RESEARCH ARTICLE

Cytohistologic Discrepancy of High-Grade Squamous Intraepithelial Lesions in Papanicolaou Smears

Yenrudee Poomtavorn[1]*, Wanwisa Himakhun[2], Komsun Suwannarurk[1], Yuthadej Thaweekul[1], Karicha Maireang[1]

Abstract

Objectives: To evaluate the frequency of cytohistologic discrepancy of high-grade squamous intraepithelial lesions (HSILs) in Pap smears and associated factors. Methods: Medical records of 223 women with HSIL Pap smears who were treated at Thammasat University Hospital were reviewed. Data on age, parity, menopausal status, contraceptive use and colposcopic directed biopsy and loop electrosurgical excision procedure (LEEP) pathology results were recorded. Results: Mean (SD) age of patients was 38.0 (9.4) years. The majority were premenopausal (86.5%) and multiparous (83.9%). Cytohistologic discrepancy between the Pap test and colposcopic-directed biopsy histology was 45.7% and that between the Pap test and LEEP histology was 29.5%. Fifty-four (24.2%) women had no high-grade CIN on both colposcopic directed biopsy and LEEP. Nulliparity, postmenopausal status and having no oral contraceptive pills use were factors associated with cytohistologic discrepancy. Conclusion: The exact cytohistologic discrepancy rate was relatively high (24.2%). Factors associated with cytohistologic discrepancy were nulliparity and postmenopausal status and having no oral contraceptive pill use.

Keywords: Pap smear results - HSIL - cytohistologic discrepancy - LEEP

Asian Pacific J Cancer Prev, **14 (1)**, 599-602

Introduction

The Papanicolaou (Pap) smear is the most widely used screening method for cervical cancer. The 2001 Bethesda system terminology is used for cytologic classification (Solomon et al., 2002). Management of abnormal cervical cytology depends on the degree of abnormalities of cervical cytology, previous history of abnormal Pap test and age of patients.

High grade squamous intraepithelial lesion (HSIL) Pap smear carries a high risk for significant cervical pathology. Women with HSIL Pap smear have been reported to have a high-grade cervical intraepithelial neoplasia (CIN) at 53-66% and 84-97% from colposcopic directed biopsy and loop electrosurgical excision procedure (LEEP), respectively (Massad et al., 2001; Dunn et al., 2003; Kantathavorn et al., 2006; Alvarez and Wright, 2007; Sadan et al., 2007). Approximately 1-4% of women with HSIL Pap smear had invasive cervical cancer (Massad et al., 2001; Wright et al., 2007). However, previous studies showed that 8-18 % of women with HSIL Pap smear had low-grade CIN (CIN 1) from colposcopic directed biopsy (Numnum et al., 2005; Cho and Kim, 2009; Li et al., 2009), so-called cytohistologic discrepancy. Management for patients with cytohistologic discrepancy who had satisfactory colposcopic examination and negative endocervical sampling is either diagnostic excisional procedure or observation with colposcopy and cytology at 6-month interval for 1 year (Wright et al., 2007). In women with cytohistologic discrepancy but unsatisfactory colposcopic examination, immediate diagnostic excisional procedure is recommended (Numnum et al., 2005; Wright et al., 2007).

Observation with colposcopy and cytology has a disadvantage in patients with CIN 2-3 who are missed by colposcopic examination with regard to delaying the treatment. To the best of our knowledge, data on factors associated with cytohistologic discrepancy in HSIL Pap smear are limited. Therefore, we conducted this study to evaluate the factors associated with cytohistologic discrepancy in HSIL Pap smear and to determine the rate of cytohistologic discrepancy.

Materials and Methods

Medical records of women with HSIL Pap smear who were treated at Thammasat University Hospital, the tertiary hospital and referral center during the years 2005-2011 were reviewed. Inclusion criteria were women with HSIL Pap smear and had pathology reports of both

*[1]Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, [2]Department of Pathology, Faculty of Medicine, Thammasat University Hospital, Pathumthani, Thailand *For correspondence: e-mail pyenrudee@gmail.com*

colposcopic directed biopsy and LEEP. Age, parity, menopausal status, contraceptive use and pathology reports of colposcopic directed biopsy and LEEP were collected. Exclusion criteria were women who had prior hysterectomy and no histological data. Available cytologic and all histologic slides were reviewed by a single cytopathologist (W.H.). Cytohistologic discrepancy was defined as having HSIL Pap smear but less than CIN 2 histology from colposcopic directed biopsy and/or LEEP.

