

Prevalence of High-grade Cervical Lesion (CIN 2+) in Women with Low Grade Squamous Intraepithelial Lesion Cytology

Asama Vanichtantikul, MD¹, Nuttavut Kantathavorn, MD^{1,2}, Amanda Pena, BSc³, Wasanai Krisorakun, MD¹, Thanita Wetcho, MD¹, Thaniya Sricharunrat, MD⁴, Narongchai Teerayathanakul, MD⁴, Taksa Luasiripanthu, MD⁴, Siriporn Saeloo, BNS⁵, Waraphorn Krongthong, MSc⁵

¹Gynecologic Oncology Division, Woman Health Center, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

²Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

³Renaissance School of Medicine at Stony Brook University, New York, USA

⁴Pathology Division, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

⁵Data Management Unit, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

Background: The frequency of high-grade cervical intraepithelial neoplasia (CIN2+) among Thai women with abnormal cytology, including low-grade squamous intraepithelial lesion (LSIL), was previously reported as higher than in Western populations. The aim of this study was to evaluate the prevalence of underlying significant cervical lesions (CIN2+) in women with LSIL cytology.

Materials and Methods: A cross-sectional study was conducted among Thai women who participated in a screening program at the women's health clinic at Chulabhorn Hospital, Thailand, between July 2011 and August 2013. A total of 63 women with LSIL cytology were recruited for colposcopic evaluations.

Results: A total of 63 women with LSIL smear were included; the median age was 38 years (22 to 67 years). Most women were multiparous (61.9%) and premenopausal (80.9%). After colposcopic evaluations, the histological results were as follows: 7 (11.1%) cases with CIN2, CIN3 or adenocarcinoma in situ; 18 (28.6%) with CIN1; 32 (66.7%) with no epithelial lesion; and no cases with cervical cancer. No clinical factors were found to correlate with high-grade cervical lesions.

Conclusion: The rates of high-grade cervical lesion (CIN2+) at initial colposcopy following LSIL cytology in our population were lower than reported in previous studies.

Keywords: Prevalence, Cervical intraepithelial neoplasia (CIN), Low-grade squamous intraepithelial lesion (LSIL), Thailand

J Med Assoc Thai 2021;104(Suppl2): S15-9

Website: <http://www.jmatonline.com>

Despite prevention programs, cervical cancer remains a major health problem in developing countries. Conventional cytology, or Pap smear, has been the most widely used screening method for cervical cancer for decades⁽¹⁾. However, women in developing countries, including Thailand, still have difficulty in accessing the test. Additionally, prevention programs for cervical cancer have not been established⁽²⁾.

In the Bethesda system, low-grade squamous intraepithelial lesion (LSIL) cytology encompasses Human

papilloma virus (HPV) infection and mild dysplasia⁽³⁾. Several studies showed that the prevalence of cervical intraepithelial neoplasia (CIN) 2 or worse (CIN2+) among women with LSIL smears is approximately 12% to 20%⁽⁴⁻¹⁰⁾. In contrast, some studies in Thai populations revealed a greater prevalence of CIN2+ in women with LSIL (16.3% to 41.5%)⁽¹¹⁻¹³⁾.

The aim of this study was to investigate the prevalence of high-grade cervical lesion (CIN2+) in Thai women with LSIL cervical cytology. We also evaluated the risk factors for this lesion.

Materials and Methods

A hospital-based cross-sectional study was conducted in 4,487 Thai women who attended a cervical screening project, and a population-based study was performed in 1,523 Thai women at Bangkhayaeng district (suburban area), aged 20 to 70 years, who voluntarily participated in a screening program launched by Chulabhorn Hospital, Thailand between July 2011 and August 2013. Women with a history of absence of cervix, previous HPV vaccination, abnormal cytology, CIN, cervical carcinoma, prior HPV infection, active cancer or any cancer during the previous 5 years or unable to follow-up throughout the study period were excluded. Informed consent was obtained from each participant. The Ethical Committee of Human

Correspondence to:

Kantathavorn N.

Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok 12120, Thailand

Phone & Fax: +66-2-5766791

Email: nuttavutkan@pccms.ac.th

How to cite this article:

Vanichtantikul A, Kantathavorn N, Pena A, Krisorakun W, Wetcho T, Sricharunrat T, Teerayathanakul N, Luasiripanthu T, Saeloo S, Krongthong W. Prevalence of High-grade Cervical Lesion (CIN 2+) in Women with Low Grade Squamous Intraepithelial Lesion Cytology. J Med Assoc Thai 2021;104 (Suppl2): S15-9

doi.org/10.35755/jmedassocthai.2021.S02.12565

Research of Chulabhorn Hospital approved this study (EC No. 13/2554). Demographic data were collected including age, parity, menopausal status, sexually active status, number of sexual partners and contraception use. Liquid based-cytology data were gathered at the time of women's participation at the clinic. Only women with LSIL smear (n=63) from the screening project were included in the present study.

