RESEARCH COMMUNICATION

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

Nathaya Khuakoonratt[1]*, Siriwan Tangjitgamol[1,2], Sumonmal Manusirivithaya[1], Jakkapan Khunnarong[1], Kamol Pataradule[1], Thaovalai Thavaramara[1], Pachuen Suekwattana[1]

Abstract

Objective: To assess the prevalence and factors associated with a histologic diagnosis of high grade squamous intraepithelial lesion (HSIL) and invasive cervical cancer in patients with low grade squamous intraepithelial lesion (LSIL) cervical pap smear findings. Methods: Medical records (including cytology reports, colposcopic impression, and pathologic results from cervical biopsy, endocervical curetting, cervical conization or hysterectomy) of 226 women with LSIL from conventional cervical pap smears during January 2001 to December 2005, who subsequently underwent colposcopic evaluation at our institution, were reviewed. Results: Mean age of the patients was 39.0 years. The incidences of LSIL, HSIL, microinvasive cervical cancer were 58.8%, 15.0%, 1.3% respectively. No associations were found between age, parity, contraception, anti-HIV or menstrual status and the detection of HSIL/invasive cervical cancer. Conclusion: Approximately 16.3 % of LSIL pap smear cases turn out to be HSIL or invasive cervical cancer from histologic diagnosis.

Key Words: HSIL - LSIL - cervical cancer - Pap smear cervical cytology

Asian Pacific J Cancer Prev, **9**, 253-258

Introduction

Cervical cancer is the second most common cancer among women worldwide, with the estimated 493,000 new cases and 274,000 deaths in 2002 (Parkin et al., 2005). The incidence is much higher in developing countries. In Thailand, cervical cancer is the most common gynecologic cancer with the age-standardized incidence rate (ASR) of 19.5 per 100,000 per year (Pengsa and Jindawijak, 2003). Cervical cancer screening program is an important means for early cancer detection. Conventional cytologic Papanicolaou's smear (Pap smear) has been the most widely used screening method for cervical cancer for several years. In 1988, the Bethesda system was adopted to reduce widespread confusion among laboratories and clinicians (National Cancer Institute Workshop, 1989). The system has been revised in 1991, and again in 2001, based on actual laboratory and clinical experience after its implement (Bethesda Workshop, 1992; Solomon et al., 2002). Major difference of Bethesda system is the introduction of squamous intraepithelial lesions (SIL) terminology in place of cervical intraepithelial neoplasia (CIN) of the World Health Organization (WHO) classification. Squamous intraepithelial lesions are divided into low grade SIL (LSIL) and high grade SIL (HSIL) according to the abnormal cytologic morphology. Human papilloma virus (HPV) infection is incorporated into the Bethesda system and is classified as LSIL together with CIN I of previous WHO system or class III of Pap smear, while HSIL includes both CIN II and CIN III or Pap class III-IV of the former systems.

Any abnormal initial cytologic smears certainly require an attention from a physician for further investigation and management. Options of management would depend on many factors, such as, the clinical findings of the lesions, severity of cytologic abnormality, an access for colposcopic examination including an instrument and a competent clinician, and the preference or compliance of the patient (Phongnarisorn et al., 2006). In general, if the initial cytologic smear shows HSIL or invasive cancer, a direct biopsy could be carried out for any visible lesion while a colposcopic directed biopsy is required in the absence of any gross lesions. The American Society of Colposcopy and Cervical Pathology (ASCCP) 2006 has adopted a concensus guideline management of LSIL that colposcopy is generally recommended (Wright

*[1]Dept Obstetrics and Gynecology, [2]Dept Anatomical Pathology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, 681 Samsen, Dusit, Bangkok 10300, Thailand. *For Correspondence: Fax: 66-2-2437907 E mail : khua4611@yahoo.co.th*

et al., 2007) , except in special populations of adolescents in whom simply follow-up with annual cytologic testing is acceptable because evidences have shown very high rates of regression to normal (Moscikki et al., 2004), and in postmenopausal women who require the management of either repeat cytological testing at 6 and 12 months, HPV DNA testing, or colposcopy. However; not all medical practitioners follow this ASCCP guideline, some prefer an initial follow-up cytologic test and conduct a colposcopy after repeated abnormal cytology (Shafi et al., 1997; Soutter et al., 1986)

