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ORIGINAL ARTICLE

The importance of HPV types and endocervical curettage in colposcopic examination for the diagnosis of cervical lesions

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ABSTRACT

Objective: Cervical cancer is the third most common gynecologic cancer diagnosis. It is a type of cancer that can be predicted with effective screening because there is a factor such as human papillomavirus (HPV), which can be considered etiologically responsible. The main objectives of our study are to investigate whether high-risk HPV (hrHPV) 16, 18 and other hrHPV genotypes revealed by HPV genotyping require a different approach and to evaluate whether simultaneous endocervical curettage (ECC) is required during colposcopy.

Material and Methods: HPV genotypes, colposcopic biopsy, and ECC results of HPV DNA-positive patients between the ages of 25–65 years. HPV types other than HPV 16 and 18 were grouped as hrHPV types. Smear results, biopsy results, and ECC results were compared. The correlation between colposcopic biopsy and ECC results was evaluated.

Results: The mean age of the 111 patients included in the study was 44.48±8.34 years. There was a statistically insignificant relationship between HPV 16 and/or 18 and other genotypes (p=0.067). A similar trend was present in terms of ECC (p=0.072). In the comparative evaluation of the patients who underwent ECC with colposcopic biopsy, it was found that colposcopic biopsy was significantly more effective in diagnostic terms (p<0.001). However, cervical intraepithelial neoplasia (CIN) was detected in ECC in 6.8% of the patients whose colposcopic biopsy did not reveal CIN.

Conclusion: Even if the lesion margins are clear during the biopsy of the lesion in colposcopy examination, ECC may increase diagnostic accuracy.

Keywords: Cervical cancer, colposcopy, endocervical curettage, human papillomavirus.

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INTRODUCTION

Cervical cancer is the third most common gynecologic cancer diagnosis.[1] The annual incidence is 4.0/100000, and 65% of the cases are observed between the ages of 40 and 60.[2] Unlike many other types of cancer, cervical cancer is a type of cancer that can be prevented with effective screening methods because a factor such as human papillomavirus (HPV), which is responsible for its development etiologically, has been revealed. Its development requires a process that lasts years, from benign/precancerous lesions to invasive cancer formation.[3]

The current approach in cervical cancer screening is a Papanicolaou (PAP) smear test and HPV genotyping. The incidence of invasive cancer and mortality has decreased by more than 70% with the PAP smear test, which has been widely accepted and used, especially in developed countries since the 1950s.[4] The specificity of the PAP smear test is 98%, and the sensitivity is 50%. In addition to the low sensitivity of the PAP smear test, the main limiting problem is the difficulty due to the need for a pathologist/cytologist in screening large populations. HPV genotyping is a screening method that has been increasingly and widely used by a group of countries, including our country, in recent years, that allows the screening of many patients in a short time and evaluates the presence of HPV 16, 18, and other high-risk HPV (hrHPV) with high oncogenicity potential.[5]

According to the literature and the data of our country, HPV 16 and 18 seem more critical and riskier than other HPV genotypes. In the current cervical cancer screening protocol of our country, the smear result of HPV 16 and/or 18 positivity is evaluated by colposcopy even if cytology is normal. In contrast, if the other group's smear result is normal, the evaluation is postponed to one year later.[6]

Our study aimed to investigate whether hrHPV 16 and 18 and other HPV types revealed by HPV genotyping require a different approach to evaluate whether the findings in our patient group support these predictions. For this purpose, a comparative analysis of high oncogenic HPV types and other HPV genotypes in colposcopic biopsy and endocervical curettage (ECC) results was planned. In addition, our study secondarily aimed to evaluate whether ECC is required during colposcopy.

