# Effect of Pap Smear Cytology, HPV Genotyping on the Concordance of Colposcopy and Conization Results

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## ABSTRACT

**Objective:** To evaluate the conization results performed due to human papillomavirus (HPV), smear, colposcopy results or clinician's decision and determine the factors that predict ≥CIN2.

**Study Design:** Retrospective comparative study.

**Place and Duration of the Study:** Department of Gynaecology and Obstetrics, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, between January 2011 and December 2021.

**Methodology**: Women with known HPV results who underwent conization in the Gynaecology clinic were retrospectively included. Age, HPV genotypes, conization, and colposcopy results of the patients were recorded. Patients were divided into two groups as those with and without ≥CIN2 and compared in terms of clinicopathological features.

**Results:** Four hundred and twenty eight (82.8%) of the 517 patients were premenopausal and perimenopausal, and 89 (17.2%) of the patients with a median age of 42 years (range: 30-65 years) were postmenopausal. While 374 were HPV 16/18 positive, 143 were non-16/18 HPV positive. Conization result was normal in 202 (39.1%) patients, CIN1 in 129 (25.0%) patients, and CIN 2-3 in 186 (36.0%) patients. In the HPV 16/18 positive group, conization result was normal in 38.2% of patients, CIN1 in 20.9%, and CIN 2-3 in 40.9%; these rates were 41.3%, 35.7%, and 23.1% in the HPV-other group, respectively ($p < 0.001$). In the logistic regression model, age, HPV type (16/18), and smear cytology results (≥ASC-US) were tested as independent factors predicting ≥CIN2.

**Conclusion:** HPV 16/18 positivity and smear cytology result (≥ASC-US) were the factors predicting ≥CIN2. Smear and HPV genotyping can make an important contribution to detecting false <NIC2 results as a result of colposcopy.

**Key Words:** *CIN, Colposcopy, Conization, Cervix, Cervical cancer, Neoplasia, HPV.*

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## INTRODUCTION

Cervical cancer is the most common gynaecological cancer. Almost all of cervical cancer is associated with human papillomavirus (HPV).[1] With the availability of an effective HPV vaccine, the incidence of cervical cancer has decreased in the recent years.[2] However, HPV has not yet entered the routine vaccination programme due to its cost in under-developed countries.[3] Therefore, an early diagnosis of pre-invasive lesions (cervical intraepithelial neoplasia, CIN) that may pose a risk for cervical cancer is still crucial. Historically, cytological evaluation was performed with Pap-smear for screening and treatment decisions of premalignant lesions.[4] After revealing the relationship between HPV and cervical cancer, HPV became a critical test for screening pre-invasive lesions.[5] Today, there are numerous screening triages in which HPV and smear tests are evaluated together in cervical cancer screening.[5]

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Among the strains of HPV, 16 and 18 pose a high risk for cervical cancer. On the other hand, there are strains other than HPV 16 and 18 that are oncogenic for cervical cancer (HPV 31, 33, 35, 39, etc.).[6] HPV strains can show heterogeneity between countries. In Turkey, women between 30 to 65 years are included in the cervical cancer screening program.[5] Pap-smear and HPV samples taken simultaneously from women by primary care clinicians are evaluated in two central laboratories.[7] Patients with HPV type 16/18 positivity or other HPV positivity with abnormal Pap-smear results are referred to colposcopy for further evaluation in Turkey (Turkish triage).[7] Further examination is planned according to the colposcopy results of the patients. Since colposcopy is a procedure that requires experience, a colposcopy cannot be performed sufficiently in some centres in Turkey. Diagnostic or therapeutic conization can be applied according to cytology and HPV results, especially in patients with insufficient colposcopies. Colposcopy can be performed with different indications, apart from the patients who are found to be at a risk in the cervical cancer screening.[8] Abnormal cervical findings and post--coital bleeding noticed during the examination are other colposcopy indications.[8]

Since the conversion rates of CIN1 detected to CIN3 and cervical cancer are low, a conservative approach is recommended for this group of patients.[9] On the other hand, CIN3 has a high risk of

conversion to cervical cancer, so its treatment is recommended.[9] It has been reported in the literature that approximately 50-61% of CIN2s regress spontaneously, and 10-18% of them progress to CIN3 or cervical cancer.[9] Although it is not clear which factors predict the progression of CIN2s, it has been suggested that HPV 16 and HSIL cytology may be predictors.[10] Due to these uncertainties, there is no clear consensus on the management of CIN2.

