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Comparison of Colposcopic Biopsy Results of Non-HPV 16/18 Oncogenic Type Positive Patients

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What is known on this subject?

High-risk human papillomavirus is the most common cause of cervical cancer worldwide.

What this study adds?

If gynecologists follow the algorithms recommended by guidelines, there is a risk of misdiagnosing cervical intraepithelial neoplasia 2+ lesions in 4% of those patients

ABSTRACT

Objective: This study aimed to evaluate and compare the risk in detecting cervical intraepithelial neoplasia (CIN) 2+ or higher lesions by performing immediate colposcopy in patients with positive high-risk non-human papillomavirus (HPV) 16/18 subtypes, regardless of their cytology results.

Material and Methods: A total of 264 patients with HPV-positive subtypes, aged 20-65 years, with any type of cervical cytology results were included in the study. A liquid-based cytologic cervical cancer screening with HPV testing was carried out between November 2020 and May 2021. Cytological specimens were classified according to the Bethesda system (2014), and HPV identification was analyzed with Cobas 4800 system. Colposcopy-guided endocervical curettage and endometrial biopsy were performed.

Results: A total of 123 patients had HPV non-16/18 oncogenic types, wherein 34 (69.3%) had no dysplasia, 9 (18.3%) had CIN 1, and 2 (4.08%) had CIN 2-3.

Conclusion: Colposcopic evaluation may be considered in cases of non-16/18 high-risk HPV subtypes with abnormal cytologic results. Among the patients who had negative cervical cytology and positive non-HPV-16/18, 4.08% were women with CIN 2-3. Following the algorithm according to the guidelines, there will be a risk of 4.08% of misdiagnosing CIN 2+ lesions by gynecologists. Organizing large-scale randomized controlled studies will help in understanding the meaning or importance of this topic.

Keywords: Colposcopy, cytology, genotyping, human papillomavirus subtypes

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Introduction

High-risk human papillomavirus (HR-HPV) is the most common cause of cervical cancer worldwide (1). According to the National Cancer Institute Centers for Disease Control and Prevention, HPV infection is responsible for >90% of cervical cancer cases worldwide. Almost 200,000 women are estimated to be diagnosed with precancerous cervical lesions or abnormal cells, which may lead to cancer. Of those, 11,000 women have lesions that progressed into cervical cancer as a result of chronic HPV infection. Unfortunately, over 4,000 women died because of this disease (2).

Randomized controlled trials have highlighted that HPV screening tests alone compared with cytologic interpretation were thought to facilitate an objective way of providing better protection against high-grade cancer precursors, such as cervical intraepithelial neoplasia (CIN 2+ and CIN 3+) and cervical cancer, than cytology tests, respectively (1,2).

According to the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 guidelines, co-testing after 1 year has been recommended in the presence of non-HPV 16/18 subtypes with normal cytology for women who are 30-65 years old (3). The difference between the 2012 and 2019 ASCCP guidelines is that in 2019, all positive primary HPV screening tests were recommended, regardless of genotype, to have additional reflex triage testing from the same laboratory specimen. The specificity of HPV testing in CIN 2+ and higher lesions decreased by 2-4% compared with cytology testing, and HPV testing alone would direct patients to overtreatment and over referral (4). Therefore, reflex triage testing is needed (5).

Risk-based management recommendations are the main difference that comes out at the 2019 ASCCP guidelines. The combination of present HPV results in history (including unknown history) for the surveillance, patient treatments, and colposcopy referrals immediately determined the risk for CIN 3+.

A Turkish nationwide study (6) stated that the positive predictive value for the risk of ≥ CIN 2 lesions of some other types of HPV, such as 33, 31, 35, and 45, in addition to HPV 16/18 is approximately 10%. Nevertheless, the current literature contains limited data on the risk of ≥ CIN 2 lesions in cases with non-HPV 16/18 high-risk types regardless of the cytology results.

The recent cervical cancer screening program is mainly based on searching or detecting the chronic HR-HPV subtypes. Direct colposcopic evaluation is recommended when the HPV 16/18 subtypes are detected (7). The prevalence of these HPV 16/18 subtypes may decrease due to HPV vaccination. In addition, the ATHENA study is similar to the study of Keiser and NHANES, without a sharp increase or decrease in the prevalence of HR-HPV (8) because of the underestimation in managing other high-risk non-16/18 HPV subtypes. The contribution of colposcopic evaluation toward the management of non-16/18 HPV high-risk cases is unclear.

This study aimed to evaluate and compare the risk of detecting CIN 2+ or higher lesions by performing colposcopy in patients with a positive high risk of non-16/18 HPV subtypes, regardless of their cytology results.

Material and Methods

This retrospective study was conducted between November 2020 and May 2021 in a tertiary center located in İstanbul at the Obstetrics and Gynecology Department, Oncology Division, after obtaining approval from Çam and Sakura City Hospital Human Research Ethics Committee (approval no: 2021.07.156). A total of 264 patients, aged 20-65 years, who were screened for cervical cancer with liquid-based cytology and HPV testing were included in this study. The study population was grouped according to their HPV 16/18 test results and previous history of abnormal cervical cytology or cancer. After obtaining informed consent from all participants, the colposcopy and biopsy procedures were performed. Patients who rejected the biopsy procedure and inadequate biopsy samples were excluded from the study. A total of 123 patients were retrospectively evaluated (Figure 1).

