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The Role of Colposcopy in Women with Normal Cytology and High-risk Human Papilloma Virus Positivity, Except for Types 16 and 18

Normal Sitolojisi Olan ve Tip 16 ve 18 Dışında Yüksek Riskli İnsan Papilloma Virüsü Pozitifliği Olan Kadınlarda Kolposkopinin Rolü

Necim Yalçın, Aysun Alcı, Mustafa Gökkaya, Mehmet Göksu, Tayfun Toptaş, Işın Üreyen

University of Health Sciences Turkey, Antalya Training and Research Hospital, Department of Gynecologic Oncology, Antalya, Turkey

Abstract

Objective: The main objective of present study was to evaluate the role of colposcopy in women with normal cytology and positivity for high risk human papilloma virus (HPV), excluding types 16 and 18.

Method: A retrospective analysis was conducted on a cohort of women who presented to the clinic for colposcopy between January 2018 and December 2023. These women had normal cytology and positivity for high risk HPV, excluding types 16 and 18. The demographic data and colposcopy results were obtained from the patient files and the electronic database of the gynaecological oncology clinic.

Results: A total of 1,646 women underwent colposcopy during the specified period. Four hundred-thirty (26.1%) women exhibited positivity for high risk HPV, excluding types 16 and 18, and normal cytology. A total of 41 patients (9.5%) were found to have cervical intraepithelial neoplasia (CIN)2+ (CIN2, CIN3, or invasive cancer) lesions. Among 41 women with CIN2+ lesions, 22% were found to have multiple infections, 17% had HPV other-x (subgroup could not be obtained), 17% had HPV type 31, and 12% had HPV type 51 positivity. The detection rate of CIN2+ lesions was highest in the group of women with HPV 31 positivity. Cervical biopsy and endocervical biopsy, revealed CIN2+ lesions in 21.7% (n=5/23) and 8.7% (n=2/23) of women with HPV type 31 positivity, respectively.

Conclusion: Women with high-risk HPV (excluding types 16 and 18) and normal cytology have a significantly increased risk of high-grade cervical lesions.

Keywords: Cervical cancer, cervical screening, cervical precancerous lesions, colposcopy, human papilloma virus

Öz

Amaç: Bu çalışmanın ana amacı, sitolojisi normal olan ve tip 16-18 dışı yüksek riskli human papilloma virüs (HPV) pozitifliği olan kadınlarda kolposkopinin rolünü değerlendirmektir.

Yöntem: Ocak 2018 ile Aralık 2023 tarihleri arasında kliniğe kolposkopi için başvuran kadınlardan oluşan bir kohort üzerinde retrospektif bir analiz yapılmıştır. Çalışmaya dahil edilen kadınların sitolojileri normaldi ve tip 16-18 dışı yüksek riskli HPV pozitifliği vardı. Demografik veriler ve kolposkopi sonuçları hasta dosyalarından ve jinekolojik onkoloji kliniğinin elektronik veri tabanından elde edildi.

Bulgular: Belirtilen dönem arasında toplam 1.646 kadına kolposkopi yapılmıştır. Dört yüz otuz (%26,1) kadında tip 16-18 dışı yüksek riskli HPV pozitifliği ve normal sitoloji saptandı. Kırk bir (%9,5) hastada servikal intraepitelyal neoplazi (CIN)2 ve üzeri lezyon saptandı. CIN2 ve üzeri lezyonu olan 41 kadının %22'sinde çoklu enfeksiyon, %17'sinde HPV diğer-x (alt grup elde edilemedi), %17'sinde HPV tip 31 ve %12'sinde HPV tip 51 pozitifliği saptandı. CIN2 ve üzeri lezyonların saptanma oranı HPV 31 pozitifliği olan kadın grubunda en yüksekti. HPV tip 31 pozitifliği olan kadınların sırasıyla %21,7'sinde (n=5/23) ve %8,7'sinde (n=2/23) servikal biyopsi ve endoservikal küretaj materyalinde CIN2 ve üzeri lezyonlar saptanmıştır.

