6.9 |
| | HPV 68 | 1 | 1 |
| **Final pathologic results** | Benign/LSIL | 90 | 88.2 |
| | HSIL (undetermined) | 1 | 1 |
| | HSIL (CIN 2) | 5 | 4.9 |
| | HSIL (CIN 3) | 5 | 4.9 |
| | Cancer | 1 | 1 |

**HPV:** Human Papilloma Virus
**LSIL:** Low Grade Squamous Intraepithelial Lesion
**HSIL:** High Grade Squamous Intraepithelial Lesion
**CIN:** Cervical Intraepithelial Neoplasia

**Table 3.** The relationship between isolated or combined HPV 52 infection and ≥HSIL lesion in final pathologic results

| HPV 52 infection | Benign or LSIL | ≥HSIL lesion | |
|---|---|---|---|
| | n (%) | n (%) | *p* Value |
| Isolated HPV 52 infection | 36 (90) | 4 (10) | 0.657 |
| Combined HPV 52 infection | 54 (87.1) | 8 (12.9) | |

**HPV:** Human Papilloma Virus
**LSIL:** Low-grade Squamous Intraepithelial Lesion
**HSIL:** High-grade Squamous Intraepithelial Lesion

The patient with cancer, who was found to be positive for isolated HPV 52 and diagnosed with squamous cell cancer with 2 cm tumor size. This patient underwent type III radical hysterectomy with nerve-sparing surgery, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy. The patient, classified as stage 1b1 according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system, did not receive adjuvant therapy.

The relationship between isolated or combined HPV 52 infection and ≥HSIL is shown in table 3. There was no statistically significant correlation between isolated or combined HPV 52 positivity and the presence of ≥HSIL. HSIL and more advanced lesions were observed in 4 (n:4/40, 10%) patients with isolated HPV 52 positivity and in 8 (n:8/62, 12.9%) patients with combined HPV 52 positivity (p=0.657).

## DISCUSSION

In this study, the frequency of HSIL in HPV 52 positive women and the effect of HPV 52 being isolated or found with other HR-HPV types on this risk were investigated. Our findings showed that the ≥HSIL rate was 10.8% of patients with HPV 52 positive. The presence of HPV 52 infection, whether in isolated infection or combined with other HR-HPV types infection have similar effects on the risk of ≥HSIL lesion. Only one patient in the cohort had cervical cancer, and it was stage IB1.

HPV 52 is among the HR-HPV types globally and is one of the most commonly detected type in certain regions, particularly in Asia and South America, after HPV 16 and 18 (15). In a large-scale meta-analysis conducted by Guan et al., which included data from over 115.000 HPV positive women, it was reported that HPV 52 significantly contributes to ≥CIN2 lesions. In that study, it emphasized that the association of HPV 52 with precancerous lesions was more pronounced, especially in young women (16). This indicates that the distribution and potential effects of HPV 52 may vary by age. Our findings are in line with these results, showing that HPV 52–related high-grade lesions occur at comparable rates within our cohort.

Another study highlighting the clinical significance of HPV 52 is by Li et al., who reported that the isolated of HPV 52 also carries a significant risk for high-grade lesions (17). Additionally, the findings of our study indicate that the presence of HPV 52, along with other HR-HPV types, does not pose a significantly increased risk compared to its isolated HPV 52 infection.

In our study, cervical cancer was detected in one patient with isolated HPV 52 infection. This finding highlights the need to consider not only HPV 16 and 18, but also other HR-HPV genotypes in the pathogenesis and risk assessment of cervical cancer (18).

Among the limitations of our study are its retrospective design, the fact that patients were limited to a single center, and the unknown HPV vaccination status and previous infection histories. However, the large number of patients and the fact that all cases were evaluated by gynecologic oncology specialists and experienced pathologists enhance the strength of the study.

## CONCLUSION

In conclusion, the incidence of HSIL and more advanced lesions in HPV 52 positive women is more than 10% with only 1% of patients with cancer, and this rate does not show a significant difference based on the isolated or combined HPV 52 infection. These findings may contribute to the adoption of more balanced, individualized approaches that avoid unnecessary interventions in the management of women with HPV 52 infection. In addition, the HPV 52 risk assessment models for cervical cancer screening programme could be determined. Future multicenter, and long-term follow-up data will provide more information about HPV 52 infection.

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