RESEARCH COMMUNICATION

# Is there any Clinical Advantage in Separating CIN 2 from CIN 3 in the Current Two-tiered Cytological Classification?

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## Abstract

**Aim: To investigate the practical use of description for CIN 2 or CIN 3 in HSIL cytology, the objective of the present study is to compare the prevalence of histologic CIN 2/3 or cancer (CIN 2+) between women with cytologic CIN 2 and CIN 3. Methods: The medical records of women with high-grade squamous intraepithelial lesion (HSIL) on cytology who underwent colposcopy at Rajavithi hospital between January 2001 and March 2005 were reviewed. Results: Of 152 women with HSIL, 70 and 82 had cytologic change compatible with CIN 2 and CIN 3, respectively. Women from HSIL-CIN 3 were significantly more likely to have CIN 2/3 or cancer than those from HSIL-CIN 2. Histology-proved CIN 2+ was confirmed in 64.3% and 85.4% in HSIL-CIN 2 and HSIL-CIN 3, respectively ($p<0.05$). Invasive cancer was found in 5.7% in HSIL-CIN 2 and 9.8% HSIL-CIN 3. Conclusion: The histologic outcome is obviously different between women with cytologic CIN 2 and CIN 3. However, both groups should be managed similarly because of the high prevalence of high-grade cervical lesion including invasive cancer.**

**Key Words:** Cervix cancer - CIN2/CIN3 - cytology - colposcopy - histopathological diagnosis

*Asian Pacific J Cancer Prev,* **10**, 115-118

## Introduction

Prior to the development of the Bethesda system (TBS), a spectrum of cervical intraepithelial neolplasia (CIN) traditionally classified as dysplasia system, CIN system, or the originally Papanicolaou classification. A current classification, the Bethesda system used to designate the spectrum of CIN is two-tiered system which consists of high and low-grade categories. Low-grade squamous intraepithelial lesion (LSIL) encompasses the HPV cytopathic effect and mild dysplasia/ CIN 1 and high-grade squamous intraepithelial lesion (HSIL) encompasses moderate dysplasia, severe dysplasia and carcinoma in situ/ CIN 2, 3. The distinction between HSIL and LSIL is made between CIN 1 and CIN 2.

TBS has been adopted by many countries. Nevertheless, it has also received widespread criticism; one of the criticisms has been that the dividing line between LSIL and HSIL is not properly set. It has been debated that the dividing line in this two-tiered system should be set between CIN 2 and CIN 3 (Robertson et al.,1989; Spitzer et al.,2002). There has been evidence from clinical follow-up studies, cytology, histopathology and molecular biology to place CIN 2 nearer to CIN 1 than CIN 3 with respect to its likelihood of progressing to invasive cancer and its use in analyses of precancer (Ostör et al.,1993; Spitzer et al., 2002; Schiffman et al.,2003; National Health and Medical Research Council, 2005; Herbert et al.,2008) . Robertson et al (1989) suggested that it would be more appropriate to have low grade CIN (CIN 1 and 2) and high grade CIN (CIN 3) categories. Schiffman et al. (2003) stated that there was substantial heterogeneity in the microscopic diagnosis and biologic meaning of CIN 2 lesions in particular. Some represented only acute nononcogenic HPV infection. It may therefore not be appropriate to combine CIN 2 and CIN 3 and a true precursor should be confined to CIN 3 only (Schiffman et al.,2003; National Health and Medical Research Council, 2005; Herbert et al.,2008). Herbert et al (2008) suggested that it was not reasonable if the distinction between CIN 2 and CIN 3 were lost especially in case of histopathology classification. According to this consideration, management in women with CIN 2, in some situation, can be different from CIN 3. For instance, in 2006 consensus guideline developed by ASCCP, observation is preferred in young women with histologic diagnosis of CIN 2 but treatment is recommended in case of CIN 3 (Wright et al., 2007). As well, regarding cytology, "moderate dysplasia/CIN 2" is an intermediate and unique category, compared with CIN 3, CIN 2 is more likely to have low grade or benign on histology , cytologic CIN 2 is more likely to be reversible and the risk of invasion on histology is very low (National Health Service Cervical Screening Program, 2003; Herbert, 2004; Kocjan et al.,2005; National Health and Medical Research Council, 2005). Nobbenhuis et al (2001) showed that the

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cumulative 1-year rate of cytological regression without intervention was similar in women with mild and moderate dyskaryotic cervical smears and it was more than those with severe dyskaryosis. Data from Australian Registries (National Health and Medical Research Council, 2005) showed that there were clear differences in outcomes for a cytologic CIN 2 compared to CIN 3. Laboratories should provide specific report of CIN 2 or CIN 3 when the cytologic result is HSIL (National Health and Medical Research Council, 2005; Herbert, 2004; Kocjan et al., 2005; Herbert et al., 2007).

