Original Article

Positive predictive values of cytological cervical diagnosis of high grade squamous intraepithelial lesions from the Thammasat University Hospital

Wasu Sae-Tia, Araya Sammor

Abstract

Introduction: To determine and update positive predictive values of cervical paps smear among patients who were diagnosed High-grade Squamous Intraepithelial Lesion (HSIL) for Cervical Intraepithelial Neoplasia (CIN) grades 2, 3 or invasive squamous cell carcinoma (SCC) in Thammasat University Hospital which was reported to be 84% in 2012.

Methods: For this retrospective study of patients who were diagnosed HSIL ± Human papilloma virus infection and ± glandular involvement from cytology including conventional and liquid base smear with cervical histological report within 6 months after the cytological diagnosis from 1st January 2014 to 31st December 2017. All cases which were reported less severe than CIN grade 1 are re-diagnosed by a general pathologist to confirm the discordant.

Results: There are 84 patients who specify inclusion and exclusion criteria. The positive predictive values of HSIL for CIN2 or CIN3 are 73.8% and 79.7% for CIN2+ (CIN2, CIN3 and invasive squamous cell carcinoma (SCC)).

Conclusion: The PPV of HSIL for CIN2+ is lower than the previous study from the same hospital and cytological report needs to correlate with clinical findings and colposcopic examination for the best diagnostic value. The factors that may affect the PPV in this study such as gaps between cytology and histology, biopsy procedure, cytological preparation and spontaneous regression of disease.

Keywords: High-grade Squamous Intraepithelial, Lesion Cervical cytology, Pathology.

Received: 27 November 2018 **Revised: 3 April 2019** **Accepted: 17 April 2019**

Department of Pathology and Forensic medicine, Thammasat University

Corresponding author: Wasu Sae-Tia, Department of Pathology and Forensic Medicine, Faculty of Medicine, Thammasat University, 99 Moo 18 Paholyotin Rd. KlongNheung KlongLuang Pathumthani, 12120, Thailand Tel. 02 - 926-9144 E-mail: grandia28657@gmail.com

Introduction

Cervical cancer is a fifth most common cancer in Thailand (8.23% of new cancer patients in 2015).[1] The Papanicolaou smear (Pap smear) is most widely screening tool for cervical cancer which significantly reduces the mortality.[2, 3] In Thailand, despite of liquid-based cytology (LBC), conventional cytology is still the standard screening test due to the financial support from the government. The screening measures and treatment for Cervical Intraepithelial Neoplasia (CIN) is the secondary prevention of cervical cancer.[4] Management of abnormal cervical cytology depends on the degree and severity of the lesion.[2] Colposcopic guided biopsy remains a critical diagnostic step after the cytological evaluation to identify the patient who requires treatment.[5]

"Squamous intraepithelial lesion" was first introduced in 1988 and remained in 2001 Bethesda system which has 2-tiered terminology as low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous cell intraepithelial lesion (HSIL) for spectrum of non-invasive squamous cervical abnormalities. The division of SIL reflects the progression of disease that LSIL is a transient infection with HPV, while HSIL is more often associated with viral persistent lesion with higher risk of viral progression.[6]

The positive predictive value (PPV) is the percentage of patients with a positive test who have the disease which means how many of test positives are true positives and if this number is higher (as close to 100 as possible), then it suggests that this test is doing as good as gold standard.[7] The gold standard test for diagnostic performance of cervical pap smear is histological evaluation.

In 2012, from the retrospective study by Kanjanavirojkul et al.[8], the PPV was reported to be 84% for CIN2+ (CIN2+; including CIN 2, 3 and squamous cell carcinoma) in Thammasat University Hospital. The study aims to 1) evaluate PPV of HSIL and 2) compare the result with previous study in 2015 and other recent studies.

