

Analysis of the Association Between Minor Cervical Cytological Abnormalities and Consequent Pathology Results According to HPV Types

Alper Kahraman,¹ Firat Tülek²

¹Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Istanbul, Turkey
²Department of Obstetrics and Gynecology, Memorial Ataşehir Hospital, Istanbul, Turkey

Submitted: 24.05.2021
Accepted: 06.07.2021

Correspondence: Alper Kahraman, Haseki Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Istanbul, Turkey
E-mail: alper.k@hotmail.com



Keywords: ASC-US; cervical cancer screening; human papillomavirus; LSIL.



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ABSTRACT

Objective: Human papillomavirus (HPV) infection is the leading cause of cervical cancer. Although screening programs involving cervical cytology and HPV DNA have greatly reduced the incidence of cervical cancer in the last decades, attempts to increase the accuracy of these programs are still ongoing. The objective of this study is to evaluate the association of cervical colposcopic biopsy pathology results in women with minor smear abnormalities in an HPV type-specific manner.

Methods: Women who underwent a colposcopic cervical biopsy due to HPV DNA positivity or minor cervical cytological anomalies and tested positive for HPV DNA in a single tertiary center between 2011 and 2019 were retrospectively evaluated. Three groups were formed according to the detected HPV types. The first group consists of women infected with HPV 16 or 18, the second group consists of women infected with only one type of high-risk HPV other than HPV 16/18, and the third group includes patients infected with multiple types of high-risk HPV other than HPV 16/18.

Results: Four hundred thirty patients met inclusion criteria within the selected period and were included in the study. The mean age of the population was 33.4 ± 6.6 and the mean parity was 2.1 ± 1.1 . The prevalence of \geq CIN 2 lesions in the first and third group of patients were similar, however infection with a single type of high-risk HPV, except for HPV 16/18, was significantly lower in \geq CIN 2 lesions compared to the other two groups.

Conclusion: Multiple type HPV infections in low grade cytology results even in the absence of HPV 16/18 seems to warrant a cautious approach.

INTRODUCTION

The Human papillomavirus (HPV) is the most common sexually transmitted disease worldwide, it usually infects young women under the age of 30 and generally regresses spontaneously.^[1] However, %10–15 of HPV infections progress to high-grade intraepithelial lesions, and some of these lesions eventually progress to cervical cancer. The vast majority of cervical cancers develop as a result of persistent high-risk HPV (hrHPV) infection.^[2] Screening programs aim to detect these precancerous cervical intraepithelial lesions as they emerge and treat them before progressing further. Contemporarily, effective preventive strategies like cervical cytology examination, HPV DNA detection, and subsequently early recognition and treatment of precancerous cervical lesions along with HPV vaccination have markedly decreased the incidence of cervical cancer.^[3]

Although frequently encountered in cervical cytology results, the clinical significance of low-grade cervical cytology still remains unclear.^[4] The introduction of HPV DNA partially eliminated this obscurity and increased the efficacy of screening.^[5] Currently, more than 200 HPV types have been identified 51 of which are known to infect mucosal cells. These types include 14 high risk types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), 6 possibly high risk types (HPV26, 53, 67, 70, 73, and 82) and 31 low risk HPV types (HPV6, 7, 11, 13, 30, 32, 34, 40, 42, 43, 44, 54, 61, 62, 69, 71, 72, 74, 81, 83, 84, 85, 86, 87, 89, 90, 91, 97, 102, 106, and 114).^[6] Amongst these HPV 16 and 18 are the types that make the greatest increase in the risk of progression to malignancy and are responsible for approximately 70% of cervical cancers.^[7] These two HPV types are targeted, not exceptionally, by all HPV vaccines produced. New nonavalent HPV vaccine provides protection for additional HPV types (HPV 6, 11, 31, 33, 45, 52, 58)

besides HPV 16 and 18. However, there are still uncovered high-risk HPV types and these types are candidates to be primary concerns in cervical cancer screening as HPV vaccination gets widespread. Women, particularly the young, could be simultaneously infected with more than one of these HPV types.^[8] Nevertheless, the effects of multitype high-risk HPV infection on progression to precancerous lesions are still controversial.

The present study aims to evaluate the association between minor anomalies in cervical cytology and final pathology results in women infected with various HPV types.