All cervical cytology samples were implemented using the Bethesda 2014 system (Surepath). HPV type identification was analyzed using Cobas 4800 for 14 types of HR-HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Colposcopy was performed on patients who had HR-HPV-DNA types regardless of cytology results. Patients were divided into two categories based on their cytology results as “negative cytology/non-HPV 16/18 positive types” and “positive cytology/non-HPV 16/18 positive types.”

Histological examination with colposcopy was performed in all patients following the procedure of 3-5% acetic acid solution on the cervix and upper vagina. The evaluation of the colposcopy findings is based on the solemnity of acetowhite lesions, an extension of lesion margins, and vascularity within the acetowhite lesion. Subsequently, Lugol’s solution was applied using an injector by direct installation in the same way with acetic acid. A biopsy of at least four parts from the Lugol negative and acetowhite positive areas was conducted. In the absence of abnormal lesions, a random biopsy was performed. All colposcopy-guided biopsies and

large loop electrosurgical excision (LEEP) procedures were performed by specialists in the gynecological oncology division. Endocervical curettage (ECC) was performed during the colposcopy-guided biopsy procedure. LEEP or conization procedures were executed in case of initial biopsy results with substantiated high-grade cervical lesions (CIN 2-3) or carcinoma *in situ*. The International Federation for Cervical Pathology and Colposcopy 2011 nomenclature was used for the transformation zone classification.

Statistical Analysis

All data were statistically analyzed using the SPSS software version 21. Descriptive statistics were used for demographic data. Fisher's Exact test and chi-squared association test were used for categorical data. The Student's t-test was performed for continuous data. A p value of <0.05 was considered statistically significant. Age, obstetric history, contraceptive method, smoking, cytology results, ECC, LEEP/conization, and cervical pathology results were all recorded.

According to the cervical biopsy results, those with low-grade dysplasia were considered CIN 1, and those with high-grade dysplasia were considered CIN 2-3.

Results

A total of 123 patients with non-16/18 HR-HPV subtypes were included and divided into two groups: Negative cytology group and positive cytology group. The mean ages of patients in the negative cytology and positive cytology groups were 40.8 (24-60) years and 40.4 (20-65) years, respectively (p=0.40). No significant difference was found in the demographics (Table 1).

All patients underwent colposcopy, and a colposcopy-guided cervical biopsy was performed in 45 (91.8%) patients (Table 2).

Endocervical canal curettage biopsy was performed in 36 (73.4%) patients of the negative cytology group, wherein all resulted in chronic cervicitis/inflammation (Table 3).

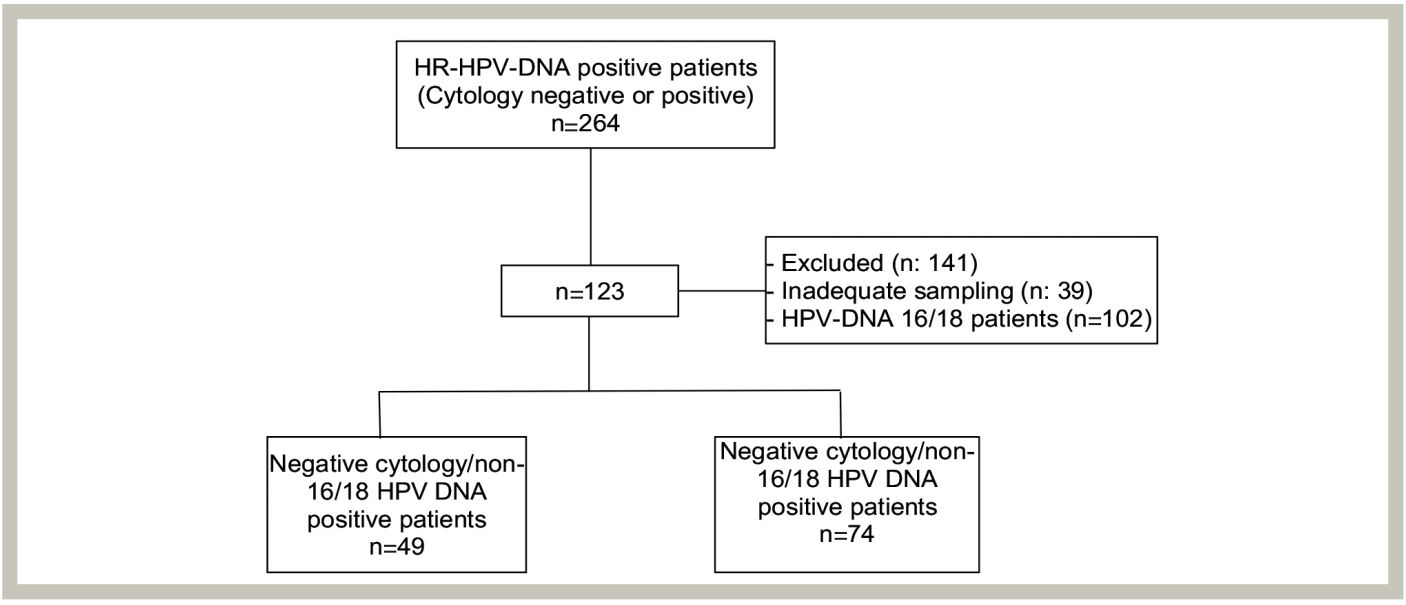

Figure 1. Flow chart of non-HPV-DNA 16/18 positive patient with negative or positive cytology

