

PREVALENCE OF HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL) AND INVASIVE CERVICAL CANCER IN PATIENTS WITH ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE (ASCUS) FROM CERVICAL PAP SMEARS

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Abstract. To determine the prevalence and factors associated with histologic diagnoses of High Grade Squamous Intraepithelial Lesions (HSIL) or invasive cervical cancer in women with a cytologic diagnosis of atypical squamous cells of undetermined significance (ASCUS), medical records of women with an ASCUS Pap smear from January 2003 to December 2006 were reviewed. Of 287 women with ASCUS Pap smears in whom data were available, 189 were annotated with "favoring a premalignant or malignant process", 74 with "favoring reactive", and 24 with "not otherwise specified". The prevalences of HSIL and invasive cervical cancer were 9.1% and 1.2%, respectively. Only subtypes of ASCUS were significantly associated with the detection of HSIL or invasive cancer, 12.7% with favoring premalignant or malignant process, 2.7% with favoring reactive, and 16.7% in with ASCUS-NOS ($p=0.034$).

INTRODUCTION

Cervical cancer is the second most common gynecologic cancer worldwide, accounting for 15% of all female cancers in developing countries (Parkin *et al*, 2002). In Thailand, cervical cancer is the most common gynecologic cancer, found in 20.9 in 100,000 women and is also the most common cause of death (Srivatanakul *et al*, 1999). One effective means to reduce mortality from cancer of the cervix is early detection and treatment of pre-invasive cervical lesions. This can be achieved by

cervical cytologic screening programs. The first system to detect and report cervical cytology was the Papanicolaou system which was developed in 1943 and has been used for many years (Papanicolaou and Traut, 1943). However, with emerging knowledge about human papilloma virus (HPV) as an important etiologic agent in cervical cancer, a new cytologic classification, the Bethesda System, was adopted in 1988 (National Cancer Institute Workshop, 1989). In the Bethesda classification, cervical intraepithelial neoplasia (CIN) was replaced by squamous intraepithelial lesion (SIL). A detection of HPV virus has been included in this new classification and is classified together with CIN I as a low grade SIL (LSIL) while CIN II and III were classified as high grade SIL (HSIL). Any cellular atypia which is more marked than those attributable to reactive changes but quantitatively and qualitatively falls short of a definitive diagnosis of SIL

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is termed as "atypical squamous cells of undetermined significance" (ASCUS). Because of the uncertain denotation of ASCUS, this term was further subcategorized in the 1991 Bethesda system (National Cancer Institute Workshop, 1993) into "reactive change", "pre-malignant/malignant" or truly "not otherwise specified". In the 2001 Bethesda system, "atypical squamous cell" (ASC) was changed (Stoler, 2002) to "atypical squamous cells of undetermined significance" (ASCUS) and "atypical squamous cells those can not exclude high grade squamous intraepithelial lesion (ASC-H)" according to the interpreting cytopathologist.

As a quality assurance not to overuse this term, the rate of ASCUS reported at any institution should be kept within the range of 3-5% (Davey *et al*, 2000; Stoler and Schiffman, 2001). However, the rates reported by many studies vary from 3.6-23.5% (Lindheim and Smith-Nguyen, 1990; Abu-Jawdeh and Wang, 1994; Auger *et al*, 1997; Williams *et al*, 1997; Kinney *et al*, 1998; Lachman and Cavallo-Calvanese, 1998; Dvorak *et al*, 1999; Lousuebsakul *et al*, 2000; Massad *et al*, 2001; Mood and Haratian, 2004; Ghaemmaghami *et al*, 2005). In harmony with the wide range of prevalence rates, final diagnoses of cervical histopathology with ASCUS may vary from normal histology at one end to HSIL or invasive cancer at the other end. Because of this, options for the management of ASCUS have been proposed: follow-up under close surveillance, HPV testing, or immediate colposcopic examination to obtain cervical biopsy for histopathologic examination. A physician taking care of a woman with ASCUS cytology may choose any of the three options depending on his experience, desire of the woman, the hospital setting and equipment. However, due to the wide range of histopathology with ASCUS, it is unclear what would be appropriate follow-up for a woman who may have a risk for HSIL or invasive cancer or simply normal

cervical histology, should it include expensive HPV testing, or a colposcopic examination (which may not be readily available). Having more data regarding the final outcomes of ASCUS would be useful. The purpose of this study was to determine the prevalence of the histologic diagnosis of HSIL, microinvasive or invasive cervical cancer in woman with ASCUS cervical Pap smear and to study factors which may be associated with the histopathologic diagnosis of HSIL or invasive cervical cancer (\geq HSIL) with ASCUS cytology.