This study aimed to evaluate the conization results performed due to HPV, smear, colposcopy results or clinician's decision and determine the factors that predict ≥CIN2. In addition, it aimed to determine the factors that may predict patients who were reported as false <CIN2 according to colposcopy.

## METHODOLOGY

Patients who underwent conization between January 2011 and December 2021, in the Department of Gynaecology and Obstetrics, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, were retrospectively scanned. Five hundred and seventeen women with known HPV results were included in the study. Being 18 years or older and conization for any reason were the inclusion criteria. Those without smear and HPV test results were excluded from the study.

HPV and smear evaluations of the patients were made in the central laboratories determined by the Turkish Ministry of Health. Smear results were classified as inadequate sampling/ASC-US/ASC-H/LSIL/HSIL/AGC/Others according to Bethesda classification.[11] A ≥ASC-US was evaluated as an abnormal cytology result. In the Turkish triage, those with HPV 16/18 or HPV non-16/18 and abnormal smear cytology are referred to colposcopy.[7]

Colposcopic examinations were performed with the Olympus colposcopy device with a green filter, capable of 40 magnification. After washing the cervix with saline during colposcopy, it was scanned at low magnification and investigated vascular pathologies with a green filter, then 3-5% acetic acid was applied and after waiting for 30-60 seconds, the cervix was scanned at small and large magnifications. Aceto-white areas and vascular pathologies were detected with the green filter. Punch biopsy was taken from the areas of acetowhite, mosaic, punctuation, erosion, leukoplakia, and atypical vascularisation. In patients whose pathological appearance could not be detected, control biopsy was taken from 4 quadrants (12, 3, 6, and 9 o'clock).

According to the conization results, the patients were divided into two groups (≥CIN2, n:186 and <CIN2, n:331). The groups were compared according to patients' age, menopausal status, smear cytology, colposcopy results, and HPV genotyping. In addition, factors that could predict ≥CIN2 were determined. Positive predictive values for ≥CIN2 of triage scenarios were investigated. The factors affecting the ≥CIN2 ratio differences between colposcopy and conization results were evaluated.

In presenting the descriptive statistics of the study, continuous variables were given as median (interquartile range), and categorical variables were given as frequency (%). Kolmogorov-Smirnov test was used to evaluate the normality of the data. Mann-Whitney U test was used to compare nonparametric data, and the Chi-square test was used to compare categorical data. A binary logistic regression model was created to detect independent factors predicting ≥CIN2. All statistical tests were performed in two ways, and a p-value of <0.05 was considered statistically significant. Statistical analyses of the study were evaluated by SPSS version 25.0.

## RESULTS

A total of 517 patients were included in the study. Majority (n=428, 82.8%) were pre-or perimenopausal and 17.2% (n=89) of the patients with a median age of 42 years (range: 30-65 years) were postmenopausal. Three hundred and seventy four (72.3%) were HPV 16 and/or 18 positive, and 143 (27.7%) were non-16/18 HPV positive.

There were 242 patients in the HPV 16/18 group with known smear cytology results. The results of the patients were reported as unsatisfactory in 3.3%, normal in 45.9%, ASC-US in 15.7%, ASCH in 5.0%, LSIL in 16.9%, HSIL in 12.4%, and AGC in 0.8%. In the HPV-other group, 102 patients had smear cytology: unsatisfactory in 1.0%, normal in 52.9%, ASC-US in 15.7%, ASCH in 3.9%, LSIL in 17.6%, HSIL in 6.9%, and AGC in 2.0%. The rates of ≥ASC-US in the HPV 16/18 group and the HPV-other group were similar (50.8% vs. 46.1%, p=0.421) as shown in Figure 1.

LEEP/conization was performed in 53 (14.2%) HPV 16/18 positive patients without colposcopy. Of the 321 patients who underwent colposcopy, 25 (7.8%) had normal results, 139 (43.3%) had CIN1, 111 (34.6%) had CIN2-3, 46 (14.3%) were inadequate. LEEP/conization was performed without colposcopy in 19 patients in the HPV–other group. Of 124 patients who underwent colposcopy, 16 (12.9%) results were normal, 60 (48.5%) had CIN1, 24 (19.3%) had CIN2-3, 24 (19.3%) were inadequate. The proportion of patients with a colposcopy result ≥CIN2 was 34.6% in the HPV 16/18 group and 19.4% in the HPV–other group (p=0.002, Figure 1).

