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Underlying Histopathology in Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) Cytology in King Chulalongkorn Memorial Hospital

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Abstract

Objective: To determine the prevalence of underlying significant cervical lesions and factors associated with such lesions in women with atypical squamous cells of undetermined significance (ASC-US) cytology.

Materials and methods: Women with ASC-US cytology undergoing colposcopy and directed biopsy at the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital between January 2007 and December 2012 were reviewed. Patients' characteristics including histopathology were collected and analyzed. Significant cervical lesions were defined as cervical intraepithelial neoplasia grade 2 (CIN2), CIN3, adenocarcinoma in situ (AIS), and invasive cervical carcinoma.

Results: During the study period 154,638 Pap smears were carried out, of which 2,136 (1.38%) were ASC-US cytology. The ratio of ASC cytology/squamous intraepithelial lesions (SIL) cytology was 1.8:1. Among 2,136 women with ASC-US cytology, 627 underwent colposcopic examination and 540 had cervical biopsy. Significant cervical lesions were noted in 46 (8.6%) women. Invasive cervical carcinoma was detected in 5 (1%) women including 3 squamous cell carcinoma and 2 adenocarcinoma.

Conclusions: The underlying significant cervical lesions in women with ASC-US cytology was 8.6% and approximately 1% had invasive cervical cancer. Diagnostic work-up with colposcopy is recommended. No significant factor predicting high-grade cervical lesions was noted in women with ASC-US cytology.

Keywords: Cervical cytology; ASC-US; Cervical cancer; Cervical histopathology

Introduction

Cervical cancer is the third most common malignancy in women worldwide with an estimation of more than 500,000 new cases per year and approximately 260,000 women die from this disease [1]. In Thailand, among female cancer, cervical cancer is the second most common after breast cancer with the estimated age-standardized incidence rate of 17.8/100,000 women-year while the estimated incidence worldwide is 7.9/100,000 women-year [1]. Each year, about 8,200 new cases are diagnosed and 4,500 die of cervical cancer [1]. Cervical cancer is now recognized as the most preventable cancer as there are various methods for prevention, i.e. primary prevention with human papillomavirus (HPV) vaccination and secondary prevention with screening test. At present, there are many methods for screening including cervical cytology, HPV testing, and visual inspection with acetic acid. The main objective of screening is to early detect and treat precancerous cervical lesions, i.e. cervical intraepithelial neoplasia grade 2 (CIN2), CIN3, and cervical adenocarcinoma in situ (AIS).

In Thailand, cervical cytology with conventional Pap smear is the most widely used for cervical cancer screening. Among the cytologic abnormalities according to the 2001 Bethesda system [2], atypical squamous cells(ASC) is the most common abnormalityaccounting for approximately 5% [3-5]. Atypical squamous cells of undetermined significance (ASC-US) is the most frequent in this category. The causes of ASC-US cytology vary widely from reactive change, reparative change, atrophic change, and inflammatory process to cervical neoplasia resulting in low reproducibility of interpretation. The risk of invasive cervical cancer in women with ASC-US cytology is low because one to two-thirds of cases are not associated with high-risk HPV infection [6,7]. In the previous reports from western countries, the prevalence of underlying high-grade cervical lesions in women with ASC-US cytology ranged from 4.4-15.4%, the risk of having invasive carcinoma was considerably low at 0.1-0.2% [8-11]. In Thailand, several reports from different regions showed a high prevalence of underlying precancerous cervical lesions ranging from 8-18%, of more importance was the high prevalence of invasive cancer ranging from2-8%% [12-16]. This study was conducted to determine the prevalence of underlying significant cervical lesions and factors associated with such lesions in women with ASC-US cytology in a university hospital in Bangkok.

Materials and Methods

After approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, the data of women with ASC-US cytology undergoing colposcopic examination between January 2007 and December 2012 at the Department of Obstetrics and Gynecology,

King Chulalongkorn Memorial Hospital were reviewed. The inclusion criteria were women aged 30-65 years with available cytology and histopathology slides. The exclusion criteria were women who had prior abnormal Pap smear, history of cervical neoplasia, pregnant women and concurrent malignancy of other organs.

Both cytologic and histopathologic slides were reviewed by two gynecologic pathologists. All cervical cytology specimens in this study were conventional method. In patients who had more than one histopathologic specimens, all the specimens were reviewed and the most severe lesion was counted. Significant cervical lesions were defined as cervical intraepithelial neoplasia grade 2 (CIN2), CIN3, adenocarcinoma in situ (AIS), and invasive cervical carcinoma. The patients' demographic data, parity, oral contraceptive usage, HIV status, and HPV status, if available were analyzed. The relative frequency of the interpretations of atypical squamous cells (ASC) and squamous intraepithelial lesions (SIL) (ASC/SIL ratio) was evaluated for quality control measurement.

Statistical analysis was carried out using SPSS software version 17 (SPSS Inc, Chicago). The descriptive statistics were used for demographic data. The chi-square or Fisher exact test was used for univariate and multivariate analysis. P-value of less than 0.5 was considered statistically significant.

