

# Improved early detection of cervical intraepithelial lesions by combination of conventional Pap smear and speculoscopy

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## Summary

**Purpose:** To evaluate the efficacy of the addition of speculoscopy to a Pap smear in cervical cancer screening.

**Methods:** All women were screened using the Pap smear plus speculoscopy (PapSure) and colposcopy in the multicenter trial. The final diagnosis of each patient was based on a histological evaluation of the colposcopic target biopsy. Results were analyzed using a proportional compare test, sensitivity, specificity and predictive value with significant value determined at less than 0.05.

**Results:** Of 1,717 eligible cases, 26 cases had LGSIL and 16 cases had HGSIL. Of the Pap smears, five cases had LSIL and 14 cases had HGSIL. Of the combination of the PapSure, 23 cases had LGSIL and 16 cases had HGSIL. The sensitivity of the Pap smear to that of PapSure was calculated at 45.2% and 92.9%, respectively ( $p < 0.001$ ). The estimated cost to detect a cervical lesion using PapSure is less than that of the Pap smear.

**Conclusion:** The addition of speculoscopy along with a Pap smear screening results in early detection of cervical lesions in comparison to the Pap smear alone. This screening combination is also more cost-effective and requires fewer visits to the clinic in comparison to a Pap smear screening alone.

**Key words:** Cervical cancer screening; Papanicolaou smear; Speculoscopy.

## Introduction

The Pap smear, introduced by George Papanicolaou in 1943, has become the most popular and important early-detection screening method for cervical cancer all over the world. However, the accuracy of the Pap smear has been questioned, with some reports finding false negative rates as high as 55%. [1] It is now widely accepted that a Pap smear does not reflect the true incidence of cervical neoplastic lesions, especially in pre-invasive forms. Various other methods have been developed to enhance the Pap smear's ability to identify women at risk for cervical cancer, with some methods addressing human errors in reading the Pap smear [2,3], and other methods adding a visual screening procedure [4], or human papilloma virus (HPV) DNA detection [5]. The combination of the Pap smear and speculoscopy, called PapSure, to screen for cervical disease has been approved by the American FDA and acts as a primary screening for cervical malignancy. [6] The purpose of this research was to evaluate the efficacy of the Pap smear, speculoscopy, and the combination of the Pap smear and speculoscopy vs colposcopy and biopsy.

## Materials and Methods

### Patients

The subjects screened were 1,829 women residing in Keelung, in northern Taiwan, who had not received a Pap smear in the past three years as confirmed by a nation-wide government database of Pap smear registration. This community outreach program was performed in different regions of Keelung

from March 2001 to November 2001. The criteria for exclusion included patients whose last Pap smear was less than three years prior to the study, whose cervix was in an unusual position and could not be properly examined, who used a vaginal suppository or had intercourse within two days before the study, who had acute cervicitis or vaginitis, or who were menstruating at the time of the study. A total of 112 cases were excluded from this study, 71 cases did not meet the criteria and the other 41 cases had positive screenings but did not receive follow-up. There were 1,717 eligible cases in this study of 1,829 women. The study was approved by the Institutional Review Boards of the Taipei Veterans General Hospital and a consent form was signed by each participant.

### Clinical examination

Five senior colposcopists and gynecologists performed the following procedures in succession on each patient in the multicenter trial. First of all, Pap smears were taken from the transformation zone of the uterine cervical surface and the cervical canal. Then a 5% acetic acid solution was applied to the patient's cervix with a cotton tip applicator. Following a time lapse of 60 seconds, acetowhite lesions were detected via speculoscopy and 5x magnified loupes. Due to the limitation of examination time constraints, a colposcopy was simultaneously performed with the screening for the first 40 cases in each section of the study day. The patient was referred to a colposcopist for a target biopsy at the abnormal acetowhite lesion within two weeks if either the speculoscopy or the Pap smear was abnormal. Three of the five doctors were assigned to perform a colposcopy and biopsy from the referred cases. One or more punch biopsies were then taken from the colposcopic lesions for histologic evaluation. Women with negative screenings or who had positive screenings but negative findings on a satisfactory colposcopy and negative endocervical curettage were assumed to have no cervical pathological lesions.