The study was approved by the Ethics Committee of Thammasat University.

Data were analyzed using SPSS version 15 program. Descriptive statistics were used for demographic data. Chi-square or Fisher's exact test, where appropriate, was used to compare the difference between groups. P <0.05 was considered statistically significant.

Results

There were 223 women who had HSIL Pap smear results recruited. Mean (SD) age was 38.0 (9.4) years. Thirty-six (16.1%) of them were nulliparous. One-hundred and ninety-three (86.5%) women were premenopausal and 46 (20.6%) women used oral contraceptive pills for birth control at the time of HSIL Pap smear discovery (Table 1).

Table 1. Clinical Characteristics of Women with High-Grade Squamous Intraepithelial Lesion (HSIL) Pap Smear (N=223)

Characteristics		N (%)
Age (years)	≤30	49 (22.0)
	>30	174 (78.0)
Parity	Nulliparous	36 (16.1)
	Multiparous	187 (83.9)
Menopausal status	Premenopause	193 (86.5)
	Postmenopause	30 (13.5)
Contraception	Pills	46 (20.6)
	Others	177 (79.4)

Table 2. Colposcopic Directed Biopsy and Loop Electrosurgical Excision Procedure (LEEP) Pathology Results in Women with High-grade Squamous Intraepithelial Lesion (HSIL) Pap Smear (N=223)

Diagnosis by colposcopic directed biopsy and LEEP	N (%)
Colposcopic biopsy ≥ CIN 2, LEEP < CIN 2	10 (04.5)
Colposcopic biopsy < CIN 2, LEEP ≥ CIN 2	48 (21.5)
Colposcopic biopsy and LEEP ≥ CIN 2	111 (49.8)
Colposcopic biopsy and LEEP < CIN 2	54 (24.2)

*CIN, cervical intraepithelial neoplasia

Histological diagnosis from colposcopic directed biopsy were no CIN in 36 (16.1%), CIN 1 or human papillomavirus (HPV) infection in 66 (29.6%), CIN 2-3 in 115 (51.6%) and cervical cancer in 6 (2.7%). Cytohistologic discrepancy between the Pap test and colposcopic directed biopsy was demonstrated in 102 (45.7%) patients. All but except 6 women who had colposcopic directed biopsy result of invasive cervical cancer underwent LEEP after colposcopic examination. Of 217 women who underwent LEEP, 144 (66.4%) had CIN 2-3 and 9 (4.1%) had invasive cervical cancer. The remaining 64 women had cytohistologic discrepancy with 19 (8.8%) had no CIN and 45 (20.7%) had CIN 1. Cytohistologic discrepancy between the Pap test and LEEP was present in 64 (29.5%) patients. Therefore, there was approximately 16% of patients who were missed the diagnosis of high grade CIN by colposcopy.

One hundred and eleven (49.8%) women had CIN 2 or greater on both colposcopic directed biopsy and LEEP specimen. Ten (4.5%) women had CIN 2 or greater on colposcopic directed biopsy but no high-grade CIN on LEEP specimen, while 48 (21.5%) women had no high-grade CIN on colposcopic directed biopsy but CIN 2 or greater on LEEP specimen. Fifty-four (24.2%) women had no high-grade CIN on both colposcopic directed biopsy and LEEP. Therefore, the exact number of cytohistologic discrepancy (less than CIN 2 on both colposcopic directed biopsy and LEEP specimens) was 24.2% (Table 2).

Univariate analysis was performed to define risk factors for cytohistologic discrepancy. Nulliparous women were more likely to have low-grade CIN than multiparous women (50% vs. 19.3%, p<0.01). In addition, postmenopausal women had more cytohistologic discrepancy (40% vs. 21.8%, p=0.03). Women who did not use oral contraceptive pills had greater cytohistologic discrepancy (28.8% vs. 6.5%, p = 0.00) (Table 3).