Since cytologic smear is only a screening test, the histopathologic results from the cervix of a patient with LSIL may not be correlated with the cytology. One way to measure the accuracy of the Pap test is to assess the cytologic-histologic correlations. Many studies reported various histopathologic diagnoses from LSIL cytology: normal, benign inflammation, LSIL or more severe lesions of HSIL and invasive cancer. The possibility of the latter two histopathologic diagnoses should worry the physicians or caregivers who are dealing with this particular group of women, leading to an immediate further management rather than a follow-up. The previous studies reported specific prevalences of HSIL in 15-30% and cancer in 0.1-3% from LSIL cytology (ASCUS-LSIL Triage Study Group 2003; Alvarez and Wright, 2007; Chute et al, 2006; Fairman et al, 2004; Law et al., 2001; Lonky et al., 1999). Knowing the final histologic diagnoses from the cervical cytologic LSIL, especially the risk of the severe lesions in each institution, would certainly facilitate the physicians in making decision how to manage their patients. The aim of this study was to evaluate the prevalence of histologic diagnoses of high grade lesions which include HSIL, microinvasive and invasive cervical cancer in women with cytologic diagnosis of LSIL in our institution. Further aim was to find factors which might associate with these high grade lesions in LSIL cytology.

Materials and Methods

This study was conducted after an approval of the Ethics Committee of our institution. Medical records of women with diagnosis of LSIL from Pap smear done at Bangkok Metropolitan Administration Medical College and Vajira Hospital during January 2001 to December 2006 were reviewed. Inclusion criteria were women who had cytologic diagnoses of LSIL and subsequently underwent colposcopic examination. Women who had history of cervical cancer or pre-invasive cervical lesions, prior hysterectomy, and incomplete medical records were excluded. Patient's clinical and pathological data were collected from the out-patient charts and the archive of the Anatomical Pathology Department. The collected data were: age, menopausal status, parity, contraceptive use, anti-Human Immunodeficiency Virus (HIV) status, and the definite cervical histology or histopathology which was referred to the most severe histologic diagnosis in this setting.

In the Department of Anatomical Pathology of our institution, Pap smear were interpreted by the cytotechnologists according to the Bethesda system 1991 and confirmed by an experienced cytopathologist, especially in those who have abnormal Pap smear. All women with LSIL or higher grade lesions were recommended to undergo colposcopic examination, which is conducted by gynecologic oncologists or fellowship in training. As a general practice guideline in our institution, any suspicious lesions would be directly biopsied under colposcope. In any cases when the colposcopy was unsatisfactory which was defined when the entire squamocolumnar junction was not comprehensively visualized, or in cases of abnormal lesions extending into cervical os, and when there were no gross cervical abnormalities, endocervical curettage (ECC) would be carried out. The women with unsatisfactory colposcopy and have negative ECC, and those who have satisfactory colposcopy with no suspicious lesion were defined as

Table 1. Clinical Characteristics of Women with Low Grade Squamous Intraepithelial Lesions (N=226)

Characteristics		N	%
Age, mean±SD (years)		39.04±1.54	
Menopause status			
	Premenopausal	173	76.5
	Postmenopausal	53	23.5
Parity	0	50	22.1
	≥ 1	176	77.9
Contraception*	Oral pill	46	21.5
	Others	168	78.5
Anti-HIV	Non-reactive	221	97.8
	Reactive	5	2.2

Table 2. Histologic or Histopathologic Diagnoses for Women with Cytologic LSIL (N=226)

Histology/ histopathology	N	%
Normal / cervicitis	56	24.8
LSIL	133	58.8
High grade lesions	37	16.3
HSIL	34	15.0
Microinvasive carcinoma	3	1.3

HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion

Table 3. Clinical Characteristics of Women with Cytologic LSIL According to Final Histopathology

Characteristics	< HSIL (%)	≥ HSIL (%)	P-value
Age			
≤ 30 years	57 (87.7)	8 (12.3)	0.294
> 30 years	132 (82.0)	29 (18.0)	
Menopausal status			
Premenopause	146 (84.4)	27 (15.6)	0.575
Postmenopause	43 (81.1)	10 (18.9)	
Parity			
0	45 (90.0)	5 (10.0)	0.168
≥1	144 (81.8)	32 (18.2)	
Anti-HIV			
Non-reactive	186 (84.2)	35 (15.8)	0.149
Reactive	3 (60.0)	2 (40.0)	
Contraception (n= 214)*			
Oral pills	39 (84.8)	7 (15.2)	0.955
Others **	143 (85.1)	25 (14.9)	

*12 cases had no data about contraception** Others included condom, intra-uterine device, implant, depot-progesterone acetate, tubal sterilization, male vasectomy

"normal colposcopy" and would simply be followed-up by a Pap smear surveillance. Subsequently, women with cervical histopathologic diagnosis of LSIL would also be periodically followed-up by Pap test while women with histopathologic diagnoses of HSIL, microinvasive cervical cancer or inconclusive diagnosis would be scheduled for cervical conization by loop electrosurgical excision procedure (LEEP).