Sonuç: Anormal sitolojisi olmayan ve tip 16-18 dışı yüksek riskli HPV taşıyan kadınlarda, yüksek dereceli servikal preinvaziv lezyon riski belirgin şekilde artmaktadır.

Anahtar kelimeler: İnsan papilloma virüsü, kolposkopi, serviks kanseri, servikal prekanseröz lezyonlar, servikal tarama

Address for Correspondence: Necim Yalçın, University of Health Sciences Turkey, Antalya Training and Research Hospital, Department of Gynecologic Oncology, Antalya, Turkey
E-mail: necimyalcin64@gmail.com **ORCID:** orcid.org/0000-0001-5980-3244
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Introduction

Historically, the understanding of the pathogenesis of cervical cancer has led to the realisation, that the application of appropriate screening methods can facilitate the detection of precancerous lesions, thereby reducing the incidence of cervical cancer with early, appropriate interventions. The discovery of the Papanicolaou (Pap) smear by Dr. George Pap and the subsequent implementation of cervical cytology for cervical cancer screening demonstrated that the incidence of cervical cancer can be reduced. Furthermore, the identification of human papilloma virus (HPV) as a viral infectious agent strongly associated with cervical cancer facilitated the development of highly sensitive HPV screening tests with or without cervical cytology for cervical cancer screening (1).

HPV is a non-enveloped double-stranded DNA virus. To date, approximately 40 distinct HPV types with a proclivity for the anogenital region have been identified. Of these, 15 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are classified as high-risk (HR), three types (26, 53, 66) are considered probable HR, and 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89) are classified as low-risk. HPV16 is associated with 50-60% of cervical cancers, while HPV18 is linked to 10-15%. The remaining HR HPV types are responsible for 25-40% of cervical cancer cases (2,3).

In the context of cervical cancer screening programmes, the majority of HPV tests examine 14 HR HPV genotypes. The combination of HR HPV positivity with cytological results has resulted in the formulation of a number of management guidelines. In this context, the American Society for Colposcopy and Cervical Pathology (ASCCP) published the initially proposed guidelines for the management of abnormal cervical cancer screening results in 2012 and subsequently updated these guidelines in 2019 (4,5). A review of cervical cancer screening programmes at the country level reveals that the majority of cases occur in women with HR HPV positivity and normal cytology results (6-8). In accordance with the aforementioned guidelines for the management of women with HR HPV positivity, the presence of HPV types 16 and 18 with normal cervical cytology necessitates a colposcopic examination. However, in the case of positivity for HR HPV, excluding types 16 and 18 (other HR HPV) and normal cervical cytology, a recommendation is made for retesting after a one-year interval (4,5). Nevertheless, the optimal management of women with positivity for other HR HPV and normal cytology remains a topic of contention.

A screening strategy based on repeated testing for women with positivity for other HR HPV may present a significant challenge due to low participation rates and loss to follow-up. Moreover, some studies have indicated that the risk of developing high-grade cervical lesions in patients with positivity for other HR HPV may be comparable or even higher than that of HPV type 18 (9, 10). Additionally, the false-negative rate of cervical cytology has been reported to be approximately 15-65% (11). This high rate raises questions regarding the follow-up of cases that test positive for other HR HPV and have normal cytology after one year by non-invasive methods, given the possibility of an increased risk for cervical high-grade lesions and cervical cancer.

In order to address these concerns, a retrospective study was conducted to evaluate the role of colposcopy in women with normal cytology and positivity for other HR HPV. Furthermore, the association of positivity for other HR HPV with high-grade cervical lesions was discussed separately.

Materials and Methods

A retrospective analysis was conducted on women who had visited the clinic for colposcopy between January 2018 and December 2023. The cohort comprised women with positivity for other HR HPV and normal cytology. The age range was determined to be from 18 to 80 years. The patients were divided into three groups according to the HPV types: HPV other-x (patients for whom the HPV other subgroup could not be obtained), HPV multiple infection (patients with more than one HPV other subgroup), and HPV 31, HPV 33, etc. (patients positive for a single known HPV other subgroup).

