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## GYNAECOLOGY

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# Histological Diagnosis of Conventional Pap Smear with Low Grade Squamous Intraepithelial Lesion (LSIL) in Chonburi Hospital

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### ABSTRACT

**Objective:** To determine the prevalence and factor associated with a histological diagnosis of high grade squamous intraepithelial lesion and invasive cervical cancer from conventional low grade cervical intraepithelial lesion (LSIL) Pap smear show in Chonburi Hospital

**Materials and methods:** Retrospective descriptive study from medical records of Chonburi Hospital that conventional Pap smears was reported as LSIL and had colposcopy and/or biopsy for tissue histology between December 2008 and May 2011.

**Results:** Two hundred and thirty patients diagnosed with LSIL from conventional Pap smear underwent colposcopy and/or tissue biopsy. The prevalence of invasive cervical cancer, HSIL, LSIL and normal/cervicitis were 0%, 16.5%, 66.5%, and 17.0% respectively. Age groups of 31 years old or older were the statistically significant factor associated with high grade lesion.

**Conclusion:** The prevalence of histological HSIL from conventional Pap smear diagnosed LSIL in Chonburi Hospital is 16.5%, no invasive cancer were found.

**Keywords:** conventional Pap smear, cervical cancer, HSIL, LSIL, colposcopy

### Introduction:

According to worldwide statistics, cervical cancer is the second most common gynecologic malignancy, second to breast cancer. As many as 529,000 women are affected, with the deaths of more than 270,000 cases each year<sup>(1)</sup>.

In Thailand, cervical cancer is also the second most common cancer, with age standardize rate at 18.1 per 100,000 population year. The International Agency for Research on Cancer (IARC) reported that Thailand has 9,999 new patients of cervical cancer per year with

5,216 deaths<sup>(1)</sup>. This means that 14 women die from cervical cancer everyday<sup>(2)</sup>. However, during these past 10 years, cervical cancer screenings could detect potentially precancerous changes and help reducing the incidence of invasive cervical cancer drastically<sup>(3,4)</sup>.

Most cases of cervical cancer were difficult to prevent at primary prevention level because of involvement of sexual behaviors. To educate people to change their behaviors are even more difficult. Moreover, Human Pappiloma Virus (HPV) vaccines are still limited and mostly unaffordable for many target

groups. Therefore, it could be said that preventions of cervical cancer at the moment are only done in secondary prevention level that is screening to identify any abnormal cytology. There is also a new technique such as liquid based cytology for screening abnormal cytology but conventional Pap smear is still the most widely used for the screening programs.

Pap smear results are currently categorized by The Bethesda system (revised 2001)<sup>(6)</sup>. When Pap smear tests show abnormal results, management guidelines will depend on many factors such as characteristics of clinical finding, severity of cytology, instrument and competent of clinicians, including compliance of patients. In general, if the initial cytology was reported as HSIL (high-grade squamous intraepithelial lesions), CIN II-III (cervical intraepithelial neoplasia II-III), they can be detected highly in histological examinations. Therefore, performing colposcopy and tissue biopsy is undoubtedly a must-perform procedure<sup>(4,6)</sup>. The American society for colposcopy & cervical Pathology (ASCCP) 2006, The American journal of obstetrics & gynecology (AJOG) consensus 2006 and the American college of obstetricians & gynecologists (ACOG) 2008 recommended that colposcopy should be done if cytology from Pap smear tests show LSIL because they can detect 15-30% of prevalence of high grade lesion (CIN II-III) and 0.1-3% of invasive carcinoma respectively<sup>(6,7)</sup>. However, some authors recommended a conservative management approach by repeating pap smear tests alone without doing any colposcopies because most of Pap smear LSIL (low grade squamous epithelial lesions) were likely to have high percentage of CIN I or HPV effect (low-grade lesion) which can be cleared or cured by itself<sup>(8,9)</sup>. Previous studies found that the prevalence of high grade lesions in cytological report of LSIL can vary from 15 to 34%<sup>(7,9-15)</sup>. The results of Pap smear screenings can also vary from pathologists to pathologists of each institute<sup>(16,17)</sup>. Based of such variations, the main objective of this study is to find the prevalence of high grade lesions (CIN II-III) in cytological report of LSIL at Chonburi Hospital. With these data, diagnosis can be decided upon and to provide more information and

resources for patients. This study also looked at the factors affecting the prevalence of high grade lesions in women with cytology LSIL.