MATERIALS AND METHODS

This study was conducted after approval by an ethics committee. Patients with a cervical cytologic diagnosis of ASCUS between January 2003 and December 2006 were identified from the archives of the Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital. The inclusion criteria were: a woman with ASCUS cytology from a conventional Pap smear performed at our institution who subsequently underwent colposcopic examination. Women with ASCUS cytology who had histology examination after fractional curettage or hysterectomy for any other coincidental pathology were also included. Women who had a history of cervical cancer or pre-invasive cervical lesions, had a prior hysterectomy, or had an incomplete medical record were excluded.

The clinical practice guideline for a woman with ASCUS cytology at Bangkok Metropolitan Administration Medical College and Vajira Hospital is to perform colposcopic examination, which is conducted by gynecologic oncologists or those in fellowship training. Tissue from colposcopic directed biopsies was obtained from any suspicious lesions. In any cases where colposcopy was unsatisfactory or where there was no gross cervical abnormality had endocervical curettage car-

ried out. Women who had satisfactory colposcopy with no suspicious lesions over ecto and endo-cervices were defined as "normal" and underwent a follow-up Pap smear. When histologic tissue biopsy revealed a lesion worse than HSIL had cervical conization by loop electrosurgical excision procedure (LEEP) or cold knife conization.

Patient clinical and pathological data were retrieved from the in-patient/out-patient charts and the archives of the Anatomical Pathology Department. Data were collected regarding age, menopausal status, marital status, parity, specific subtype of ASCUS, and the definite cervical histology. Histopathology referred to the most severe histologic diagnosis at biopsy, curettage, LEEP, or hysterectomy. Data were analyzed by parametric and nonparametric statistics, using SPSS 11.5 (Chicago, IL). Descriptive statistics were used for demographic data and summarized as frequencies, percentages, means with standard deviation (SD) and medians with ranges. Differences between variables were evaluated with the chi-square test for variables that were normally distributed and the Mann-Whitney *U* test for variables that were not normally distributed. The primary outcome was considered significant only if the *p*-value ≤ 0.05 .

RESULTS

At our institution, 11,000-12,000 women have cervical cytologic Pap smear annually. During the study period, 830/46,680 women (1.75%) had a cytologic diagnosis of ASCUS. Approximately 2/3 of them (531 women) were excluded: 66 women had a history of cervical cancer or pre-invasive cervical lesions, 32 women had a prior hysterectomy, 170 had an incomplete medical record, 275 were lost to follow-up or were self-referred to other hospitals and did not have colposcopic examination at our institution. A total of 287 women with ASCUS cytology met all the inclusion

Table 1
Clinical characteristic features of women with atypical squamous cells of undetermined significance (ASCUS) in our study (N=287).

Characteristics	<i>n</i>	(%)
Age, (years) (mean \pm SD)	46.2 \pm 14.25	
< 55 years	220	(76.7)
\geq 55 years	82	(23.3)
Marital status		
Single	17	(5.9)
Married	270	(94.1)
Parity		
0	55	(19.2)
≥ 1	232	(80.8)
Menopausal status		
Pre-menopause	172	(59.9)
Postmenopause	115	(40.1)
Anti-HIV		
Negative	283	(98.6)
Positive	4	(1.4)

HIV=Human immunodeficiency virus

criteria and were included in the study. The specific subtypes of ASCUS were: not otherwise specified (NOS) in 24 cases (8.4%), favor reactive process in 74 cases (25.8%), and favor premalignant/malignant process in 189 cases (65.9%).

The mean age of the women was 46.2 \pm 14.25 years. More than half of them (59.9%) were premenopausal. Most of them were multiparous, with a median parity of 2 (range 1-11). The clinical characteristics of the women in the study are shown in Table 1. Of 287 women, colposcopy was performed in 277 women (96.5%). Colposcopic examination was noted as satisfactory in 172 women (62.1%) while the transformation zone of the cervix was not entirely seen or the operator (colposcopist) made unsatisfactory notes in 106 women (38.3%). Cervical biopsy was performed in 138 women (48.1%), while endocervical curettage (ECC) was performed in 107

Table 2
Histologic or histopathologic results of women with atypical squamous cells of undetermined significance (ASCUS) ($N=287$).