Methods

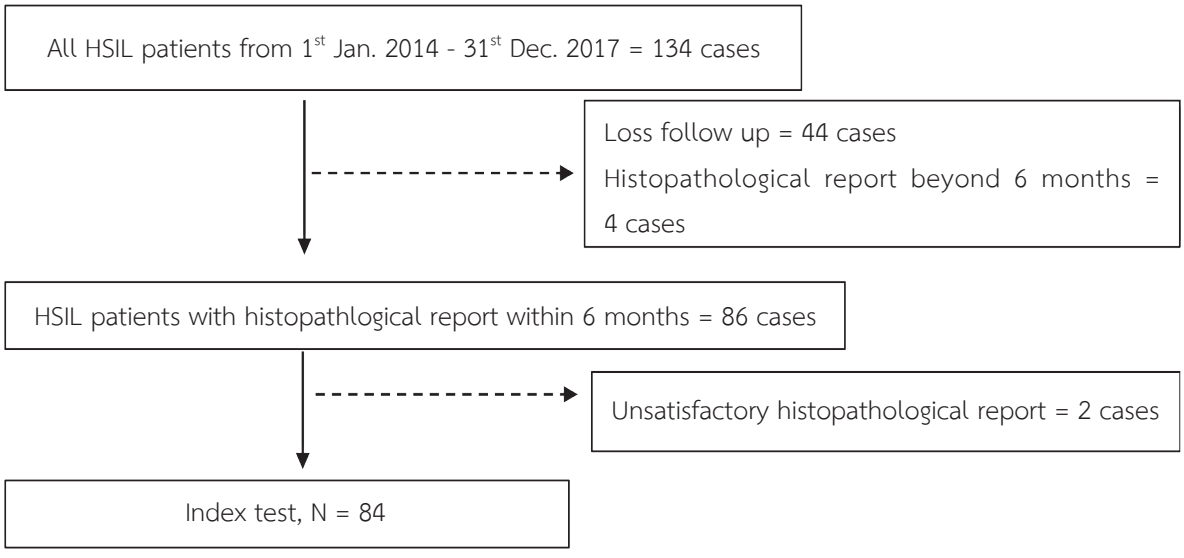
This retrospective study collected the patient data who had screening cytological diagnosis as HSIL ± glandular involvement ± Human papillomavirus infection at cervix from either conventional and liquid base smear at Thammasat University Hospital during 1st January 2014 - 31st December 2017. The cytological and histological results were report based on the Bethesda System 2001 and WHO Classification of Tumors of Female Reproductive Organs 2014, respectively. The inclusion criteria are as follows: 1) Patient had first histological diagnosis either from colposcopic biopsy or LEEP within 6 months after the cytological diagnosis and 2) the diagnosis was done by Thammasat University Hospital pathologist. The exclusion criteria are as follows: 1) The paraffin block, cytological or histological slide was disappeared and 2) the histological diagnosis showed unsatisfactory.

The patient data was collected from the electronic database. The data consists of age, type of cytological preparation, and gap between the cytological and histological evaluation, cytological diagnosis and histological diagnosis. All slides from the HSIL patient who had pathological diagnosis less severe than CIN2 were reviewed by a general pathologist to confirm the discordant. The PPV of HSIL for CIN2, 3 and CIN2+ (CIN2+=CIN2, CIN3 or SCC) was calculated by using 2×2 tables with the standard formula. The gold standard test in this study is first time histopathological report either from colposcopic biopsy or LEEP.