The HPV test employed was Hybrid Capture 2 (Qiagen), which is the reference test routinely utilised in numerous laboratories. In cases where the Hybrid Capture2 (Qiagen) test indicated the presence of HPV, genotyping was conducted using the CLART kit (Genomica). The analysis excluded patients who had undergone hysterectomy, those diagnosed with gynaecological cancer, those younger than 18 years of age, those older than 80 years of age, and for whom colposcopy results were not available. Data on patients who underwent colposcopy in our institution were collected from patient files and the electronic database systems. The demographic data, including age, menopausal status, pathological results of colposcopically directed biopsies, and endocervical curettage (ECC) were obtained. The study was initiated following the approval of the Ethics Committee of the University of Health Sciences Turkey,

Antalya Training and Research Hospital, dated 10 October 2024 and numbered 2024-319. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

The colposcopic examination database was evaluated to ascertain whether the colposcopy was conducted adequately. All colposcopies were conducted by gynaecological oncologists during the specified period. A colposcopic evaluation was conducted subsequent to the administration of a 3% acetic acid solution to the cervix. Cervical biopsies were taken in the presence of lesions suspicious for cervical intraepithelial neoplasia (CIN) on colposcopic examination. Additionally, random biopsies were sometimes taken at the discretion of the colposcopist in the absence of abnormal colposcopic findings. When colposcopy was inadequate, ECC was performed in cases where the cervix was obscured by haemorrhage, inflammation, or scar tissue; when the squamocolumnar junction was not visible or only partially visible; when the transformation zone was type 3; or when the visualised lesion extended into the endocervical canal. Additionally, ECC was performed at the discretion of the colposcopist in the absence of the aforementioned factors. ECC was performed with a Novak curette, whereby the entire endocervical canal was scraped and subsequently processed as a histopathological specimen.

In this manuscript, the pathological results of the specimens, either cervical biopsies or ECC, were assessed in two categories in accordance with the threshold for treatment at our centre: Those below the CIN2 level and those at or above the CIN2 level, including CIN2, CIN3 and invasive cancer (CIN2+).

Statistical Analysis

SPSS version 22.0 was used for the analysis of the data. Descriptive statistics were used. The binary variables were reported as counts and percentages.

Results

A total of 1,646 women underwent colposcopy between the specified period. Of these, 333 (20.2%) women exhibited HPV 16/18 positivity and normal cytology, and 430 (26.1%) women exhibited positivity for other HR HPV and normal cytology. The data set comprised 430 women, obtained from the electronic records of the institution. The analysis was conducted on a total of 430 women. The median age of the cohort was 44 years (range, 30-65 years). Amongst the women whose menopausal status was known, 63% were premenopausal. The distribution of HPV subtypes is presented in Table 1.

The colposcopic findings were reported as normal in 207 women (48.1%), inadequate in 12 women (2.8%), and abnormal in 211 women (49.1%). A total of 41 (9.5%) patients were found to have CIN2+ lesions. Cervical biopsy revealed CIN2+ lesions in 29 women (6.7%), while ECC revealed CIN2+ lesions in 12 women (2.8%) (Tables 2, 3).

Table 1. The distribution of HPV subgroups

HPV type	n	(%)
HPV other-x*	110	25.6
HPV multiple**	125	29.1
HPV 31	23	5.3
HPV 52	31	7.2
HPV 56	22	5.1
HPV 35	16	3.7
HPV 33	7	1.6
HPV 51	36	8.4
HPV 68	12	2.8
HPV 45	14	3.3
HPV 39	11	2.6
HPV 58	18	4.2
HPV 59	5	1.2
Total	430	100

*: Patients whose HPV other subgroup couldn't be obtained, *: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus

Table 2. The distribution of cervical biopsy results with regard to HPV subtypes

	Cervical biopsy, n (%)		
HPV type	Not performed	Negative	CIN2+CIN3
HPV other-x*	65 (59.1)	39 (35.5)	6 (5.5)
HPV multiple**	54 (43.2)	65 (52)	6 (4.8)
HPV 31	8 (34.8)	10 (43.5)	5 (21.7)
HPV 52	10 (32.3)	18 (58.1)	3 (9.7)
HPV 56	11 (50)	9 (40.9)	2 (9.1)
HPV 35	7 (43.8)	8 (50)	1 (6.3)
HPV 33	5 (71.4)	1 (14.3)	1 (14.3)
HPV 51	20 (55.6)	13 (36.1)	3 (8.3)
HPV 68	6 (50)	6 (50)	0 (0)
HPV 45	7 (50)	5 (35.7)	2 (14.3)
HPV 39	6 (54.5)	5 (45.5)	0 (0)
HPV 58	13 (72.2)	5 (27.8)	0 (0)
HPV 59	1 (20)	4 (80)	0 (0)
Total	213 (49.5)	188 (43.7)	29 (6.7)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia

No women presented with invasive cancer. Conization was recommended for 41 women (9.5%) and was performed on 34 women (7.9%).

Tables 2, 3 present the details of the cervical biopsy and ECC results with regard to HPV subtypes. Of the 41 patients with CIN2+ lesions, 22% were found to have multiple infections, 17% had HPV other-x (subgroup could not be obtained), 17% had HPV type 31, and 12% had HPV type 51 positivity. The detection rate of CIN2+ lesions was highest in the group of women with HPV 31 positivity. Cervical biopsy and ECC revealed CIN2+ lesions in 21.7% (n=5/23) and 8.7% (n=2/23) of women with HPV type 31 positivity, respectively (Tables 2, 3). Overall, a CIN2+ lesion was identified in seven (30.4%) of the 23 women with HPV type 31-positive disease.

Conization identified a CIN2+ lesion in 24 (72.7%) of the 34 women who underwent this procedure. The results of conisation according to the HPV subtypes are presented in Table 4.

Table 3. The distribution of ECC results with regard to HPV subtypes

	ECC, n (%)		
HPV type	**Not performed**	**Negative**	**CIN2+CIN3**
HPV other-x*	36 (32.7)	73 (66.4)	1 (0.9)
HPV multiple**	29 (23.2)	91 (72.8)	5 (4)
HPV 31	8 (34.8)	13 (56.5)	2 (8.7)
HPV 52	6 (19.4)	25 (80.6)	0 (0)
HPV 56	5 (22.7)	16 (72.7)	1 (4.5)
HPV 35	2 (12.5)	14 (87.5)	0 (0)
HPV 33	0 (0)	6 (85.7)	1 (14.3)
HPV 51	5 (13.9)	29 (80.6)	2 (5.6)
HPV 68	3 (25)	9 (75)	0 (0)
HPV 45	5 (35.7)	9 (64.3)	0 (0)
HPV 39	5 (45.5)	6 (54.5)	0 (0)
HPV 58	4 (22.2)	14 (77.8)	0 (0)
HPV 59	1 (20)	4 (80)	0 (0)
Total	109 (25.3)	309 (71.9)	12 (2.8)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia, ECC: Endocervical curettage

Discussion

In the present study, CIN2+ lesions were identified in 41 of 430 (9.5%) women with positivity for other HR HPV and normal cervical cytology. Furthermore our study revealed that 17% of women with CIN2+ lesions were HPV type 31 positive, and that CIN2+ lesions developed in 7 (30.4%) of 23 patients with HPV type 31 positivity.

Table 4. Pathology of conisation results according to HPV subgroups

	Pathology of conisation		Total
HPV type	**Negative**	**CIN2+**	
HPV other-x*	2 (28.6%)	5 (71.4%)	7 (100%)
HPV multiple**	2 (33.3%)	4 (66.7%)	6 (100%)
HPV 31	0 (0%)	5 (100%)	5 (100%)
HPV 52	2 (66.7%)	1 (33.3%)	3 (100%)
HPV 56	2 (66.7%)	1 (33.3%)	3 (100%)
HPV 35	0 (0%)	1 (100%)	1 (100%)
HPV 33	0 (0%)	1 (100%)	1 (100%)
HPV 51	0 (0%)	5 (100%)	5 (100%)
HPV 45	1 (50%)	1 (50%)	2 (100%)
Total	9 (27.3%)	24 (72.7%)	33 (100%)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia

In cervical cancer screening programmes, the most frequently observed positive screening results are HR HPV positivity with normal cytology. The rate in the literature ranged from 6.7% to 14.9% (12-15). In settings where colposcopy services are inadequate, referring women with HR HPV positivity, with normal cytology, to colposcopy will present a substantial challenge for healthcare systems. It is therefore of great importance to ensure that women who are to be referred for colposcopy are selected appropriately. In the present study, 20.2% of the women who were referred for colposcopy tested positive for HPV 16/18 and had normal cytology, while 26.1% tested positive for positivity for other HR HPV and had normal cytology. Although a higher proportion was identified in the present study than in previous literature, this was because only women who underwent colposcopy were included. Nevertheless, in the present study, a significant proportion of the total colposcopy load consisted of women with HR HPV positivity and normal cytology, as reported in the literature.

In the 2019 ASCCP guideline on risk-based management of abnormal cervical cancer screening results, the clinical action threshold for colposcopy was set at an immediate CIN3+ risk above 4%. In this guideline, the immediate risks of CIN 2+ and CIN 3+ lesions for women with HPV type 16 positivity and normal cytology are 7.82% and 5.30%, respectively, compared to 5.56% and 3% for women with HPV type 18 positivity and normal cytology, respectively (5). Although the immediate risk of CIN3+ for HPV type

18 positivity and normal cytology remains below the clinical action threshold for colposcopy, there is a rationale for excluding HPV18 as the second most important carcinogenic type. This is because HPV18 is linked to cervical adenocarcinoma, which is not effectively identified by cytology. In the present study, the rate of CIN2+ lesion detection in women with other HR HPV positivity was found to be 9.5%. A review of the literature revealed a considerable range in the reported rate, with figures varying between 5% and 15% (16-19). It is believed that this extensive range can be attributed to the number of patients included in the studies (97 to 1,332 women). However, it is hypothesised that a significant proportion of high-grade cervical lesions may go undetected in women with other HR positivity for HPV, and normal cytology, who do not undergo colposcopic examination.

In April 2014, the US Food and Drug Administration approved the cobas® 4800HPV test as an option for primary screening. This test provides genotyping information for HPV16/18 and also allows the identification of the other 12 high risk HPV types (20). The use of genotyping has enabled the determination of the prevalence of HR HPV genotypes in different geographical regions. The studies investigating the distribution of HR HPV genotypes in women with normal cervical cytology in Asian and African populations found that the five most frequently detected genotypes were 16, 52, 58, 18, and 33, and 16, 58, 52, 35 and 18, respectively (21,22). In the present study, the frequency distribution of the five most common HR positivity types of HPV in individuals with normal cytology was as follows: Multiple infection (29.1%), HPV other-x (genotyping could not be obtained) (25.6%), HPV type 51 (8.4%), HPV type 52 (7.2%), and HPV type 31 (5.3%). The identification of the distribution of oncogenic HR HPV genotypes in different regions highlights the need to develop management guidelines tailored to these variations. We believe this approach is crucial for the effective management of abnormal results from the cervical cancer screening programme, including women who are positive for other HR HPV, with normal cytology.