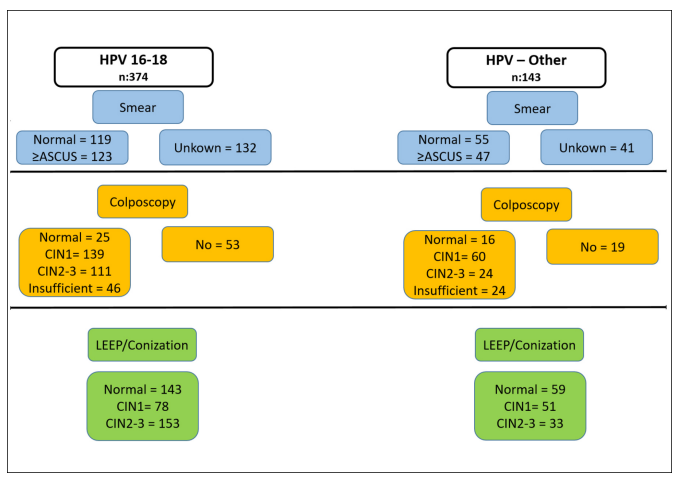


**Figure 1: Smear, colposcopy, LEEP/conization results of the patients.**

**Table I: Cone biopsy results of patients according to different triage scenarios and positive predictive values (PPV, %).**

| | n | Normal | CIN1 | ≥CIN2 | PPV % ≥CIN2 |
|---|---|---|---|---|---|
| Any HPV (%) | 517 (100) | 202 (39.1) | 129 (25.0) | 186 (35.9) | 35.9 |
| HPV 16/18 (%) | 374 (100) | 143 (38.3) | 78 (20.8) | 153 (40.9) | 40.9 |
| HPV non 16/18 (%) | 143 (100) | 59 (41.2) | 51 (35.7) | 33 (23.1) | 23.1 |
| Any HPV + Smear triage | | | | | |
| ≥ ASC-US (%) | 170 (100) | 63 (37.1) | 33 (19.4) | 74 (43.5) | 43.5 |
| ≥ LSIL (%) | 100 (100) | 35 (35.0) | 21 (21.0) | 44 (44.0) | 44.0 |
| ≥ HSIL (%) | 41 (100) | 11 (26.9) | 4 (9.7) | 26 (63.4) | 63.4 |
| HPV 16/18 and/or other HPV + abnormal smear ≥ ASC-US (Turkish triage) (%) | 421 (100) | 163 (38.7) | 93 (22.1) | 165 (39.2) | 39.2 |
| HPV 16/18 + abnormal smear ≥ ASC-US (%) | 123 (100) | 43 (35.0) | 18 (14.6) | 62 (50.4) | 50.4 |

*CIN: Cervical intraepithelial neoplasia, PPV: Positive predictive value, HPV: Human papillomavirus, ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion.*

**Table II: Comparison of patients with and without CIN2 lesions according to cone biopsy.**

| | ≥CIN1 n = 331 | ≥CIN2 n = 186 | p-value* |
|---|---|---|---|
| Age, median, year (IQR) | 43 (38-49) | 39 (34-44) | <0.001 |
| Age, categorical n (%) | | | |
| <45 | 185 (55.9) | 143 (76.9) | <0.001 |
| ≥45 | 146 (44.1) | 43 (23.1) | |
| Menopausal status, n (%) | | | |
| Premenopausal/Perimenopausal | 265 (80.1) | 163 (87.6) | 0.029 |
| Postmenopausal | 66 (19.9) | 23 (12.4) | |
| Smear cytology, n (%) ** | | | |
| | 136 (58.6) | 38 (33.9) | <0.001 |
| ≥ASC-US | 96 (41.4) | 74 (66.1) | |
| HPV type, n (%) | | | |
| 16/18 | 221 (66.8) | 153 (82.3) | <0.001 |
| Other | 110 (33.2) | 33 (17.7) | |
| Colposcopy, n (%) | | | |
| Yes | 259 (78.2) | 186 (100) | <0.001 |
| No | 72 (21.8) | 0 (0) | |

*CIN: Cervical intraepithelial neoplasia, IQR: Interquartile range, HPV: Human papillomavirus, ASC-US: Atypical squamous cells of undetermined significance, *Mann-Whitney U and Chi-square tests were used. **A total of 344 patients whose smear results are known.*