Results

A total of 134 cervical HSIL patient's data was collected. 44 patients were lost to follow up. 6 patients had a histological diagnosis is beyond 6 months after cytological diagnosis, 2 patients were diagnosed unsatisfactory on histological report. There are only 84 patients who met the requirement of inclusion and exclusion criteria (n = 84) (Figure 1). The pathological reports after reviews the discordant cases of all HSIL patients are described as reactive in

11 cases, CIN1 in 6 cases, CIN 2 in 20 cases CIN 3 in 42 cases and squamous cell carcinoma (SCC) in 5 cases (Table 1). The positive predictive value (PPV) for CIN2 and CIN3 is 73.8% and for CIN2+ (CIN2+=CIN2, CIN3 or SCC) is 79.7%. The patients were divided into 2 groups for comparing the demographic data. The first group is the patients who had discordant between cytological and pathological report (cytological diagnosis is HSIL but histological diagnosis is less severe than CIN2) (Figure 2) and the second group is the patients who had concordant between cytological and histological diagnosis (Table 2).



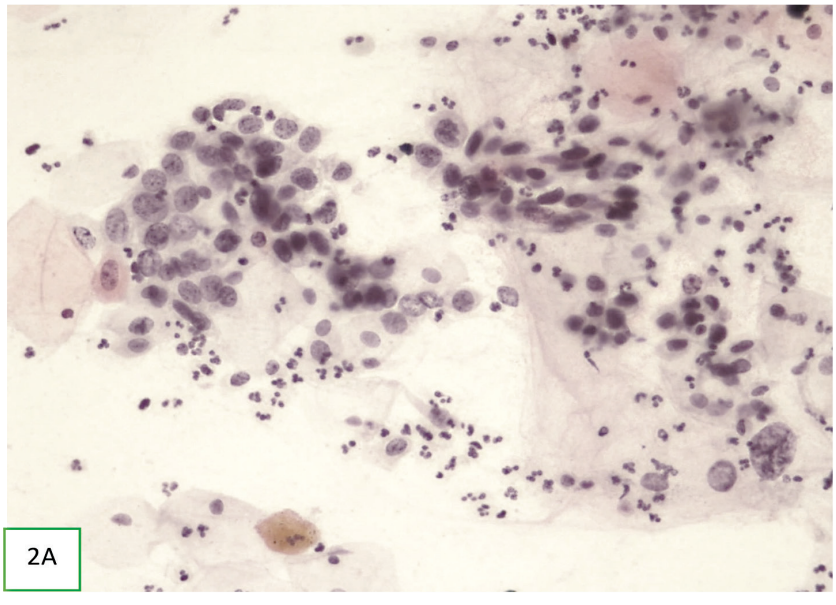


Figure 1 Diagram of the study flow

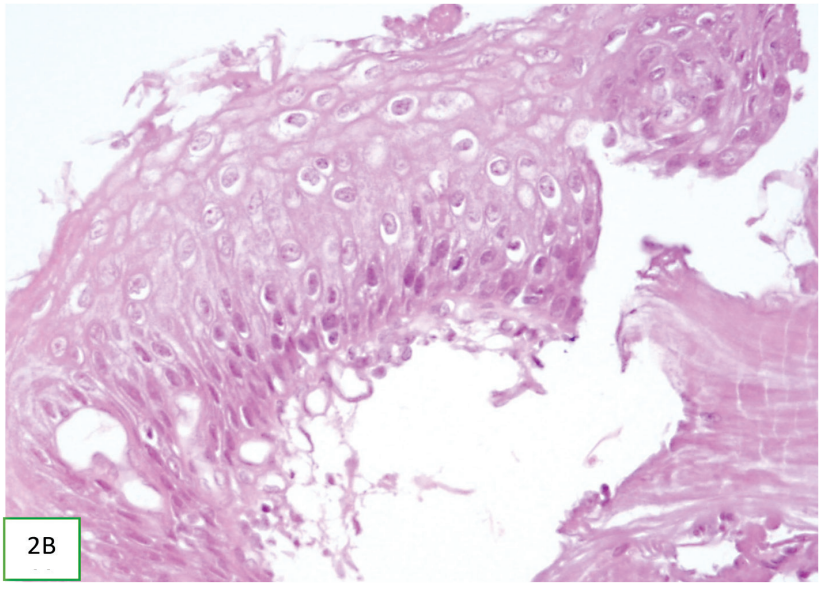


Figure 2 Slides from the discordant case between cytological and histological diagnosis. 2A) Conventional pap smear slide reveals high-grade dysplastic squamous cells and 2B) Histological slide from the same patient shows CIN 1 with koilocytic change without evidence of CIN2, CIN3 or SCC.

