

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

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**Background:** The prevalence of high-grade cervical intraepithelial neoplasia (CIN2+), especially invasive cancer, among Thai women with high-grade squamous intraepithelial lesion (HSIL) cytology was reported higher than in Western populations. The aim of this study was to evaluate the prevalence of underlying significant cervical lesions (CIN2+) in women with HSIL cytology.

**Materials and Methods:** A total of 4,487 women from the Woman Health Centre of Chulabhorn Hospital, Bangkok and 1,523 women from Bangkhayaeng District of Pathumthani province, Thailand, who participated in a cervical cancer screening program between July 2011 and August 2013, were recruited into the study. A total of 22 women (14 from Chulabhorn Hospital and 8 from Bangkhayaeng District) with HSIL cytology were recruited for colposcopic evaluations.

**Results:** Of the 22 women with HSIL cytology, the median age was 42 years (22 to 67 years). The majority of patients were multiparous (90.9%) and premenopausal (72.7%). Final pathological results were as follows: 20 (91.0%) with CIN 2, CIN3 or adenocarcinoma in situ; 0 (0%) with CIN 1; 1 (4.5%) with no epithelial lesion; and 1 (4.5%) with cervical cancer. No clinical factors were associated with CIN2+.

**Conclusion:** Rates of CIN 2+ at initial colposcopy following HSIL cytology in our population were very high (95.5%) and support the “see-and-treat” strategy for HSIL cytology management.

**Keywords:** Prevalence, Cervical intraepithelial neoplasia (CIN), High-grade squamous intraepithelial lesion (HSIL), See and treat, Thailand

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Cervical cancer is the second most prevalent cancer among women in developing countries<sup>(1,2)</sup>. In Thailand, cervical cancer is the second most prevalent cancer among women after breast cancer<sup>(3,4)</sup>. The incidence of cervical cancer is decreasing in Thailand due to preventative screening measures, such as Pap smears and visual inspection with

acetic acid-cryotherapy<sup>(4)</sup>.

Currently, Pap smear is the recommended screening test for early detection of cervical cancer<sup>(5)</sup>. In the Bethesda system (cytology report), Pap smears can have several outcomes: normal or abnormal as high-grade squamous intraepithelial lesions (HSIL) cytology, which shows moderate to severe changes that can be representative of a precancerous or cancerous state<sup>(6)</sup>. To determine if the lesions are precancer or cancer, further analysis with a cervical biopsy should be done. Biopsy results are represented with a grading system comprising cervical intraepithelial neoplasia (CIN) 1, CIN2, CIN3 and cancer. Low-risk abnormal results indicate CIN1. High-risk abnormal results can indicate CIN2, CIN3, adenocarcinoma in situ (AIS) and cancer.

Conventionally, after a HSIL cytology result is reported, the patient is followed-up with a colposcopic examination and biopsy. After pathological results are determined, the results and treatment plans are discussed, followed by the treatment. The “see-and-treat” approach forgoes the biopsy step, and treatment is performed after a high-grade lesion is discovered at colposcopy. The aim of this

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study was to understand the disease burden (CIN2+) among Thai women to evaluate whether alternative treatment approaches such as the “see-and-treat method” may continue to be beneficial and appropriate for women with HSIL cytology.

## Materials and Methods

Between July 2011 and August 2013, a total of 4,487 women were recruited to participate in a hospital-based cross-sectional cervical cancer screening study at the Chulabhorn Hospital, Bangkok, Thailand, and 1,523 women were recruited into a population-based cervical cancer screening at Bangkhayaeng District, Pathumthani province, Thailand using Pap smears and HPV screening tests.

Inclusion criteria were Thai nationality and age 20 to 70 years. Informed consent was obtained from each participant. The Ethical Committee of Human Research of Chulabhorn Hospital approved this study (EC No. 13/2554). Exclusion criteria were as follows: identification of advanced cervical carcinoma after the first Pap smear, diagnosis with cervical carcinoma in the previous year, HPV vaccination, no cervix, pregnant, history of any cancer within the last 5 years, previous diagnosis or treatment for precancerous lesions and cervical carcinoma, Eastern Cooperative Oncology Group (ECOG) performance status greater than or equal to 2, other diseases that may prevent patients from participating in the study and refusal to participate with a signed consent form. The following demographics were collected from the patients: age, parity, menopause status, marital status, oral contraceptive pill use and education level.

Liquid based-cytology data were received at the time of patient participation at the clinic. Samples were obtained by gynecologic oncologists of Chulabhorn Hospital using SurePath (BD, Diagnostics-Tripath, Burlington, NC, USA) liquid-based cytology, and the cytology was interpreted by pathologists at Chulabhorn Hospital using the Bethesda 2001 report system<sup>(7)</sup>. Participants with HSIL cervical cytology underwent colposcopic examinations with 5% acetic acid solution to the cervix and upper vagina to visualize

the lesions for biopsy; the colposcopic finding was documented and colposcopic directed biopsies (CDBs) were taken from the worst affected areas. Patients usually went for the conization procedure (Loop Electrosurgical Excision Procedure) for diagnosis and treatment. The final diagnosis was based on the most aggressive pathology result.