**Table III: Multivariate analyses for predictive factors of ≥CIN2 lesions detected by cone biopsy.**

| | All patients n = 517 | | Patients with n = 310 | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age, <45 | 2.297 (1.154-4.570) | 0.018 | 1.695 (0.832-3.455) | 0.146 |
| Menopausal status | 1.489 (0.633-3.505) | 0.362 | - | - |
| HPV type, 16/18 | 2.629 (1.470-4.699) | 0.001 | 3.273 (1.432-7.479) | 0.005 |
| Smear cytology, ≥ASC-US | 2.662 (1.640-4.320) | <0.001 | 1.787 (0.921-3.467) | 0.086 |

*CIN: Cervical intraepithelial neoplasia, OR: Odds ratio, CI: Confidence interval, HPV: Human papillomavirus, ASC-US: Atypical squamous cells of undetermined significance.*

Conization/LEEP was performed in all patients. Conization result was normal in 202 (39.1%) patients, CIN1 in 129 (25.0%) patients, and CIN 2-3 in 186 (36.0) patients. In HPV 16/18 positive group, conization pathology result was normal in 38.2% of patients, CIN1 in 20.9%, and CIN 2-3 in 40.9%, while these rates were 41.3%, 35.7%, and 23.1% in the HPV-other group, respectively (p <0.001). The rate of ≥CIN2 was higher in the HPV 16/18 group compared to the HPV-other group (40.9% vs. 23.1%, p <0.001, Figure 1).

Of the 72 patients who had conization without colposcopy (because of vaginal bleeding), 50 (70.4%) had normal results, 22 (30.6%) had CIN1 and there was no patient with ≥CIN2. When the LEEP/conization histopathologies of the entire patient group were evaluated, the rate of ≥CIN2 was significantly higher in those who underwent colposcopy compared to those who did not (41.8% *vs.* 0%, p <0.001, Figure 1).

Triage scenarios were done according to the HPV and smear results of the patients. The triage scenario with the highest positive predictive value was smear ≥HSIL and any HPV positivity (PPR: 63.4%, Table I).

The clinical features, HPV, and smear results of the patients were compared in <CIN2 (Group A) and ≥CIN2 (Group B) groups formed according to the conization result. Group A

had a higher median age than Group B (43 vs. 39, p <0.001). The rate of postmenopausal patients was higher in Group A than in B (19.7% vs. 12.8%, p=0.029). While the rate of smear result ≥ASC-US was 41.1% in Group A, it was 66.4% in Group B (p <0.001). The rate of HPV 16/18 positive patients in Group B was significantly higher than in Group A (82.4% vs. 66.7%, p <0.001). While the rate of colposcopy was 100% in Group B, it was 78.2% in Group A (p <0.001, Table II).

As a result of the logistic regression model created with age, menopausal status, HPV type, and smear cytology variables, age, HPV type, and smear cytology results were tested as independent factors predicting ≥CIN2 (Table III).

The conization result was ≥CIN2 in 79 (25.5%) of 310 women whose colposcopy results were <CIN2. In this subgroup, ≥CIN2 lesion rates were higher in the young compared to the elderly (31.3% vs. 16.1%, p=0.003). While the rate of ≥CIN2 was 29.3% in those with ≥ASC-US smear results, whereas it was 17.7% in those without such results (p=0.044). The rate of ≥CIN2 was higher in those who were HPV 16/18 positive compared to those who were not (30.0% vs. 16.0%, p=0.008). No relationship was found between menopausal status and ≥CIN2 (p=0.303). HPV 16/18 positivity was the only independent predictive factor that could detect ≥CIN2 lesion in patients whose colposcopy result was false <CIN2 (Table III).

The ≥CIN2 ratio was significantly lower in the elderly group compared to the young. In the elderly group,≥CIN2 was higher in HPV 16/18 positive patients than negative patients (28.9% vs. 9.8%, p=0.003). In the HPV-other group, ≥CIN2 was significantly higher in young patients compared to the elderly (32.9% vs. 9.8%, p=0.001). In the same patient group, the rate of ≥CIN2 was 25.5% in those with smear cytology results ≥ASC-US, while it was 12.7% in those with <ASC-US (p=0.098).

## DISCUSSION

In this study, patients' age, HPV genotyping, and smear cytology results were predictive factors of ≥CIN2 lesions detected by conization, independent of colposcopy results. In addition, it was observed that approximately one-fourth of the patients had false <CIN2 as a result of colposcopy. It has been shown that the presence of HPV 16/18 in patients with false <CIN2 as a result of colposcopy can predict ≥CIN2.