Samples were obtained by gynecologic oncologists of Chulabhorn Hospital using the SurePath (BD, Diagnostics-Tripath, Burlington, NC, USA) Pap test kit for liquid-based cytology. The results were interpreted by pathologists at Chulabhorn Hospital using the Bethesda 2001 report system⁽³⁾. Participants with LSIL cervical cytology underwent colposcopy; the colposcopic finding was documented and colposcopic directed biopsies (CDB) were taken from the worst affected area after applying 3% acetic acid. The final diagnosis was based on the worst histology according to the Bethesda 2001 classification⁽³⁾.

Statistical analysis was performed with STATA version 12.1 for window (StataCorp, Lake station, TX, USA). The Pearson's Chi-square (χ^2) or exact test was used for comparison of categorical variables on demographic characteristic data. Comparison of continuous variables was

made using Student's t-test. Univariate and multivariate analyses were performed using logistic regression analysis. The $p < 0.05$ was considered statistically significant.

Results

During the study period, 63 women with LSIL cytology (1.0%; 63/6,010) were recruited for colposcopic evaluations, including 48 patients (1.1%; 48/4,487) from the hospital-based cohort and 15 patients (1.0%; 15/1,523) from the suburban area (Bangkhayaeng district). Table 1 shows the baseline characteristics of the patients. The mean age of the women was 40.1 ± 10.8 years (median 38 years; range, 22 to 67 years). Almost two-thirds of the patients were multiparous (61.9%). Most women were premenopausal (80.9%). Forty-one (65.1%) women were current users of oral contraceptive pills. All demographic data were comparable between the hospital-based and suburban groups except study level. A greater proportion of women in the hospital-based cohort had a higher level of education than the women in the suburban area ($p = 0.001$). LSIL positivity in the two groups was equal as shown Table 2.

After colposcopic evaluations, CDBs were taken from the worst affected area. Table 2 shows the final histological results: 7 (11.1%) cases were CIN2, CIN3 or

Table 1. Demographic characteristics for patient with LSIL pap smears in Chulabhorn hospital and in Bangkhayaeng district

Demographics	Total (n=63) n (%)	Chulabhorn Hospital (n=48)	Bangkhayaeng Cohort (n=15)	p-value
Age				
Mean (years) \pm SD	40.1 \pm 10.8	40.3 \pm 10.2	39.6 \pm 12.7	0.840 ¹
Range (years)	22 to 67	22 to 60	22 to 67	
20 to 30 years	15 (23.8)	12 (25.0)	3 (20.0)	
31 to 70 years	48 (76.2)	36 (75.0)	12 (80.0)	
Parity				0.371 ²
Nulliparous	24 (38.1)	20 (41.7)	4 (26.7)	
Multiparous	39 (61.9)	28 (58.3)	11 (73.3)	
Menopause				0.457 ²
Pre-menopause	51 (80.9)	40 (83.3)	11 (73.3)	
Post-menopause	12 (19.1)	8 (16.7)	4 (26.7)	
Marital status				0.277 ²
Single	22 (34.9)	19 (39.6)	3 (20.0)	
Married	30 (47.6)	20 (41.7)	10 (66.7)	
Divorced	11 (17.5)	9 (18.7)	2 (13.3)	
Contraceptive pill use				1.000 ²
No	22 (34.9)	17 (35.4)	5 (33.3)	
Yes	41 (65.1)	31 (64.6)	10 (66.7)	
Education				0.001 ^{2*}
Primary education	9 (14.3)	4 (8.3)	5 (33.3)	
High school	11 (17.5)	5 (10.4)	6 (40.0)	
Vocation school	8 (12.7)	6 (12.5)	2 (13.3)	
Bachelor degree	24 (38.1)	22 (45.8)	2 (13.3)	
Postgraduate	11 (17.5)	11 (22.9)	0 (0.0)	

¹ Independent samples t-test, ² Exact test, * $p < 0.05$

LSIL = low-grade squamous intraepithelial lesion; SD = standard deviation

adenocarcinoma in situ (AIS); 18 (28.6%) cases were CIN1; 32 (66.7%) cases had no epithelial lesion; and no cases had cervical cancer.