HR-HPV: High-risk human papillomavirus

Table 1. Comparison of demographics of patients with positive non-16/18 HPV DNA with negative or positive cytology

	Negative cytology (n=49)	Abnormal cytology (n=74)	p value*
Age (mean)	40.8 (24-60)	40.4 (20-65)	0.40
Gravida (mean)	2.38	2.43	0.45
Parite (mean)	1.93	1.9	0.45
Smoker	11(22.4%)	16 (21.6%)	0.82
Contraceptive pill usage	1 (2.05%)	2 (2.70%)	0.06

HPV: Human papillomavirus

Table 2. Comparison of colposcopy-guided cervical biopsy

	Negative cytology (n=45)	Abnormal cytology (n=73)	p value
Chronic cervicitis, inflammation	34 (69.3%)	40 (54.05%)	0.02
Low-grade dysplasia, CIN 1	9 (18.3%)	17 (22.97%)	
High-grade dysplasia (CIN 2-3)	2 (4.08%)	16 (21.6%)	

CIN: Cervical intraepithelial neoplasia

Table 3. Comparison of endocervical canal curettage biopsy results

	Negative cytology (n=36)	Abnormal cytology (n=63)	p value
Chronic cervicitis, inflammation	36 (100%)	60	0.94
Low-grade dysplasia, (CIN 1)	-	2	
High-grade dysplasia (CIN 2-3)	-	1	

CIN: Cervical intraepithelial neoplasia

Discussion

This retrospective cohort study demonstrated that non-16/18 HR-HPV subtypes cause nearly 15% of CIN 2+ lesions. This probability increased to 21.6% with abnormal cytologic results. The subtype analysis of the non-16/18 HR-HPV group in cases, which resulted in CIN 2+ lesions, was not defined.

Gultekin et al. (6) stated that the ratio of CIN 2+ lesions for the non-16/18 HPV subtypes was reported to be nearly 17%, which were nearly 24% of the HPV 16/18 subtypes. They put forward the necessity of reflex cytologic tests for the non-16/18 HPV subtypes to prevent unnecessary colposcopic evaluations. Our results correspond with this research. Our study found that the detection rate of CIN 2+ lesions statistically increased with abnormal cytology.

Aydoğmuş and Aydoğmuş (9) reported that the ratio of CIN 2+ lesions in cases of normal cytology results with non-16/18 HPV subtypes was 15.6%. Conversely, in another research, this ratio was reported as 0.01% (10). Our research detected CIN 2+ lesions 4% of patients with negative cytology. Interestingly, Çöl Madendağ et al. (11) reported that the detected CIN 2+ lesions with normal cytology were higher in cases of non-16/18 HPV subtypes, contrary to 16/18 HPV subtypes. Yalcin et al. (12) stated that the colposcopic evaluation of the normal cytologic results of the HPV 16 cases did not increase the detection rate of cervical cancer. Conflicting results are reported in the literature in cases of negative cytology results with positive non-16/18 HPV subtypes. The regional differences and the possible effect on the virulence or the behavior of the non-16/18 HPV subtypes may cause these conflicting results.

The reported cases demonstrated that even with the normal cytology results, non-16/18 HPV subtypes may cause higher dysplastic lesions at the uterine cervix (6,9,10). Colposcopic evaluation seems logical in cases with abnormal cytology results with non-16/18 HR-HPV subtypes. Colposcopic evaluation is considered to be a burden in the healthcare system; however, as a new and modern gynecologic oncology department, our oncology experts can carry out colposcopic examinations. Colposcopic evaluations are easily accessible and applicable. This is the major strength of this research. This research provides information about the management of the non-16/18 HR-HPV-positive cases.

Study Limitations

One of the limitations of this study is the colposcopic evaluation. Reid's colposcopic index was not found in the patients' colposcopy reports. Retrospective design and limited data is also a limitation of this study.

Conclusion

Organizing large-scale randomized controlled studies would be beneficial in understanding the importance of this topic.

Ethics

Ethics Committee Approval: Çam and Sakura City Hospital Human Research Ethics Committee approved (approval no: 2021.07.156).

Informed Consent: Approval received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.E.D., Ö.K., H.T., Concept: H.T., Design: N.A.V., H.T., Data Collection or Processing: N.A.V., G.N.K., H.T., Analysis or Interpretation: N.A.V., G.N.K., O.K., Literature Search: N.A.V., G.N.K., O.K., Writing: N.A.V., G.N.K., O.K., Ş.E.D.

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