There is clinical usefulness in retaining a subdivision between CIN 2 and CIN 3 for cytologic reporting of HSIL. In the authors' institute, Rajavithi hospital, TBS 2001 has been used for many years. However, this two-tiered system is still used in practice in combination with traditional CIN system which separates HPV from CIN 1 and CIN 2 from CIN 3 for reporting cervical cytology. The authors investigate whether dividing HSIL cytology to CIN 2 and CIN 3 has differently predictive significance in term of the histological outcome. The present study should also emphasize the clinical usefulness of retaining CIN 2 and CIN 3 in HSIL in Thailand. The objective of the present study is to evaluate and compare the prevalence of histologic CIN 2/3 or cancer (CIN 2+, high-grade cervical lesions) between cytologic HSIL-CIN 2 and HSIL-CIN 3 of Thai women.

## Materials and Methods

Upon a retrospective study from January 2001 through March 2005, all women who had a referral cytological interpretation of HSIL in colposcopy clinic, Rajavithi hospital were identified, extracted and reviewed by computer search. During the study period, clinical data were prospectively stored in a computerized database of colposcopy clinic (On-Dysplay version 2.10.7, Oncoserve sytems, Melbourne, Victoria, Australia).

Most women enrolled in the present study had HSIL following a Pap smear in the authors' institute , the remainder were referred from other clinics. They were counseled regarding the option of immediate loop electrosurgical procedure (LEEP), (Surgitron F.F.P.F generator, Ellman international, New York, USA) and signed an informed consent for colposopy and additional procedure.

Colposcopy was performed using standard technique. The colposcopic finding was documented and colposcopically directed biopsy (CDB) was taken from the worst affected area using 3% acetic acid according to standard of practice. Lugol's staining was optional. In the patients with unsatisfactory finding, LEEP or conization was performed as appropriate. Tissue specimens were interpreted by the Department of pathology at the same institution. The final diagnosis was based on the worst histology. Data was analysed by SPSS version 11.5 (Statistical Package for the Social Science, SPSS Inc, Illiois, USA).The association between the cytologic and histologic results were examined using the Chi square Mantel- extension test and $p < 0.05$ was considered statistically significant.

**Table 1. Cytohistologic Association Between HSIL Cytology and Final Histology**

| Cytology | Final histology diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | Negative | CIN1 | CIN2 | CIN3 | Cancer | All |
| HSIL-CIN2 | 15 (21.4) | 10 (14.3) | 13 (18.6) | 28 (40.0) | 4 (5.7) | 70 |
| HSIL-CIN3 | 8 (9.7) | 4 (4.9) | 5 (6.1) | 57 (69.5) | 8 (9.7) | 82 |
| HSIL-total | 23 (15.1) | 14 (9.2) | 18 (11.8) | 85 (55.9) | 12 (7.9) | 152 |

## Results

Mean age of the 152 women with HSIL undergoing colposcopy was 56 years with range of age 18-72 years. Seventy three (48%) were nulliparous. Satisfactory colposcopy was noted in 112 (73.7%) women. Seventy women and 82 women had cytologic change compatible with CIN 2 and CIN 3, respectively. Of 152 women, 134 had histology from CDB. The remainder (18) underwent immediate LEEP after initial colposcopy. Of 134 women, the histological diagnosis from CDB in women with HSIL was negative in 17(12.7 %), CIN 1 in 19 (14.2%), CIN 2 in 16 (11.9%), CIN 3 in 76 (56.7%) and invasive cancer in 6 (4.5%). Using an initial colposcopy and CDB in women with HSIL could identify histology- proved CIN 2+ in 98 (73.1%) cases.