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### *Papanicolaou smear*

For each Pap smear, an Ayre's spatula and an endocervical cytobrush were used to take smears from the transformation zone and endocervical canal of the cervix, respectively. The cells from the spatula and brush were smeared onto separate slides, two slides per patient. The tip of the smeared cytobrush was placed in a tube containing 5 ml of DNA reserved solution (diluted from 50x TE sterile solution, USB, Ohio, USA) for HPV DNA study (results not shown). The slides were evaluated according to the Bethesda system. Cytology was considered positive if the cells showed squamous intraepithelial lesions, atypical squamous intraepithelial lesions (ASUS), or glandular intraepithelial lesions (AGUS). Cytology was considered negative if the cells showed normal, atrophy, metaplasia, or inflammatory changes. All slides were rechecked by one senior cytopathologist. A positive Pap smear was defined as ASCUS/AGUS or worse.

### *Speculoscopy*

Following the Pap smear, a blue-white chemiluminescent light was activated by bending a speculite and then attaching the speculite (Trylon Corp., Torrance, CA, US) on the lower dilator blade of a vaginal speculum, prior to speculum insertion. Room lights were dimmed and the speculum inserted into the vagina. The cervix was then carefully observed using 5x magnification glass-mounted binocular loupes to detect the presence or absence of acetowhite lesions and both the site and size of the lesions were noted. Positive speculoscopy was defined as a marked acetowhite lesion with sharp margins.

### *Colposcopy*

A total of 1,082 cases were examined with colposcopy, which included 214 subjects who had positive screenings and 868 randomly sampled cases from the other negative screenings. Women with either positive Pap smear results or cervical lesions visible by speculoscopy were subjected to colposcopy for further investigation. Colposcopic findings were considered abnormal if a marked acetowhite lesion had characteristics of a sharp margin, irregular surface, or atypical vessel patterns (coarse punctuations, mosaic, etc.). Abnormal squamous metaplasia was defined as a weak intensity of the acetowhite and/or blurred margin. Women with either satisfactory or unsatisfactory colposcopies underwent punch biopsies taken from the acetowhite lesion and other suspicious areas. Endocervical curettage (ECC) should be performed for those patients who have unsatisfactory colposcopies. Specimens of biopsy tissue taken from the abnormal acetowhite lesion on the cervix and ECC were fixed in 10% formalin-saline solution and sent for histological examination.

### *Histology*

Biopsy specimens were embedded in paraffin, and 6-8  $\mu$ m tissue slices were taken and stained with haematoxylin-eosin using standard criteria. Histological slides were evaluated by different pathologists and the final diagnosis of all slides was reconfirmed by one senior pathologist.

### *Cost-effectiveness*

The cost-effective analysis was applied to examine and compare the expense of each screening method needed to find a positive case as well as total cost needed for the entire population. The estimation of related direct costs of examinations, such as Pap smear, speculoscopy, colposcopy, cervical punch biopsy, and histological studies was 578 NT (new Taiwan yuan), 1,000 NT, 360 NT, 430 NT, and 700 NT, respectively.

The cost of each examination was listed by Taiwan's Bureau of National Health Insurance. The indirect costs for each visit include one round-trip city bus transportation of 30 NT and two hours of time spent at the hospital equal to 132 NT (66 NT for one-hour base hourly wage).

### *Statistical analysis*

The reference standard was colposcopy with target biopsy, a commonly used and accepted reference standard for cervical cancer screening studies. The reports of normal and cervicitis in the histological study were referred to as test-negative. The results of negative or inflammatory Pap smears combined with negative findings in speculoscopy were referred to as test-negative as well. Results revealing a flat condyloma, low-grade squamous intraepithelial lesion (LGSIL) or worse in the histological study were considered test-positive. A proportional compare test, likelihood ratio test, positive/negative predictive value, sensitivity, specificity, and predictive value were performed by SPSS (SPSS Base 8.8, SPSS Inc., Chicago, IL) and MedCalc (Version 5, MedCalc software, Broekstraat, Belgium) software.