Data were analysed by parametric and nonparametric statistics, using SPSS 11.5 (Chicago, IL). Descriptive statistics were used for demographic data and summarized as number of frequency and percentage, mean with standard deviation (SD), or median with range. Differences between variables were evaluated with Chi-square or Fisher's exact test as appropriate. The primary outcome was considered significant only if p value < 0.05.

Results

From January 2001 to December 2006, a total of 72,087 women had conventional cervical cytologic smear in our institution. Out of this, 691 women (0.9%) had cytologic diagnosis of LSIL. However; only 226 women underwent colposcopic examination and were included in the study. Thirteen women did not have colposcopic examination but came back months later for follow-up Pap smears. The remaining 452 women were lost to follow up, or were referred to have colposcopic examination or Pap smear follow up in other hospitals upon their request base upon financial reimbursement or personal reasons. Mean age of the 226 women was 39±1.5 years. Approximately two-third of them were premenopausal. The characteristic features of women included in the study are shown in Table 1. Colposcopic examinations in 226 women were noted as satisfactory in 157 women (69.5%) while 69 women (30.5%) had unsatisfactory result. Overall, 132 patients underwent colposcopic directed biopsy (CDB), 67 patients without any visible lesions had only endocervical curettage (ECC), and seven patients had both procedures. Twenty patients who had satisfactory colposcopic examination without any suspicious lesions were reassured of their normal clinical findings and were only scheduled for periodic cytologic surveillance. After colposcopic examination, 46 women underwent LEEP; 15 of which were considered as diagnostic procedures while 31 were for therapeutic intention.

Our study found that 133/226 patients (58.9%) of cytology LSIL had correlated pathologic diagnosis of CIN I or LSIL. The remaining 93 patients (41.1%) had discordant pathologic diagnoses; 56 patients (24.8%) were diagnosed as cervicitis or normal cervical tissue while 37 patients (16.3%) were pathologically diagnosed as having more severe lesions. From these 37 cases, 34 cases (15%) were reported as HSIL and three (1.3%) as microinvasive cervical cancer. The details of histologic or histopathologic diagnoses of lesions from the cytologic LSIL patients are shown in Table 2.

Some clinical characteristics were studied to evaluate whether there would be any factors associated with the high grade outcomes of the cytologic LSIL. We found that there were no factors, which we studied, had any significant association with the HSIL or higher outcomes (Table 3).

Discussion

Cervical cancer is the most common malignancy and a major cause of cancer-death in Thai women. This may due to a limitation of primary health services not covering all areas of the country, leading to a less than satisfactory screening program achievement. Furthermore, an appropriate management of abnormal cytology is still a main problem due to lack of special instrument, colposcope in particular, medical personnel including cytopathologists and gynecologic oncologists.

In general, the management for patients with abnormal cytology depends mainly on the severity of lesions. HSIL is an immediate precancerous lesion carrying a high risk of progression to invasive disease if left untreated, so its cytologic report should be investigated immediately for its specific histopathology. Investigations and managements of HSIL base on clinical findings whether the lesion is clearly visible, or it needs a colposcope to visualize and select the area of lesion to be biopsied for histologic examination. Although the ASCCP in 2006 released a consensus guideline for management of women with LSIL cytology for a colposcopy (Wright et al., 2007), taking into consideration that only few numbers of LSIL would progress to cancer and the majority of LSIL can regress spontaneously (Moscikki et al., 2004) one may question about the cost-effective of the procedure. Furthermore, the colposcopy or experienced personnel may not be readily available especially in developing countries with low resource setting. Close follow up of a patient with LSIL until it spontaneously resolves may be an alternative option of management assuming that incidence of cervical cancer is low in the area and the patients are expected to have good compliance. On the other hand, a follow up option of abnormal cytology in the area with high incidence of cervical cancer may not be appropriate and would delay proper treatment. The most important reason to guide how the women with LSIL cytology should be managed is probably the prevalence of HSIL or higher histopatholgy of their cervical lesions.

