

# The Correlation between Squamous Cell Abnormalities by Liquid based Cytology and Histopathology

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## Abstract

**Objective:** To evaluate the correlation between squamous cell abnormalities by liquid-based cytology and histopathology, and to evaluate the accuracy of liquid-based cytology in detecting cervical squamous cell abnormalities.

**Methods:** A total of 943 patients with squamous cell abnormalities by liquid-based cytology underwent colposcopic examination from June 2014 until May 2017. The final histopathology was defined as the most severe lesion from colposcopic directed biopsy, excision procedure or hysterectomy.

**Results:** A majority of abnormal cytology was LSIL (45.6%), followed by ASCUS, HSIL, ASC-H and SCC (29.6%, 13.5%, 9.7%, and 1.7%, respectively). LSIL/ASCUS cytology was confirmed to be CIN1 or less in approximately 90% of patients but coexisting high-grade lesions (CIN2/3) occurred in about 10% and invasive cancer was less than 1%. HSIL and ASC-H cytology yielded about 50% and 25% high-grade lesions, respectively; coexisting invasive cancer was diagnosed in 10.2% and 1.1%, respectively. Invasive cancers were diagnosed in 43.8% of patients with SCC cytology. The accuracy of liquid-based cytology for detecting cervical squamous cell abnormalities was 79.8%. There was a moderate correlation between cervical cytology and histopathology ( $\text{Kappa}=0.43$ , 95% CI=0.36-0.50).

**Conclusion:** The correlation between cervical cytology and histopathology remained moderate. Despite, acceptable accuracy rate, it should only be used as a screening test. About 10% of the high-grade lesion was found in low-grade cytology and 10% of invasive lesion co-existed in high-grade cytology. Therefore, pathological confirmation should be made before definitive management especially in areas with high incidence of cervical cancers.

**Keywords:** Cervical cytology; Cervical cancer correlation; Histopathology; Liquid-based cytology; Squamous cell abnormalities

## Introduction

Cervical cancer is the second most common female cancer in developing countries. It causes about 265,672 deaths each year and has become the fourth most common leading cause of cancer deaths worldwide. According to the well-established screening program by using Papanicolaou testing, the rates of cervical cancer have decreased over the past 40 years in developing countries [1]. Cervical cytology has been used in many cervical cancer screening programs including the ACS, ASCCP or ASCP guidelines [2]. Previous data shows that liquid-based cytology produced a better quality slide and had higher sensitivity for detecting low-grade disease compared to conventional cytology [3-7]. However, all guidelines still include both conventional cytology and liquid-based cytology as cervical cancer screening techniques [2,8,9].

Although cervical cytology plays an important role in the screening and prevention of cervical cancer, there is limited data about the accuracy of cytological examination compared with the gold standard using histopathology of the cervix. Several studies have evaluated the correlation between cytology and histopathology of cervical lesions. However, there was a variety of cytological sampling methods and a different definition of low-grade cytology. Some studies included only LSIL but some included ASCUS as low-grade cytology. As the result, the overall agreement between cytology and histopathology ranges widely between 58%-79% [10-14].

This study aims to evaluate the correlation between squamous cell abnormalities by liquid-based cytology and histopathology and to evaluate the accuracy of liquid-based cytology in detecting cervical squamous cell abnormalities.

## Materials and Methods

A retrospective review was conducted in women with squamous cell abnormalities by liquid-based cytology that underwent colposcopic examination between June 2014 and May 2017. Patients with a previous history of cervical or endometrial cancer and patients without a histopathologic diagnosis were excluded from this study.

Colposcopic examinations were performed by experienced gynecologic oncologists or gynecologic oncology fellows. Suspicious areas on the cervix were biopsied and sent for histopathologic evaluation. In patients with normal colposcopic findings, random biopsy or endocervical curettage was performed. Patients who had cytopathologic discrepancy received further excision procedure. The most severe lesions either from colposcopic directed biopsy, excisional procedure or hysterectomy were considered as the final histopathologic diagnosis.

## Statistical Analysis

SPSS version 22 (SPSS Inc, Chicago, IL, USA) was used for statistical

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**Received** January 09, 2019; **Accepted** January 31, 2019; **Published** February 07, 2019

**Citation:** Areeruk W, Manchana T (2019) The Correlation between Squamous Cell Abnormalities by Liquid based Cytology and Histopathology. J Integr Oncol 8: 222.

