

# CORRELATION BETWEEN CYTOPATHOLOGY AND HISTOPATHOLOGY IN WOMEN WITH SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

## КОРЕЛАЦИЈА ПОМЕЃУ ЦИТОПАТОЛОШКИТЕ И ХИСТОПАТОЛОШКИТЕ НАОДИ КАЈ ЖЕНИ СО СКВАМОЗНИ КЛЕТОЧНИ АБНОРМАЛНОСТИ НА ГРЛОТО НА МАТКАТА

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### ABSTRACT

**Objective:** The aim of the study was to correlate the results of cervical cytology and cervical biopsy in women with squamous cell abnormalities of the uterine cervix.

**Materials and Methods:** This comparative retrospective study was conducted in a series of 184 sexually active women, aged 20 to 60, who came to their annual gynecological exam at the University Clinic for Gynecology and Obstetrics in Skopje between September 2015 and March 2016. In all 184 patients with cytologically diagnosed squamous cell abnormalities of the uterine cervix, a colposcopic cervical biopsy with endocervical curettage for histopathological analysis was taken, with was analyzed at the University Clinic for Radiotherapy and Oncology in Skopje. The results of the liquid-based cytology smears and cervical biopsies were compared to evaluate the diagnostic agreement between the cytology findings and the biopsies.

**Results:** Cytopathologically, there were 118 (64.13%) ASC-US, 22 (11.96%) LSIL, 38 (20.65%) HSIL and 6 (3.26%) invasive carcinoma cases. Histopathologically, there were 108 (58.70%) non-neoplastic lesions, 24 (13.04%) LGSIL cases, 42 (22.83%) HGSIL cases and 10 (5.43%) invasive squamous cell carcinomas. Including all squamous cell abnormalities, the sensitivity of the smear test in low-grade and higher grade lesions was 58.70% (108/184) and the false positivity was 41.30% (76/184). Excluding ASC-US lesions, the sensitivity of the smear test was 78.80% (52/66) and the false positivity was 21.21% (14/66). After evaluating cervical cytopathological correlation the positive predictive value was found to be 100% (6/6) in invasive carcinoma, 68.42% (26/38) in HGSIL and 31.82% (7/22) in LGSIL.

**Conclusions:** The high sensitivity of the cervical smear test for high-grade squamous lesions shows that it is an effective screening test for cervical cancer and precursor lesions.

**Key words:** cytopathology, histopathology, squamous cell abnormalities, liquid-based cytology, cervical biopsies

### INTRODUCTION

Cervical cancer is the third most common malignancy in women worldwide, annually with 500.000 newly diagnosed cases and almost 250.000 deaths [1]. About 90% of cervical cancer cases are squamous cell carcinomas, 10% are adenocarcinomas and a small number are other types [2]. Various forms of squamous cell abnormalities precede the appearance of the cervical cancer, which include a lot of progressive morphological changes, from

productive human papillomavirus (HPV) infection-mild dysplasia to carcinoma in situ [3].

A significant decrease in the incidence and mortality of cervical cancer can be realized with effective cervical cytology screening programs [4]. The aim of the Papanicolaou (PAP) smear test is to detect precancerous cervix lesions before they become invasive cancer. The accuracy of the PAP smear test is evaluated using: sensitivity, specificity and predictive value. Evaluating the correlation between cervical cytology and biopsy is the best method of the determining the PAP smear test accuracy. However, it is not a perfect methods due to the potential sampling and interpretation errors [5].

The aim of the study was to correlate the results of cervical cytology and cervical biopsy in women with squamous cell abnormalities of the uterine cervix.

## MATERIAL AND METHODS

This comparative retrospective study was conducted in a series of 184 sexually active women, aged 20 to 60, who came to their annual gynecological exam at the University Clinic for Gynecology and Obstetrics in Skopje between September 2015 and March 2016. In all 184 patients with cytologically diagnosed squamous cell abnormalities of the uterine cervix, a colposcopic cervical biopsy with endocervical curettage for histopathological analysis was taken, with was analyzed at the University Clinic for Radiotherapy and Oncology in Skopje. The results of the liquid-based cytology smears and cervical biopsies were compared to evaluate the diagnostic agreement between the cytology findings and the biopsies.

### Criteria of inclusion

This study included 184 sexually active women with squamous cell abnormalities of the uterine cervix of the PAP smear.