Of total 152 women, the final histological diagnosis for women with HSIL was negative in 23(15.1%), CIN 1 in 14 (9.2%), CIN 2 in 18 (11.8%), CIN 3 in 85 (55.9%) and invasive cancer in 12 (7.9%).Therefore, the positive predictive value of histology- proved CIN 2+ in women with HSIL was 75.6%. Table 1 shows cytohistologic association between HSIL cytology and final histology. Of the 134 women who had histology from CDB, 36 of 60 (60%) of women with HSIL-CIN 2 had histologic CIN 2+ while 62 of 74 (83.8%) of women with HSIL-CIN3 had histologic CIN 2+. The histology-proved invasive cancer was observed in 4 of 70 (5.7%) and 8 of 82 (9.8%) of women with HSIL-CIN 2 and HSIL-CIN 3, respectively. The analysis revealed a significant difference ($p<0.05$) between HSIL-CIN 2 and HSIL-CIN 3 in terms of the biopsy results (Table 2). Of the total 152 women with HSIL cytology, 45 of 70 (64.3%) who had HSIL-CIN 2 cytologic feature on smear had CIN 2+ at final histological diagnosis, compared with 70 of 82 (85.4%)

**Table 2. Cytohistologic Association between Cytology HSIL and Histologic Significant Result from CDB**

| Cytology | Colposcopically directed biopsy (134) | | p-value* |
|---|---|---|---|
| | CIN 1 or less (36) | CIN 2+(98) | |
| HSIL-CIN2 | 24 (40.0) | 36 (60.0) | 0.002 |
| HSIL-CIN3 | 12 (16.2) | 62 (83.8) | |

* Chi square Mantel-extension test

**Table 3. Histologic CIN 2/3 or cancer (CIN2+) and Cytologic CIN2 and CIN 3**

| Cytology | Final histology diagnosis (152) | | p-value* |
|---|---|---|---|
| | CIN 1 or less (37) | CIN 2+(115) | |
| HSIL-CIN2 | 25 (35.7) | 45 (64.3) | 0.003 |
| HSIL-CIN3 | 12 (14.6) | 70 (85.4) | |

* Chi square Mantel-extension test

whose smears were compatible with HSIL-CIN 3 cytologic feature. This difference was also statistically significant ($p<0.05$). The result was shown in Table 3. Therefore, the positive predictive value (PPV) for CIN 2+ on histology was 67.3% and 85.4% for HSIL-CIN 2 and HSIL-CIN 3, respectively.

## Discussion

The PPV of HSIL for histologic CIN 2+ in the present study is in agreement with data from previous studies showing that initial colposcopy or LEEP identified CIN 2+ in 53-97% of women with HSIL (National Health Service Cervical Screening Program, 2003; Wadehra et al., 2003; National Health and Medical Research Council, 2005; Wright Jr et al., 2007). The significant difference in prevalence of histology-proved CIN 2+ observed in the present study confirmed that in routine clinical practice, the cytologic distinction between CIN 2 and CIN 3, although rather subjective, has cytologic prediction of underlying high-grade cervical lesion.

As known, severe dysplasia is generally thought to be a more robust diagnosis than moderate dysplasia. Data from Australian Registries showed that results of predictive value of histology-proved CIN 2+ for HSIL-CIN 2 and CIN 3 were approximately 61-65% and 83-88%, respectively and the predictive value of invasive cancer were approximately 0-0.2% and 1-5%, respectively (National Health and Medical Research Council, 2005). Previous meta-analysis of studies of women with screen detected abnormalities referred for colposcopy revealed that a results of predictive value of CIN 2+ for mild dysplasia, moderate dysplasia and severe dysplasia cytology were 42%, 66.9% and 92.2% , respectively and the predictive value of cancer were 0.1%, 0.1% and 6.2% , respectively (National Health Service Cervical Screening Program, 2003). A recent study revealed 70% of final histology of CIN 2+ in HSIL-CIN 2 (Harry et al.,2008) which is similar to the present study. These support that the predictive value for high-grade cervical lesions or invasive cancer of cytology HSIL-CIN 2 is clearly different from HSIL-CIN 3. Anderson et al (2004) showed that the PPV for histologic CIN 2 and 3 were similar for two-and three-tier systems, whether or not there was moderate dysplasia category. This study also showed that the intra and interobserver agreement was moderate using both grading system, but the agreement between cytology grade and final histology was worse using two-tier system than when the three-tier system was used. In addition, they demonstrated a reluctance to use the term of HSIL for all cytological changes otherwise reported as moderate dysplasia category.