Univariate analysis was performed with factors including age, parity, menopausal status, marital status and contraceptive pills used (Table 3). None of these factors were significant predictors for high-grade disease on final histological results.

Discussion

Cervical cytology remains the standard screening method to prevent cervical cancer. In LSIL cytology, the recommended management is colposcopy or reflex HPV

testing or cytological follow-up^(1,2). However, immediate colposcopy might be appropriate for Thai women whose compliance is suboptimal⁽¹⁴⁾.

The present study demonstrated that the prevalence of histologically confirmed high-grade cervical lesion (CIN2+) at CDB among women with LSIL is 11.1%, which is lower than previous reports⁽⁴⁻¹³⁾. The frequency of high-grade cervical intraepithelial neoplasia (CIN2+) among Thai women with LSIL cytology was higher than that in Western populations (11% to 41.5% and 12% to 20%, respectively)⁽⁴⁻¹³⁾. One study from the north region of Thailand reported a prevalence of high-grade lesion as high as 41.5% among women with LSIL on Pap smear, including

Table 2. Prevalence of high-grade cervical lesion (CIN 2+) in LSIL cytology in Chulabhorn hospital and in Bangkhayaeng district

LSIL on cytology	Chulabhorn Hospital (n=4,487) n (%)	Bangkhayaeng Cohort (n=1,523) n (%)	Total (n=6,010) n (%)
LSIL positive	48 (1.1)	15 (1.0)	63 (1.0)
No CIN	32 (66.7)	6 (40.0)	38 (60.3)
CIN1	11 (22.9)	7 (46.7)	18 (28.6)
CIN2, CIN3 or AIS	5 (10.4)	2 (13.3)	7 (11.1)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)

LSIL = low-grade squamous intraepithelial lesion; CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ

Table 3. Factors to predict high-grade cervical lesion (CIN 2+) compared to low-grade lesion in LSIL cytology

Demographics	Total (n=63)	Less than CIN2 n (%)	CIN2+ n (%)	Crude OR (95% CI)
Age				
20 to 30 years	15	13 (86.67)	2 (13.3)	1
31 to 70 years	48	43 (89.58)	5 (10.4)	0.75 (0.13 to 4.36)
Parity				
Nulliparous	24	21 (87.5)	3 (12.5)	1
Multiparous	39	35 (89.74)	4 (10.3)	0.80 (0.16 to 3.93)
Menopause				
Pre-menopause	51	44 (86.27)	7 (13.7)	1
Post-menopause	12	12 (100)	0 (0.0)	n/a
Marital status				
Single	22	19 (86.36)	3 (13.6)	1
Married	30	27 (90)	3 (10.0)	0.70 (0.13 to 3.87)
Divorced	11	10 (90.9)	1 (9.1)	0.63 (0.06 to 6.91)
Contraceptive pill use				
No	22	20 (90.9)	2 (9.1)	1
Yes	41	39 (95.12)	5 (12.2)	1.39 (0.25 to 7.82)

CIN = cervical intraepithelial neoplasia; LSIL = low-grade squamous intraepithelial lesion; OR = odds ratio; CI = confidence interval; n/a = not available

36.4% of CIN2+ and 5% of carcinoma⁽¹³⁾. Compared with results from other studies in Thailand⁽¹¹⁻¹³⁾, our prevalence of CIN2+ was in the low range. One probable reason is that CDB was taken for every patient in our study, while in the other studies, the biopsy was only taken in suspicious cases. Colposcopy is a sensitive, but non-specific, method for detection of high-grade intraepithelial lesions⁽¹⁵⁾. Previous reports showed that only approximately two-third of cases of biopsy-confirmed CIN2+ among women with LSIL were identified at initial colposcopy, and false-negative rates for colposcopy ranged from 15% to 31% for CIN2 and CIN3 lesions⁽¹⁶⁾. A higher detection rate of CIN2+ is confirmed with more reliable procedures including conization⁽¹⁰⁾. However, in the present report, CDB was conducted in all cases, including in the group of women who had negative colposcopic findings, so the more correct histological diagnoses were initially diagnosed. Another possible explanation of our low prevalence is that a liquid-based cytology was used for primary screening, which has more accuracy than conventional Pap smear.

Previous studies showed that the risk of high grade lesion or cervical cancer was increased in younger patients^(17,18), multiparous women^(13,19), patients with premenopausal status⁽¹⁰⁾ and contraceptive pill use⁽²⁰⁾. However, our study showed that these factors had no statistical difference between groups with CIN2+ and lesser severity. One limitation of the present study is that the sample size was too small to evaluate the significant risk factors for the lesion.

