Screening of Cervical Neoplasia by Using Pap Smear with Speculoscopy Compared with Pap Smear Alone

Sathone Boonlikit, MD*, Wisit Supakarapongkul, MD*,
Nisa Preuksaritanond, MD*, Charoen Vipupinyo, MD*,
Suphet Tuipae, MD*, Somsamorn Mangclaviras, MD*,
Saowanee Karnplumjid, MD*, Picharn Chantarawiroj, MD*

** Department of Obstetrics and Gynecology, Rajavithi Hospital*

Objective: *The objective was to compare the sensitivity and specificity of Pap smear plus speculoscopy with Pap smear alone.*
Material and Method: *The study was conducted in the Gynecology Clinic, Rajavithi hospital, Thailand between February 1st and July 31st 2003. Women who made a request for cervical screening underwent a Pap smear, speculoscopy and colposcopy. Colposcopically directed biopsies were obtained from women who had a positive colposcopy. Analytical methods were applied.*
Results: *Of 257 women recruited to the study, Pap smear plus speculoscopy could increase sensitivity from 6.67% with Pap smear alone and to 33.33% when Pap smear plus speculoscopy is used. The false negative rate was reduced from 93.33% with Pap alone and to 66.67% with Pap smear plus speculoscopy. In using Pap smear alone compared with combination of two tests, the specificity decreased from 97.52% to 77.68% and false positive rate increased from 2.48% to 22.31%, respectively.*
Conclusion: *Adding speculoscopy to the Pap smear is able to significantly increase the sensitivity of the cervical screening. It also reduces the "false negative" result. However, as expected, the specificity slightly decreases, due to the false positive from speculoscopy itself. One solution is to defer colposcopy for 6 months and to perform colposcopy only if either Pap smear or speculoscopy is positive.*

Keywords: *Speculoscopy, Cervical screening, Chemiluminescent light, Adjunctive test, Pap smear*

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For more than 50 years the Papanicolaou smear has been the mainstay of cervical screening resulting in a dramatic decrease in death from cervical cancer. However, the Pap smear does have certain disadvantages. It has a low sensitivity and high false negative rate. The data reveals that some of the false-negative Pap smears rarely contain any abnormal cells on the slide[1,2]. So far, an effort to seek an explanation for this matter has been focused on either the incomplete transfer of cells from collection devices to the slide or inadequate sampling. This results in the development of liquid-based cytology technique[2,3]. Additionally, one of the emerging explanations is the lack of exfoliation of dysplastic cell (shedder and non-shedder hypothesis)[4,5]. Data from some studies have been shown to the effect that there is an abnormal expression of the adhesion molecules in a subset of dysplastic lesions of the cervix [4,5]. It can prevent detection by any test requiring exfoliated abnormal cell, including liquid-based technique. Despite the non-shedding behavior, those lesions can be identified by visual test[4]. There have been a number of visual tests which investigated for primary screening or used as adjunctive test of cytology method. These tests include cervicography, visual inspection with acetic acid (VIA), speculoscopy. At the present time, cervicography has a limited role as a primary screening or an adjunct to Pap smear[6-8]. However, as a triaging strategy for patients with ASCUS Pap smear, it is still a promising technique[9,10]. Direct inspection is the

Correspondence to : Boonlikit S, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Rajavithi Hospital, 2 Phayathai Rd, Rajatevee, Bangkok 10400, Thailand. Phone: 0-2354-8165-74, Fax: 0-2354-8084

other method based on applying acetic acid to the cervix and then visualizing it. It can be done under incandescent light with or without magnification or the chemiluminescent light [11,12]. This chemiluminescent light is of low intensity. It is diffuse and produces minimal reflective glare from normal tissue. There are studies showing that the use of chemiluminescent light allows the examiner to identify acetowhitening better than the incandescent light does[12-16]. Speculoscopy is developed for cervical screening by using chemiluminescence and low-power magnification to examine the cervix after applying an acetic acid. It can detect acetowhite dysplastic lesions and has been reported to be effective in detecting cervical intraepithelial lesions when combined with the Pap smear[11,12,15,17-23]. Presently, new technologies such as liquid-based cytology, HPV DNA test have been introduced, however, they are very expensive and need a well-maintained cyto-pathological laboratory support. The ideal screening test in Thailand should be inexpensive, practical and suitable for infrastructure. In this situation, visual screening tests have many of the advantages of cytologic screening. They seem to be easier to learn than cytology. The results of the visual tests are instantly known which can decrease the problem in transportation and unreliable women for follow up. VIA is now being studied in Thailand with its potential as a low-cost primary screening technique[24]. The other tests, however, have not been adequately studied.