### Criteria of exclusion

This study did not include: pregnant women, women with previous surgery on the uterine cervix (cervical conization, carbon dioxide laser vaporization and total hysterectomy) and also previous abnormal cytological and histopathological findings of the uterine cervix.

### Methods of examination

All samples for cytology were taken using Thin Prep PAP smear cytology and were analyzed in the Cytology laboratory of the University Clinic for Gynecology

and Obstetrics in Skopje by a doctor-cytopathologist. Cytological results were classified according to the revised Bethesda classification [6,7], such as: Atypical Squamous Cells of Undetermined Significance-ASC-US; Low-grade Squamous Intraepithelial Lesion-LSIL (productive HPV infection, Cervical Intraepithelial Neoplasia grade 1-CIN1); High-grade Squamous Intraepithelial Lesion-HSIL (CIN2, CIN3, CIS) and invasive squamous cell carcinoma.

Samples for histopathological analysis were taken at the University Clinic for Gynecology and Obstetrics in Skopje and were analyzed at the University Clinic for Radiotherapy and Oncology in Skopje, at the Department of Histopathology and Clinical Cytology by an experienced expert in histopathology. According to the morphology determined in biopsiesamples, cervical findings were characterized as: normal finding (non-specific cervicitis); Low-Grade Squamous Intraepithelial Lesion-LGSIL (Flat condyloma, cervicitis chronicavirosa, mild dysplasia); High-Grade Squamous Intraepithelial Lesion-HGSIL (moderate dysplasia, severe dysplasia, carcinoma in situ) and invasive squamous cell carcinoma.

### Statistical analysis

Data were analyzed by a specific software for databases (Excel). Statistical analysis of the established statistical series was made with the statistical program SPSS (Statistical Package for the Social Sciences), version 22.0.

The structure of numerical signs was analyzed by determining the measures of central tendency (arithmetical mean) and measures of dispersion (standard deviation).

The Spearman correlation test, ANOVA test, one-way variance analysis and the Tamhane test were used for statistical evaluations. Two-way comparisons were used to create 2x2 tables and calculate the positive predictive values.

A p value <0.05 was considered significant for statistical evaluation.

## RESULTS

The study included 184 women, aged 20 to 60 years (39.81±9.26). The cases aged of the cytopathological diagnostic groups were compared and the difference was found to be significant (p=0.001). A significant difference was found between the age of ASC-US and invasive cancer cases (p<0.03). There was also a significant difference between the age of LSIL and HSIL women (p<0.03) (Table 1).

**Table 1.** Distribution of mean age of cytopathological diagnostic groups

Cytopathological diagnosis	n	%	mean	sd
ASC-US	118	64.13	37.30	8.00
LSIL	22	11.96	34.63	8.53
HSIL	38	20.65	41.75	9.68
Invasive carcinoma	6	3.26	45.56	10.26
Total	184	100	39.81	9.26

Legend: ASC-US-atypical squamous cells of undetermined significance; LSIL-low grade squamous intraepithelial lesion; HSIL-high grade squamous intraepithelial lesion; n-number; sd-standard deviation

Cytopathologically, there were: 118 (64.13%) ASC-US, 22 (11.96%) LSIL, 38 (20.65%) HGSIL and 6 (3.26%) invasive carcinoma cases.

We found a significant difference between the age of the nonneoplastic group and LGSIL women ( $p=0.001$ ). There was also a significant difference between the age of LGSIL and squamous cell carcinoma women ( $p=0.002$ ) (Table 2).

**Table 2.** Distribution of mean age of histopathological diagnostic group

Histopathological diagnosis	n	%	mean	sd
Nonneoplastic	108	58.70	38.73	7.21
LGSIL	24	13.04	33.11	8.51
HGSIL	42	22.83	43.22	11.00
Invasive carcinoma	10	5.43	44.16	10.30
Total	184	100	39.81	9.26

Legend: LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion, n-number; sd-standard deviation

Histopathologically, there were 108 (58.70%) nonneoplastic lesions, 24 (13.04%) LGSIL

cases, 42 (22.83%) HGSIL cases and 10 (5.43%) invasive squamous cell carcinomas (Table 3).

