RESEARCH COMMUNICATION

Prevalence of High-grade Cervical Lesion in Women with LSIL and HSIL Cytology and Prevalence of Invasive Cancer in Women Cytologically Positive for Malignancy

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Abstract

Aim: To determine the prevalence of high-grade cervical lesion (CIN 2 or worse, CIN 2+) and the prevalence of invasive cancers in women with LSIL, HSIL and positive for malignancy on cytology, respectively. Methods: A retrospective study of patients undergoing colposcopy in Rajavithi hospital between 2003-2004 was performed. The final diagnosis was based on colposcopy and histology. Results: Among 250 women with LSIL and 152 women with HSIL, 28 (11.20%) and 112 (75.70%), respectively, had histology-confirmed high-grade cervical lesions. Invasive cancer was diagnosed in 12 (7.9%) of women with HSIL but in none of the LSIL cases. Among 19 women with positive smears for malignancy, only 7 (36.8 %) had histology-confirmed invasive cancer. Conclusion: The present study confirms that women with HSIL have high prevalence of high-grade cervical lesions and malignancy. Women with LSIL may be managed less aggressively because of the negligible risk of more advanced lesions. Smears positive for malignancy are inconsistent predictors of invasive cancer.

Key Words: LSIL - HSIL - smear positive for malignancy - CIN 2 or worse - CIN 2+

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Introduction

Cervical cancer is the most common cancer in Thailand with the age standardized incidence rate (ASR) of 19.5 per 100,000 person-years (Pengsaa et al., 2003). Although HPV testing has been accepted as an effective cervical screening, cytology is still the mainstay of screening at the present time in this country. The 2001 Bethesda System terminology is presently used for cytological classification. This terminology utilizes the terms low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) which is much different from the previous cytologic classification (Solomon et al., 2002). This same two-tiered system is also applied to the histology. Notably, cytologic LSIL and HSIL are not equivalent to histological HPV/CIN1 and CIN 2/3, respectively. The goal of cervical cancer screening is not to prevent CIN but to prevent and detect early invasive cancer. The detection of CIN 2 or CIN 3 is not a screening failure but rather the primary goal. Therefore, management of women with abnormal cytology in each category is based on the severity of the cytology and the level of risk of high-grade cervical lesion (CIN 2 or worse, CIN 2+) on final histology. Literature indicates that the prevalence of CIN 2 or worse identified at single colposcopy among women with LSIL and HSIL is 12-20% and 53-77%, respectively (Kinney et al., 1998; Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004; Fairman et al., 2004; Alverez et al., 2007; Wright Jr. et al., 2007).The purpose of the present study is to investigate the prevalence of high-grade cervical lesion in women with LSIL and HSIL cervical cytology. Furthermore, the author also examines the prevalence of an invasive cancer in women with positive for malignancy from cervical cytology.

Materials and Methods

From January 2003 to December 2004 , all women who had a referral cytological interpretation of LSIL, HSIL and positive for malignancy in colposcopy clinic, Rajavithi hospital were reviewed. In the author's hospital, all women with abnormal cervical cytology (ASC-US or worse) were counseled and underwent colposcopy. The colposcopic finding was documented and colposcopically directed biopsies (CDB) were taken from the worst affected area using 3% acetic acid according to standard of practice. The final diagnosis was based on the worst histology according to the Bethesda classification. In case of LSIL, a considerable number of women were examined by colposcopies without biopsies, especially in the group of women who had negative colposcopic findings. Since

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the biopsy was not performed in all cases, therefore, the histology in those cases were not known. In the present study, the author used the combination of colposcopy and histology (colpohistology) as the criterion standard for diagnosis in LSIL category, negative colpohistologic diagnosis included two conditions : 1) Women with negative colposcopy (and no biopsy) were accepted as negative finding , 2) The histology from CDB was negative. Positive colpohistologic diagnosis was based on histology. In case of HSIL, an immediate large loop excision of the transformation zone (LLETZ) after colposcopy was performed in some women which were included in the present study. Cases were eligible in the present study if they met inclusion criteria. These criteria included LSIL, HSIL and positive for malignancy on cytology. Women with cytology performed during pregnancy and women who did not have colposcopy performed were excluded from the present study. Women who appeared with apparent cervical cancer were also excluded. The data were analyzed using the statistical package for the social sciences (SPSS) version 11.5.