## Materials and methods

This was a descriptive study. Data was collected from medical records of all patients who came for cervical cancer screening programs at Chonburi Hospital during December 1, 2009 and May 31, 2011. This study was approved by The Ethics Committee for Human Research of Chonburi Hospital. Patients came for cervical cancer screening programs with conventional Pap smear tests with results of cytology diagnosis "LSIL" then underwent colposcopy examinations were included. Women who were definite diagnosed with cervical cancer as well as those with a history of hysterectomy or incomplete data records were excluded.

All recorded files at registration contained information of ages, parity, contraception and menopausal status, including results of HIV tests. Patient's names and hospital numbers were separated from this research study's running numbers and filled separately.

Screenings was done by conventional Pap smear tests. According to Bethesda system 2001, cytological results were evaluated and interpreted by cytotechnologists and certified by pathologists at Chonburi Hospital. Patients were required to undergo colposcopy and/or biopsy by qualified gynecologic oncologists or gynecologists with colposcopic trainings experience. Colposcopic examination was performed following the application of 5% acetic acid solution to the cervix and upper vagina. Biopsy was obtained from the most abnormal appearing area of each separate lesion. As for endocervical curettage, it was only done on patients with unsatisfied colposcopy's results. The women with satisfactory colposcopy without suspicious lesion were defined as normal colposcopy and biopsy was not performed.

According to our Institute's guideline, if pathological results from biopsies show LSIL or HPV effect or CIN I equivalent, patients will be advised to repeat Pap smear every 6 months. If pathological results from biopsies show HSIL (CIN II, CIN III), LEEP

or CKC will be recommended. If pathological results from biopsies show carcinoma, staging and management of cervical cancer will be started.

Data was analyzed using SPSS version 11.5. Descriptive statistics such as characteristics of population were presented in numbers, mean and percentages between those used Chi-square test and those used Fischer's exact test as appropriated. The outcome was considered significant if p-value < 0.05.

## Results

During the period of 18 months between December 1, 2009 to May 31, 2011, 230 results were reported as LSIL and consequently, underwent colposcopy and/or biopsy. The average age of these women was 35.4 years (16-68) with 91.3% of premenopausal women and 16.5% of nulliparous. Characteristics of population were described in Table 1.

**Table 1.** Characteristic of women with low grade squamous intraepithelial lesion (n=230)

Characteristic	N	Percentage
Mean age(±SD) year	35.4(± 9.68)	
Menopausal status		
- pre menopausal	210	91.3
- post menopausal	20	8.7
Parity		
- nulliparous	39	16.9
- multiparous	191	83.0
Contraception		
- Pills	58	25.2
- DMPA	26	11.3
- Condom	25	10.8
- TR	108	46.9
- No contraception	14	6.01
Anti HIV		
- Positive	88	38.3
- Negative	142	61.7
Previous PAP		
- Yes	73	31.7
- No	157	68.2

The mean period from Pap smear to colposcopy was 31.8 days. Colposcopy was performed by gynecologists at Chonburi Hospital and 32 percent of patients underwent colposcopy by gynecologic oncologists of Chonburi Hospital. Colposcopic examinations were noted as satisfactory in 225 women (98%). Out of 5 women with unsatisfied colposcopy, one patient with no suspicious lesion have had ECC,

while the other 4 patients had abnormal lesion and biopsies were obtained. Thirty seven women went on to be treated with LEEP or CKC, among those, 9 women were reported no visible abnormal lesion from colposcopy.

Our study also found that among screened patients who had cytology of LSIL, high grade lesion diagnosed by colposcopy and histologic tissues were

16.5 % (CIN II 12.1% and CIN III 4.3%). None of these patients had invasive disease or AIS. Prevalence of low grade lesion (mild dysplasia or HPV change) was 66.52%. Patient with normal histology, diagnosed of cervicitis, and patient with no lesion who biopsy wasn't performed were 17.0% as indicated in Table 2.

Regarding the secondary objective of this study was to examine the associated factors in those cytology with LSIL but histology showed high grade lesions.

Table 3 showed statistically significant differences between women who are younger 31 years old and women who are 31 years old or more ( $p = 0.013$ ).

