

## RESEARCH ARTICLE

# Incidence of High Grade Squamous Intraepithelial Lesions in Patients with Atypical Squamous Cells of Undetermined Significance Papanicolaou Smears at Naresuan University Hospital

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### Abstract

**Purpose:** To determine the incidence of high-grade cervical intraepithelial neoplasia (CIN2-3) among patients with atypical squamous cells of undetermined significance (ASC-US) Papanicolaou (Pap) smears. **Materials and Methods:** One-hundred and eighty-seven patients with ASC-US Pap smears who underwent colposcopy with histological study were enrolled between September 2007 and August 2015. Patient factors (including age, parity, current pills used, HIV status, age at first sexual intercourse and number of sexual partners) were obtained. Logistic regression analysis was used to evaluate clinical factors associated with CIN2-3. **Results:** CIN was diagnosed in 92 of 187 women (49.2%). Sixty-one of these (32.6%) had CIN1 and 31 (16.6%) had CIN2-3. There was no woman who had invasive cancer. There was no correlation of high-grade CIN with factors in this study including age, parity, current pills used, HIV status, age at first sexual intercourse and number of sexual partners. **Conclusions:** Data from this study showed no invasive cervical cancer was found in patients with ASC-US. There was no patient factor associated with high grade intraepithelial neoplasia in patients with ASC-US Pap smears.

**Keywords:** Cervical cytology - Pap smear - colposcopy - CIN

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### Introduction

Cervical cancer still remains the major health problem in Thailand. Data from GLOBOCAN 2012, cervical cancer incidence (age-standard incidence rates; ASR) in Thailand was 17.8 per 100000 (Ferlay et al., 2013). Cervical cancer is the most common female genital malignancy. Cervical cancer screening is the effective method to decrease cervical cancer. Nowadays, cervical cytology and high-risk human papilloma virus (HR-HPV) testing have important role for cervical cancer screening. In Thailand, HR-HPV testing is not widely available, so cervical cytology is still mainly in cervical cancer screening method.

Atypical squamous cells of undetermined significance (ASC-US) is the most frequent abnormal cervical cytology. Incidence rate of ASC-US was 9.0% in previous study (Katki et al., 2013). Catteau et al., (2014) found ASC-US was 59.3% of abnormal Papanicolaou (Pap) smear result. Previous studies showed 5-10% of women with ASC-US Papanicolaou (Pap) smear had cervical intraepithelial neoplasia (CIN) 2-3 on histology (Wright

et al., 1995; Kinney et al., 1998). Incidence of CIN2+ in women who had ASC-US Pap smear alone was 6.9% in 5 years (Katki et al., 2013). Katki et al. (2013) reported cumulative risk of invasive cervical cancer was 0.16% in 5 years. Women with HPV-negative ASC-US have very low absolute risk of subsequently detected CIN3 or worse in 2 years, similar to women with a negative cytology in the absence of HPV testing (Safaian et al., 2007). Acceptable managements in women with ASC-US Pap smear are HPV testing and repeat cytology at 1 year interval (Massad et al., 2013).

Colposcopic directed cervical biopsy is the diagnostic procedure for women who have abnormal Pap smear but it causes patient discomfort and uses more resources. Adherence to follow-up and cost of procedures should be outweighed risk and benefit of each modality of treatment. Accuracy of abnormal Pap smear is important because HR-HPV testing is not widely used in Thailand.

This study aimed to determine the prevalence of high-grade CIN and other lesions among patients with ASC-US Pap smear undergoing investigation in Naresuan University Hospital, Thailand.

## Materials and Methods

All patients with ASC-US Pap smear who attended at the colposcopic clinic, Naresuan University Hospital from September 2007 to August 2015 were enrolled. The data was collected by retrospective chart review. Exclusion criteria included patients with pregnancy, post-hysterectomy, history of abnormal Pap smear who had undergone colposcopy before and patients with no histological diagnosis. The study was approved by the Naresuan University Institutional Review Board, Naresuan University.

Patients who had abnormal Pap smear underwent registration to colposcopic clinic. They were scheduled for colposcopy within 4 weeks after registration. Colposcopists in this study were separated in 2 groups, first group was general gynecologist before 2012 and another group was gynecologic oncologist in 2012 and year after. After apply 3% acetic acid, lesion at cervix was biopsied in the most severe lesion. Endocervical curettage was performed when inadequate colposcopy. Random biopsy of cervix or endocervical curettage or both of them was done when negative colposcopy. Final histological diagnosis was made on the most severe histological results of tissue biopsy, loop electrosurgical procedure or hysterectomy specimens. Patient who had no tissue for pathology were exclude from the study.

The statistical analysis was carried out using SPSS computer software (SPSS, Chicago, IL, USA). Demographic data of patients were analyzed by number, mean, and frequency of patients. The chi-square or Fisher exact test was used whenever appropriate to compare between groups. A P-value of less than 0.05 was considered statistically significance. Univariate analysis of risk factors of patient was calculated using logistic regression analysis and described as odds ratio.

## Results

There were 187 patients with ASC-US Pap smear enrolled in this study. Table 1 shows patient's characteristics including age, parity, current pills used, HIV status, age at first sexual intercourse and number of sexual partners. Mean age of the patient who had ASC-US Pap smear was 41.2 (16-84) years old. One-hundred and fifty two (81.3%) patients were multiparous. There were 23 (13%) patients who current pills used. In this study had only 3 (1.6%) patients had positive anti-HIV. Mean age at first sexual intercourse was 21.4 (15-35) years old. Sixty-four patients (66%) had only 1 sexual partner.