Table 1 Histopathological diagnosis for HSIL patients.

Cytological diagnosis	Histopathological diagnosis (gold standard)					
HSIL***	Reactive	CIN*1	CIN2	CIN3	SCC**	Total
	11	6	20	42	5	84

* Cervical Intraepithelial neoplasia, ** Squamous cell carcinoma and *** High-grade squamous intraepithelial lesion.

Table 2 Demographic data of patients of discordant and concordant groups.

	Histological diagnosis	
	≤ CIN1	CIN2+
Number of case (n=84)	17	67
Mean age ± S.D.	40.9 ± 10.2	44.5 ± 15.1
Smear preparation		
Conventional smear	15	60
Liquid base smear	2	7
Histological procedure		
Cervical biopsy	17	64
LEEP	0	3
Time gap between reports (months)	2.6	2.4

Discussion

The results of the positive predictive values (PPV) for CIN2+ in cervical pap smear in the literature regardless of the type of cytological preparation (conventional or liquid-based cytology) are about 57 - 100%[8 - 16] in which the average PPV is about 85.2%.[8 - 16] The PPV reported by Kanjanavirojkul et al.[8] from 75 HSIL patients in the Thammasat University Hospital (same hospital with this study) was 84%. Despite lower than the average and the previous study (see Table 3), PPV in this study (79.7%) is in the range of previous research. According to discordant between cytology (HSIL) and histology (less severe than HSIL) false-positive cytology and false-negative histology are the conditions that may affect PPV.[10] After reviewing the diagnosis of 17 cases, the cytology of all cases met the criteria for diagnosis of HSIL and for the histological diagnosis, there is no evidence of CIN2+ which is distinct in H&E stain. So, all discordant cases have no false-positive cytology and no false-negative histology in this study. The factors that may cause the variation of PPV in different studies are described as follows: 1) Time of biopsy procedure; the gold standard test in this study is the first histopathological diagnosis within 6 months after cytological diagnosis. Multiple followed up biopsy can reveal the lesion about 42.5% of the negative cases from the first biopsy.[17] According to the previous studies which had higher PPV than this study, Cobucci[9] (PPV = 99%) used all histological reports from every procedure as a gold standard. Kanjanavirojkul[8] (PPV = 85%) used the final histological as a gold standard. 2) Type of procedure. LEEP has higher yield than colposcopic biopsy.[18] Van Hemel[12] (PPV = 97%) used the histopathological diagnosis to calculate PPV only from LEEP and hysterectomy procedures. In this study, the specimens are almost colposcopic biopsy (81 from 84 cases). However, Pimple[11] (PPV = 89.4%) and Mukhopadhyay[14] (PPV = 100%) used the histopathological diagnosis only from colposcopic biopsy specimen still showed higher PPV than this study but no how many times of biopsy was described. 3) Type of cytological smear; in this study the cytological specimens are almost conventional smear (74/84 cases) comparing to van Hemel[12] study (PPV = 97%) which all cytological reports were interpreted from liquid base smears. Liquid-based cytology is generally assumed to produce better-quality slide than conventional method; which relate to sensitivity, specificity and higher positive predictive value.[19, 20] However, the results was controversy in Longatto-Filho[15] and Singh[21] reports. In Thailand, some studies suggested that the liquid base cytology has better sensitivity[22], specificity[22, 23] and positive predictive value[23] comparing to conventional smear. 4) Dysplastic lesion can spontaneous regress.[24] Most high-grade lesions are thought to be much more likely to persist than to regress. However, rates of spontaneous regression vary from 6% to 50%, depending on diagnostic criteria, and length of follow-up.[25] 28% of CIN2 and CIN3 lesions may spontaneously regress in 15 weeks (3.8 months).[25] In this study, the gap between cytological and histological diagnosis of discordant and concordant patients are 2.6 and 2.4 months. Unfortunately, it is impossible to compare this factor because the other studies did not purpose the gap. 5) Air-dry artifact can disturb the cytological evaluation.[9] Only one case from discordant patients that had air-dry artifact and still diagnosed as HSIL due to there were some remaining dysplastic squamous cells which met the HSIL criteria outside the air-dry artifact area. The other factors that did not describe in this study such as experience and the skill of the pathologist.[26, 27]

