Do HPV 16 positive/ASC-H cervical cancer screening results predict CIN 2+ better than other high-risk HPV subtypes?

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Abstract

Objective: To determine whether patients with atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia (ASC-H) cytology have a correlation between high-risk human papillomavirus (HPV) type and CIN 2+[1] lesion in final pathology.

Material and Methods: The study was conducted retrospectively, using data from three tertiary gynecologic oncology centers located in various regions of Turkey. Data from 5,271 patients who had colposcopy between January 2003 and January 2021 were analyzed.

Results: A total of 163 patients who had ASC-H cervical cytology test results, based on the Bethesda 2014 classification were eligible, and of these 83 (50.9%) who tested positive for HPV were included in the study. There was no correlation between the occurrence of CIN 2+ lesions and age (p=0.053). If there was any HPV 16 positivity (only HPV 16, HPV 16 and 18, HPV 16 and others) the presence of CIN 2+ lesions in the final pathology increased significantly. In HPV 16 positive ASC-H patients, the probability of CIN 2+ lesions in the final pathology were 72.5% while this rate was 48.1% in HPV 16 negative group (p=0.033).

Conclusion: The guidelines do not provide a comprehensive definition of the role of the HPV test in managing ASC-H. Positive high-risk HPV types, especially HPV 16, together with an ASC-H smear result should bring to mind the possibility of high-grade dysplasia. (J Turk Ger Gynecol Assoc 2024; 25: 90-5)

Keywords: ASC-H, cervical cancer, HPV

[1]CIN 2+ lesions were HSIL (CIN 2/CIN 3), micro-invasive cancer, adenocarcinoma in situ, and cervical cancer.

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Introduction

GLOBOCAN 2020 reported approximately 604,000 new cases of cervical cancer and 342,000 deaths attributed to the disease globally (1). Cervical cancer ranked as the fourth most prevalent cancer among women (2). The global occurrence and mortality rates differ among countries, based on factors such as the presence of cervical cancer screening programs and the frequency of human papillomavirus (HPV) vaccination. The components of cervical cancer screening include cervical cytology and/or testing for oncogenic subtypes of the HPV (3,4). Although an HPV test is first option for cervical screening, triage with cervical cytology is recommended for some subtypes (5). Furthermore, cervical cytology may be the only choice in undeveloped and some developing countries (6). Therefore, cytologic evaluation and management still have an important value in a cervical screening program (6).

The Bethesda 2014 classification uses the term "atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia (ASC-H)" to describe cytological specimens that do not meet the necessary criteria for high grade squamous intraepithelial lesion (HSIL), but cannot definitively rule it out (7). Therefore, ASC-H cytology should be considered as suspicious for HSIL. ASC-H cytology results account for 10% of all ASC tests reported (8,9), and can be seen in approximately 0.2-0.3% of all cervical cytology tests (10).

HPV positivity has been reported as 68-84% in ASC-H cases (8,9). The prevalence of cervical intraepithelial neoplasia 2+ (CIN 2+) lesions in cases of HPV positive ASC-H is estimated to be between 30% and 47% (8,11). Nevertheless, the existing literature lacks sufficient evidence concerning the correlation between HPV subtypes and the likelihood of CIN 2+ lesions in ASC-H cytology. The aim of the present study was to assess the correlation between CIN 2+ lesions and high-risk HPV subtypes among patients who presented with HPV-positive ASC-H cytology.