MATERIAL AND METHODS

This study was conducted at a university hospital. The Clinical Research Ethics Committee approved the study (Ethics Committee decision no: 2018/514/140/11). The medical data of HPV DNA-positive female patients between the ages of 25 and 69 who applied to our clinic between December 01, 2016 and February 01, 2017 were evaluated retrospectively. The inclusion criteria in the study were between the ages of 25 and 69, HPV positive, having ECC and colposcopic biopsy together, and an informed consent form was obtained. The exclusion criteria were that HPV-negative colposcopy was performed, only colposcopic biopsy was performed, or cervical biopsy was not needed during colposcopy, and only ECC was performed. In addition, the patients with positive HPV 16 and 18 and positive hrHPV were excluded from the study. Furthermore, the patients with type 3 transformation zones where the transformation zone could not be monitored were excluded from the study. Under the criteria above, 111 of the 208 patients were included in the study, and their medical data were evaluated. Primarily, HPV genotypes (grouped as HPV 16, HPV 18, HPV 16 and 18, and hrHPV), colposcopic biopsy, and ECC results were evaluated in the patients for the main purposes of our study. Other parameters evaluated in our study are age, smoking, PAP smear results, pregnancy history (gravida and parity numbers), and the age of first coitus. Informed consent was obtained from each patient for colposcopy, and gynecologist-oncology specialists performed the procedure. All the parameters used in the study are routinely used in the follow-up and treatment of the patients who underwent colposcopic examination and biopsy. The study was concluded after the information of the patients who met the criteria was collected and statistically evaluated, and the expected number of patients was reached. In this study, correlation analysis was performed regarding possible risk effects of cervical pathologies and other parameters, and it investigated whether HPV genotypes differed in terms of PAP smear, colposcopic biopsy, and ECC results. Comparison and correlation analyses of cervical pathology results were performed to evaluate the necessity of simultaneous ECC with colposcopic biopsy, which is one of the other main objectives of the study.

Table 1: Demographic characteristics of the patients included in the study

	Mean±SD	Median (range)
Age (years)	44.49±8.34	
Gravida		2 (0–11)
Parity		2 (0–8)
Age at first intercourse (years)	20.03±4.48	

SD: Standard deviation.

Statistical Analysis

SPSS 20.0 statistical software was used to evaluate the statistical data. Continuous variables were indicated by mean (±SD), Student's t-test was used to compare the data, categorical variables were expressed as a ratio (%), and the Chi-square or Mann–Whitney-U test was appropriately used. One-way ANOVA test was used to evaluate three or more groups, and the Spearmen-rho test was used in the correlation analysis. P value was considered statistically significant if it was <0.05 (double-sided).

RESULTS

The demographic characteristics of 111 patients are shown in Table 1. The smoking rate was 34.2%, and 65.8% of the patients did not smoke. As shown in Table 2, there were no significant differences between the biopsy results of the patients and coitus age, age, gravida, and parity.

It was found in the evaluation of the smear results of the patients that 76.6% (n=85) of the patients were normal, 11.7% (n=13) were atypical squamous cells of undetermined significance (ASCUS), and 11.7% (n=13) were low-grade squamous intraepithelial lesion (LGSIL). In the evaluation performed according to HPV

Table 2: Biopsy results and demographic data

	Normal (n=73)	LSIL (n=25)	HSIL (n=12)	Cancer (n=1)	p
Age (years)	45.45±8.39	42.84±8.32	41.58±7.73	50	0.281
Age at first intercourse (years)	19.78±3.75	20.56±6.7	20.42±3.09	20	0.885
Gravida	3.3±1.9	3.4±1.5	2.8±1.5	2	0.678
Parity	3.3±1.9	2.5±1.4	2.3±1.1	2	0.962

Data are expressed as mean±SD. LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion.

Table 3: Comparison of colposcopic biopsy and endocervical curettage biopsy

ECC biopsy results (n)	Colposcopic biopsy results (n)				
	NILM	LSIL	HSIL	Cancer	Total
NILM	68	21	12	0	101
LSIL	3	4	0	0	7
HSIL	2	0	0	0	2
Cancer	0	0	0	1	1
Total	73	25	12	1	111

ECC: Endocervical canal curettage; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; NILM: Negative for intraepithelial lesion or malignancy.

types, the smear was normal in 6 (66.7%) of a total of 9 patients with HPV genotype 18 positive, ASC-US was detected in one patient (11.1%), and LGSIL was detected in two patients (22.2%). In 41 patients with HPV genotype 16 positive, the smear results of 34 patients (82.9%) were normal, three patients (7.3%) had ASCUS, and four patients (11.8%) had LSIL. Cervical smear was normal in all four patients with both HPV 16 and 18. Apart from HPV 16 and 18, 41 (71.9%) of 57 patients with HPV types had a normal smear, nine (15.8%) had ASCUS, and seven (12.3%) had LGSIL. There was no significant relationship between the HPV types and smear results (p=0.649).