For the patients who had cytological diagnosis as HSIL and histological diagnosis as no dysplasia, it is important for clinicians to repeat the colposcopy and re-evaluate the squamocolumnar junction, endocervix and vagina. If the lesion is grossly absence, except in cytology with HSIL, conization with endocervical curettage emerges as a diagnostic and therapeutic possibility[10] and for the HSIL patient with histopathological diagnosis as CIN1, reviewing of

cytologic and histologic slides is an interesting approach to diminish the possibility of errors in interpretation. The repeated biopsy of the cervix might have been obtained at a site other than that of the most serious lesion.[10]

Table 3 PPV from various studies.

Author,Year	Case number (n)	PPV for CIN2+* (%)
Kanjanavirojkul[8], 2012	75	84
Cobucci[9], 2016	418	99
Aschau[10], 2011	216	89.8
Pimple[11], 2010	106	89.4
van Hemel[12], 2009	171	97
Repše-Fokter[13], 2011	695	82.6
Mukhopadhyay[14], 2013	56	100
Longatto-Filho[15], 2005	56	68.1
Nishio[16], 2018	140	57
This study, 2018	84	79.7

*CIN2+ = Cervical Intraepithelial Neoplasia grade 2, grade 3 or invasive squamous cell carcinoma

Conclusion

The PPV of HSIL for CIN2+ obtained from this study was 79.7% and lower than the previous studies. The factors that may affect the PPV in the difference studies are such as gaps between cytological and histological evaluations, biopsy procedure, cytological preparation and spontaneous regression of disease. The screening cytological report needs to correlate with clinical and colposcopic examination for the best diagnostic value.

Acknowledgments

This study is supported by a grant from Thammasat University. The authors gratefully acknowledge the staffs of the Department of Pathology, Faculty of Medicine Thammasat University Hospital for counsels.

Reference

1. กลุ่มงานเทคโนโลยีสารสนเทศสถาบันมะเร็งแห่งชาติ. ทะเบียนมะเร็งระดับโรงพยาบาล พ.ศ. 2558. กรุงเทพมหานคร:บริษัท พรทรัพย์การพิมพ์ จำกัด; 2560.
2. Poomtavorn Y, Himakhun W, Suwannarurk K, Thaweekul Y, Maireang K. Cytohistologic discrepancy of high-grade squamous intraepithelial lesions in Papanicolaou smears. Asian Pacific Journal of Cancer Prevention. 2013;14:599-602.
3. Kingnate C, Supoken A, Kleebkaow P, Chumworathayi B, Luanratanakorn S, Kietpeerakool C. Is age an independent predictor of high-grade histopathology in women referred for colposcopy after abnormal cervical cytology? Asian Pacific Journal of Cancer Prevention. 2015;16:7231-5.