Multivariate analysis using logistic regression model was performed and confirmed that nulliparity, postmenopausal status and having no oral contraceptive pills use were associated with cytohistologic discrepancy (Table 3).

Discussion

Cytohistologic discrepancy between Pap test and colposcopic directed biopsy was greater (45.7%) than that

Table 3. Univariate and Multivariate Analyses for Prediction of Cytohistologic Discrepancy

Characteristics		CIN 1 from colposcopic directed biopsy and LEEP, N (%)	Univariate		Multivariate	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	≤30	9 (18.4)	0.65 (0.29-1.43)	0.28	0.54 (0.21-1.36)	0.19
	>30	45 (25.9)				
Parity	Nulliparous	18 (50.0)	4.19 (1.99-8.86)	<0.01	5.45 (2.34-12.67)	<0.01
	Multiparous	36 (19.3)				
Menopause	No	42 (21.8)	0.42 (0.19-0.94)	0.03	0.39 (0.16-0.94)	0.04
	Yes	12 (40.0)				
Contraception	Others	51 (28.8)	5.80 (1.72-19.55)	0.01	3.76 (1.07-13.14)	0.04
	Pills	3 (06.5)				

*LEEP, loop electrosurgical excision procedure; OR, odds ratio; 95%CI, 95% confidence interval

between Pap test and LEEP (29.5%). This result indicated that high-grade CIN could be missed by colposcopic examination. Due to the fact that accurate colposcopic diagnosis depends on many factors such as colposcopic findings i.e. size of lesion; satisfactory or unsatisfactory colposcopy and an experience of colposcopists.

Our study demonstrated the exact percentage of cytohistologic discrepancy as high as 24.2. Previous studies demonstrated a lower frequency. (Numnum et al., 2005; Cho and Kim, 2009; Li et al., 2009). Li et al (Li et al., 2009) and Numnum et al (Numnum et al., 2005) reported the prevalences of cytohistologic discrepancy of 7.8% and 16%, respectively. Greater cytohistologic discrepancy found in our study could be a matter of cytologic interpretation error of Pap test, resulting in an overdiagnosis of HSIL. As almost half of the patients were referred from other hospitals, cytologic slides for review were not available.

Cytologic error was reported to be the major cause of cytohistologic discrepancy (Tzeng et al., 1999; Moss et al., 2010). Cytologic errors included cytologic sampling error, poor specimen preservation, suboptimal staining quality and cytologic interpretation error.

By using univariate and multivariate analyses, our study showed that nulliparity postmenopausal status and having no oral contraceptive pills use were associated with cytohistologic discrepancy. Our study agrees with the previous studies which reported multiparity and current use of contraceptive pills were significantly associated with high-grade CIN (Parazzini et al., 1992; De Vet et al., 1993; Clements et al., 2011; Gargano et al., 2012).

The option for managing women with HSIL Pap smear but low-grade CIN on colposcopic directed biopsy is either immediate diagnostic excisional procedure or observation with colposcopy and cytology at 6-month interval (Wright et al., 2007). Diagnostic excisional procedure carries a risk of perioperative hemorrhage, infection and adverse pregnancy outcomes including preterm delivery, premature rupture of membrane and low birthweight (Crane, 2003; Kietpeerakool et al., 2006; Kyrgiou et al., 2006; Sjoborg et al., 2007; Simoens et al., 2012). Therefore, if clinical factors associated with low risk for high-grade CIN are present, observation with colposcopy and cytology may be the appropriate option. We would suggest to observe and perform colposcopy and cytology at 6-month interval in nulliparous, postmenopausal women and women who do not use oral contraceptive pills.

Strength of our study is that final histological diagnosis was confirmed on LEEP specimens. However, there were some limitations. As it was a retrospective study, data on other factors which may be associated with cytohistologic discrepancy such as sexual behavior, previous history of Pap testing, were lacking. In addition, half of patients were referred from other hospitals, therefore, review of cervical cytology was not possible.