The relationships of HPV genotypes with colposcopic biopsy were evaluated. Cervical intraepithelial neoplasia (CIN)1 lesions were evaluated as LGSIL, CIN2, and three lesions were evaluated as HGSIL. In the hrHPV group, a biopsy was reported as normal in 42 (73.7%) of 57 patients, ten patients (17.5%) had LGSIL, and five patients (8.8%) had high-grade dysplasia (HGSIL). Biopsy was normal in five (55.6%) of nine patients with HPV type 18 positive, LGSIL was determined in two patients (22.2%), HGSIL in one patient (11.1%), and cervical cancer in one patient (11.1%). Of the 41 patients with HPV type 16 positive, 24 (58.5%) had a normal biopsy, 11 (26.8%) had LGSIL, and six (14.6%) had HGSIL. Biopsy was normal in two of the four HPV 16+18 positive patients and LGSIL was detected in two patients. No statistically significant result was obtained in evaluating the relationship between colposcopic biopsy results and HPV high and other genotypes of the patients (p=0.067).

When ECC and HPV types were compared, 53 (93%) of 57 patients with hrHPV types had normal ECC, while only four (7%) had LGSIL. Seven of the nine HPV 18 positive patients had normal ECC, one had LGSIL, and one had cervical cancer. In 41 patients with HPV 16 positive, ECC was normal in 37 patients (90.2%), LGSIL in two patients (4.9%), and HGSIL in two patients (4.9%). ECC was normal in four of the four patients who were positive for HPV 16 and 18. The evaluation of ECC biopsy pathological results in terms of HPV high and other genotypes was not statistically significant (p=0.072).

Comparisons of colposcopic biopsy and ECC biopsy are shown in Table 3. In the comparative evaluation of the patients who underwent colposcopic biopsy and ECC, the colposcopic biopsy was significantly more effective in terms of diagnosis (p<0.001). In contrast, its results correlated at a nearly significant level (correlation analysis, p=0.059).

DISCUSSION

Cervical cancer is the third most common cancer among gynecological cancers worldwide. It ranks fourth among all cancers in terms of cancer-related deaths.[1] Especially in developed countries with a good cancer screening policy, a significant decrease in the incidence and prevalence of cervical cancer has been noted because of the widespread use of the PAP smear test and other advanced diagnostic methods such as colposcopy, cervical biopsy, and ECC since the 1950s. In this way, cervical cancer development has decreased by more than 80% in developed countries.[7]

As a result of the developments in biotechnology and the performance of HPV genotyping in more detail, those with a high oncogenic potential of HPV genotypes have been revealed. Cervical cancer screening policies based on the presence of HPV genotypes 16 and 18, which are high oncogenic types, have become prominent over time. Because scanning with HPV DNA reduces the need for labor and experienced health personnel and provides fast results without a need for interpretation, large masses can be scanned healthily and reliably. In a newly published study by Gültekin et al.,[8] including one million women, it was demonstrated that the number of women screened for cervical cancer in Türkiye increased 5–6 times in the year following the transition to the screening system based on HPV genotyping in 2014, while the screening in terms of cervical cancer was at the level

of 2% since the beginning of the 2000s. Today, the recommendations of various health organizations may differ in screening; the European Union, IARC, and the World Health Organization (WHO) prioritize screening with HPV DNA genotyping in primary screening, while others recommend the use of PAP cytology and HPV testing together.[9,10] In our study, the PAP smear cytology results of HPV high oncogenic genotypes and other HPV types were compared, and no significant difference was found in ASCUS and LGSIL presence.

According to the 2019 guidelines of the American Society for Colposcopy and Cervical Pathology, colposcopy is recommended for HPV genotypes 16 and 18, as in our country, in the management of negative cytology and positive HPV test. In our country, the age of the beginning of HPV screening was determined as 30 years, and the ending age was defined as 69 years if the previous tests were normal. Again, if HPV 16 and 18 are positive, the patient is referred to colposcopy, and if the smear is normal in the presence of other hrHPV types, the patient is called for a follow-up to be re-evaluated after 1 year.[11] In our study, all HPV genotypes were evaluated by colposcopy, whether high-risk or not, and it was examined whether there was a difference between HPV genotype 16 and HPV 18 positive group and the group with other HPV types in terms of biopsy and ECC biopsy results. In the presence of HPV 16 and 18 genotypes, more CIN was detected in both ECC biopsies and colposcopic biopsies at a level close to statistical significance.

