RESEARCH COMMUNICATION

Risk Factors for High-Grade Cervical Intraepithelial Neoplasia in Patients with Atypical Squamous Cells of Undetermined Significance (ASC-US) Papanicolaou Smears

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Abstract

Objective: To determine risk factors of high-grade cervical intraepithelial neoplasia (CIN 2-3) among women with atypical squamous cells of undetermined significance (ASC-US) Papanicolaou (Pap) smears. Methods: Two-hundred and sixty-six women with ASC-US Pap tests who underwent a colposcopy with histologic study were enrolled between August 2008 and June 2010. Patient data including age, education, income, parity, current pills used, number of vaginal deliveries, number of sexual partners, age at first sexual intercourse, history of sexually transmitted diseases, history of pelvic inflammatory disease and smoking habits were obtained. Logistic regression analysis was used to evaluate factors associated with CIN 2-3. Results: CIN was diagnosed in 134 of 266 women (50.4%). Ninty-seven of these (72.4%) had CIN 1 and 37 (27.6%) had CIN 2-3. Frequency of the latter was lower in women who had at least bachelor's degree graduation as compared to those having less than primary school graduation (odds ratio (OR) 0.085, 95% confidence interval (CI) 0.013-0.557). In addition, those with a higher income (5,000-20,000 baht per month) had less frequent CIN 2-3 (OR 0.378, 95% CI 0.147-0.970), whereas women who had 3 or more sexual partners were more likely to develop CIN 2-3 (OR 3.181, 95% CI 1.316-7.687). Conclusions: Women with ASC-US Pap smears who had 3 or more sexual partners, low education and low income were at an increased risk of CIN 2-3. Therefore, this group of patients deserve a high priority for immediate colposcopy in order for early detection of high-grade CIN.

Keywords: Pap smear - ASCUS - colposcopy - cervical intraepithelial neoplasia - cervical cancer

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Introduction

The acceptable options in managing women with atypical squamous cells of undetermined significance (ASC-US) Papanicolaou (Pap) smear are immediate colposcopy with biopsy, follow-up cytology study at 4-6 months interval and human papillomavirus (HPV) DNA testing. Previous studies showed 5-10% of women with ASC-US Pap smear had cervical intraepithelial neoplasia (CIN) 2-3 on biopsy (Wright et al., 1995; Kinney et al., 1998).

A repeat of Pap smear within 4-6 months had a sensitivity of 85% (Solomon et al., 2001). This approach potentially reduces the cost of colposcopy but may result in delay in diagnosis and treatment in patients with high-grade CIN. HPV DNA testing had a sensitivity of 96% for detecting high-grade dysplasia and a negative predictive value of 98% (Wright et al., 1995). Approximately 40 percent of women with ASC-US Pap smear who had negative for high risk HPV could avoid an unnecessary colposcopy (Solomon et al., 2001). Although HPV DNA testing has been shown to be a promising tool in primary cervical cancer screening as it is more sensitive in detecting CIN lesions than using only cytology, HPV DNA testing is more expensive than cytologic study.

Colposcopic directed cervical biopsy is the diagnostic procedure and provides histological diagnosis but it causes patient discomfort. In managing patients with ASC-US Pap smear, consideration of Pap test history, risk factors of cervical cancer, adherence to follow-up and cost together with risk and benefit of each modality of treatment is crucial.

This study aimed to determine risk factors of high-grade CIN among patients with ASC-US Pap smear.

Materials and Methods

All patients with ASC-US Pap smear who attended the colposcopy clinic, Thammasat University Hospital from August 2008 to June 2010 were enrolled. Exclusion criteria included patients with pregnancy, post-hysterectomy and patients with no histological diagnosis. The study was

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approved by the Ethics Committee of Faculty of Medicine, Thammasat University. Informed consent was obtained from all participants.

All enrolled patients were interviewed by attending physicians. Demographic and lifestyle data including age, education, income, menstrual status, parity, number of vaginal delivery, age at first sexual intercourse, number of lifetime sexual partners, current pills used, smoking habit, history of sexually transmitted diseases (STDs) and history of pelvic inflammatory disease (PID) were recorded.