## **Results**

Of the 1,717 eligible cases the mean age was  $51.67 \pm 14.60$  (range 25-89, median 50). Mean parity was  $3.39 \pm 2.02$  (range 0-13, median 3). There were 818 postmenopausal cases and only 51 cases receiving regular hormonal replacement therapy.

In the 42 cases with positive biopsies, 16 cases were diagnosed with HGSILs (high grade squamous epithelial lesions) (CIN2 or CIN3) and 26 cases with LGSILs (flat condyloma or CIN1). Of the 31 positive Pap smears, 19 corresponded with positive histological findings and were considered correctly identified. All 23 false negatives in the Pap smears were diagnosed by biopsies as LGSIL (21 cases) and HGSIL (2 cases). Only three false negatives in the PapSure were found to be LGSILs (Table 1). The detection rate of cervical lesions was 1.11% in the Pap smear, 1.57% in speculoscopy, and 2.27% in PapSure. The total rate of disease was 2.44% (Table 2).

The sensitivity increased dramatically from 45.2% in the Pap smear to 92.9% when combining speculoscopy with the Pap smear, proportion test  $p < 0.001$ , when taking the LGSIL as the reference test. The advantage of adding speculoscopy to the Pap smear in screening for cervical lesions, in this case HGSIL, is shown whereby the rate increases from 87.5% in the Pap smear to up to 100% in PapSure, proportion test  $p < 0.001$ . However, the specificity of PapSure screenings, either LGSIL or HGSIL, was lower than the Pap smear alone (proportion test  $p < 0.001$ ) (Tables 3 and 4).

False negatives were present not only in both screening methods but also in colposcopy. Nine cases of LGSIL and four cases of HGSIL were presented as abnormal squamous metaplasia with less intensity of the acetowhite and lack of sharp margins (Table 5).

Considering the goal of identifying 90.5% of all SILs, and assigning costs to Pap smears, speculoscopy, colposcopy, and biopsy studies, the cost per case of finding a SIL lesion in a 4-consecutive Pap smear protocol would be \$3,870 compared to \$2,482 with the use of the

Table 1. — Reasons for patient exclusion from the study.

Items	Cases	Notes
Intercourse in past 2 days	17	
Acute vaginitis	15	
Menstruation period and bleeding	6	bleeding during sampling in 3 cases
Vaginal douche in past 2 days	1	also had intercourse
Vaginal suppository in past 2 days	1	also had intercourse
Inadequate observation	19	abnormal cervical position
Lack of Pap smear	11	slides broken
Lack of Speculscopy	6	lack of data
Lost to follow-up	41	Pap smear: HGSIL (3), SCC (1) Speculscopy positive (37)
<b>Total cases</b>	<b>112</b>	<b>Excluded from the study</b>

Table 2. — Detection rates of various screening methods.

Screening Methods	Results	Diagnosis			Total	Detection rate
		Negative	LGSIL	HGSIL		
Pap smear	Negative	1,663 (96.9%)	21 (1.2%)	2 (0.1%)	1,686 (98.2%)	1.11%
	Positive	12 (0.7%)	5 (0.3%)	14 (0.8%)	31 (1.8%)	
Speculscopy	Negative	1,503 (87.5%)	7 (0.4%)	8 (0.5%)	1,518 (88.4%)	1.57%
	Positive	172 (10.0%)	19 (1.1%)	8 (0.5%)	199 (11.6%)	
PapSure*	Negative	1,494 (87.0%)	3 (0.2%)	0	1,497 (87.2%)	2.27%
	Positive	181 (10.6%)	23 (1.3%)	16 (0.9%)	220 (12.8%)	
<b>Total</b>		1,675 (97.6%)	26 (1.5%)	16 (0.9%)	1,717 (100.0%)	2.44%

\*PapSure = Pap smear plus speculscopy

Positive result:

- Pap smear: atypia or worse
- Speculscopy: marked acetowhite lesion with sharp margin
- PapSure: either positive Pap smear or speculscopy

Table 3. — Sensitivity and specificity of different modalities in cervical cancer screening with LGSIL as the reference test\*.