Results

During the study period, 154,638 Pap smears were performed, of which 2,136 (1.38%) smears were ASC-US cytology. The ratio of ASC-US cytology/squamous intraepithelial lesions (SIL) cytology was 1.8:1. Of the 2,136 ASC-US smears, 627 (29.3%) women underwent colposcopic examination and colposcopically directed biopsy was performed in 540 patients. Eighty seven women underwent colposcopic examination without biopsy taken due to no lesion seen and were excluded from the study. Mean age of the patients was 40.1 years with a range of 25-63 years. One hundred and twenty three (22.8%) women were post-menopause. Seventeen (3.1%) women had HIV infection. Fifty-five patients were tested for HPV status in which 49 were HPV-positive. The follow-up period ranged from 0-84 months after colposcopy. The median follow up time was 23 months. During follow-up, high-grade cervical lesions were detected in 3 women. Among 49 women who were HPV-positive, 4 (8.2%) had high-grade lesions (Figure 1). No CIN was noted in 6 women who were HPV-negative.

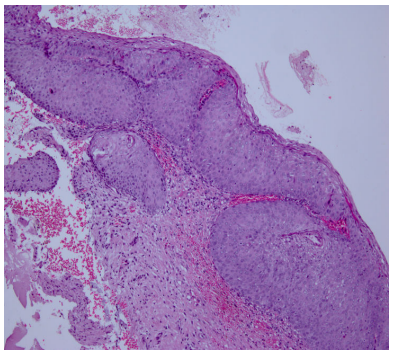

Figure 1: High grade lesions (CIN3 with glandular involvement) with koilocytic change in superficial cells.

Table 1 shows the underlying histopathology of women with ASC-US cytology undergoing colposcopically directed biopsy. Forty one (7.6%) had precancerous cervical lesions and 5 (0.92%) had invasive carcinoma in which 3 were stage IA1 squamous cell carcinoma (Figure 2) and 2 were stage IB1 adenocarcinoma of the cervix (Figure 3), One of them had concurrent CIN 3. Overall, the prevalence of significant cervical lesions, i.e. CIN 2, CIN3, adenocarcinoma in situ (AIS) and invasive cervical carcinoma was 8.6%.

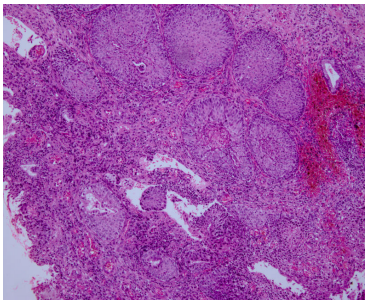

Figure 2: Frank invasive squamous cell carcinoma, obtaining from a patient with ASC-US on prior Pap smear.

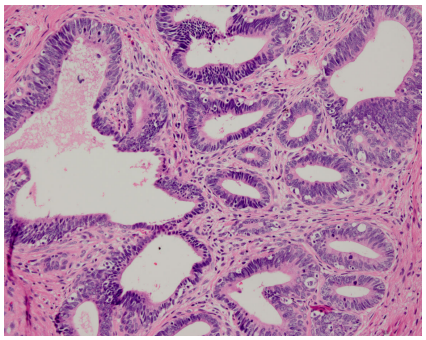

Figure 3: Endocervical adenocarcinoma.

In 41 precancerous lesions, 73.2% (30 cases) and 80% (4/5) of invasive cervical carcinoma showed superficial koilocytic change.

Histopathology	Number (%)
Normal	82 (15.2)
HPV effect	321 (59.4)
CIN 1	85 (15.7)
CIN 2, CIN 3 and AIS	41 (7.6)
Squamous cell carcinoma	3 (0.6)
Adenocarcinoma	2 (0.4)
Inadequate tissue sampling	6 (1.1)
Total	540(100)

Table 1: Underlying histopathology of 540 women with ASC-US cytology. CIN: Cervical Intraepithelial Neoplasia; AIS: Adenocarcinoma In Situ.

Univariate analysis for predicting significant cervical lesions including age, parity, menopausal status, oral contraceptive usage, and HIV status was carried out. Only age ≤40 years was found to have p-value of less than 0.10 in the univariate analysis. Multivariate analysis using a logistic regression model of this significant covariate was performed. No statistical significance was noted for this factor to predict significant cervical lesions as shown in Table 2.

Variables		<CIN 1	>CIN 2	p-value	OR* (95%CI)	p-value
Age	≤40	249	31	0.03	1.85 (0.79-3.71)	0.12
	>40	239	15			
Parity	Nulliparous	372	40	0.10	-	-
	Multiparous	116	6			
Menopause	Pre-menopause	373	40	0.10	-	-
	Post-menopause	115	6			
Oral contraceptives	Yes	76	4	0.21	-	-
	No	412	42			
HIV status	Negative	372	45	0.68	-	-
	Positive	16	1			

Table 2: Univariate and multivariate analyses for predicting significant cervical lesions (>CIN 2). CIN: Cervical Intraepithelial Neoplasia; *Multivariate adjusted odds ratio; CI, confidence interval.