MATERIALS AND METHODS

We analyzed data of patients who underwent a colposcopy following HPV DNA positivity or minor cytological changes, including atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL), and tested positive for HPV DNA in a single tertiary center between 2011 and 2019. Institutional review board approval was obtained (61351342/2020-327) for this study. Colposcopic examinations were performed by four different practitioners throughout the selected period. Two to four colposcopic cervical biopsies were taken in each patient from aceto-white areas, atypical vascularization zones or any other colposcopic abnormalities. In the absence of colposcopic abnormalities, 2 to 4 random biopsies were taken at the physicians' discretion. All HPV DNA-positive specimens were underwent HPV genotype analysis. The prevalence of HPV types was assessed. The study population was divided into three groups for further analysis on HPV types. The first group consisted of women infected with either HPV 16 or HPV 18, the second group included women infected with a single high-risk HPV type other than HPV 16 or 18, and the third group included women infected with multiple high-risk HPV types other than HPV 16 and HPV 18. HPV DNA detection was performed using the Hybrid capture 2 test (Qiagen HC2) and genotyping was carried out by CLART kit (Genomica). Specimens were collected by cyto-brush and preserved in Thin-Prep fixative solution (Hologic Inc., Bedford, Mass) and tested for 19 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68a, 68b, 69, and 82)

and 17 low-risk HPV types (6, 11, 30, 32, 40, 42, 43, 44, 54, 55, 62, 70, 72, 81, 84, 90, and 91).

Cytology specimens were classified according to the 2001 Bethesda System. Cervical biopsies were classified according to the World Health Organization classification.

Statistical analysis

Data were analyzed by the IBM Statistical Package for Social Sciences (SPSS) version 23 (London, UK). Descriptive statistics were expressed in mean±standard deviations for normally distributed data and median (min-max) for non-normally distributed data. The significance of the differences was assessed with the ANOVA test among groups. Categorical variables were evaluated with Pearson chi-square test and Fisher's exact test. P<0.05 value is considered significant.

RESULTS

A total of 598 cervical biopsies were carried out and they were taken within the selected period, and 430 of them had positive HPV DNA tests. The mean age of the population was 33.4±6.6 and the mean parity was 2.1±1.1. Of these 430 HPV positive biopsies, 198 were diagnosed with CIN 1, 62 were found to be CIN 2 or CIN 3 (≥CIN 2) and 147 biopsies were negative. Cytology studies of these subjects revealed that of these 430 women biopsied, 216 had atypical squamous cells of undetermined significance (ASC-US), 201 had low-grade squamous intraepithelial lesion (LSIL) and 13 had negative cytology. HPV genotype analysis was performed for all HPV DNA-positive subjects. One-hundred-ninety-seven of were found to be infected with multiple types of HPV and 233 with a single HPV type. The most common HPV type in study population was HPV 16 (133/430, 30.9%), followed by HPV 51 (64/430, 14.8%), HPV 18 (52/430, 12.9%) and HPV 39 (48/430, 11.1%). The prevalence of HPV types among the study population is shown in Table 1.

The total number of ASC-US cytology results was 216. In ASC-US cytology, 9% (24/77) of patients infected with HPV 16 or 18 were revealed to have negative biopsy results, 59.7% (46/77) had CIN 1 and 9% (7/77) had ≥CIN

Table 1. Frequency of HPV types among study population

| HPV type | Number (%) | HPV type | Number (%) | HPV type | Number (%) | HPV type | Number (%) |
|----------|------------|----------|------------|----------|------------|----------|------------|
| HPV 16 | 133 (30.9) | HPV 45 | 25 (5.8) | HPV 73 | 8 (1.8) | HPV 42 | 2(0.4%) |
| HPV 51 | 64 (14.8) | HPV 6 | 22 (5.1) | HPV 11 | 6 (1.4) | HPV 86 | 2(0.4%) |
| HPV 18 | 52 (12) | HPV 59 | 20 (4.6) | HPV 62 | 5 (1.1) | HPV 26 | 1(0.2%) |
| HPV 39 | 48 (11.1) | HPV 58 | 20 (4.6) | HPV 61 | 5 (1.1) | HPV 36 | 1(0.2%) |
| HPV 53 | 45 (10.4) | HPV 68 | 17 (3.9) | HPV 40 | 4 (0.9) | HPV 58 | 1(0.2%) |
| HPV 31 | 43 (10) | HPV 66 | 15 (3.4) | HPV 34 | 3 (0.7) | HPV 64 | 1(0.2%) |
| HPV 56 | 40 (9.3) | HPV 44 | 14 (3.2) | HPV 56 | 2 (0.4) | HPV 41 | 1(0.2%) |
| HPV 52 | 36 (8.3) | HPV 33 | 13 (3) | HPV 83 | 2 (0.4) | HPV 54 | 1(0.2%) |
| HPV 35 | 31 (7.2) | HPV 82 | 8 (1.8) | HPV 38 | 2 (0.4) | | |