Screening Methods	Sensitivity (range)	Specificity (range)	Positive LR	Negative LR	PPV	NPV
Pap smear	45.2% (29.9-61.3)	99.2% (98.7-99.6)	58.32%	0.55%	59.4%	98.6%
Speculscopy	64.3% (48.0-78.4)	89.7% (88.2-91.1)	6.26%	0.40%	13.6%	99.0%
PapSure	92.9% (80.5-98.4)	89.1% (87.6-90.6)	8.55%	0.08%	17.6%	99.8%

\* Positive: Flat condyloma/LGSIL/HSIL or more severe; Negative: Normal/Cervicitis. Proportion test: Pap smear vs PapSure: Sensitivity,  $p < 0.001$ ; Specificity,  $p < 0.001$ . LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

Table 4. — Sensitivity and specificity of different modalities in cervical cancer screening with HGSIL as the reference test\*.

Screening Methods	Sensitivity (range)	Specificity (range)	Positive LR	Negative LR	PPV	NPV
Pap smear	87.5% (61.6-98.1)	98.9% (98.3-99.4)	82.74%	0.13%	43.8%	99.9%
Speculscopy	50.0% (24.7-75.3)	88.8% (87.2-90.2)	4.46%	0.56%	4.0%	99.5%
PapSure	100.0%	88.0% (86.3-89.5)	8.30%	0%	7.2%	100.0%

\* Positive: HGSIL or more severe; Negative: Normal/Cervicitis/Flat condyloma/LGSIL. Proportion test: Pap smear vs PapSure: Sensitivity,  $p < 0.001$ ; Specificity,  $p < 0.001$ . LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

Table 5. — Results of screening and histological diagnosis of 1,717 screened women undergoing colposcopy.

Results screening test	Cases (%)	Number of Colposcopies (%)	Target biopsy	Histological Diagnosis		
				Negative	LGSIL	HGSIL
<i>Pap smear</i>						
SCC	3 (0.18)	3 (100.0)	3	0	0	3
HGSIL	7 (0.41)	7 (100.0)	7	0	0	7
LGSIL	3 (0.18)	3 (100.0)	3	1	2	0
ASCUS	18 (10.5)	18 (100.0)	16	9	3	4
Inflammatory	423 (24.64)	284 (67.1)	63	57	6	0
Negative	1,263 (73.56)	767 (60.7)	173	156	15	2
<i>Speculscopy</i>						
Positive	199 (11.59)	193 (97.0)	184	157	19	8
Negative	1,518 (88.41)	889 (58.6)	81	66	7	8
<i>PapSure</i>						
Positive	220 (12.81)	214 (97.3)	203	164	23	16
Negative	1,497 (87.19)	868 (58.0)	62	59	3	0
<i>Colposcopy</i>						
SCC		1	1	0	1	0
HGSIL		4	4	1	0	3
LGSIL		170	170	145	16	9
SM*		90	90	77	9	4
Negative		817	0	0	0	0
<b>Total cases</b>	<b>1,717 (100.0)</b>	<b>1,082 (63.0)</b>	<b>265</b>	<b>223</b>	<b>26</b>	<b>16</b>

SCC= squamous cell carcinoma; SM\*= abnormal squamous metaplasia favoring SIL.

Table 6. — Estimation of detection rate in consecutive Pap smear screenings.

The order of Pap smear screening	Cases found in each Pap smear	Calculation
The first Pap	19.0 cases	42 x 0.4524 = 19
The second Pap	10.4 cases	(42-19) x 0.4524 = 10.4
The third Pap	5.7 cases	(42-19-10.4) x 0.4524 = 5.7
The fourth Pap	3.1 cases	(42-19-10.4-5.7) x 0.4524 = 3.1
<b>Total</b>	<b>38 cases</b>	<b>90.5% (38/42)</b>

A single Pap smear can detect 19 of 42 cases (19/42 = 45.24%). Detection rate of 4-consecutive Pap smears is equal to one PapSure screening Total number of screenings in 4-consecutive screenings for all 1,717 subjects: 1,717 + (1,717-19) + (1,717-19-10.4) + (1,717-19-10.4-5.7) = 6,784 screenings.