The present study was undertaken to evaluate the potential of combining the Pap smear with speculoscopy (PAPSURE®). The objective was to compare the sensitivity and specificity of this test with the Pap smear alone. It is the first study in Thailand designed to investigate in normal women presenting for annual screening.

Material and Method

The present study was conducted in a Gynecolgy clinic between February 1st and July 31st 2003. The study was open to any woman who presented for routine a Pap smear and pelvic examination. Women with a history of cervical carcinoma or known case of CIN were excluded. The other exclusion criteria included pregnancy, previous cervical operation or total hysterectomy, women with cervical abnormality such as cervical myoma, women who had pelvic radiotherapy. After the details of the present study were explained, if the woman refused the offer, she was sent to have a Pap smear and internal examination routinely performed. The women who wanted to participate read the information brochure and signed an informed consent form. A clinical history was then taken. Each woman was individually counseled again and then subjected to three screening tests respectively. The first and second tests were Pap smears and speculoscopy. After being positioned on the examination couch, Speculite was activated by bending the plastic tube. Bending the tube broke the small internal capsule, resulting in the mixing of various chemicals. The blue white, non toxic light was produced from this tube. The speculite was now attached to the upper blade of the speculum and inserted into the vagina. After performing a Pap smear, the cervix was washed with 5% acetic acid. Then, room light was dimmed and the physician started the observation of the cervix with the aid of 6x magnification and the results were recorded. After completing the test, each woman was sent to another room. She then underwent a colposcopy and pelvic examination by a colposcopist who was blinded as to the speculoscopy result of each woman in the present study. At colposcopy, colposcopically directed biopsy (CDB) was done only if there was a lesion compatible with a pre-invasive or invasive lesion. The woman with normal colposcopic finding and no significant lesion was considered to be disease-free and was not biopsied. The colposcopic finding was then recorded on a data-collection form. All of the specimens were sent to the hospital laboratory. Laboratory personnel were blinded as to the speculoscopy results. The Pap slides were read by cytotechnologists using the 2001 Bethesda system. Pap smears showing CIN, ASC-US, ASC-H, invasive cancer, abnormal glandular intraepithelial lesion such as AIS and HPV infection were considered as positive, whereas those with features of metaplasia, inflammatory atypia without HPV feature were considered as negative. Speculoscopy was considered to be positive if the examiner observed a distinct acetowhite area on the cervix. Otherwise, it was considered negative. The Pap plus speculoscopy screening test was considered to be positive if either the Pap smear or the speculoscopy was positive. The Pap plus speculoscopy screening test was negative only if both were negative. Colposcopic examination showing atypical transformation zone compatible with pre-invasive lesion or invasive cancer was considered to be positive. The abnormalities outside the transformation zone such as vaginal condyloma or HPV vaginitis without the pre-invasive or invasive lesions in transformation zone were considered negative. Biopsies with features of

Table 1. Results of Pap test, speculoscopy and Pap plus speculoscopy compared with colposcopic-histologic diagnosis*

Colposcopy-histology	Pap Test		Speculoscopy		Pap plus Speculoscopy	
	Positive	Negative	Positive	Negative	Positive	Negative
Positive**	1	14	4	11	5	10
Negative***	6	236	49	193	54	188

* Biopsies were performed when colposcopy revealed atypical transformation zone compatible with pre-invasive lesion; no biopsy were performed in cases of normal colposcopy

** Positive results were based on histology

*** Negative results included two conditions 1) Normal colposcopy and no biopsy 2) Colposcopy was positive but biopsy was negative for pre-invasive/ invasive lesion