In their study published in 2005, Khan et al.[12] monitored women with negative cytology results for 10 years and reported CIN 3 and cancer development as 17% in the women with HPV 16 positive, 14% with HPV 18 positive, and only 3% in the presence of other risky HPV genotypes. In our study, high-grade CIN detected in colposcopic biopsy with HPV genotype 16 or 18 positivity was 14.6% in the patients with HPV genotype 16 positivity and 11.1% in the patients with HPV genotype 18 positivity, and it was 8.8% in other HPV genotypes. Although our findings did not have statistical significance, it is seen that they are similar to this study.

Multiparity and smoking, which are thought to play a facilitating role when accompanied by HPV infection in the development of cervical cancer, were also evaluated in our study. Various studies in the literature suggest that smoking may cause the development of cervical cancer with local inflammation and HPV persistence,[13,14] In a review published by the International Agency for Research on Cancer (IARC) in 2004, it has been reported that the relationship between squamous cervical cancer and smoking is evident, and its relationship with adeno and adenosquamous cervical cancers has not yet become definite.[15] In contrast to these studies, in our study, we observed that our ECC and colposcopic biopsy results did not correlate with smoking in terms of both HGSIL and cancer. However, we found that the only patient with adenocarcinoma did not have a smoking history. Similarly, our study did not find any correlation in parity numbers. Cross-sectional studies with a higher number of patients are needed to evaluate the relationship between cervical neoplasia and cancer development with co-factors such as smoking and multiparity and to reveal this difference.

According to the report published by IARC, which reveals the relationship between HPV and cervical cancer, 69% of cervical cancers are squamous cell cervical cancer, 25% are adenocarcinoma, and 6% are cervical cancers of other types, mainly adenosquamous cell carcinoma.[16] In a study published by Bulk et al.[17] in the British Journal of Cancer in 2006, it was demonstrated that HPV genotype 18 was associated with cervical adenocarcinoma and rapidly progressing cervical cancers. HPV genotype 16 was associated with squamous cell cervical cancers. Although there was only one case for whom we detected cervical cancer, HPV genotype 18 was positive in the adenocarcinoma patient we detected similarly.

In the guidelines published by ACOG in 2008, it has been predicted that ECC can only be performed with the practitioner's decision if the colposcopy is insufficient or the colposcopy is sufficient, but the lesion is not identified.[18] Schorge et al.[19] reported the necessity of using ECC in the follow-up of these patients if conization was performed for adenocarcinoma in situ. Although it was widely used in the review published by Abu in 2005, it was stated that there were no randomized studies supporting the routine use of ECC.[20] In our present study, ECC was applied to all patients during colposcopy. Thus, we aimed to evaluate the importance of ECC in case of HPV positive. Thanks to ECC applied in addition to colposcopic biopsy, LGSIL was detected in 4.1% of the patients whose colposcopic biopsy was normal, and HGSIL was detected in 2.7% of such patients. We found that ECC could only detect the presence of CIN in 6.8% of the patients. Even in our patient group with a limited number of patients in our study, we thought that the presence of many patients with low or high-grade lesions resulted from ECC. However, the colposcopic biopsy result was normal, which could increase both procedures' diagnostic accuracy and precision.

CONCLUSION

HPV genotypes 16 and 18 persistent infections are the most important factors of cervical cancer. Our study showed that the frequency of CIN increased in the patients infected with these high oncogenic HPV genotypes. Another important finding from our study was that 6.8% of patients had CIN when ECC was added to the diagnostic approach in patients with no pathology detected in colposcopy examination. Therefore, although colposcopy is the gold standard among diagnostic approaches, performing it with ECC can increase diagnostic accuracy and precision even when the lesion margins are visible during the colposcopic biopsy.

Statement

Ethics Committee Approval: The Kartal Lütfi Kırdar Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 31.10.2018, number: 2018/514/140/11).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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