Our study found that 691/72,087 women who had conventional cervical cytologic smears during the study period (0.9%) had cytologic diagnosis of LSIL. Other studies reported LSIL in the range of 0.7-2.9% (Wright et al., 2007; Law et al., 2001). The prevalence of LSIL may increase as high as 18% if the cytology is studied by liquid-based cytology (ASCUS-LSIL Triage Study Group, 2003). Having mentioned earlier that among various histopathologic diagnoses of the LSIL cytology, which ranged from normal cervical tissue to HSIL or invasive cervical cancer, the prevalence of the high grade lesions carry more serious problem and should call for an immediate management. The prevalence of HSIL or greater histologic diagnoses in our study was 16.3% (37 women): 15% as HSIL and 1.3% as microinvasive cervical cancer. Fortunately, no invasive lesion was found in our study. Our results of high grade lesion in LSIL cytology were in the range as those reported in previous studies

which ranged from 15.0-41.4 %; 0.1-5% of which were invasive cancers (Phongnarisorn et al., 2006; Wright et al. 2007, Chute et al., 2006; Law et al., 2001; Lonky et al., 2001; Massad et al., 1996; Lee et al., 1998). Compared to other studies, our prevalences of high grade lesions were close to the figures reported in the studies of Lonky and Massad et al. (Lonky et al., 2001 ; Massad et al., 1996), which were in the lower range among these reports. Lonky et al. (Lonky et al., 2001) reported that 327/1784 (18.3%) of LSIL cytology had histologic diagnoses of HSIL and two cases (0.1%) had invasive cervical cancers while Massad et al (Massad et al., 1996) found 17% HSIL without any cases of invasive cervical cancer in their series from 700 LSIL Pap smear. Other studies reported higher prevalence of higher grade lesions (Phongnarisorn et al., 2006; Law et al., 2001; Lee et al., 1998). Law et al. (Law et al., 2001) reported that 145 cases out of 877 LSIL Pap smear (27%) had histologic diagnosis as HSIL, and 16 cases (3%) had microinvasive cervical lesion while 543 cases (72%) had correlated CIN1 as the final histopathology. Another study by Lee et al. reported that 45/145 of LSIL cytology (31%) were found to have HSIL while LSIL was confirmed on biopsy in 83/145 (57.2%) (Lee et al., 1998). One study from the northern part of Thailand, which is notorious for a high incidence of cervical cancer also showed high prevalence of high grade lesions from LSIL cytology, in 91/220 women (41.4%): 80 women (36.4%) had histologically confirmed HSIL, nine women (4.1%) had microinvasive while two (0.9%) had invasive cervical lesions (Phongnarisorn et al., 2006). The differences among these studies might be due to different characteristic features or the overall prevalence of cervical cancer in each study. In a clinical point of view, this particular group of women would have a delayed proper management if only a follow-up plan is conducted without an immediate colposcopic examination.

These discordant results between the cytologic findings and tissue histopathology support the practice guideline in our institution that colposcopic examination should be performed in all women with LSIL. Aside from this possibility, we are also aware of the other reasons e.g. poor compliance for a follow up of a woman, or any psychological distress caused by abnormal cervical cytology without intervening action. Moreover the cost of colposcopic examination in our country is not as high as in western countries.

One may argue that our prevalence of higher grade lesions in our study may be underestimated because 20 women (8.8%) with LSIL who had no suspicious lesions (with satisfactory colposcopy) did not have tissue pathologic diagnosis. However, we tended to insist on our result because all of these 20 women had normal Pap smear results from serial followed-up.

A number of factors have been reported to be associated with the prevalence of HSIL and cancer in general population. These high risk factors are: older age of the individuals, younger age at first intercourse, smoking habits, high parity, more number of sexual partners, oral contraceptive use, infection of high-risk type of Human Papilloma Virus (HPV), and low cellular immune response (Maiman et al., 1998; Ho et al, 1998; Koutsky et al., 1992). Maiman et al. found that severe immunodeficiency in women with CD4 counts < 200 cells/m3 was the strongest predictor of an abnormal cervical cytology (Maiman et al., 1998).

However, only few studies reported about the factors which were associated with high grade lesions in patients with LSIL cytology. Petry et al. reported significantly higher risk of CIN3 and cancer among women with Pap results of CIN1 or 2 in women with > 5 lifetime-partners, smokers, and HPV-16 infection while age at first intercourse or age of the patient at abnormal cytology detection showed no association (Petry et al., 1994). Our study also found that age was not associated with the detection of high grade lesion. Limited by being retrospective in nature of our study, we have no data concerning age at first intercourse, number of partners, smoking history and HPV infection. Our data showed that patients with parity ≥ 1 or anti-HIV positive had higher prevalence of high grade lesions than the other comparative subgroups. However, the differences were not significant probably due to small number of cases.