Table 2. Association of HPV types and pathology results in study population

| Cytology result | Pathology result | HPV 16/18 | Single type HPV excluding HPV 16/18 | Multiple type HPV excluding HPV 16/18 | Total number |
|-------------------|------------------|-------------------------|-------------------------------------|---------------------------------------|--------------|
| Negative cytology | Negative bx | 5 | 3 | 0 | 8 |
| | CIN I | 3 | 1 | 1 | 5 |
| | ≥CIN 2 | 0 | 0 | 0 | 0 |
| | Total number | 8 | 4 | 1 | 13 |
| ASC-US | Negative bx | 24 (25.2%) | 52 (54.7%) | 19 (20%) | 95 |
| | CIN I | 46 (47.4%) | 22 (22.7%) | 29 (29.9%) | 97 |
| | ≥CIN 2 | 7 (29.1%) | 8 (33.3%) | 9 (37.5%) | 24 |
| | Total | 77 (35.6%) | 82 (38%) | 57 (26.4%) | 216 (100%) |
| LSIL | Negative bx | 14 (26.9%) | 21 (40.4%) | 17 (32.7%) | 52 |
| | CIN I | 22 (42.3%) | 56 (50.5%) | 34 (30.6%) | 111 |
| | ≥CIN 2 | 17 (32.6%) | 9 (23.7%) | 12 (31.6%) | 38 |
| | Total | 52 | 86 | 63 | 201 (100%) |
| Total population | Negative bx | 39 (29.5%) | 80 (45.5%) | 36 (29.6%) | 155 |
| | CIN I | 69 (52.2%) | 79 (44.9%) | 65 (53.3%) | 213 |
| | ≥CIN 2 | 24 (18.1%) ^b | 17 (9.7%) ^a | 21 (17.2%) ^b | 62 |
| | Total | 132 | 176 | 122 | 430 (100%) |

^aPrevalence of single type infection excluding HPV 16/18 is significantly lower in comparison to HPV16/18 infection and multiple type HPV infection excluding HPV16/18 ($p=0.034$). ^bPrevalence of HPV 16/18 infection is not significantly different from multiple type HPV infection excluding HPV16/18 ($p=0.259$)

2 lesions. Eighty-two patients were infected with single a high-risk HPV other than HPV 16 or 18, of which 63.4% (52/82) had negative cytology, 26.8% (22/82) had CIN I, and 9.8% (8/82) had ≥CIN 2 lesions. Fifty-seven patients were found to be infected with multiple high-risk HPV other than HPV 16 or 18, 33% (19/57) of their biopsy results were negative, 50.9% (29/57) of them was found to have CIN I and 15.8% (9/57) of them was found to have ≥CIN 2 biopsy results.

The total number of LSIL cytology results was 201. Among these LSIL cytologies, 26.9% (14/52) of patients infected with HPV 16 or 18 were found to have negative biopsies, 40.3% (21/52) had CIN I and 32.6% had (17/52) ≥CIN 2 lesions. Among the patients infected with a single high-risk HPV other than HPV 16 or 18, 24.4% (21/86) had negative biopsies, 65.1% (56/86) had CIN I and 10.5% (9/86) had ≥CIN 2 lesions. Sixty-three patients were found to be infected with multiple high-risk HPV types other than HPV 16 and 18, 27% (17/63) of which had negative biopsy results, 54% (34/63) had CIN I, and 19% (12/63) had ≥CIN 2 lesions.