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analysis. Data were presented as mean±SD, frequencies, and percentages. The overall agreement between cytology and histopathology results was analyzed using the Kappa coefficient.

## Results

84,461 liquid-based cytology tests were done during the study period. Squamous cell abnormalities were found in 3,478 cases (4.1%). A total of 943 patients with squamous cell abnormalities by liquid-based cytology underwent colposcopic examination were included in the study. Mean age of the patients was 40.7 ± 12.1 years. Most were multiparous, premenopause and did not use hormonal contraception (Table 1). A majority of abnormal cytology was LSIL (45.6%), followed by ASCUS, HSIL, ASC-H and SCC (29.6%, 13.5%, 9.7%, and 1.7%, respectively).

Low-grade lesions (CIN1/HPV infection) was the most common histopathological diagnosis, the incidence was 61.6%. High-grade lesions (CIN2/3) were detected in 17.6% of patients and 2.6% of patients had invasive cervical cancers. Table 2 shows cytologic results in relation to the histopathologic results. ASCUS cytology yielded a diagnosis of low-grade lesions in 68.8%, CIN2/3 in 11.2% and invasive cancer in 1.1% of the cases. LSIL cytology was confirmed to be CIN1 or no intraepithelial lesions in 90% of patients but coexisting high-grade lesions (CIN2/3) occurred in 9.7% and invasive cancer in 0.2%. HSIL and ASC-H cytology yielded high-grade lesions in 49.6% and 24.2%, respectively; coexisting invasive cancer was diagnosed in 10.2% and 1.1%, respectively. CIN3 was diagnosed in 50% of patients with SCC cytology, but 43.8% of these patients had invasive cancers (37.5%

Cytology	Histopathology		
	Low grade	High grade**	Total
Low grade*	632 (89.1%)	77 (10.9%)	709
High grade*	113 (48.3%)	121 (51.7%)	234
Total	745 (79.0%)	198 (21.0%)	943

\*Low grade cytology included ASCUS, LSIL  
 \*High grade cytology included ASC-H, HSIL, SCC  
 \*\*High grade pathology is defined as CIN2+

**Table 3:** Cytologic results in relation to the histopathologic results, comparing between low grade and high grade cytology.

squamous cell carcinoma and 6.3% adenocarcinoma). There was one case of SCC cytology with biopsy results showing VIN1 (6.3%). This patient was post-hysterectomy due to a pre-invasive lesion of the cervix and she was followed with cytology every 6 months.

Table 3 compares cytologic results and histopathologic results between low grade and high-grade cytology. The accuracy of liquid-based cytology for detecting cervical squamous cell abnormalities was 79.8%. By defining high-grade cytology as ASC-H or higher grade cytology, there was a moderate correlation between cervical cytology and histopathology (Kappa=0.43, 95% CI=0.36-0.50).

## Discussion

Among cervical cancer patients, squamous cell carcinoma remains the most common pathology. Therefore, detection and treatment of pre-invasive cervical squamous cell lesions are important for the prevention of invasive cervical cancers. Several studies have evaluated the performance of cytology in detecting pre-invasive cervical lesions, but the results still varied. This variation was due to various methods of cervical cytology sampling and cut off reference for positive cytology such as ASCUS cytology was excluded in some studies. Moreover, the incidence of high-grade cervical lesions varies among different regions of the world. Therefore, our study aimed to evaluate the performance of liquid-based cytology in detecting cervical squamous cell abnormalities in central Thailand.

A previous study reported a high rate of significant high-grade lesions in low-grade cytology among Northern Thais, which was 10% high-grade lesions and 0.2% invasive lesions in low-grade cytology [15]. This is consistent with our study that also detected about 10% high-grade lesions and 0.6% invasive lesions in low-grade cytology. Another study in Asia also demonstrated this high rate of high-grade lesions (13%) in low-grade cytology, whereas the incidence was lower in the USA which reported about 2.6% high-grade lesions and 0% invasive lesion in low-grade cytology [10,16]. According to this data, health care providers should pay attention to patients with low-grade cytology to exclude high grade or invasive lesion especially in areas with high incidence of cervical cancers.