In the context of the development of precancerous and cancerous lesions, a comprehensive understanding of the geographical distribution of HR HPV genotypes, as well as their oncogenic potential, is of great importance. The prevalence of oncogenic HR HPV genotypes in precancerous and cancerous lesions can be employed as an indicator of oncogenic potential. In the present study, the most frequently identified other HR HPV genotypes in women with normal cytology and CIN2+ lesions were HPV multiple infection (26%), HPV other-x positivity (17%), HPV type 31 (17%) and HPV type 51 (12%), in descending order of prevalence. Furthermore, it is noteworthy that a CIN2+ lesion was identified in seven (30.4%) of the 23 women with HPV type 31-positive disease. The development of high-grade cervical lesions in women who are positive for other HR HPV types and normal cytology has been the subject of only a limited number of studies. However, in the majority of these studies, positivity for other HR HPV was grouped together, and their association with high-grade cervical lesions was subjected to statistical analysis as a single group (16,18,19). In accordance with the findings of the present study, a previous study conducted by Kabaca et al. (17) investigated women with normal cytology and positivity for other HR HPV. HPV type 31 and HPV type 51 positivity were observed in 19.5% and 10.6% of those with CIN2+ lesions, respectively. In studies conducted by Schiffman et al. (23) and Zhang et al. (24) on women with HR HPV infection and normal cytological findings, Schiffman et al. (23) observed that the most common HPV types after HPV type 16 in women with CIN3+ lesions were HPV types 31 and 52, with a frequency of 13.9% and 11.2%, respectively. Similarly, Zhang et al. (24) observed that the most common HPV types after HPV type 16 in women with CIN2+ lesions were HPV types 52 and 58, with a frequency of 13.7% and 12.7%, respectively (23). In the light of the data mentioned above, it can be suggested that some HR HPV genotypes may exhibit a higher prevalence and a greater oncogenic capacity than HPV type 18, considering both geographical distribution and oncogenic potential. Consequently, these genotypes with non-invasive methods may permit the omission of unnecessary follow-up procedures for cervical high-grade lesions. In this respect, the present study emphasises the need to reconsider the role of colposcopy in women with other HR HPV positivity and normal cytology, particularly HPV type 31, which has a comparable risk to HPV 18. It requires that these women be evaluated by colposcopy and, if suspected, cervical biopsies, rather than retesting by co-test one year later, contrary to current management guidelines.

Study Strengths

One of the strengths of the current study is that it is one of the few studies to specifically evaluate colposcopy outcomes in women with other HR HPV types positivity, and normal cytology.

Furthermore, the present study is important for understanding the distribution of other HR HPV genotypes

and their oncogenic potential, as it categorises other HR HPV genotypes into specific groups and subjects them to statistical analysis.

The present study contributes to the management of women infected with other HR HPV in the absence of abnormal cytology, as it presents data from a cohort of women referred for colposcopy from a specific region of Turkey, thereby providing valuable insights into the distribution of other HR HPV genotypes.

Study Limitations

The limitations of the present study are firstly, that the study population was relatively small and limited to patients admitted to a single center. As a result, the findings of the current study cannot be generalised beyond this context. Secondly, the retrospective design of the study did not allow for an adequate analysis of prognostic variables and management strategies.

Furthermore, HPV genotyping using the CLART kit (Genomica) revealed that a significant proportion of the study population exhibited a HR HPV type labeled as other-x (where the genotype could not be obtained), precluding the possibility of establishing a correlation with HPV-specific genotypes.

Conclusion

The risk of high-grade cervical preinvasive lesions is markedly increased in women positive for other HR HPV in the absence of abnormal cytology. It is crucial not to ignore this risk. The necessity of retesting these women after one year, in accordance with established guidelines, is open to question, particularly in view of regional differences in the incidence of HR HPV genotypes and the need to consider the capacity of individual genotypes to develop preinvasive lesions. The findings of this study indicate that, despite the potential increase in the number of colposcopies performed, referring women with normal cytology infected with other HR HPV to colposcopy results in a higher incidence of high-grade cervical preinvasive lesions being detected. It can be reasonably assumed that this will result in a reduction in the incidence of cervical cancer, which is the primary goal of cervical cancer screening programmes.

Ethics

Ethics Committee Approval: The study was initiated following the approval of the Ethics Committee of the University of Health Sciences Turkey, Antalya Training and Research Hospital, dated 10 October 2024 and numbered 2024-319. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.Y., A.A., M.G., Me.G., T.T., I.Ü., Concept: N.Y., Me.G., T.T., I.Ü., Design: N.Y., A.A., M.G., T.T., I.Ü., Data Collection or Processing: N.Y., A.A., M.G., Me.G., Analysis or Interpretation: N.Y., Me.G., T.T., I.Ü., Literature Search: N.Y., A.A., M.G., Writing: N.Y., I.Ü.

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