Material and Methods

The study was conducted retrospectively, using data from three tertiary gynecologic oncology centers located in various regions of Turkey. The study was approved by the University of Health Sciences Turkey, Ankara City Hospital Clinical Research Ethics Committee (approval number: 7, date: 29.01.2021). Between January 2003 and January 2021, the data of 5,271 patients who underwent colposcopic examination in the gynecological oncology outpatient clinics of the participating centers were analyzed. Among this cohort, patients who had ASC-H cervical cytology test result were investigated. Patients who had positive HPV test result and ASC-H simultaneously were included. Every patient provided their explicit consent for the institution to utilize their clinical data. The liquid-based thin-layer slide preparation technique was used for all ASC-H cervical cytology. NOVAprep® liquid-based cytology systems (NOVAprep Inc., Russia) and Max-prep® cytology systems (Corebiotech Co., Korea) were used for the liquid-based cytology preparation. The age, HPV test results, and histopathological reports of the colposcopic biopsy and endocervical curettage (ECC) were analyzed. HPV-DNA was isolated by using QIAsymphony® DSP virus/pathogen MIDI kit, HPV-DNA was detected and typed by QIAscreen HPV-PCR kit (Qiagen Inc., Germany). Three tertiary gynecological oncology clinics implemented the American Society for Colposcopy and Cervical Pathology (ASCCP) recommendations for the management of pre-invasive lesions. Colposcopic examination was routinely performed in patients with ASC-H cytology in the centers included in this study. ECC was also performed. Conization was performed in patients who had HSIL, micro-invasive cancer, or adenocarcinoma in situ (AIS) on colposcopic biopsy and who had discordance between biopsy and clinical evaluation. HSIL (CIN 2/CIN 3), micro-invasive cancer, AIS, and cervical cancer were defined as CIN 2+ lesions.

Statistical analysis

The SPSS, version 22.0 was used for all statistical analyses (IBM SPSS Inc., Chicago, IL, USA). Descriptive values are expressed as arithmetic mean ± standard deviation, median and percent. The chi-square test was used to analyze categorical variables. A p-value <0.05 was deemed statistically significant.

Results

There were 163 cases with ASC-H cytology findings, and of these 83 (50.9%) patients who had positive HPV test result and ASC-H simultaneously were included. The mean patient age was 45±9.21 years. HPV 16 was the most prevalent type of HPV. There were 36 patients (43.4%) with HPV 16 only, four patients (4.8%) with both HPV 16 and 18, and eleven patients (13.3%) who had HPV 16 and HPV types other than HPV 18 simultaneously. HPV type was undetermined in five (6%) patients. The patients' characteristics are presented in Table 1.

Colposcopy was performed in all patients. Colposcopic biopsy was performed in 80 patients who had suspicious lesions on colposcopic examination. Colposcopic examinations of the other three patients were normal. HSIL was the most common pathology in 42/80 (52.5%) among the colposcopic biopsy and ECC results of the patients. The remaining diagnoses included squamous cell carcinoma in two patients, micro-invasive cancer in two patients, and AIS in one patient. Conization was performed in 47 patients. Eight patients with HSIL biopsy results refused conization. Among the pathological results of conization, the most common pathology was HSIL in 31/47

(66%). On final pathological diagnosis, CIN 2+ lesion was reported in 51 (61.4%) patients and HSIL was the most common (55.4%) type among these results (Table 1).

The association between CIN 2+ lesions and age or HPV type in patients with ASC-H cytology is summarized in Table 2. The incidence of CIN 2+ lesions was 73% among patients aged <44 years, compared to 52.2% among patients aged ≥44 years (p=0.053). It was significantly more likely that the final pathology would show CIN 2+ lesions in patients who had HPV 16 positivity (only HPV 16, HPV 16 and 18, or HPV 16 and others). The incidence of CIN 2+ lesions, as determined by the final pathological diagnosis, was 72.5% in patients who tested positive for both HPV 16 and had ASC-H cytology simultaneously. In contrast, the incidence was 48.1% in patients who tested positive for a type of HPV other than HPV 16 (p=0.033).

HPV 16 positivity in patients with ASC-H cytology predicted CIN 2+ lesions with 74% specificity, 50% sensitivity, 72.5% positive predictive value, and 51.9% negative predictive value. Statistics were not analyzed for other HPV types excluding HPV 16 because the number of patients for other subtypes was insufficient.