For HPV genotyping, linear array HPV testing (Roche, USA) was used. This kit is capable of identifying 37 HPV types (i.e., HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108) including 12 high-risk, 8 probable high-risk and 17 low-risk types, classified by oncogenic potentiality<sup>(8-10)</sup>.

Demographic data and biopsy results were analyzed with STATA version 12.1. The Exact test was used for comparison of categorical variables on demographic characteristic data. Comparison of continuous variables was performed using independent samples t-test. The significance level was set at 5%.

## Results

During the study period, 22 women were found to have HSIL cytology (0.4%) and were recruited for colposcopic evaluation. Of the 22 women, 14 patients (0.3%) were from the hospital-based cohort and 8 patients (0.5%) were from the suburban area (Bangkhayaeng District). No difference in the HSIL positive rate was found in the groups. Of the 22 women with HSIL cytology, one woman from Chulabhorn Hospital had no CIN in her biopsied lesions, 13 women (92.9%) had CIN2+, which included CIN2, CIN3 and AIS. Eight women (100%) from the Bangkhayaeng District had CIN2+, one of whom had stage IA cervical cancer (4.5%). A combined total of 21 women (95.5%) had CIN2+ from these two cohorts. No significant difference ( $p > 0.05$ ) was found between the prevalence of CIN2+ in HSIL cytology among the two cohorts. A summary of these data is shown in Table 1.

The characteristics of women with HSIL cytology are depicted in Table 2. The mean age was 44.3 years, with

**Table 1.** Prevalence of high-grade cervical lesion (CIN 2+) in HSIL cytology

HSIL on Cytology	Total	Chulabhorn Hospital	Bangkhayaeng District	p-value <sup>1</sup>
Total patients	6,010	4,487	1,523	
HSIL positive rate, n (%)	22 (0.37)	14 (0.31)	8 (0.53)	1.000
No CIN	1 (4.5)	1 (7.1)	0 (0.0)	
CIN1	-	-	-	
CIN2+	21 (95.5)	13 (92.9)	8 (100.0)	
CIN2, 3 or AIS	20 (91.0)	13 (92.9)	7 (87.5)	
Cancer	1 (4.5)	0 (0.0)	1 (12.5)	

<sup>1</sup> Fisher's exact test

CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; AIS = adenocarcinoma in situ

**Table 2.** Characteristics of patient with HSIL pap smears at Chulabhorn Hospital and Bangkhayaeng District

Characteristics	Total	Chulabhorn Hospital	Bangkhayaeng District	p-value
Total HSIL patients	22	14	8	
Age				
Mean (years) $\pm$ SD	44.3 $\pm$ 9.7	43.8 $\pm$ 9.2	45.1 $\pm$ 11.1	0.763 <sup>1</sup>
Median (years)	42.0	42.0	43.5	
Parity				0.515 <sup>2</sup>
Nulliparous	2 (9.1)	2 (14.3)	0 (0.0)	
Multiparous	20 (90.9)	12 (85.7)	8 (100.0)	
Menopause				0.624 <sup>2</sup>
Pre-menopause	16 (72.7)	11 (78.6)	5 (62.5)	
Post-menopause	6 (27.3)	3 (21.4)	3 (37.5)	
Marital status				0.353 <sup>2</sup>
Single	3 (13.6)	3 (21.4)	0 (0.0)	
Married	12 (54.6)	6 (42.9)	6 (75.0)	
Divorced	7 (31.8)	5 (35.7)	2 (25.0)	
Contraceptive pills used				0.351 <sup>2</sup>
No	6 (27.3)	5 (35.7)	1 (12.5)	
Yes	16 (72.7)	9 (64.3)	7 (87.5)	
Educational attainment				0.371 <sup>2</sup>
No education	1 (4.5)	1 (7.1)	0 (0.0)	
Primary school	8 (36.4)	3 (21.4)	5 (62.5)	
High school	2 (9.1)	1 (7.1)	1 (12.5)	
Vocation school	3 (13.6)	3 (21.4)	0 (0.0)	
Bachelor's degree	6 (27.3)	4 (28.6)	2 (25.0)	
Postgraduate	2 (9.1)	2 (14.3)	0 (0.0)	

<sup>1</sup> Independent samples t-test, <sup>2</sup> Exact test.

HSIL = high-grade squamous intraepithelial lesion; SD = standard deviation

a range of 34.6 to 54 years of age. Almost all women were multiparous (90.9%). Most women were premenopausal (72.7%). Almost half (54.6%) were married and 31.8% were divorced. Sixteen (72.7%) women used oral contraceptive pills. Approximately three-fifths of patients completed below a bachelor's degree. No differences in the various characteristics were found in the two patient groups, as shown in Table 2.