**Table 2.** Colpo- histological diagnosis for women with LSIL (n= 230)

Colpo-histological diagnosis	n	percentage
Normal/ Cervicitis/ No lesion	39	17.0%
Low grade lesion (CIN I or HPV infection)	153	66.5%
High grade lesion	38	16.5%
- Moderate dysplasia (CIN II )	28	12.1%
- Severe dysplasia/carcinoma in situ ( CIN III )	10	4.3%
Invasive carcinoma	0	0.0%

**Table 3.** Comparison of clinical characteristic between histology HSIL and Normal/LSIL of women with the cytology LSIL (n=230)

Characteristic	HSIL (%)n=38	Normal ,LSIL (%) n=192	p-value
AGE (years)			
age < 31	19(50.00%)	134(69.8%)	0.013*
age ≥ 31	19(50.00%)	54(28.1%)	
Menopausal status			
pre menopausal	37(97.4%)	173(90.1%)	0.21
post menopausal	1(2.6%)	19(9.9%)	
Parity			
Nulliparous	8(21.1%)	30(15.6%)	0.47
Multiparous	30(78.9%)	162(84.4%)	
Contraception			
pills	13(34.2%)	45(23.4%)	0.58
DMPA	3(7.9%)	23(12.0%)	
condom	4(10.5%)	20(10.4%)	
TR	17(44.7%)	91(47.4%)	
None	1(2.6%)	13(6.8%)	
Anti HIV			
Positive	20(52.6%)	68(35.4%)	0.06
negative	18(47.4%)	124(64.6%)	
Previous PAP			
Yes	9(23.7%)	64(33.3%)	0.34
No	29(76.3%)	128(66.7%)	

## Discussion

Cervical cancer is one of the leading causes of cancer deaths in women. In Thailand, cervical cancer deaths are only second to breast cancer deaths, making cervical cancer one of the major problems of the country's public health.

Consensus guidelines for the management of women with abnormal cervical screening tests, for example, ASCCP 2006 Consensus guidelines recommends that colposcopy should be done if Pap smear tests demonstrate cytology of LSIL<sup>(6)</sup>. However, Thailand is a developing country with problems in public health's systems. Medical services are not accessible to everyone. On top of this, we lack human resources and adequate equipment. Therefore, performing colposcopy to all cytology LSIL patients may increase work load for central hospital.

Management of precancerous lesions varies in accordance to characteristics of pathology. High grade lesions can progress to severe precancerous and cancerous lesions. In contrast, most cases of low grade squamous intraepithelial lesion (CIN I or HPV infection) usually regress spontaneously occurring within 2 years follows up<sup>(18)</sup>. This means that the prevalence of high grade lesions in cytology LSIL is an important factor to choose the management options.

Analyzing and evaluating Pap smear tests sometimes has variation. External variable is, such as, the experience of cytotechnologists and internal variable is, for example, insufficiency of staffs while there are too many slides waiting to be examined each day. All of these factors create variables which result from

variation in diagnosis.

During this study, from conventional Pap smear LSIL data of total 230 samples, prevalence of high grade lesions (CIN II, CIN III) is 16.5% with no invasive or micro invasive detected. The results of this study are characteristically closed and similar to those done prior to this study. For example, report from Lonky et al<sup>(13)</sup> showed that 327/1784 (18.3%) of cytology LSIL had histologic diagnoses of HSIL and two cases (0.1%) had invasive cervical cancers. Massad et al<sup>(19)</sup> found that 17% of HSIL without any cases of invasive cervical cancer in their series of 700 case of cytology LSIL from Pap smear.

In Thailand, prevalence from other studies was also different. While this study shows 16.5% of HSIL without any lesions of invasive or micro invasive detected, one study from Chiangmai University<sup>(14)</sup> showed that high grade lesions were as high as 36.4% with 5% of MIC; and another study from Vajira Hospital<sup>(15)</sup> showed that prevalence of high grade lesions were only 15.3% with only 1.3% of MIC (Table 4).

These studies were done in Thai population. However, the differences of prevalence could be due to population's characteristics and the prevalence of CA cervix which vary according to the regions. Interpretation could also be different due to pathologists.