Histologic/ histopathology	<i>n</i>	(%)
Normal	84	29.3
Inflammation/ cervicitis	50	17.4
LSIL	122	42.5
HSIL		
CIN II	10	3.5
CIN III	16	5.6
Primary cervical cancers	3	0.9
Squamous cell carcinoma	1	0.3
Adenocarcinoma	1	0.3
Lymphoma	1	0.3
Metastatic ovarian adenocarcinoma	1	0.3

CIN=cervical intraepithelial neoplasia; HSIL=high grade squamous intraepithelial lesion; LSIL=low grade squamous intraepithelial lesion

women (37.1%). LEEP was subsequently performed in 30 women (10.4%) who had HSIL on cervical biopsy or ECC. After obtaining histopathologic diagnosis, various types of hysterectomy were performed: simple hysterectomy (11 cases), vaginal hysterectomy (4 cases) and radical hysterectomy (2 cases).

Ten women who had been appointed for colposcopic examination did not have the test because hysterectomy or fractional curettage was performed prior to the schedule. Hysterectomy was performed for the following reasons: leiomyoma with bleeding complications ($n=2$), prolapsed uterus ($n=1$), and ovarian tumor ($n=2$). Fractional curettage was performed in five cases due to co-incidental abnormal uterine bleeding. All ten women were examined by a gynecologic oncologist before

Table 3
Histopathology of HSIL or higher according to clinical characteristics and subtypes of atypical squamous cells of undetermined significance (ASCUS) ($N=287$).

Characteristics	Histopathology		p-value
	Normal/LSIL	HSIL/cancer	
Age			
< 55 y ($n = 220$)	195 (88.6%)	25 (11.4%)	
≥ 55 y ($n = 82$)	77 (93.9%)	5 (6.1%)	0.174 ^a
Marital status			
Single ($n = 17$)	15 (88.2%)	2 (11.8%)	
Married ($n = 270$)	242 (89.6%)	28 (10.4%)	0.694 ^a
Parity			
0 ($n = 55$)	49 (89.1%)	6 (10.9%)	
≥ 1 ($n = 232$)	208 (89.7%)	24 (10.3%)	1.00 ^a
Menopausal status			
Premenopause ($n = 172$)	153 (89%)	19 (11%)	
Postmenopause ($n = 115$)	104 (91.4%)	11 (9.6%)	0.694 ^a
ASCUS subtype			
NOS ($n = 24$)	20 (83.3%)	4 (16.7%)	
Favor reactive ($n = 74$)	72 (97.3%)	2 (2.7%)	0.034 ^a
Favor PM/M ($n = 189$)	165 (87.3%)	24 (12.7%)	
Anti-HIV			
Negative ($n = 283$)	254 (89.8%)	29 (10.2%)	
Positive ($n = 4$)	3 (75%)	1 (25%)	0.359 ^b

p-values by chi-square test^a, Fisher's exact test^b

Favor PM/M=favor premalignant/malignant process; HIV=human immunodeficiency virus; HSIL=high grade squamous intraepithelial lesion; LSIL=low grade squamous intraepithelial lesion; NOS=not otherwise specified.

Table 4
Prevalence of atypical squamous cells with undetermined significance (ASCUS) and histology/histopathology outcomes including high grade lesions or cancer.

Reference	N	Prevalence of ASCUS (%)	Histopathology (%)		
			LSIL	HSIL	Cancers
Lindheim and Smith-Nguyen, 1990	101	NA	12.9	19.7	0.99
Abu-Jawdeh and Wang 1994	97	NA	18	13	0
Massad <i>et al</i> , 2001	399	23.5	22	17	1
Auger <i>et al</i> , 1997	52	1.3	27	10	4
Lousuebsakul <i>et al</i> , 2000	421	2.34	43	4	1
Lachman <i>et al</i> , 1998	560	36.1	19.5	16.8	0
Williams <i>et al</i> , 1993	84	4.5	13	9	0
Mood and Haratian, 2002	98	2.76	33.6	3.1	2
Dvorak <i>et al</i> , 1999	249	3.8	54	18	0
Our study 2007	287	1.75	42.5	9.1	1.2

HSIL=high grade squamous intraepithelial lesion; LSIL=low grade squamous intraepithelial lesion; NA=not available

hysterectomy and invasive cancer was not evident on gross cervical inspection.