The performance of LSIL in our study yielded CIN1 and CIN2/3 in about 70% and 10%, respectively, and only 0.2% had invasive cervical cancer. These numbers were similar to ASCUS cytology, and this could probably support the suggestion that LSIL is equivalent to ASCUS [10]. The performance of HSIL in our study yielded invasive cancer in 10%, which was higher than other studies done in low cervical cancer incidence countries but lower than the study done in Northern Thailand where the incidence of cervical cancer is very high [10,17,18]. Our study revealed 10.2% invasive cancers and 55.1% high-grade lesions in HSIL, whereas another study conducted in the USA reported only 2% invasive cancers but 65% high-grade lesions [17]. The reviewed study in Thailand reported as high as 16.6% invasive cancers and 68.4%

Characteristics		
Mean age (years ± SD)		40.7 ± 12.1
Parity	Nulliparous	281 (29.8%)
	Multiparous	511 (54.2%)
	Missing	151 (16.0%)
Menopausal status	Premenopause	693 (73.5%)
	Postmenopause	222 (23.5%)
	Missing	28 (3.0%)
Transitional zone	Type1	556 (59.0%)
	Type2	106 (11.2%)
	Type3	224 (23.8%)
	S/P Hysterectomy	45 (4.8%)
	Not address	12 (1.3%)
Contraception	Oral contraceptive pills	75 (8.0%)
	Others	192 (20.4%)
	None	579 (61.4%)
	Unknown	97 (10.3%)

**Table 1:** Baseline characteristics.

Cytology	Histopathology					
	Benign (N=170)	CIN1/HPV (N=575)	CIN2 (N=9)	CIN3 (N=164)	SCCA (N=24)	AdenoCA (N=1)
ASCUS (N=279)	53 (19.0%)	192 (68.8%)	1 (0.4%)	30 (10.8%)	3 (1.1%)	0
LSIL (N=430)	86 (20.0%)	301 (70.0%)	4 (0.9%)	38 (8.8%)	1 (0.2%)	0
ASC-H (N=91)	23 (25.3%)	45 (49.5%)	0	22 (24.2%)	1 (1.1%)	0
HSIL (N=127)	8 (6.3%)	36 (28.3%)	4 (3.1%)	66 (52.0%)	13 (10.2%)	0
SCC (N=16)	0	1 (6.3%)	0	8 (50.0%)	6 (37.5%)	1 (6.3%)

**Table 2:** The histopathological results according to different cytologic categories.

high-grade lesions in HSIL cytology. The highest incidence was found in Northern Thailand and the suburban area of Bangkok, showing up to 20% invasive cancers in HSIL cytology [7,15,18]. Therefore, invasive cervical cancer should be another point of concern in taking care of high-grade cytology in high cervical cancer incidence countries.

The accuracy of liquid-based cytology for detecting cervical squamous cell abnormalities in this study was slightly higher than several studies that used conventional cytology which reported about 58%-79% [11-14]. This can be explained by the probability of confounding from inflammation or obscuring blood in conventional cytology that leads to under-reporting of cytology results. Liquid-based cytology also produces better slide quality, lowers unsatisfactory specimens and retains specimen for further investigation such as HPV testing [3-7]. However, data on the accuracy of liquid-based cytology were sparse, and our study showed that the accuracy rate was slightly lower than one previous study; that is, 79.8% compared to 85.4% [10].

Whereas a previous study reported a weak correlation between conventional cytology and histopathology ( $\text{Kappa}=0.10-0.23$ ) [17,19], our study showed a moderate correlation between liquid-based cytology and histopathology ( $\text{Kappa}=0.43$ , 95%  $\text{CI}=0.36-0.50$ ). These findings suggest that liquid-based cytology is acceptable for the screening and detection of pre-invasive cervical lesions.

The strength of our study is a large number of cases, including nearly a thousand patients with squamous cell abnormalities. Moreover, we used all abnormal squamous cell cytological categories including ASCUS in the detection of abnormal squamous cell abnormalities. The limitation is that we used only cases with histopathologic diagnosis. Some patients with normal colposcopic findings or having lesions in the endocervical canal might be missed. However, random biopsies were performed in all patients with negative colposcopic findings aiming to confirm a true negative result.

In conclusion, the correlation between cervical cytology and histopathology remained moderate. Despite, acceptable accuracy of liquid-based cervical cytology, it should be used only as a screening test. About 10% of high-grade lesions were found in low-grade cytology and 10% of co-existing invasive cancers were found in high-grade cytology. Therefore, pathological confirmation should be made before definitive management especially in areas with high incidence of cervical cancers.

## Conflicts of Interest

The authors declared no conflicts of interest.

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