Among HSIL-positive women in both groups, 20 women (90.9%) were HPV-positive, and 18 (81.8%) were infected with high-risk HPV. Three women (18.6%) were infected with probable high-risk HPV genotype and six women (27.3%) were infected with a low-risk HPV genotype, as shown in Table 3.

## Discussion

The data from the Chulabhorn Hospital represent a hospital-based study and the data from the Bangkhayaeng District represent a population-based study. The study

showed that 95.5% of the women with HSIL cytology had biopsy results of CIN2+, which is comparable to other studies in Thailand<sup>(11-18)</sup> and slightly higher compared with rates in developed countries, as shown in Table 4<sup>(19-24)</sup>.

Previous data reported the prevalence of CIN2+ and invasive cancer in HSIL cytology among populations living in low cervical cancer incidence areas, such as Western countries like the United States or Australia, ranging from 42.0% to 97.0% and 1.1% to 3.0%, respectively, as shown in Table 4<sup>(19-24)</sup>. In Thailand, although the prevalence of CIN2 to 3 and AIS in women with HSIL smears (62% to 74%) was comparable to reports of other populations, the prevalence of invasive cancer was higher, ranging from 9.2% to 25.8%, as shown in Table 4<sup>(11-18)</sup>. Our study showed a lower prevalence of invasive cancer (4.5%) but a higher rate than those reported from Western countries. Therefore, intensive evaluation of Thai women with HSIL cytology is still mandatory to exclude occult invasive lesion.

Our biopsy results were expected to be higher than

**Table 3.** Prevalence of HPV positivity in HSIL cytology

	Total n (%)	Chulabhorn Hospital n (%)	Bangkhayaeng District n (%)
HSIL positive women	22	14	8
HPV positive	20 (90.9)	12 (85.7)	8 (100.0)
High-risk HPV	18 (81.8)	10 (71.4)	8 (100.0)
Probable HR HPV	3 (13.6)	3 (21.4)	0 (0.0)
Low-risk HPV	6 (27.3)	4 (28.6)	2 (25.0)

HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; HR = high risk

**Table 4.** Comparison of prevalence of CIN2+ and invasive cancer in HSIL cytology between Thai and Western studies

Study location	Author	Year	n	Percentage of CIN2+	Percentage of invasive Cancer
Thailand					
	Kantathavorn et al (12)	2006	681	94.4%	20.7%
	Boonlikit S (13)	2008	152	75.7%	7.9%
	Sripipattanakut M (14)	2011	179	81.6%	17.9%
	Aue-aungkul et al (15)	2011	124	88.7%	25.8%
	Ingkapiroj et al (16)	2012	302	74.2%	9.3%
	Srisuwan et al (17)	2014	197	87.7%	9.2%
	Kingnate et al (18)	2016	143	74.8%	12.6%
	This study	2019	22	95.5%	4.5%
Western countries					
	Massad et al (20)	2001	377	42.0%	3.0%
	Dunn et al (21)	2003	100	97.0%	3.0%
	Alvarez et al (22)	2007	225	52.9%	N/A
	Smith et al (23)	2016	369	82.0%	1.1%
Australia	Blain et al (24)	2016	137	81.3%	2.7%

CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; N/A = not available

those of Western countries because there is a higher prevalence of cervical cancer in Thailand<sup>(1)</sup>. No significant difference in the prevalence of CIN2+ in HSIL cytology was found between women from Chulabhorn Hospital and Bangkhayaeng District.

A disadvantage of the present study is the low number of participants who had HSIL cytology results, which could be a limitation to complete interpretation of our biopsy results. For example, 4.5% of the women with HSIL cytology in our study had invasive cancer, which does not reflect data from literature showing a much higher prevalence among Thai women<sup>(11-18)</sup>.

An advantage of this study is that every participant with HSIL cytology was followed-up with biopsy and excisional procedure. Results from examinations and

procedures were reliable as they were performed by highly trained and experienced gynecological oncologists.

### Conclusion

A large percentage (95.5%) of HSIL cytology results in this study showed CIN2+ with an invasive cancer prevalence of 4.5%, which will undergo treatment in the future. Immediate colposcopy evaluation with the “see-and-treat” method for treating HSIL cytology continues to be appropriate for Thai women.

### What is already known on this topic?

Rates of high-grade cervical lesion (CIN2+) and invasive cancer in Thai women at initial colposcopy following HSIL cytology were high at 42.0% to 97.0% and 7.9%

to 25.8%, respectively.

### What this study adds?

This study found a 95.5% prevalence of histologically confirmed high-grade lesion (CIN2+) among women with HSIL, which is comparable to previous reports. This finding confirms the continued use of the “see-and-treat” approach for HSIL cytology management in Thailand.

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### Potential conflicts of interest

The authors declare no conflict of interest.

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