The final histology/histopathology from the cervixes with ASCUS cytology in our studied population varied from normal findings to invasive cancer. The details of histology/histopathology are shown in Table 2. In brief, 84 cases (29.3%) of ASCUS had normal histologic findings, while 30 cases had HSIL or invasive cancers (10.3%). Of the four cases of invasive cancer, one case was squamous cell carcinoma, two were adenocarcinoma of the cervix or metastatic ovarian carcinoma (one case each), and the remaining case was primary cervical lymphoma.

We studied whether any clinical or cytopathologic subtypes of ASCUS were associated with the histopathology of \geq HSIL in patients with ASCUS cytology. We found that age, marital status, menopausal status, parity, and positive anti-HIV serology were not associated with \geq HSIL. Only the specific subtypes of ASCUS were significantly associated with \geq HSIL ($p=0.034$); the women whose

ASCUS cytology were denoted as "not otherwise specified" or "favor premalignant/malignant process" had a higher association with \geq HSIL (Table 3).

DISCUSSION

Since the Bethesda system was adopted in 1988, cytotechnologists and pathologists in the department of Anatomical Pathology at our institution have incorporated this new system into their reports. The diagnostic category of ASCUS is a new terminology which was introduced in order to reduce confusion and unnecessary colposcopic referrals associated with previous vague diagnoses of atypical categories. Three specific subtypes of ASCUS are used, based on the judgment of cytopathologist: not otherwise specified, favor reactive process, favor pre-malignant/malignant process. According to the latest revision of Bethesda in 2001 (Stoler, 2002), report of atypical squamous cells is divided into 2 categories: ASC-undetermined significance (ASC-US) and ASC-high grade lesion could not be

excluded. These minor changes have also been modified.

During the study period, the ASCUS rate at our institution was 1.75%, which is in the range recommended for ASCUS in a low risk population, which should be < 5% (Ergenneli *et al*, 2001). Other studies (Abu-Jawdeh and Wang, 1994; Auger *et al*, 1997; Dvorak *et al*, 1999; Ghaemmaghami *et al*, 2005; Kinney *et al*, 1998; Lachman and Cavallo-Calvanese, 1998; Lindheim and Smith-Nguyen, 1990; Lousuebsakul *et al*, 2000; Massad *et al*, 2001; Mood and Haratian, 2004; Williams *et al*, 1997) reported rates ranging from 3.6-23.5%. The different prevalences of ASCUS are due to: characteristics of the patient population, such as a high rate in a high risk population *eg*, old age (Massad *et al*, 2003), underscreened populations, patients with sexually transmitted diseases including human immunodeficiency virus (HIV) infection (Holcomb *et al*, 1999), the type of cytologic study (conventional Pap smear or liquid base cytology) (Saslow *et al*, 2002) and the experience and skill of the cytopathologists. The pathologists and clinicians at each institution who are dealing with women with ASCUS should be aware of these limitations.

For the management of women with ASCUS cervical cytology, the American Society for Colposcopy and Cervical Pathology recommends the following (Wright *et al*, 2002): to repeat the Pap smear in 4-6 months, to have HPV DNA testing or to have colposcopy. The decision varies by institution, generally based on the availability of medical personnel, experience, equipment, the cost-effectiveness of the option, and financial resources. Of these factors, the possibility of severe histopathology is one of the most important factors influencing decision making. Although a follow-up Pap smear is a low cost option, a disadvantage is its low sensitivity. Ghaemmaghami *et al* (2005) found that a single repeat Pap smear did not decrease the frequency of referral for colposcopy. A repeat Pap smear also requires fre-

quent visits, which may be inconvenient for some patients leading to poor compliance and a delay in detecting important lesions. Another study by Ergenneli *et al* (2001) reported LSIL in 14 % and HSIL in 11% of patients who underwent colposcopic directed biopsies for their evaluation of ASCUS. They concluded that ASCUS was a marker for the detection of SIL and an immediate colposcopy-directed biopsy is appropriate management.