A standardized colposcopic examination was performed by gynecologic oncologists. All patients were subjected to a complete colposcopic evaluation with directed biopsy when an abnormal lesion was present and endocervical curettage was performed when colposcopic finding was unsatisfactory and/or no abnormal lesion was seen. Histologic findings were classified as followed: no dysplasia, low-grade dysplasia (CIN 1 or HPV infection) and high-grade dysplasia (CIN 2-3).

Associations among clinical variables and high-grade dysplasia were assessed by logistic regression analysis.

Results

There were 266 patients with ASC-US Pap smear enrolled in the study. Table 1 shows characteristics of patients including age, parity and their highest education. There were 134 of 266 patients (50.4%) having CIN. Of 134 patients, 97 (72.4%) had CIN 1 and 37 (27.6%) had CIN 2-3.

Education and income were associated with the frequency of high-grade dysplasia or CIN 2-3 (Table 2). In comparison with patients who had a highest education of less than primary school, patients who had a highest education of primary and secondary schools, diplomas and at least bachelor's degree had lower risk of high-grade dysplasia (odds ratio [OR] 0.086 (95% confidence interval [CI] 0.013-0.584), 0.145 (0.022-0.968), 0.085 (0.013-0.557), respectively). In addition, high-grade dysplasia in patients having higher income (5,000-20,000 baht per month) was less frequent than patients with low income (less than 5,000 baht per month), OR was 0.378 (95% CI 0.147-0.970). In contrast, there was no correlation between age and the occurrence of high-grade dysplasia.

Reproductive history in association with colposcopic biopsy results is presented in Table 3. There were no associations among parity, menopausal status, current pills used, number of vaginal delivery and the frequency of high-grade dysplasia.

Table 4 demonstrates the relation among colposcopic biopsy results and sexual habits. In comparison with women having 1 or 2 sexual partners, frequency of high-grade dysplasia was greater in women having more than 2 partners (OR 3.181, 95% CI 1.316-7.687). However, no association between the frequency of high-grade dysplasia and age at first sexual intercourse and history of STDs and PID.

There was no correlation between smoking history and high-grade dysplasia (Table 5). OR of high-grade dysplasia was 0.478 (95% CI 0.048-4.721) in never-smoking patients in comparison with current smokers.

Table 1. Characteristics of Patients According to Age Groups, Parity and Education

Characteristics	Number of patients (n)	Frequency (%)
Age (years)		
20-30	73	27.4
31-40	95	35.7
41-60	98	36.9
Parity		
Nulliparous	69	25.9
Multiparous	197	74.1
Educational level		
Less than primary school	5	1.9
Primary & secondary schools	79	29.7
Diplomas	67	25.2
At least bachelor's degree	115	43.2

Discussion

The frequency of high-grade dysplasia in patients with ASC-US Pap smear was approximately 14%. Previous studies reported varied rate of high-grade dysplasia. Parazzini et al., (1995) and Shlay et al., (2000) reported the prevalence of high-grade dysplasia at 25% and 7.7%, respectively. The difference in these findings may be attributable to different clinical factors of the study populations such as age groups, parity, number of sexual partners, age at first sexual intercourse as well as difference in ASC-US diagnosis experience of pathologists and colposcopic accuracy by colposcopists.

By using logistic regression analysis, high-grade dysplasia was frequent in patients with low education, low income and more than 2 sexual partners. These results are in agreement with previous studies (Parazzini et al., 1995; Shlay et al., 2000). Parazzini et al., (1995) reported a higher prevalence of high-grade dysplasia in low-educated women, women with multiparity, smokers and women with more sexual partners. However, 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 were found to be associated with high-grade dysplasia.