It is known that HPV 16 and 18 are among the important risk factors for cervical cancer.[12] Studies have shown that HPV 16 positivity may also be a risk factor for the progression of CIN2.[10,13,14] Reflex triage is applied in Turkey for cervical cancer screening. In this triage application, an advanced examination and treatment of the patients were planned according to the results of smear cytology in those with HPV non-16/18.[5,7] In this study, both HPV 16/18 and smear cytology result ≥ASC-US were independent factors predicting ≥CIN2 supported the importance of reflex triage. In a study in which the results of approximately 4 million women were evaluated in the national screening programme conducted in Turkey, the PPV for ≥CIN2 was 18.8% in any HPV positivity, 27.3% in HPV 16/18 positivity, 24.3% in the Turkish triage (HPV 16/18 or non-16/18 + abnormal smear ≥ASC-US).[5] In the present study, the PPV was 35.9% in any HPV positivity, 40.9% in HPV 16/18 positivity, 23.1% in HPV non-16/18 positivity, and 39.1% in Turkish triage. The higher detection of PPVs in this study compared to the screening programme was associated with the inclusion of patients with various symptoms. On the other hand, the fact that the PPV of the Turkish triage was higher compared to HPV non-16/18 supported the results of the Turkish national screening programme.

In a study conducted in Italy, which included 1186 women, ≥CIN2 was significantly lower in those older than 41 years.[15] In the same study, as a result of multivariate analysis, the age of patient was an independent predictive factor for ≥CIN2.[15] A Japanese study showed that among women with cytology HSIL, ≥CIN2 was lower in the elderly (>50 years) women than in the young.[16] However, HPV was not evaluated in that study.[16] In this study, ≥CIN2 was significantly lower in the elderly than in the young. On the other hand, ≥CIN2 in the elderly patients included in this study was significantly higher in HPV 16/18 positive patients than in those HPV non-16/18. This result show the need to be more careful in HPV 16/18 positive elderly patients, although it was known that CIN2 lesions are less likely to progress to cancer in a 40-year-old.[13,17,18]

Conization without colposcopy does not seem appropriate, as it may cause obstetric complications in young women. In this study, the fact that ≥CIN2 lesion was not detected in any of the women without colposcopy supported this claim. A clinician's experience is crucial in colposcopic evaluation. For example, several real-life studies of Swedescore, developed by colposcopic assessment for prediction ≥CIN2 lesions, have not been as successful as the original study.[19] This result was thought to be related to the experience of colposcopists.[19] This suggests that colposcopic evaluation alone may not be sufficient to detect ≥CIN2 lesions. In a study conducted in Australia, the authors stated that 18% of women, whose smear cytology was HSIL and <CIN2 was detected in colposcopy, had ≥CIN2 lesions in their subsequent colposcopies or conizations.[20] In the present study, approximately one-fourth of the women with a colposcopy result of <CIN2 had a conization result of ≥CIN2. The rate of ≥CIN2 lesions was higher in patients with smear cytology ≥ASC-US and HPV 16/18 positive.

This study had some limitations too. Although HPV vaccination was not included in the routine programme in Turkey, there was a possibility that some of the women included in this study had HPV vaccination. The smear result of a signifi-

cant part of patients could not be reached. In addition, conization was performed in approximately 14% of the patients without colposcopy. Although this situation seems wrong, it is a fact that many centres and clinicians are insufficient in smear evaluations and colposcopies. Another limitation is that the authors could not obtain data on why this procedure was performed on patients who underwent conization without colposcopy.

## CONCLUSION

HPV 16/18 positivity and smear cytology result (≥ASC-US) were the factors predicting ≥CIN2. Smear and HPV genotyping can make an important contribution to detect false <CIN2 results as a result of colposcopy.

### ETHICAL APPROVAL:

The study was approved by the Ethical Committee of the University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey.

### PATIENTS' CONSENT:

Due to the retrospective nature of the study and the use of stored and de-identified samples, patients' consent was not required.

### COMPETING INTEREST:

The authors declared no competing interest.

### AUTHORS' CONTRIBUTION:

HS, FA: Substantial contribution to conception and design, acquisition of data, interpretation of data, and drafting and revising of the manuscript.

All authors have approved the final version of the manuscript to be published.

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