The limitations of this study were the limited number of women with LSIL included in the study. This was because some did not have colposcopy in our institution despite an abnormal screening Pap smear due to personal or financial reasons as we have mentioned earlier.

In conclusion, our study found 0.9% prevalence of LSIL cytologic diagnosis. The prevalence of high grade lesions was 16.3%. This data may serve as basic information in counseling the patients about the likelihood of histologic abnormalities after an abnormal cytologic diagnosis classified under the Bethesda system and her prognosis. Our study with small number of women of LSIL, particularly in each subgroup, could not demonstrate any significant factors which could predict the women who would have higher risk of high grade lesions. Further studies may focus on these women especially those with anti-HIV positive to better predict the certain group of women at risk.

References

Alvarez RD, Wright TC (2007). Effective cervical neoplasia detection with a novel optical detection system: a randomized trial. *Gynecol Oncol*, **104**, 281-9.

ASCUS-LSIL Triage Study (ALTS) Group (2003). A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol*, **188**, 1393-400.

Bethesda Workshop (1992). The 1991 Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda Workshop. *JAMA*, **267**, 1892.

Chute DJ, Covell J, Pambuccian SE, Stelow EB (2006). Cytologic-histologic correlation of screening and diagnostic Papanicolaou tests. *Diagn Cytopathol*, **34**, 503-6.

Fairman A, Tan J, Quinn M (2004). Women with low-grade abnormalities on Pap smear should be referred for colposcopy. *Aust N Z J Obstet Gynaecol*, **44**, 252–5.

Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD (1998). Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*, **338**, 423-8.

Koutsky LA, Holmes KK, Critchlow CW, et al (1992). A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med*, **327**, 1272-8.

Law KS, Chang TC, Hsueh S, et al (2001). High prevalence of high grade squamous intraepithelial lesions and microinvasive carcinoma in women with a cytologic diagnosis of low grade squamous intraepithelial lesions. *J Reprod Med*, **46**, 61–4.

Lee SS, Collin JR, Pun CT, Cheng KD, Ngan YH (1998). Conservative treatment of low grade squamous intraepithelial lesions (LSIL) of the cervix. *Int J Gynecol Obstet*, **60**, 35-40.

Lonky NM, Sadeghi M, Tsadik GW, Petitti D (1999). The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol*, **181**, 560–6.

Maiman M, Fruchter RG, Sedlis A, et al (1998). Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Gynecol Oncol*, **68**, 233-8.

Massad LS, Halperin CJ, Bitterman P (1996). Correlation between colposcopically directed biopsy and cervical loop excision. *Gynecol Oncol*, **60**, 400-3.

Moscikki AB, Shiboski S, Hill NK, et al (2004). Regression of low-grade squamous intra-epithelial lesions in young women. *Lancet*, **364**, 1678-83.

National Cancer Institute Workshop (1989). The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. *JAMA*, **262**, 931-4.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics 2002. *CA Cancer J Clin*, **55**, 74-108.

Pengsaa P, Jindawijak S (2003). Cervix uteri. In : Sriplung H, Sontipong S, Martin N et al, editors. Cancer in Thailand Vol. IV, 1998-2000 Bangkok: Bangkok Medical Publisher, 49-50.

Petry KU, Scheffel D, Bode U, et al (1994). Cellular immunodeficiency enhances the progression of human papillomavirus–associated cervical lesions. *Int J Cancer*, **57**, 836-40.

Phongnarisorn C, Srisomboon J, Siriaungkul S, et al (2006). 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*, **16**, 1565-8.

Shafi MI, Luesley DM, Jordan JA, et al (1997). Randomised trial of immediate versus deferred treatment strategies for the management of minor cervical cytological abnormalities. *Br J Obstet Gynaecol*, **104**, 590-4.

Solomon D, Davey D, Kurman R, et al (2002). The 2001 Bethesda System: Terminology for reporting results of cervical cytology. *JAMA*, **287**, 2114-9.

Soutter WP, Wisdom S, Brough AK, Monaghan JM (1986). Should patients with mild atypia in a cervical smear be referred for colposcopy? *Br J Obstet Gynaecol*, **93**, 70–4.

Wright TC, Massad LS, Dunton CJ, et al (2007). 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*, **197**, 346-55.