4. Wongtiraporn W, Laiwejpithaya S, Sangkarat S, Benjapibal M, Rattanachaiyanont M, Ruengkhachorn I et al. Long term outcomes of laser conization for high grade Cervical Intraepithelial Neoplasia in Thai women. Asian Pacific Journal of Cancer Prevention. 2014;15:7757-61.
5. Wright T, Cox J, Massad L, Twiggs L, Wilkinson E. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. Journal of the American Medical Association 2002;287:2120-9.
6. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M et al. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. Journal of the American Medical Association 2002;287:2114-9.
7. Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. Indian Journal of Ophthalmology. 2008;56:45-50.
8. Kanjanavirojkul N, Muanglek R, Yanaqihara L. Accuracy of abnomal pap smear at Thammasat University Hospital. Journal of the Medical Association of Thailand. 2012;95:S79-82.
9. Cobucci R, Maisonnette M, Macêdo E, Santos Filho F, Rodovalho P, Nóbrega M et al. Pap test accuracy and severity of squamous intraepithelial lesion. Indian Journal of Cancer. 2016;53:74-6.
10. Anschau F, Guimarães Gonçalves M. Discordance between cytology and biopsy histology of the cervix: What to consider and what to do. Acta Cytologica. 2011;55:158-62.
11. Pimple S, Shastri S, Amin G, Goswami S. Evaluation of colposcopy vs cytology as secondary test to triage women found positive on visual inspection test. Indian Journal of Cancer. 2010;47:308.
12. Van Hemel B, Buikema H, Groen H, Suurmeijer A. Accuracy of a low priced liquid-based method for cervical cytology in 632 women referred for colposcopy after a positive Pap smear. Diagnostic Cytopathology. 2009;37:579-83.
13. Repše-Fokter A. Accuracy of the Papanicolaou test in the detection of high-grade cervical lesions. International Journal of Gynecology and Obstetrics. 2011;112:65-6.
14. Mukhopadhyay S, Ray S, Dhar S, Bandyopadhyay R, Sinha SK. Evaluation of the category high-grade squamous intraepithelial lesion in The Bethesda System for reporting cervical cytology. Journal of Cytology. 2013;30:33-5.
15. Longatto-Filho A, Maeda M, Eržen M, Branca M, Roteli-Martins C, Naud P et al. Conventional pap smear and liquid-based cytology as screening tools in low-resource settings in Latin America. Acta Cytologica. 2005;49:500-6.
16. Nishio H, Iwata T, Nomura H, Morisada T, Takeshima N, Takano H et al. Liquid-based cytology versus conventional cytology for detection of uterine cervical lesions: a prospective observational study. Japanese Journal of Clinical Oncology. 2018;48:522-8.
17. Zhang H, Xiao J, Tao X, Zhou X, Wang L. [Consistency of diagnosis between cervical cytology and colposcopic biopsy diagnosis]. Chinese Journal of Pathology 2018;47:444-8.
18. Yang B, Pretorius R, Belinson J, Zhang X, Burchette R, Qiao Y. False negative colposcopy is associated with thinner Cervical Intraepithelial Neoplasia 2 and 3. Gynecologic Oncology. 2008;110:32-6.
19. Strander B, Andersson-Ellström A, Milsom I, Rådberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program. Cancer. 2007; 111:285-91.
20. Zhu J, Norman I, Elfgren K, Gaberi V, Hagmar B, Hjerpe A, et al. A comparison of liquid-based cytology and Pap smear as a screening method for cervical cancer. Oncology Reports. 2007;18:157-60.