It is the clinical practice of our institution, a tertiary cancer center, that all women with ASCUS cytology receive colposcopic examination. Similar to other cancer centers with a high number of women with abnormal cervical cytology, there is a long waiting list for colposcopy. It may take several weeks to months before the procedure may actually be performed. The fact that women with HSIL or suspicious for invasive cancer cytology need prompt investigation raises the need for individualized, appropriate care for women with cervical lesions. To have quality assurance at our institution and refine the management of women with abnormal cervical cytology, we focused on the outcomes of \geq HSIL with ASCUS cytology (Massad *et al*, 2003).

We found the prevalence of HSIL/invasive cancer with ASCUS cytology at 10.3%. This figure is in the range reported in other studies, which found the pathology of HSIL and invasive cancers ranged from 4-20% and 0-4%, respectively (Lindheim and Smith-Nguyen, 1990; Abu-Jawdeh and Wang, 1994; Auger *et al*, 1997; Williams *et al*, 1997; Kinney *et al*, 1998; Lachman and Cavallo-Calvanese, 1998; Dvorak *et al*, 1999; Lousuebsakul *et al*, 2000; Ergenoli *et al*, 2001; Massad *et al*, 2001; Mood and Haratian, 2004; Ghaemmaghami *et al*, 2005). The prevalence of ASCUS and the correlation with the final histology/histopathology results are summarized in Table 4. One may question whether our results truly reflect the prevalence of \geq HSIL with ASCUS cytology because we included only women who

underwent colposcopy or had biopsies. This limitation is due to the retrospective nature of our study. Hence, women with ASCUS pathology who might also have \geq HSIL would be missed in our study. However, this circumstance is probably encountered in routine gynecologic services in other hospitals where patients may not follow medical advice (to have colposcopy) (Auger *et al*, 1997; Lousuebsakul *et al*, 2000; Mood and Haratian, 2004).

The rate of HSIL or invasive cancer in our study pointed out that histologically proven cervical lesions are important if the physician does not want to miss severe cervical lesions with ASCUS cytology. This information supports our guidelines for management in our institution that women with ASCUS should undergo colposcopic evaluation to select an area for tissue sampling.

The 10% (4-20% in other studies) rate of HSIL/cancer must be reevaluated by physicians outside the hospital, in primary health care units, or in lower-resource settings to determine whether it is justified to refer all women with ASCUS to see a colposcopist for immediate colposcopy. The ASCUS -LSIL Triad Study (ALTS trial) (Kim *et al*, 2002) reported in favor of HPV DNA testing because it is less costly than repeated cytology or colposcopic examinations. It yielded a high sensitivity. In Thailand, where HPV-DNA testing is expensive and not readily available in all areas, we believe this option has limitation.

Due to the limitations of this retrospective study, only HSIL or cancer in ASCUS cytology were studied. Our study found the prevalence of \geq HSIL was not different between women \geq 55 years old and those younger. This is different from the results of Massad *et al* (2003) who found that older women (\geq 50 years) with ASCUS had higher numbers of CIN III and cancer than younger women (25% vs 15%, respectively) while younger women with ASCUS had higher numbers of cellular atypia, CIN I and CIN II than

older women (64% vs 40%, respectively).

We found that only "not otherwise specified" and "favor premalignant/malignant lesions" had a higher association with \geq HSIL lesions (16.7% and 12.7% respectively), while those with reactive ASCUS had minimal risk for \geq HSIL lesions (2.7%), similar to a study by Mood and Haratian (2004) which showed almost all women with reactive ASCUS had benign histology without HSIL or cervical cancer.

These findings emphasize the importance of sub-classification of ASCUS to refine recommendations for colposcopy. Those with ASCUS "not otherwise specified" or with premalignant/malignant lesions should undergo immediate colposcopy while "reactive" ASCUS should be followed by interval Pap smear.

In conclusion, this study found 10.3% of women with ASCUS cytology actually had HSIL or invasive cervical cancer. The prevalences were higher in the ASCUS subtypes of "not otherwise specified" and "favor premalignant/malignant lesions", at 16.7% and 12.7% respectively. ASCUS "favor reactive process" had a low prevalence of \geq HSIL lesions in 2.7%.

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