Conclusion

The current study found an approximate 11% prevalence of histological confirmed high-grade lesion (CIN2+) among women with LSIL. Immediate colposcopy evaluations with CDB might be an appropriate option. However, with careful assessment and good compliance, women with LSIL on liquid-based cytology may be managed less aggressively.

What is already known on this topic?

The rates of high-grade cervical lesion (CIN2+) at initial colposcopy following LSIL cytology in Thai women are higher than those of Western populations (11% to 41.5% and 12% to 20%, respectively).

What this study adds?

The present study found a prevalence of only 11% of histological confirmed high-grade lesion (CIN2+) among women with LSIL, which is lower than previous reports. The probable reasons are that a liquid based-cytology was used for primary screening and colposcopic directed biopsies were taken for every patient in our study.

Acknowledgements

This research project is supported by Chulabhorn Royal Academy. We would like to extend our special thanks to participants, the medical and nursing staff of Woman

Health Center, Chulabhorn Hospital for their kind assistance and support towards the success and accomplishment of this study.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Wright TC Jr. The new ASCCP colposcopy standards. *J Low Genit Tract Dis* 2017;21:215.
2. Kietpeerakool C, Tangjitgamol S, Srisomboon J. Histopathological outcomes of women with abnormal cervical cytology: a review of literature in Thailand. *Asian Pac J Cancer Prev* 2014;15:6489-94.
3. Apgar BS, Zoschnick L, Wright TC Jr. The 2001 Bethesda System terminology. *Am Fam Physician* 2003;68:1992-8.
4. Alvarez RD, Wright TC. Effective cervical neoplasia detection with a novel optical detection system: a randomized trial. *Gynecol Oncol* 2007;104:281-9.
5. Benedet JL, Matisic JP, Bertrand MA. An analysis of 84244 patients from the British Columbia cytology-colposcopy program. *Gynecol Oncol* 2004;92:127-34.
6. Fairman A, Tan J, Quinn M. Women with low-grade abnormalities on Pap smear should be referred for colposcopy. *Aust N Z J Obstet Gynaecol* 2004;44:252-5.
7. Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. *Obstet Gynecol* 1998;91:973-6.
8. Lonky NM, Sadeghi M, Tsadik GW, Petitti D. The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol* 1999;181:560-6.
9. Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol* 2001;82:516-22.
10. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007;197:346-55.
11. Khuakoonratt N, Tangjitgamol S, Manusirivithaya S, Khunnarong J, Pataradule K, Thavaramara T, et al. Prevalence of high grade squamous intraepithelial lesion (HSIL) and invasive cervical cancer in patients with low grade squamous intraepithelial lesion (LSIL) at cervical pap smear. *Asian Pac J Cancer Prev* 2008;9:253-7.
12. Kiatyosnusorn R, Suprasert P, Srisomboon J, Siriaree S, Khunamornpong S, Kietpeerakool C. High-grade histologic lesions in women with low-grade squamous intraepithelial lesion cytology from a region of Thailand with a high incidence of cervical cancer. *Int J Gynaecol Obstet* 2010;110:133-6.
13. Phongnarisorn C, Srisomboon J, Siriaungkul S, Khunamornpong S, Suprasert P, Charoenkwan K, et al.

Women in a region with high incidence of cervical cancer warrant immediate colposcopy for low-grade squamous intraepithelial lesion on cervical cytology. *Int J Gynecol Cancer* 2006;16:1565-8.

14. Rattanalappaiboon D, Kietpeerakool C, Kleebkaow P, Chumworathayi B, Launratanakorn S, Santipongsupakorn T. Factors affecting compliance in the first year of postcolposcopy surveillance among women with a high incidence of cervical cancer. *Int J Gynaecol Obstet* 2014;124:160-3.
15. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol* 1998;91:626-31.
16. ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol* 2003;188:1393-400.
17. Barreth D, Schepansky A, Capstick V, Johnson G, Steed H, Faught W. Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H): a result not to be ignored. *J Obstet Gynaecol Can* 2006;28:1095-8.
18. Louro AP, Roberson J, Eltoum I, Chhieng DC. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion. A follow-up study of conventional and liquid-based preparations in a high-risk population. *Am J Clin Pathol* 2003;120:392-7.
19. 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 Pac J Cancer Prev* 2015;16:7231-5.
20. Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodhill A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007;370:1609-21.