21. Singh V, Gupta N, Nijhawan R, Srinivasan R, Suri V, Rajwanshi A. Liquid-based cytology versus conventional cytology for evaluation of cervical Pap smears: Experience from the first 1000 split samples. Indian Journal of Pathology and Microbiology. 2015;58:17-21.
22. Phaliwong P, Pariyawateekul P, Khuakoonratt N, Sirichai W, Bhamarapravatana K, Suwannarurk K. Cervical cancer detection between conventional and liquid based cervical cytology: a 6-year experience in Northern Bangkok, Thailand. Asian Pacific Journal of Cancer Prevention. 2018;19:1331-6.
23. Arunratsamee P, Siwadune T. Arunratsamee P, Siwadune T. Comparison of diagnostic efficacy between Cytoneph® liquid-based cytology and conventional pap smear cytology in colposcopic clinic at Chonburi hospital. Thai Journal of Obstetrics and Gynaecology. 2012;20:41-7
24. Holowaty P, Miller A, Rohan T, To T. Natural history of dysplasia of the uterine cervix. Journal of the National Cancer Institute. 1999;91:252-8.
25. Trimble C, Piantadosi S, Gravitt P, Ronnett B, Pizer E, Elko A, et al. Spontaneous regression of high-grade cervical dysplasia: Effects of human papillomavirus type and HLA phenotype. Clinical Cancer Research. 2005;11:4717-23.
26. Chacho M, Mattie M, Schwartz P. Cytohistologic correlation rates between conventional Papanicolaou smears and ThinPrep cervical cytology: A comparison. Cancer. 2003;99:135-40.
27. Milne D, Wadehra V, Mennim D, Wagstaff T. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. British Journal of Obstetrics and Gynaecology. 1999;106:38-41.

บทคัดย่อ

ค่าทำนายผลบวกทางเซลล์วิทยาของผู้ป่วยที่มีเซลล์ปากมดลูกผิดปรกติระดับรุนแรงของโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

วสุ แซ่เตีย, อารยา สามหมอ
ภาควิชาพยาธิวิทยาและนิติเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

วัตถุประสงค์: เพื่อศึกษาค่าทำนายผลบวกของผู้ป่วยที่ได้รับการวินิจฉัยแล้วเป็น High-grade Squamous Intraepithelial Lesion (HSIL) จากการตรวจเซลล์วิทยาปากมดลูก ของโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติซึ่งเคยรายงานไว้ที่ 84% ในปี พ.ศ. 2555

วิธีการศึกษา: เก็บข้อมูลย้อนหลังนับตั้งแต่วันที่ 1 มกราคม พ.ศ. 2557 ถึงวันที่ 31 ธันวาคม พ.ศ. 2560 จากผู้ป่วยหญิงที่ได้รับการวินิจฉัยทางเซลล์วิทยาว่าเป็น HSIL และมีผลการตรวจชิ้นเนื้อภายใน 6 เดือน แล้วทำการตรวจวินิจฉัยซ้ำในรายที่มีผลชิ้นเนื้อรุนแรงน้อยกว่าเท่ากับ Cervical Intraepithelial Neoplasia (CIN) grade 1

ผลการศึกษา: ผู้ป่วยที่ผ่านเกณฑ์คัดอาสาสมัครเข้าและออก จำนวน 84 ราย มีค่าทำนายผลบวกของ HSIL สำหรับ CIN2 หรือ CIN3 เท่ากับ 73.8% และค่าทำนายผลบวกผู้ป่วย HSIL สำหรับ CIN2, CIN3 หรือ invasive squamous cell carcinoma เท่ากับ 79.7%

สรุปผลการศึกษา: ค่าทำนายผลบวกของผู้ป่วย High-grade Squamous Intraepithelial Lesion มีค่าน้อยกว่าเทียบกับการศึกษาล่าสุดและค่าเฉลี่ยที่ได้จากงานวิจัยที่ผ่านมา ปัจจัยที่ทำให้ค่าทำนายผลบวกแตกต่างกัน ได้แก่ ระยะห่างของการส่งตรวจเซลล์วิทยากับชิ้นเนื้อ, ลักษณะของชิ้นเนื้อ, วิธีการเตรียมเซลล์วิทยา และการทุเลาลงของรอยโรค เป็นต้น การตรวจเซลล์วิทยาควรใช้ร่วมกับข้อมูลทางคลินิกอื่น เพื่อให้ได้ประโยชน์สูงสุด

คำสำคัญ: เซลล์เยื่อบุปากมดลูกผิดปรกติระดับรุนแรง, การตรวจเซลล์วิทยาปากมดลูก, พยาธิวิทยา