HPV, CIN, AIS or glandular dysplasia, invasive cancers were considered positive. The absence of those features or features of metaplasia, non specific atypia without HPV characteristic were considered as negative. The gold standard was based on the association between colposcopy and/or histology (colposcopic-histologic diagnosis). Since the biopsy was not performed in the absence of the lesion, therefore, in the present study, negative colposcopic-histologic diagnosis included two conditions: 1) Women with negative colposcopy (and no biopsy) were accepted as negative findings, 2) Colposcopy was positive but the histology from CDB was negative. Positive colposcopic-hisologic diagnosis was based on histology from CDB. The data were analysed by using Ministat software. Descriptive statistics were used to describe the women's characteristics. The statistics used included mean, median, standard deviation, percentage. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate (FPR) and false negative rate (FNR) were calculated.

Results

A total of 257 women were recruited to the present study. The age of the women ranged from 18 to 69 years (mean $\pm$ SD = 41.44 $\pm$ 8.82 years). The mean age at first intercourse ranged from 12-38 years (mean $\pm$ SD = 22.86 $\pm$ 4.47 years). Forty-two women (16.34%) were nulliparous, 215 (83.66%) were multiparous. The mean parity was 1.66 (median = 2), with a range of 0 to 6. Smoking was reported by 13 (5.06%) of the women. Sixty-two women (24.12%) were either taking oral contraceptives or had taken them in the past. Nineteen women (7.39%) had been diagnosed with STD in the past. Forty-two (16.34%) women had unsatisfactory colposcopy. Of these 257 women, 37 (14.40%) had positive results to the colposcopy, 53 (20.62%) to the speculoscopy, 7 (2.72%) to the Pap smear and 59 (22.96%) to the combination of two latter tests (Table 1). Almost all of the combinations of two tests had a positive result for only one of the two tests independently (Table 2). Among the 37 women with positive colposcopy, colposcopically directed biopsy were done. Thirteen women (35.14%) had HPV infection, one woman (2.7%) had CIN 1. There was one woman having CIN 3. She was treated by LLETZ and the histology revealed CIN 3, none had cancer. Thus, only 15 (40.54%) of this group had significant pathology.

The Pap smear plus speculoscopy could increase sensitivity from 6.67% with the Pap smear alone to 33.33% when the Pap smear plus speculoscopy was used, specificity decreased from 97.52% to 77.68% respectively. Combination of those two tests could reduce the false negative rate from 93.33% with the Pap alone to 66.67% with Pap smear plus speculoscopy (Table 3).

There were 52 women with a positive speculoscopy and a negative Pap smear. In this group, after colposcopy (and CDB if colposcopy were positive) were done, 48 women were considered normal, either by colposcopy impression or abnormal colposcopy impression but the subsequent pathology from CDB showed negative results. Only 4 women had

Table 2. Correlation between the result of Pap smear, speculoscopy, Pap plus speculoscopy and colposcopic-histologic diagnosis

Test result	Colposcopy-histology		Total
	Positive	Negative	
Either one or both tests +ve			
▪ Pap +ve Speculoscopy -ve	1	5	6
▪ Pap -ve Speculoscopy +ve	4	48	52
▪ Pap +ve Speculoscopy +ve	0	1	1
Both tests -ve	10	188	198
Total	15	242	257

Table 3. Comparison of the results of Pap smear, speculoscopy and combined test

Test	Sensitivity	Specificity	PPV	NPV	FPR	FNR	Accuracy
1. Pap smear	6.67	97.52	14.28	94.40	2.48	93.33	92.22
2. Speculoscopy	26.67	79.75	7.55	94.61	20.25	73.33	76.65
3. Pap smear plus Speculoscopy	33.33	77.68	8.47	94.95	22.31	66.67	75.10

PPV = Positive predictive value, NPV = Negative predictive value, FPR = False positive rate, FNR = False negative rate

abnormal histology. All of them were diagnosed as LGL (low-grade lesion).