Results

During the study period, 752 referral cytological tests were received at colposcopy clinic, 421 tests were eligible for the present study. The 250 women with LSIL and 152 women with HSIL ranged in age from 16 to 61 years (mean, 35.6 years) and 19 to 66 years (mean, 42.6 years), respectively. Age range in 19 women with positive for malignancy on cytology was 35 to 68 years (mean, 53.8 years). The mean parities of women with LSIL, HSIL and positive for malignancy on cytology were 1.5, 2.4 and 3.6 children, respectively. Tests for anti-HIV were positive in 6 women Tables 1 and 2 show the results of final histology in each group. Of the 250 women with LSIL , a colpohistologic diagnosis of CIN 2 or worse was rendered in 28 cases (11.20 %) and no invasive cervical cancer was identified in this group. For those 152 women with HSIL , 115 cases (75.0 %) had histological diagnosis of CIN 2 or worse and 12 cases (7.9 %) had invasive cervical cancer. Regarding cases positive for malignancy on cytology, 7 of 19 (36.8 %) had invasive cervical cancer diagnosed by histology. Among the remainder, 10 women (52.6 %) had CIN 2,3 and 2 women (10.5%) had negative final histology.

Table 1. Presenting Cytology versus Colpohistology Diagnosis and Predictive Values

Colpohistology result	Cytology result			Total
	LSIL	HSIL	Malignancy	
Negative†	98 (39.2)	23 (15.1)	2 (10.5)	123
HPV/CIN 1	124 (49.6)	14 (9.2)	0 (0.0)	138
CIN 2/3	28 (11.2)	103 (67.8)	10 (52.6)	141
Invasive cancer	0 (0.00)	12 (7.9)	7 (36.8)	19
Total	250 (100)	152 (100)	19 (100)	421
Predictive value ‡	60.8%	84.9%	89.5%	
Negative	39.2%	15.1%	10.5%	
HPV/CIN 1	49.6%	9.2%	-	
CIN 2/3	11.2%	67.8%	52.6%	
Invasive cancer	-	7.9%	36.8%	

LSIL =Low-grade squamous intraepithelial lesion , HSIL= High-grade squamous intraepithelial lesion† In case of LSIL cytology , negative result was based on the association between colposcopy and /or histology which included 2 conditions : 1) Absence of colposcopic lesion and no CDB was performed or 2) CDB was performed and histology revealed a benign result.‡ Disease defined as any CIN, microinvasive or invasive cancer

Table 2. Prevalence of High-grade Cervical Lesion (CIN 2+) in LSIL/HSIL

Colpohistology result	Cytology result		Total
	LSIL	HSIL	
CIN1 or less †	222 (88.8)	37 (24.3)	239
CIN 2+ ‡	28 (11.2)	115 (75.7)	143
Total	250 (100)	152 (100)	382

†CIN 1 or less includes CIN 1, HPV infection, reactive change and negative‡ CIN 2 + includes CIN2 , CIN3, microinvasive and invasive cancer

Discussion

The result presents the traditional cytology-colposcopy-histology system currently used in Thailand. It can be used to counsel women with abnormal cytology regarding the likelihood of histologic abnormality. The present study illustrates that the prevalence of histological confirmed CIN 2 or worse identified at initial colposcopy among women with LSIL is 11.2 % which is similar to previous reports of 12-20 % (Kinney et al., 1998; Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004; Fairman et al., 2004; Alverez et al., 2007; Wright Jr. et al., 2007) and no invasive cervical cancer in this group as compared to 0 – 0.3 % (Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004) in the literature. However, a previous study in Thailand showed different result. The study performed in the region with high incidence of cervical cancer demonstrated that CIN2+ was diagnosed histologically in 41.5% of women with LSIL and 5% had microinvasive or frankly invasive carcinoma (Phongnarisorn et al., 2006). This study (Phongnarisorn et al., 2006) as well as the earlier data previously reported a relatively high prevalence of CIN 2+ (Wright et al., 2002). However, the figure of the present study resembles and supports most recent published reports (Kinney et al., 1998; Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004; Fairman et al., 2004; Alverez et al., 2007; Wright Jr. et al., 2007) which showed the relatively low prevalence of CIN 2+ (11-20%) and invasive cancer (0-0.3%) (Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004).