**Table 3.** Correlation between results of cervical cytology and cervical biopsy

Cytopathological diagnosis	Histopathological diagnosis									
	Nonneoplastic		LGSIL		HGSIL		Invasive carcinoma		Total	
	n	%	n	%	n	%	n	%	n	%
ASC-US	94	51.08	12	6.52	12	6.53	0	0	118	64.13
LSIL	11	5.99	7	3.80	4	2.17	0	0	22	11.96
HSIL	3	1.63	5	2.72	26	14.13	4	2.17	38	20.65
Invasive carcinoma	0	0	0	0	0	0	6	3.26	6	3.26
Total	108	58.70	24	13.04	42	22.83	10	5.43	184	100

Legend: ASC-US-atypical squamous cell of undetermined significance; LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion; n-number; %-percent

The relationship between cytopathological and histopathological results was significant ( $r=0.9992$ ,  $p<0.00001$ ,  $p<0.05$ ).

When all the squamous cell abnormalities in the cervical cytology was included, the sensitivity of the PAP test for LSIL and higher grade lesions was 58.70% (108/184) while false positivity was 41.30% (76/184). When ASC-US were excluded, the sensitivity was 78.80% (52/66) and false positivity 21.21% (14/66).

We were unable to calculate sensitivity, specificity and negative predictive value for the women groups as there were no real negative or false negative groups. The correlation was calculated using the positive predictive value (PPV) according to our study data.

The cyto-histopathological correlation increased in parallel to the grade of PPV and was 100% for invasive squamous cell carcinoma, 68% for HSIL and 32% for LSIL (Table 4).

**Table 4.** Positive predictive value of cyto-histopathological diagnosis

Cytopathological diagnosis	Histopathological diagnosis	PPV
LSIL	LGSIL	0.32
HSIL	HGSIL	0.68
Invasive carcinoma	Invasive carcinoma	1

Legend: PPV-positive predictive value; LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion

The cyto-histopathological comparison for cervical intraepithelial lesions and invasive carcinoma revealed that the PAP test predictive value increased as the epithelial abnormality of the lesion increased and was 20% for ASC-US, 50% for LSIL, 92% for HSIL and 76% for LSIL+HSIL (Table 5).

**Table 5.** Positive predictive value of cytology groups

Cytopathological diagnosis	PPV
ASC-US	0.20
LSIL	0.50
HSIL	0.92
LSIL+HSIL	0.76

Legend: PPV-positive predictive value; ASC-US-atypical squamous cell of undetermined significant; LSIL-low squamous intraepithelial lesion; HSIL-high squamous intraepithelial lesion

## DISCUSSION

The aim of using the cervical smear test is screening sexually active women to enable early detection and treatment of precancerous lesions and prevent mortality due to cervical cancer. There is a relationship between the widespread use of the cervical smear test and decreased mortality due to invasive squamous cancer. Screening programs have therefore been developed all over the world. Cases where a cytological abnormality has been detected undergo biopsy from the suspect lesions under colposcopy for a definite diagnosis [8].

It is difficult to definitely establish PPV of the PAP smear test preinvasive lesions. The literature figures are 50-90% for sensitivity and 31-90% for specificity [9]. The PPV is 17-89% for preinvasive or microinvasive lesions and almost 100% for squamous cell carcinoma [10,11].

A study where the cyto-histopathological correlation of 374 cases was analyzed showed full match between the cytology and biopsy in 43.10% of the cases while this rate was 48.38% and 62.50% for low-grade and high-grade lesions, respectively. Cervical cytology sensitivity was 77.31% [12].

We found increased cyto-histopathological correlation with the cervical intraepithelial lesion as the degree of epithelial cell abnormality increased. The PPV was 20% for ASC-US, 50% for LSIL, 92% for HSIL and 76% for LSIL+HSIL. We evaluated the cervical cytology and cervical biopsy correlation again after matching the Bethesda terminology counterpart of the smear results with the SIL terminology results of the biopsy results. The PPV again showed an increase with the lesion degree and was 32%, 68% and 100% for LSIL, HSIL and invasive carcinoma cases, respectively.

Cervical precancerous lesions can be detected approximately 10 years before they become cancerous with the PAP smear screening. Comparison of the age of our patients revealed a significant difference between LGSIL and invasive carcinoma. The mean age for LGSIL group was 33.11 while the squamous cell carcinoma group had a mean age of 44.16 with a difference of over 10 years. This indicates that a period where lesions can be detected and treated before they become cancerous exists.