Previous study reported that there was significantly higher risk of CIN III and cancer among women with Pap results of CIN I or II in women with more than 5 lifetime partners, who were smokers and HPV-16 infection while age at first intercourse or age of the patients with abnormal cytology detection showed no

**Table 4.** Comparison of Prevalence of colpo - histologic diagnosis in Thai women with Pap smear LSIL

Colpo - histologic diagnosis	C. Pongnarisorn 2006 (n= 220)	N.Khuanooralt 2008 (n=226)	This study (n=230)
Normal /cervicitis /no lesion	17.7 %	24.9 %	17.0 %
LSIL	40.9%	58.8 %	66.5 %
HSIL	36.4%	15.0 %	16.5 %
MIC/Invasive carcinoma	5.0%	1.3 %	0.0 %

association<sup>(20)</sup>. This study was a descriptive study and all information data came from the records. Some information about risk factors, such as the age of first intercourse, age of first pregnancy, number of sexual partners and smoking, were not available. Moreover, we do not know whether these patients had been examined or had received treatments in other hospitals before came to our hospital.

However, this study found that the age of 31 years old or more was associated with detection of higher grade lesions. This finding might this study reflected the prevalence of people in our area.

From our study, we found 16.5% of incidence of histological high grade lesions in cytological LSIL and supported doing colposcopy on all patients with Pap smear's LSIL results as recommended by ASCCP 2006. We have also changed methods of diagnoses and treatments in our hospital. We hope to do further study to include subgroups of teenagers and pregnant women, which will help us improve much better methods of diagnoses and treatment in order to allow us to be able to provide more information and resources for the patients.

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## ผลการวินิจฉัยทางพยาธิวิทยา หลังการตรวจคัดกรองมะเร็งปากมดลูกชนิด Low grade squamous intraepithelial lesion (LSIL) ในโรงพยาบาลชลบุรี

สุขสรรค์ ชัยวิรัตน์, จิตติวรรณ ลมดี

**วัตถุประสงค์ :** เพื่อศึกษาความชุก และปัจจัยเสี่ยง ในการตรวจพบ รอยโรคก่อนการเป็นมะเร็งปากมดลูกขั้นสูง จากชิ้นเนื้อในกลุ่มผู้ป่วย ที่คัดกรองมะเร็งปากมดลูก ด้วยวิธี conventional Pap smear รายงานผลว่าเป็น Low grade squamous intraepithelial lesion (LSIL)

**วัสดุและวิธีการ :** การศึกษานี้เป็นการศึกษาเชิงพรรณนา เก็บรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยนอกของโรงพยาบาลชลบุรี ที่ตรวจคัดกรองมะเร็งปากมดลูกโดยวิธี conventional Pap smear ที่รายงานผลว่า LSIL และ ได้รับการส่องกล้อง Colposcope และ/หรือ สุ่มเก็บชิ้นเนื้อในช่วงเวลาดังแต่เดือนธันวาคม 2552 ถึง เมษายน 2554

**ผลการศึกษา :** กลุ่มตัวอย่างจากผู้รับบริการในโรงพยาบาลชลบุรีทั้งสิ้น 230 คน ที่ได้รับการวินิจฉัยจากการตรวจคัดกรองมะเร็งปากมดลูก โดยวิธี conventional Pap smear ว่า "LSIL" และได้รับการส่องกล้อง colposcope, ความชุกของมะเร็งปากมดลูก, รอยโรคก่อนการเป็นมะเร็งขั้นสูง (HSIL), รอยโรคก่อนการเป็นมะเร็งขั้นต่ำ (LSIL) และผลการส่องกล้องไม่พบรอยโรค หรือผลตรวจชิ้นเนื้อปกติ หรือมีการอักเสบของปากมดลูก คิดเป็นร้อยละ 0, 16.5, 66.5, และ 17.0 ตามลำดับ กลุ่มอายุที่มากกว่าหรือเท่ากับ 31 ปี เป็นปัจจัยเสี่ยงที่ทำให้ตรวจพบรอยโรคก่อนการเป็นมะเร็งปากมดลูกขั้นสูงอย่างมีนัยสำคัญทางสถิติ

**สรุป :** ความชุกของการตรวจพบรอยโรคก่อนการเป็นมะเร็งขั้นสูงจากชิ้นเนื้อในกลุ่มผู้ป่วยที่ Pap smear รายงานผลว่าเป็น Low grade squamous intraepithelial lesion (LSIL) ในโรงพยาบาล ชลบุรี คือ 16.5 % และไม่มีการตรวจพบมะเร็งปากมดลูกในการวิจัยนี้

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