Final cervical histological report in patients with ASC-US Pap smear. There were 92 of 187 (49.2%) patients having CIN. Of all patients, 61 (32.6%) had CIN 1 and 31 (16.6%) had CIN2/3/AIS. There was no invasive cervical cancer in patients with ASC-US Pap smear.

The univariate analysis about correlation of high grade cervical intraepithelial neoplasia (CIN 2/3) and clinical factors (which included age, parity, current oral contraceptive pills used, age at first sexual intercourse, number of sexual partners, HIV status) was performed and showed in Table 2. There was no significant correlation between the clinical factors and incidence of high grade

**Table 1. Demographic Data for Patients with ASC-US Pap Smears**

Characteristics	Total	Number	Frequency (%)
Age (years)	187		
< 30		34	18.2
31-40		57	30.5
41-50		60	32
> 50		36	19.3
Parity	187		
Nulliparous		35	18.7
Multiparous		152	81.3
Current pills used	165		
No		142	86.1
Yes		23	13.9
Age (years) at first sexual intercourse	93		
< 18		14	15
> 18		79	85
HIV status	187		
Negative		184	98.4
Positive		3	1.6
Number of sexual partners	97		
1		64	66
2		17	17.5
>2		16	16.5

**Table 2. Correlation of High Grade Cervical Intraepithelial Neoplasia (CIN 2/3) and Patient Factors**

	No CIN/ CIN 1	CIN 2/3	OR (95% CI)	P-value
Age				
< 30	26	8	1*	
31-40	46	11	0.78 (0.28-2.18)	0.631
41-50	51	9	0.57 (0.20-1.66)	0.305
> 50	33	3	0.30 (0.07-1.23)	0.093
Parity				
Nulliparous	28	7	1*	
Multiparous	128	24	0.75 (0.29-1.91)	0.547
Current pills used				
No	115	27	1*	
Yes	21	2	0.41 (0.09-1.84)	0.241
Age at 1st SI				
< 18	9	5	1*	
> 18	65	14	0.39 (0.11-1.34)	0.133
No of partners				
1	51	13	1*	
2	14	3	0.84 (0.21-3.37)	0.806
> 2	11	5	1.78 (0.53-6.04)	0.353

cervical dysplasia in ASC-US Pap smear women.

## Discussion

There was no cervical cancer in patients with ASC-US Pap smear in this study. The frequency of high grade dysplasia in patients with ASC-US Pap smear was 31 in

187 patients (16.6%). Previous studies reported vary rates of high grade dysplasia (6.9-26.4%) in patients with ASC-US (Katki et al., 2013; Kietpeerakool et al., 2014; Won et al., 2015). In U.S., ASC-US Pap smear women had cumulative risk in 5 years for CIN2+ was 6.9%, risk for CIN3+ was 2.6% and risk for cancer was 0.16% (Katki et al., 2013). Won et al., (2015) reported CIN2+ was found in 11.3% of ASC-US patients in Korea. Study in Thailand reported rate of high grade dysplasia (including invasive cancer) in ASC-US Pap smear women was 8.0-26.4% (Kietpeerakool et al., 2014). In agreement with our study, prevalence of CIN2+ in Thai women with ASC-US was higher than the report from U.S. One of the most important reason, Thai women do not regularly take Pap smear.

No clinical factor was associated with high grade intraepithelial neoplasia in patient with ASC-US in this study. By using logistic regression analysis, there was no statistical significance correlation of high grade dysplasia and clinical factors including age, parity, current pills used, age at first sexual intercourse, number of sexual partners and HIV status. Previous studies showed various risk factors of developing CIN such as STDs, young age at first sexual intercourse, oral contraceptive pills used, cigarette smoking and high parity (Parazzini et al., 1992; De Vet et al., 1993). Shlay et al., (2000) demonstrated an association of high grade dysplasia and high risk HPV (OR 110.08, 95% CI 8.35-999) but no clinical factors was found to be associated with high grade dysplasia. However, our study showed different results as there was no correlation between younger age at first sexual intercourse and high-grade CIN. This study is retrospective study that may have many confounding factors. Future study is needed to determine effects of these factors on clinical outcome of women with ASC-US Pap smear.

Two options in management women with ASC-US are HPV test and repeat cytology at 1 year interval. HPV testing is now recommended to triage women with ASC-US and as an adjunct to cytology when screening women > 30 years old. Ibanez et al., (2012) reported sensitivity to detect CIN2+ of HR-HPV test was 97.2% and specificity was 68.3% among ASC-US patients. Risk of women with HPV-negative ASC-US had very low of subsequent CIN3 (Safaeian et al., 2007). Cumulative risk in 5 years for CIN2+ in women who had ASC-US Pap smear with positive HPV test was 16%, women who had ASC-US Pap smear with negative HPV test was 1.1%, (Katki et al, 2013). Wright et al., (2015) reported the sensitivity for CIN3+ of cytology was 47.8% compared to 61.7% for the hybrid strategy (cytology in 25-29 years old women and cotesting in > 30 years old women). The specificity for CIN3+ was 97.1% and 94.6% for cytology and hybrid strategy, respectively.

In many countries, the benefit of using HPV test would be outweighed by excess colposcopy. Owing to the high cost of the HPV test in Thailand, our study was limited to use this test as an adjunct to cytology. However, from our study, the findings support that the use of repeated cytology is one of the effective management options for ASC-US patients, especially in unavailable HPV test areas.

Data from this study showed frequency of high grade

intraepithelial neoplasia in patients with ASC-US was 16.6%. There was no invasive cervical cancer was found in this group of patient. No clinical factor was associated with high grade intraepithelial neoplasia in patients with ASC-US Pap smear.

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*Suttichai Heng and Daranee Sirichaisutdhikorn*

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