In the total study population, 29.5% (39/132) of patients infected with HPV 16 or 18 had negative biopsy results, 52.2% (69/132) had CIN I and 18.1% (24/132) had ≥CIN 2 lesions. 45.5% (80/176) of patients infected with single high-risk HPV other than HPV 16 or 18 were found to have negative biopsies, 44.9% (79/176) of them had CIN I lesions and 9.7% (17/176) had ≥CIN 2. Of the patients infected with multiple HPV types other than HPV 16 or

18, 29.6% (36/122) were found to have negative biopsy results, 53.3% (65/122) had CIN I and 17.2% (21/122) had ≥CIN 2 lesions.

The distribution of HPV type groups within biopsy results was given in Table 2. The rates of infection with HPV 16 or 18 and infection with multiple other high-risk HPV types were similar in the overall study population. However, the rate of infection with a single high-risk HPV other than HPV 16 or 18, was found to be significantly lower than the other two groups ($p=0.034$).

DISCUSSION

Cytology based screening has dramatically reduced cervical cancer rates since first described by Papanikolaou. However, studies indicate cervical cancer incidence reached a plateau despite the widespread implementation of cytologic screening.^[3] Contemporarily, HPV DNA is introduced to screening suggestions in order to further reduce the incidence of cervical cancer.^[9] To date, 14 high-risk HPV types have been identified, with one one which persistent infection leads to development of cancer. Of these types, HPV 16 and 18 constitute 70% of the cases.^[7] HPV-based screening has been shown to be %60 more efficient in preventing cervical cancer compared to cytology-based screening alone, and HPV DNA is recommended for primary cervical cancer screening.^[5,10] Attempts to properly classify screened women according to HPV types are still ongoing.^[11] Co-infection with multiple HPV types usually occur in young women.^[8] Studies on the association of

multiple HPV types and pre-invasive cervical lesions have conflicting results in literature. Some of these studies showed similar rates of pre-invasive lesion development in women infected with multiple HPV types in comparison to a single HPV type, whereas others indicate a higher risk in multi-type HPV infection.^[12,13]

Several types of assays are used to detect HPV in clinical settings. Some of the U.S. Food and Drug Administration (FDA) approved assays are hybrid capture 2 (HC2), Cervista HPV test and Roche Cobas 4800 HPV test that detects HPV DNA, and RNA-based Aptima HPV assay that detects E6/E7 protein mRNA.^[14,15] Studies indicate that the choice of test used to detect HPV infection might slightly affect the rate of HPV positivity. Several studies showed that hrHPV prevalence varies between 3.6% and 16.2% in separate populations with different tests and methodologies.^[14,16–19] In a study conducted by Huijsmans et al.^[14] hrHPV detection rates of HC2, Cobas, and Aptima tests were compared. The prevalence of hrHPV positive results by HC2, Cobas, and Aptima were found as 8.5%, 8.1%, and 7.5% respectively. Although the Kappa coefficients indicate substantial agreements among the tests, the rate of hrHPV detection of HC2 was found to be significantly higher than the Aptima test. Studies also indicate that hrHPV detection rates of Cervista were also similar to the HC2 test.^[15] In our study, we evaluated the results obtained by one of the most widely studied HPV tests among the FDA-approved tests mentioned before, HC2. However, the use of different diagnostic modalities to detect HPV might lead to slight discrepancies among studies, and this factor should be taken into account in assessing different studies. The frequency of HPV types varies geographically. Comprehensive studies define the most common types worldwide as HPV 16 and 18.^[20] Following these two types, HPV type 31 seems to be more frequent in Europe and Latin America, whereas HPV type 52 prevalence is higher in North America and Asia.^[21] Gultekin et al.^[22] demonstrated that the most common HPV types in Turkey are HPV 16, 51, 31, 52, and 18 and this distribution appears to represent a mixture of the most common types seen in Europe, Asia, and Africa. In parallel with this study, we found that the most common HPV types are 16, 51, 18, 39, 53, and 31. Our study population was derived from the province of Istanbul. Connecting Europe to Asia, Istanbul is one of the world's most populous metropolises, attracting large numbers of national and international visitors, migrants, workers, and students. These unique features of the region might have contributed to the different frequencies of HPV types compared to other national or regional studies. As HPV vaccination rates increase, HPV types not covered by vaccines and their management may be of greater concern in the near future. In our study population, HPV type 51, which is not covered by any currently available vaccine, was found to be the second most common HPV type and HPV 39 as the fourth most common HPV type in women with low-grade cytological abnormalities followed by a colposcopic biopsy.