Discussion

The present study is the first practice-based clinical study of Pap smear plus speculoscopy screening performed in Thailand. The present study indicates that using the Pap smear plus speculoscopy as a screening test significantly increases the detection of preinvasive lesion compared with screening using the Pap smear alone. In fact, the present study also shows that even using speculoscopy alone has more sensitivity than using the Pap smear alone, specificity, however, is inferior. This study's findings are in agreement with data from other studies of visual tests, such as cervicography, VIA[7,25,26]. Comparison of the results obtained with VIA with cervical cytology indicates that the sensitivity of VIA is equally or more sensitive than cytology but less specific[11,26]. Many studies have confirmed that the combination of VIA or cervicography and cytology can detect more lesions than cytology alone[8,10,25]. In addition, the presented data also support the findings of earlier studies of women using a Pap smear plus speculoscopy[11,15,17,20,21].

Based on previous studies, the cervical cytology tests reported as ASC-US in the present study are classified as "positive"[11,19,20]. There were 4 women having ASC-US cytology. Three of them had negative speculoscopy and colposcopy. One woman had postive colposcopy and speculoscopy but the pathology of CDB subsequently revealed only metaplastic epithelium. In fact, speculoscopy has also been proposed as a triage test for colposcopy for women with ASC-US Pap smears. They could benefit from performing speculoscopy as the effective triage without requiring an additional clinic visit or laboratory test, potentially decreasing costs[15]. In women who have ASC-US results and negative speculoscopy, they are considered to be "low risk", those who have ASC-US results and positive speculoscopy results are considered to be "high risk". Colposcopy is recommended in the high risk group. This is a possible value of speculoscopy[15].

Three additional cases of positive Pap smear were CIN 1, ASC-H and CIN 2. All of them had negative speculoscopy. There will be several explanations regarding this result. For example, the transformation zone might be located deeply inside the endocervical canal, therefore, the abnormality cannot be detected by speculoscopy. In contrast, the Pap smear can collect the cells scraped from the endocervical canal[12,15]. In addition, in women with subclinical HPV infection, which has a subtle epithelial change without acetowhitening (minimally expressed papilloma virus infection, MEPI) possibly have normal speculoscopic findings. In the present data, the woman who had ASC-H Pap smear was found to have only vaginal condyloma without atypical transformation zone (negative colposcopy). The other women with CIN 1 Pap smear, colposcopic examination showed normal transformation zone. There was only one woman who had an abnormal Pap smear (CIN 2) and negative speculoscopy was subsequently found to have atypical transformation zone by colposcopy (CIN 3 by histology). Importantly, almost all "positive" combinations of two tests were positive for only one of the two tests independently. This suggests that both tests are sensitive in different mechanisms and they are synergistic to each other.

Obviously, the combination of the Pap smear and speculoscopy has less specificity than the Pap smear alone. The specificity decreases from 97.52% to 77.68%. The present finding is in agreement with data from other studies[11,15,17,20]. In fact, increasing sensitivity of any screening test will certainly result in decreasing the specificity. Adding speculoscopy to the Pap smear increases identification of cervical change due to a nonpathologic condition, such as reparative change, immature squamous metaplasia. The areas showing such changes usually consist of epithelial cells with high nuclear/cytoplasmic ratio. Using visual tests such as speculoscopy, VIA, cervicography, even colposcopy can show acetowhite areas

that do not have the significant pathology. Nevertheless, the small decrement in specificity of screening tests strongly have a large impact on the cost due to increasing false positive results and excessive use of colposcopy can result in overdiagnosis and overtreatment of women[27]. To overcome this problem, the use of speculoscopy as an adjunctive test in a screening program might need particular algorithms for managing those patients with "positive" speculoscopy but negative Pap smear. In practice, one approach is to defer colposcopy for 6 months and to perform colposcopy only if either the Pap smear or speculoscopy is positive[11,15,28]. One study showed that after waiting for 6 months, 29% of women had positive speculoscopy results reverted to normal. In women who had persistently positive results by speculoscopy but negative cytology, 81% were found to have biopsy-confirmed CIN 1 and 8% had CIN 2, 3[11,28]. In the current study, of 52 women having a negative Pap smear and positive speculoscopy, all of them were normal or only LGL by colposcopic-histologic diagnosis. That means most of the women in this group can have results reverted to normal in the next 6 months. Therefore, using those approaches, the diagnostic efficacy can be improved. However, deferral should only be considered for women who are reliable for follow up. Another concern regarding those approaches is patients' anxiety from waiting a long time.