Table 1. Characteristics of entire cohort (n=83)

Characteristics		**Mean ± SD**	**Median (range)**
Age		45±9.21 years	44 (24-66) years
		n	**%**
Age	<25 years	1	1.2
	≥25 years	82	98.8
HPV type	Type 16 only	36	43.4
	Type 18 only	2	2.4
	Types 16 with 18	4	4.8
	Other types	24	28.9
	Type 16 with other types	11	13.3
	Type 18 with other types	1	1.2
	Unknown types	5	6
Colposcopic examination	Normal (no biopsy)	3	3.6
	Abnormal (with biopsy)	80	96.4
Results of pathological reports obtained by colposcopy (n=80)[1]	Benign	15	18.8
	LSIL (CIN 1)	18	22.5
	HSIL (CIN 2)	25	31.3
	HSIL (CIN 3)	13	16.3
	HSIL (undetermined)	4	5
	AIS	1	1.3
	Micro-invasive cancer	2	2.5
	SCC	2	2.5
Histopathological results of conization (n=47)	Benign	9	19.1
	LSIL	6	12.8
	HSIL	31	66
	Cancer	1	2.1
Results of final pathologicaldiagnosis (n=83)	Benign	16	19.3
	LSIL	16	19.3
	HSIL	46	55.4
	Micro-invasive cancer	2	2.4
	SCC	2	2.4
	Adenocarcinoma	1	1.2

[1]Results from 80 patients who underwent colposcopic biopsy and endocervical curettage. SD: Standard deviation, LSIL: Low-grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia, HSIL: High-grade squamous intraepithelial lesion, AIS: Adenocarcinoma in situ, SCC: Squamous cell cancer, HPV: Human papillomavirus

Table 2. The relationship between final pathological diagnosis and HPV, and age in patients with ASC-H cytology

Parameters		Final pathological diagnosis				p-value
		Benign and LSIL		CIN 2+		
		n	%	n	%	
Age[1]	<44 years	10	27	27	73	0.053
	≥44 years	22	47.8	24	52.2	
HPV 16 (n=78)[2]	Negative	14	51.9	13	48.1	**0.033**
	Positive	14	27.5	37	72.5	

CIN: Cervical intraepithelial neoplasia, CIN 2+ lesions were HSIL (CIN 2/CIN 3), micro-invasive cancer, adenocarcinoma in situ, and cervical cancer, HPV: Human papillomavirus, LSIL: Low-grade squamous intraepithelial lesion, [1]Median value, [2]Five patients with unknown type were excluded, ASC-H: Atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia

Pathological findings of the five patients whose final pathological diagnosis was cancer are shown in Table 3. All but one (80%) had HPV 16 positivity and HPV 31 was positive in the other patient. The final pathological diagnosis was that four patients had squamous cell carcinoma, while one patient had adenocarcinoma.

Discussion

In the present study, patients with ASC-H cytology who tested positive for high-risk HPV, specifically HPV 16, had a significantly higher incidence of CIN 2+ lesions. HPV 16 positivity in patients with ASC-H cytology predicted CIN 2+ lesions with good specificity and positive predictive value but only moderate sensitivity and negative predictive value.

ASC-H refers to atypical squamous cells in the cervix that exhibit the features of a focal high-grade intraepithelial lesion, but are not definitive for diagnosis. It is important to manage ASC-H cytology carefully due to this potential presence of a high-grade intraepithelial lesion. The occurrence of CIN 2-3 lesions in patients with ASC-H cytology ranged from 10% to 85% in the biopsy findings reported in the literature (12-17). Galliano et al. (12) found that 63.8% of patients with ASC-H cytology had high-grade intraepithelial lesions, regardless of their HPV status.

Patton et al. (18) highlighted that age was important for the development of dysplasia in ASC-H cases. However, when predicting high-grade dysplasia in individuals with ASC-H cytology, Kietpeerakool et al. (19) did not find a significant difference between women under 40 and those over 40 years. Gilani et al. (20) also found no difference in the risk of both low-grade and high-grade dysplasia between patients under 30 and those over 49 years. The present study also demonstrated that there was no significant disparity in the likelihood of CIN 2+ lesions among patients with ASC-H cytology based on age.