In a previous study, Vintermyr et al.^[23] showed that ASC-US and LSIL cytology with HPV16 infection and multiple HPV-type infections other than HPV 16 or 18 carry a similar CIN 2 progression risk, and Spinillo et al.^[24] demonstrated that multiple type HPV infections are a significant risk factor for progression to \geq CIN 2 lesions. Supporting these findings, we found a comparable prevalence of multiple type HPV infection except for HPV 16 and 18 and HPV 16 or 18 infection within \geq CIN 2, but a significantly lower prevalence of single HPV type infection other than HPV 16 or 18. In a recent study, a high HPV viral load was found to be associated with CIN 2 progression.^[25] The high frequency of multiple type HPV infection in \geq CIN 2 lesions in our study may represent a cumulative result of oncogenic effects of HPV, the inadequacy of immune response to suppress the infection, and the resulting high viral load. Nevertheless, multiple type HPV infections in low-grade cytology results even in the absence of HPV 16 or 18 seem to deserve a cautious approach.

Ethics Committee Approval

This study approved by the Üsküdar University Non-Interventional Research Ethics Committee (Date: 30.06.2020, Decision No: 61351342/2020-327).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: F.T.; Design: A.K.; Supervision: F.T.; Fundings: A.K.; Materials: F.T.; Data: F.T.; Analysis: A.K.; Literature search: A.K.; Writing: A.K.; Critical revision: F.T.

Conflict of Interest

None declared.

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Minör Servikal Sitolojik Değişikliklerin Servikal Biyopsi Patoloji Sonuçlarıyla İlişkinin HPV Alt Tipleri Dahilinde İncelenmesi

Amaç: Persistan human papillomavirus (HPV) enfeksiyonları serviks kanserinin başta gelen sebebidir. Günümüzde HPV DNA çalışmalarının da dahil edildiği tarama programları sayesinde serviks kanseri insidansında ciddi azalmalar görülmektedir. Ancak tarama programlarının daha da geliştirilmesi için çalışmalar devam etmektedir. Bu çalışmada minor servikal sitolojik anormallikler ile nihai servikal biyopsi sonuçlarının HPV alt tiplerine göre incelenmesi amaçlanmıştır.

Gereç ve Yöntem: 2011–2019 yılları arasında üçüncü basamak bir merkezde HPV DNA pozitifliği veya minor servikal bozukluklar nedeniyle servikal biyopsi alınan hastalar geriye dönük olarak incelenmiştir. Hastalar saptanan HPV alttiplerine göre üç gruba ayrılmıştır. Birinci grupta HPV16/18 ile enfekte olan hastalar, ikinci grupta HPV16/18 dışında tek bir yüksek riskli HPV alttipi ile enfekte olan hastalar, üçüncü grupta HPV16/18 dışında birden fazla sayıda yüksek riskli HPV alttipi ile enfekte olunan hastalar alınmış ve sonuçlar karşılaştırılmıştır.

Bulgular: Seçilen çalışma döneminde çalışma kriterlerini karşılayan 430 hasta olduğu saptanarak çalışmaya dahil edilmiştir. Çalışma grubunun ortalama yaşı 33.4 ± 6.6 , ortalama paritesi 2.1 ± 1.1 olarak saptanmıştır. Birinci ve 3. gruplarda \geq CIN 2 servikal lezyon görülme oranlarının benzer olduğu ancak HPV16/18 dışında tek yüksek riskli HPV tipi ile enfekte olan hastalarda \geq CIN 2 lezyon görülme oranlarının anlamlı ölçüde daha düşük olduğu görülmüştür.

Sonuç: Servikal sitolojisinde minor değişiklikler olan hastalarda HPV16/18 dışında kalan yüksek riskli HPV tiplerinin eş zamanlı çoklu enfeksiyonu dikkatli inceleme gerektiren bir durum gibi görünmektedir.

Anahtar Sözcükler: ASC-US; human papilloma virus; LSIL; serviks kanseri taraması.