`In women with HSIL, histology-confirmed CIN 2+ was identified in 75.70 % of cases. This is in agreement with data from previous studies showing that an initial colposcopy identified CIN 2+ in 50-77% of women with HSIL (Kinney et al ., 1998; Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al ., 2004; Alverez et al., 2007; Wright Jr. et al., 2007). A higher detection rate of CIN 2+ was observed in studies of women using a more reliable specimen such as LLETZ or

conization (Kantathavorn et al., 2006; Wright Jr. et al., 2007). However, the prevalence of an invasive carcinoma, 7.9% is greater than expected. In general, approximately 0.1-3% of women with HSIL have invasive cancer (Lonky et al., 1999; Jones et al., 2000; Massad et al., 2001; Benedet et al., 2004; Wright et al., 2002; Wright Jr. et al., 2007), however, one study previously reported in the same country showed higher prevalence at 20% (Kantathavorn et al., 2006). Several plausible explanations may account for this significant difference such as some women in the author's study did not have CDB and had a final histology from a "see and treat" intervention which was likely to reveal more severe histology than CDB from an initial colposcopy. In addition, some women included in the study probably had early cervical cancer at the time cytological sampling.

In women with positive for malignancy on cytology, invasive cervical cancer were identified in 36.84%. It is similar to most studies previously reported (Lonky et al., 1999; Johnson et al., 2001; Massad et al., 2001; Charoenkwan et al., 2006). In any case, few studies (Jones et al., 2000; Uyar et al., 2003) reported high prevalence (80-90%) whereas the other showed very low prevalence (Benedet et al., 2004). It has been shown that the results varies considerably from study to study and may be influenced by various factors such as patient population, methodology, the method of reference test and cytological interpretation. Johnson et al. (Johnson et al., 2001) reported different positive predictive value (PPV) of three reporting categories used when features suggestive of invasion were seen in cervical smears. His categories were described by strength of suspicion (frank invasion, suspicion of invasion and microinvasion). The PPV for any invasive disease on histology were 55.7%, 22.3% and 17.2% for frank invasion, suspicion of invasion and microinvasion, respectively. It reflects that in group of women with positive for malignancy on cytology, it is actually composed of heterogeneous groups of degree of cytological suspicion. For example, in some cases, invasive carcinoma and HSIL cannot be reliably separated from each other, cytologically. This situation may occur when there are highly pleomorphic HSIL cells with keratinized cytoplasm but no background feature of invasion is identified. Conversely, there may be features suggesting tumor diathesis but malignant cells are not identified (Wright et al., 2004). Assuredly, a number of such equivocal cases especially those referred from community are reported as "positive for malignancy" as well as those who have apparently cytological feature of invasion. Regarding this, the 2001 Bethesda System emphasizes this entity by providing the new category of "HSIL with features suspicious for invasion" for this matter (Wright et al., 2004).

Certainly, limitations of the present study do exist. First, its retrospective nature precludes standardization of protocol. Secondly, a substantial number of colposcopies in women with LSIL were performed without biopsies, especially in the group of women who had negative colposcopic findings. Therefore, the true histological diagnoses in those cases were not known. In fact, colposcopy is a highly subjective investigation, with the accuracy dependent upon experience of colposcopists. For many years, it was believed that colposcopy was a sensitive, but rather non specific, method for detection of high-grade squamous intraepithelial lesion. Although one meta-analysis of the performance of colposcopy confirmed this idea (Mitchell et al., 1998), literature reported false-negative rates for colposcopy ranging from 15% to 31% for CIN 2,3 lesions (Skehan et al., 1990). The ALTS trial (ASCUS-LSIL Triage Study (ALTS) Group, 2003) found that only 67% of the cumulative cases of biopsy-confirmed CIN 2,3 among women with LSIL were identified at initial colposcopy. As for HSIL, colposcopy can miss a significant number of CIN 2,3 lesions as well , failure to detect CIN 2,3 at colposcopy in women with HSIL does not necessarily mean a CIN 2,3 lesion does not exist (Wright Jr. et al., 2007). A higher detection rate of CIN 2+ is confirmed when the result of more reliable procedure (LLETZ, conization) is available (Kantathavorn et al., 2006; Wright Jr. et al., 2007). In the present study, some women did not have CDB and had a final histology directly from a "see and treat" LLETZ which possibly revealed more severe histology than CDB. This fact results in the methodological bias due the unreliability of the reference test. In addition, the lack of central review of all referral cytology by pathologists working in academic institute may be one of the limitations of the present study. Finally, it is possible that the samples in the present study are too small.

In conclusion ,the present study indicates that women with HSIL are highly prevalent of high-grade cervical lesion and the prevalence of an invasive carcinoma is greater than previous reports. Immediate colposcopy and colposcopically directed biopsy is mandatory. Women with LSIL have low prevalence of high-grade cervical lesion and the negligible risk of invasive cancer. Women in this group may be managed less aggressively. More than half of the positive for malignancy smears in the present study are associated with these lesser severity of histological diagnosis. However,careful assessment by pelvic examination and colposcopy still remain an important approach.

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