The similar problem has been recognized by the Australian National Cervical Screening Program Guidelines Review Group and suggests that laboratories may wish to continue to provide specific description of CIN 2 or CIN 3 when the cytology is HSIL (National Health and Medical Research Council, 2005). Likewise, the proposed new 2-tier system by British Society for Clinical Cytology still allow the use of free-text description for moderate or severe dyskaryosis (Harry et al., 2008). A recent study (Harry et al.,2008) investigated the role of the moderate dyskaryotic smear in women with moderate dyskaryotic smears referred for colposcopy. These smears were reviewed and reclassified using a 2-tier system, eliminating central "moderate" category. From the figure in this study, it revealed that in group of women whose moderate dyskaryosis was reclassified as low-grade dyskaryosis, there were a considerable number of cases with CIN 2+ on final histology. Those cases are at risk for under treatment when eliminating central "moderate" category. On the other hand, this study also demonstrated the likelihood of overtreatment when using 2-tier system as well. However, in their report, it was concluded that there was no clinical benefit in retaining the category of moderate dyskaryosis in clinical practice.

In the present study, the prevalence of CIN 2+ and invasive cancer in HSIL-CIN 2 was significantly high, compared to those in LSIL from literature (National Health Service Cervical Screening Program, 2003; Wright Jr.et al., 2007) and it was closer to that of HSIL-CIN 3 than LSIL. In addition, data regarding cytological interpretation revealed that distinction between CIN 1 and CIN 2 was good with a moderate agreement, but the distinction between CIN 2 and CIN 3 was fair and sometimes it is difficult to distinguish cytologically (National Health and Medical Research Council, 2005; Kocjan et al.,2005). In view of that, it seems rational to group CIN 2 into HSIL. Management should be the same in cytology showing HSIL-CIN 2 or HSIL-CIN 3 as there is a significant risk of high-grade cervical lesion. In any event, the authors still recognized that the descriptor of "moderate category" should be reserved for several purposes. Firstly, the important of the central category is that CIN 2 is like a buffer, giving a very different spectrum of outcome compared with either CIN 1 or CIN 3. It is an intermediate entity that may include over-called CIN 1 and under-called CIN 3 (Herbert et al.,2008; Schiffman et al.,2003; Herbert,2004; Kocjan et al.,2005). Secondly, it allows correlation between cytologic different systems especially with systems that link moderate dysplasia/CIN 2 with mild dysplasia/ CIN 1 such as Munich system used in Europe links moderate dysplasia with mild dysplasia, separating them from severe dysplasia and carcinoma in situ (Spitzer et al.,2002; Herbert ,2004; Kocjan et al.,2005; Herbert et al.,2007). According to such system, some clinicians would therefore differently manage patients with CIN 2 and CIN 3 on cytology. In addition, the evidence showing a stronger association of high-grade cervical lesions with HSIL-CIN 3 than HSIL-CIN 2 can apply in the clinical practice. In fact, in colposcopy clinic, women with HSIL-CIN 3 on cytology tend to be treated by a see and treat policy more often than those with HSIL-CIN 2 who tend to be treated at the second visit after biopsy confirmation (Harry et al., 2008). In Thailand, most of the cytopathology laboratories still include a text report favoring CIN 2 or moderate dysplasia to inform the clinician when the results are HSIL.

In conclusion, although the authors recognize the limitations of the present study, the retrospective design with the small number of patients and lack of concurrent pathological review, the data showed that the predictive

value for high-grade cervical lesion of HSIL-CIN 2 was statistically different from HSIL-CIN 3. Nevertheless, it seems that there is no significant distinction regarding clinical management. Both cytological results should be managed in the same way because the rate of detection of high-grade cervical disease and invasive cancer in both of them is too high to allow a conservative follow-up protocol only. The authors believed that the descriptor of "moderate category" should be reserved in the Bethesda system.

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