The clinical results of patients diagnosed as ASC-US by cervical smear can show great variety, from clearly benign lesions to potentially serious lesions and it is therefore not possible to provide a definite classification. In our study the total rate of cervical intraepithelial lesions among cases with an ASC-US smear result was 20.34%. According to a study by Massad et al., on the basis of histological results of cytological finding, 22.3% of ASC-US finding really are histologically positive [13]. Various laboratories report a SIL rate of 15-30% among ASC-US cases [14,15].

In our study, women with LSIL cytology results had a dominant histological LGSIL results (50%), whereas the HGSIL results was confirmed in 18.18%. Our results corresponding with results in study by Milenkovic et al. [16].

Studies show that, with a cytological HSIL result, more than 50% of the women will have HGSIL and 2% will have invasive carcinomas [17]. In our study 68.42% of cytological



HSIL results had a histological HGSIL results and 10.55% had a invasive cervical carcinomas. Data also show that between 20% and 30% of HSIL results are not diagnosed by cervical cytology [18].

In our study the sensitivity of the PAP smear test in LGSIL and higher grade lesions was 58.70% and the false positivity was 41.30%. Excluding ASC-US lesions, the sensitivity of the PAP smear test was 78.80% and the false positivity was 21.21%. Another study on cyto-histopathological correlation found a false positivity rate of 3.5% and a false negativity rate of 5.3%. The most common cause of false negativity was sampling error [19].

## CONCLUSION

Increased degree of neoplasia in cervical lesions increases the correlation between PAP smear and biopsy. The high sensitivity of the PAP smear test for high-grade lesions shows that it is an effective screening test for cervical cancer and precursor lesions.

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## КОРЕЛАЦИЈА ПОМЕЃУ ЦИТОПАТОЛОШКИТЕ И ХИСТОПАТОЛОШКИТЕ НАОДИ КАЈ ЖЕНИ СО СКВАМОЗНИ КЛЕТОЧНИ АБНОРМАЛНОСТИ НА ГРЛОТО НА МАТКАТА

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### АБСТАРКТ

**Вовед:** Целта на студијата беше да направиме корелација помеѓу цервикалните цитолошки наоди и цервикалните биоптични наоди кај жени со сквамозни клеточни абнормалности на грлото на матката.

**Материјал и методи:** Оваа компаративна ретроспективна студија беше направена на серија од 184 сексуално активни жени, на возраст од 20 до 60 години, кои дојдоа на редовен годишен гинеколошки преглед на Универзитетска Клиника за Гинекологија и Акушерство во Скопје, во периодот од Септември 2015 година до Март 2016 година. Кај сите 184 жени со цитолошки наод на сквамозни клеточни абнормалност на грлото на матката, беше направена цервикална биопсија со ендоцервикална киретажа за хистопатолошка анализа, која беше направена на Универзитетска Клиника за Радиотерапија и Онкологија во Скопје. Резултатите од liquid-based ПАП размаските и од цервикалните биопсии беа споредени и евалуирани за дијагностичка точност помеѓу цитопатолошките и хистопатолошките наоди.

**Резултати:** Цитопатолошки беа: 118 (64.13%) случаи на ASC-US, 22 (11.96%) случаи на LSIL, 38 (20.65%) случаи на HSIL и 6 (3.26%) случаи на инвазивен сквамозен карцином на грлото на матката. Хистопатолошки беа 108 (58.70%) случаи на нормален наод, 24 (13.04%) случаи на LGSIL, 42 (22.83%) случаи на HGSIL и 10 (5.43%) случаи на инвазивен сквамозен карцином на грлото на матката. Вклучувајќи ги сите сквамозни клеточни абнормалности, сензитивноста на ПАП тестот за лезиите од низок степен и за повисоките степени беше 58.70% (108/184) и лажно позитивноста беше 41.30% (76/184). Исклучувајќи ги ASC-US лезиите, сензитивноста на ПАП тестот беше 78.80% (52/66) и лажно позитивноста беше 21.21% (14/66). После направената цервикална цитопатолошка корелација, позитивната предиктивна вредност беше 100% (6/6) за случаите со инвазивен карцином, 68.42% (26/38) за HGSIL случаите и 31.82% (7/22) за LGSIL случаите.

**Заклучок:** Високата сензитивност на ПАП тестот за сквамозните интраепителни лезии од висок степен, кажува дека ПАП тестот е ефективен скрининг тест за цервикалниот карцином и неговите преканцерозни лезии.

**Клучни зборови:** цитопатологија, хистопатологија, сквамозни клеточни абнормалности, liquid-based размаска, цервикални биопсии