The present study has some limitations. The first limitation is that a biopsy is taken only in women with positive colposcopy. In case of negative colposcopy, biopsies are not done. Therefore, there is no way of knowing the true histological diagnosis in women who have negative colposcopy. This fact could result in the methodological bias due to the absence of reliable reference test. The second limitation is that the sample size is small. Those problems could affect the accuracy, sensitivity and specificity of the diagnostic tests in the present study. Compared to similar studies[17,21], all of the presented tests have lower sensitivity and specificity. Despite these limitations, however, the present study demonstrates that adding speculoscopy to the routine Pap smear is able to significantly increase the sensitivity of the cervical screening. It also reduces a "false negative" result. However, the specificity slightly decreases, due to the false positive from speculoscopy itself. The test can be easily performed by clinicians and the result is immediately known without the necessity of complicated laboratory service. Currently, many new technologies have expanded the number of adjunctive tests to clinicians worldwide. Nevertheless, the infrastructure in each country will determine which screening test is most suitable.

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การศึกษาการใช้แป๊พเสมียร์ร่วมกับสเปคูโลสโคปีเปรียบเทียบกับการใช้แป๊พเสมียร์ในการตรวจคัดกรองมะเร็งปากมดลูก

สธน บุญลิขิต, วิสิทธิ์ สุภัครพงษ์กุล, นิสา พฤกษะริตานนท์, เจริญ วิภูภิญโญ, สุเพ็ชร ทุ้ยแป, สมสมร มังคละวิรัช, เสาวนีย์ การปลื้มจิตต์, พิชาญ จันทรวิโรจน์

การศึกษาเพื่อเปรียบเทียบผลความไวและความจำเพาะของการตรวจคัดกรองมะเร็งปากมดลูกด้วยแป๊พเสมียร์ (Papanicolaou smear) ร่วมกับสเปคูโลสโคปี (speculoscopy) กับการตรวจด้วยแป๊พเสมียร์เพียงอย่างเดียว ในสตรีที่มารับการตรวจคัดกรองมะเร็งปากมดลูกจำนวน 257 คน ที่โรงพยาบาลราชวิถีระหว่างวันที่ 1 กุมภาพันธ์ถึง 31 กรกฎาคม พ.ศ. 2546 ในด้านความไว ความจำเพาะ ค่าการทำนายผลบวก (PPV) ค่าการทำนายผลลบ (NPV) อัตราผลบวกลวง (FPR) อัตราผลลบลวง (FNR) และความแน่นอน (accuracy) พบว่าการตรวจด้วยแป๊พเสมียร์ร่วมกับสเปคูโลสโคปี สามารถเพิ่มความไวได้อย่างมากเมื่อเทียบกับการตรวจด้วยแป๊พเสมียร์เพียงอย่างเดียว (ร้อยละ 33.33, 6.67 ตามลำดับ) อัตราผลลบลวงลดลง (ร้อยละ 66.67, 93.33 ตามลำดับ) แต่ความจำเพาะลดลง (ร้อยละ 77.68, 97.52 ตามลำดับ) และอัตราผลบวกลวงสูงขึ้น (ร้อยละ 22.31, 2.48 ตามลำดับ) การใช้สเปคูโลสโคปีร่วมกับการตรวจด้วยแป๊พเสมียร์ (adjunctive test) สามารถเพิ่มความไวและลดผลลบลวงของการตรวจด้วยแป๊พเสมียร์ ปัญหาเรื่องความจำเพาะลดลงและอัตราผลบวกลวงสูงขึ้นโดยเฉพาะในรายที่มีผลตรวจสเปคูโลสโคปีผิดปกติเพียงอย่างเดียว สามารถแก้ไขได้โดยนัดตรวจซ้ำใน 6 เดือนและส่งตรวจคอลโปสโคปีในรายที่ยังมีผลการตรวจผิดปกติ