The prevalence of HPV positivity ranges from 38% to 84% among women with ASC-H cytology (8,13,21,22). Chen et al. (22) reported that among patients with positive high-risk HPV test and ASC-H cytology, the occurrence of CIN 2+ lesions was 55%, based on cervical biopsy or loop electrosurgical excisional procedure specimens. In contrast, the incidence was only 9% among those negative for high-risk HPV. These authors found that women who had both positive high-risk HPV and ASC-H cytology were six times more likely to have high-grade dysplasia compared to those who were negative for high-risk HPV (22). The meta-analysis conducted by Xu et al. (9) examined ASC-H triage and found that the high-risk HPV test had a sensitivity of 93% and a specificity of 45% in detecting CIN 2+ lesions. Data from Keiser Permanente Northern California showed that the likelihood of immediate CIN3+ was

Table 3. Clinical-pathological findings of patients with cervical cancer

Patient no	Age	Cytology	HPV type	ECC result	Colposcopic biopsy result	Conization	Conization result	Final pathological diagnosis
1	49	ASC-H	HPV 16	Benign	HSIL (CIN 2)	Performed	Adenocarcinoma	Adenocarcinoma
2	49	ASC-H	HPV 16	Benign	Micro-invasive SCC	Performed	HSIL (CIN 2)	Micro-invasive SCC
3	52	ASC-H	HPV 31	HSIL (CIN 2)	Micro-invasive SCC	Performed	HSIL (CIN 2)	Micro-invasive SCC
4	28	ASC-H	HPV 16	SCC	SCC	Not performed	-	SCC
5	55	ASC-H	HPV 16	Benign	SCC	Not performed	-	SCC

HPV: Human papillomavirus, ECC: Endocervical curettage, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell cancer, CIN: Cervical intraepithelial neoplasia, ASC-H: Atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia

26% for patients with HPV positive ASC-H and 3.4% for patients with HPV negative ASC-H (23). However, the cancer risk was approximately same. Therefore, ASCCP 2019 guideline recommended colposcopic biopsy for ASC-H, regardless of HPV status, as was recommended in the earlier 2012 guideline (23,24). However, the new guideline focused on HPV type in the presence of HSIL cytology. Patients who tested positive for HPV 16 and had HSIL cytology had an immediate risk of CIN 3+ greater than 60%. This threshold was established to justify expedited treatment, which consisted of excisional biopsy without colposcopic biopsy for non-pregnant patients aged 25 years and older (23). The present study found that the risk of CIN 2+ lesions increased significantly from 48% to 72.5% in patients who had both ASC-H cytology and a positive high-risk HPV test, specifically for HPV 16 type. The high-risk HPV test, which includes the HPV 16 type, has a sensitivity of 74% and a specificity of 50% for detecting CIN 2+ lesions in patients with ASC-H cytology. Therefore, our findings suggest that expedited treatment may be considered for patients with ASC-H cytology and HPV 16 positivity.

Study limitations

The advantages of our study were that colposcopic and excisional procedures were all performed by gynecological oncology specialists. The patients were followed up by the same clinic. The present study aimed to elucidate the significance of high-risk HPV type in patients presenting with ASC-H cytology, a previously unidentified component of cervical pathological lesions. Pathology samples of the patients were examined by pathologists specialized in gynecological pathology. One of the limitations of our study is its retrospective design. Furthermore, due to the limited sample size, subgroups of other high-risk HPV types, excluding HPV 16 and 18, were not investigated.

Conclusion

Patients with ASC-H cytology should be managed carefully. This finding has a strong correlation with dysplasia at any level, and particularly with high-grade dysplasia. The HPV type is not fully defined in the management of ASC-H in the literature. The presence of positive high-risk HPV and ASC-H cytology significantly increased the risk of CIN2+ lesion in our cohort. Furthermore, this risk was increased over the 60% in the presence of HPV 16 positivity for ASC-H cytology. Therefore, the expedited treatment can be kept in mind for patients with ASC-H cytology and concurrent HPV 16 positivity. Nevertheless, additional research, especially with larger sample sizes, is necessary to draw definitive conclusions.

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