In conclusion, cytohistologic discrepancy rate in our study was relatively high at 24.2%. Nulliparity, postmenopausal status and having no oral contraceptive pills use were associated with cytohistologic discrepancy. Therefore, we suggest to observe and perform colposcopy and cytology at 6-month interval in HSIL Pap test patients who have these factors.

Acknowledgements

This study was supported by a research grant from the Faculty of Medicine, Thammasat University Hospital.

References

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

Cho H, Kim JH (2009). Treatment of the patients with abnormal cervical cytology: a "see-and-treat" versus a three-step strategy. *J Gynecol Oncol*, **20**, 164-8.

Clements AE, Raker CA, Cooper AS, et al ., 2011. Prevalence and patient characteristics associated with CIN 3 in adolescents. *Am J Obstet Gynecol*, **204**, 1-7.

Crane JM (2003). Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. *Obstet Gynecol*, **102**, 1058-62.

De Vet HC, Knipschild PG, Sturmans F (1993). The role of sexual factors in the aetiology of cervical dysplasia. *Int J Epidemiol*, **22**, 798-803.

Dunn TS, Burke M, Shwayder J (2003). A "see and treat" management for high-grade squamous intraepithelial lesion pap smears. *J Low Genit Tract Dis*, **7**, 104-6.

Gargano JW, Nisenbaum R, Lee DR, et al.,2012. Age-group differences in human papillomavirus types and cofactors for cervical intraepithelial neoplasia 3 among women referred to colposcopy. *Cancer Epidemiol Biomarkers Prev*, **21**, 111-21.

Kantathavorn N, Phongnarisorn C, Srisomboon J, et al., 2006. Northern Thai women with high grade squamous intraepithelial lesion on cervical cytology have high prevalence of underlying invasive carcinoma. *Asian Pacific J Cancer Prev*, **7**, 477-9.

Kietpeerakool C, Srisomboon J, Khobjai A, Chandacham A, Tucksinsook U (2006). Complications of loop electrosurgical excision procedure for cervical neoplasia: a prospective study. *J Med Assoc Thai*, **89**, 583-7.

Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al.,2006. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*, **367**, 489-98.

Li ZG, Qian de Y, Cen JM, Chen GD, Shu YH (2009). Three-step versus "see-and-treat" approach in women with high-grade squamous intraepithelial lesions in a low-resource country. *Int J Gynaecol Obstet*, **106**, 202-5.

Massad LS, Collins YC, Meyer PM (2001). Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol*, **82**, 516-22.

Moss EL, Moran A, Douce G, et al., 2010. Cervical cytology/ histology discrepancy: a 4-year review of patient outcome. *Cytopathology*, **21**, 389-94.

Numnum TM, Kirby TO, Leath CA 3rd, et al (2005). A prospective evaluation of "see and treat" in women with HSIL Pap smear results: is this an appropriate strategy? *J Low Genit Tract Dis*, **9**, 2-6.

Parazzini F, La Vecchia C, Negri E, et al.,1992. Risk factors for cervical intraepithelial neoplasia. *Cancer*, **69**, 2276-82.

Sadan O, Yarden H, Schejter E, et al (2007). Treatment of high-grade squamous intraepithelial lesions: a "see and treat" versus a three-step approach. *Eur J Obstet Gynecol Reprod Biol*, **131**, 73-5.

Simoens C, Goffin F, Simon P, et al,. 2012. Adverse obstetrical

outcomes after treatment of precancerous cervical lesions: a Belgian multicentre study. *BJOG*, **119**, 1247-55.

Sjoborg KD, Vistad I, Myhr SS, et al.,2007. Pregnancy outcome after cervical cone excision: a case-control study. *Acta Obstet Gynecol Scand*, **86**, 423-8.

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

Tzeng JE, Chen JT, Chang MC, Ho WL (1999). Discordance between uterine cervical cytology and biopsy: results and etiologies of a one-year audit. *Kaohsiung J Med Sci*, **15**, 26-31.

Wright TC Jr, 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.