Discussion

The prevalence of underlying high-grade cervical lesions in 540 women with ASC-US cytology undergoing colposcopincally directed biopsy in this study (7.6%) was within the previously reported ranges of 4.4-15.4% in the western countries where the incidence of cervical cancer was considerably low [8-11]. Such prevalence was a little bit lower than those of 8-18% in the previous reports from Thailand [12-16]. However, the risk of having invasive cancer among women with ASC-US smears in this study (1%) was much higher compared with those of 0.1-0.2% in the western countries [8-11], but was in line with the risk of 0-8% in the previous studies in Thailand [12-16]. These findings imply the appropriate management of women with ASC-US cytology in the area with a high incidence of cervical cancer.

Management of women with abnormal cervical cytology, in general depends on the risk of having high-grade lesions and invasive cancer. For each abnormal screening result, recommended approach is based on the 5-year risk of CIN3 or greater [17]. If the risk is higher than 5%, immediate colposcopy is recommended, but if the risk is between 2-5%, repeating the screening test in 6-12 months is recommended. Since the risk of harboring significant cervical lesions in women with ASC-US smears in our study was high at 8.6%, immediate colposcopy is warranted.

According to the consensus guidelines for the management of abnormal cervical cancer screening tests of the American Society for Colposcopy and Cervical Pathology (ASCCP), the preferred strategy for managing women with ASC-US cytology is to perform HPV testing and refers the patient for colposcopy in case of HPV-positive. Alternatively, repeating cervical cytology in 1 year is an acceptable option for ASC-US cytology, if the repeating smear shows ASC-US or more severe cytologic abnormality, colposcopy should be performed. Colposcopy is not recommended as an initial diagnostic work-up for ASC-US cytology [17]. In the area with high incidence of cervical cancer and high prevalence of underlying significant lesions in women with ASC-US cytology, immediate colposcopy is an appropriate strategy to early detect and treat precancerous cervical lesions, particularly in women with poor compliance to follow-up. Furthermore, the expense of colposcopic procedure in Thailand is much lower than that in the western countries. Importantly, colposcopy provides immediate information for counseling the patients and helps relieve stress and anxiety about developing cancer.

In the present study, 4 (8.2%) cases of high-grade cervical lesions were detected in 49 women with ASC-US cytology who were HPV-positive and no CIN was found in 6 women who were HPV-negative. Although the number was too small, further study on the influence of HPV status and the risk of underlying significant lesions in women with ASC-US cytology is proposed in our institute. Currently, it is well established that HPV is the main cervical carcinogen. HPV is detected in nearly 100% of cervical cancer [18,19]. Therefore, the data of cervical HPV status are certainly useful in managing ASC-US smears. A meta-analysis on management of women with ASC-US cytology showed that HPV testing had a higher sensitivity for detecting high-grade cervical lesions compared with repeat cytology (91% vs. 72%) [20]. The 5-year risk of CIN2 or greater in women with ASC-US/HPV-positive results was 18% compared with 1.1% in those with ASC-US/HPV-negative results [7]. The findings suggest that women with ASC-US/HPV-positive results should be referred to colposcopy. In a meta-analysis, the prevalence of HPV positivity in women with ASC-US cytology varied widely between 23% and 74% [21]. Triaging ASC-US smears with HPV testing could reassuringly identify women who need further colposcopic work-up and reduce workload of such procedure.

No significant predictors for underlying high-grade cervical lesions were noted in the univariate and multivariate analyses of this study. The predisposing factors or co-factors of cervical carcinogenesis included age, parity, menopausal status, oral contraceptive usage, and HIV status. Oral contraceptives have been considered as a strong co-factor of persistent HPV infection and progression to precancerous lesions. Among women with ASC-US cytology, oral contraceptive use was reported as a significant independent predictor for having CIN2+ or more severe [12]. Women with HIV infection also have an increased risk of co-infection with HPV, persistent HPV infection, and development of cervical neoplasia [22,23]. HIV-infected women with abnormal cervical cytology had approximately 2.6 folds the risk of having high-grade cervical lesions compared to HIV-negative women. HIV-positive women with any degree of abnormal cytology warrant further management with immediate colposcopy [24].

The strength of this study includes the high number of women with ASC-US cytology and analysis of only women undergoing colposcopically directed biopsy. All cytologic and histopathologic slides were reviewed by two gynecologic pathologists. The limitation of this study is the retrospective by nature, some data are missing, especially the HPV status. Not all women with ASC-US cytology underwent colposcopy and directed biopsy. However, the findings from this study could be applied in planning management of women with ASC-US cytology in the area with high incidence of cervical cancer.

In conclusions, the underlying significant cervical lesions in women with ASC-US cytology was 8.5% and approximately 1% had invasive cervical cancer. Diagnostic work-up with colposcopy is recommended. No significant factor predicting high-grade cervical lesions was noted in women with ASC-US cytology.

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