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). However, our study showed different results such as there was no correlation between younger age at first sexual intercourse and high-grade CIN. This may be explained by a relatively small number of women who had the first sexual intercourse at younger age. Moreover, immune status, duration of pills used, duration of smoking and history of abnormal Pap testing may affect occurrence of CIN. Further study is needed to determine effects of these factors on clinical outcome of women with ASC-US Pap testing. Larger population of women who had history of STDs are necessary to demonstrate the association between high-grade lesion and STDs.

As previously mentioned, ASC-US Pap smear result may be triaged using repeated cytology, colposcopy or HPV testings (Etherington and Shafi, 1996; Cuschieri et

Table 2. Colposcopic Biopsy Results According to Age Groups, Educational Level and Income

Characteristics	Number of patients			OR (95% CI), high and low-grade dysplasia
	Low-grade		High-grade	
	No CIN (n=132)	CIN 1 (n=97)	CIN 2-3 (n=37)	
Age (years)				
20-30	28	30	15	1*
31-40	56	28	11	0.506 (0.217-1.181)
41-60	48	39	11	0.489 (0.210-1.139)
Educational level				
Less than primary school	2	0	3	1*
Primary & secondary school	40	30	9	0.086 (0.013-0.584)
Diplomas	36	19	12	0.145 (0.022-0.968)
At least bachelor's degree	54	48	13	0.085 (0.013-0.557)
Income (baht/month)				
<5,000	15	8	8	1*
5,000-20,000	79	58	18	0.378 (0.147-0.970)
>20,000	38	31	11	0.458 (0.164-1.278)

*Reference category; OR = odds ratio; CI = confidence interval

Table 3. Colposcopic Biopsy Results According to Reproductive Factors

Characteristics	Number of patients			OR (95% CI), high and low-grade dysplasia
	Low-grade		High-grade	
	No CIN (n=132)	CIN 1 (n=97)	CIN 2-3 (n=37)	
Parity				
Nulliparous	34	22	13	1*
Multiparous	98	75	24	0.598 (0.285-1.251)
Menopause				
Yes	24	12	8	1*
No	108	85	29	1.479 (0.626-3.494)
Current pills used				
Yes	38	20	10	1*
No	94	77	27	0.916 (0.418-2.006)
Number of vaginal deliveries				
0	51	38	17	1*
1	28	27	6	0.732 (0.259-2.066)
2	36	26	8	0.418 (0.122-1.433)
>2	17	6	6	0.495 (0.155-1.580)

*Reference category; OR = odds ratio; CI = confidence interval

Table 4. Colposcopic Biopsy Results According to Sexual Habits

Characteristics	Number of patients			OR (95% CI), high and low-grade dysplasia
	Low-grade		High-grade	
	No CIN (n=132)	CIN 1 (n=97)	CIN 2-3 (n=37)	
Age (years) at first sexual intercourse				
<18	25	12	5	1*
≥18	107	85	32	0.811 (0.296-2.217)
Number of sexual partners				
1	80	66	17	1*
2	34	22	10	1.534 (0.662-3.551)
>2	18	9	10	3.181 (1.316-7.687)
History of PID				
No	124	85	30	1*
Yes	8	12	7	2.438 (0.951-6.254)
History of STDs				
No	112	88	35	1*
Yes	20	9	2	0.394 (0.090-1.726)

*Reference category; OR = odds ratio; CI = confidence interval; PID = Pelvic inflammatory disease; STD = Sexually transmitted disease

Table 5. Colposcopic Biopsy Results According to Smoking Habits

Characteristics	Number of patients			OR (95% CI), high and low-grade dysplasia
	Low-grade		High-grade	
	No CIN (n=132)	CIN 1 (n=97)	CIN 2-3 (n=37)	
Current smokers	0	3	1	1*
Never smokers	132	94	36	0.478 (0.048-4.721)

*Reference category; OR = odds ratio; CI = confidence interval

al., 2004; Trottier et al., 2006). Our findings support the use of immediate colposcopic evaluation if patients with ASC-US Pap testing have low-education, low income and more than 2 sexual partners. However, balance between risks and benefits of alternative modalities, patient's concern about natural history and severity of the disease and patient's adherence to follow-up should be taken into account in caring this group of patients.

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