### Discussion

Cervical cancer is the leading gynecological malignancy in Taiwan. The data of cervical cancer in 1998 showed that the total cases of invasive cervical carcinoma to be 2,796 and the incidence rate as 24.07/100,000. The total cases of carcinoma in situ of the uterine cervix was

PapSure protocol. The estimated cost shows the direct and indirect cost savings to be approximately 17.2 million US dollars when adding speculscopy to a Pap smear screening in comparison to a Pap smear alone in order to achieve a 90.5% detection rate for the entire female population of Taiwan (Tables 6 and 7).

Table 7. — Estimation of cost to find 90.5% of cervical lesions from 1,717 case screenings in Pap smear and PapSure.

Items	Pap smear*	PapSure*	Notes
Number of screenings	6,784	1,717	To achieve 90.5% of detection rate in SIL
Screening(s)	578 NT x 6,784 = 3,921,152 NT***	1,578 NT x 1,717 = 2,709,426 NT	One Pap smear costs 578 NT One speculscopy 1,000 NT
Positive in screenings	True positive 38 False positive 47	True positive 38 False positive 172	False positive: 47 in 4 consecutive Pap smears 172 in one PapSure screening
Colposcopy	360 NT x (47+38) = 30,600 NT	360 NT x (172 +38) = 75,600 NT	One colposcopy costs 360 NT (false positive + true positive)
Biopsy + Histology	1,130 NT x (47+38) = 96,050 NT	1,130 NT x (172+38) = 237,300 NT	Cervical biopsy costs 430 NT Histology 700 NT (false positive + true positive)
2 hours spent per visit	132 NT x 6,784 = 895,488 NT	132 NT x 1,717 = 226,644 NT	Base hourly wage in Taiwan 66 NT / Hour
Transportation fee	30 NT x 6,784 = 203,520 NT	30 NT x 1,717 = 51,510 NT	30 NT for a round-trip city bus
Cost to find a SILs	135,442.4 NT (\$3,870)	86,854.7 NT (\$2,482)	To find 38 SILs from 1,717 subjects
Estimated cost for all population	1,678,633,400 NT (\$47,960,950)	1,076,452,400 NT (\$30,755,780)	Goal: To detect 90.5% of SILs from 5,600,000 women, age >30

The issues of lesion regression and progress were not considered in the estimation. To detect 90.5% of SILs in the entire female population of Taiwan, the expenditure of 602,181,000 NT (about 17.2 million US dollars) may be saved if speculscopy was added along with a Pap smear.

\*It was estimated that 6,784 Pap smears (4 consecutive Pap smears) can achieve a 90.5% detection rate, with 38 cases of SILs detected from 42 SILs

\*\*PapSure is a Pap smear combined with Speculscopy

\*\*\*NT, new Taiwan yuan (1 US \$ = 35 NT)

3,095 and the incidence rate was 25.25/100,000. In an official report of 4,921,887 Pap smears taken from January 1997 to December 1999, the abnormal Pap smear rate was 1.78%, including atypia, SIL, and malignancy [7]. In this study, the positive findings were 1.81%, 12.81% and 2.44% in Pap screening alone, Pap smear plus speculscopy and confirmed by colposcopic biopsy, respectively. The prevalence of SILs was less than that of the study done by Denny *et al.* in South Africa on 2,944 women who had never had cervical cancer screenings, with LGSIL as 3.6% vs 1.5% and with HGSIL 2.8% vs 0.9% [8]. The prevalence of both studies was far less than that of 9.2% in Benedet *et al.*'s report. [9] Theoretically, detecting the true incidence of cervical disease in a population should be based on the Pap smear, colposcopic examination, and/or target biopsy. The most common cervical cancer encountered is the squamous cell lesion, and preinvasive lesions can be identified by visual screening due to the characteristic acetowhite appearance. A visual examination of the uterine cervix can easily detect most of an acetowhite lesion. PapSure, which combines the Pap smear with speculscopy to screen for cervical cancer, has been approved by the United States FDA and has shown very high sensitivity and negative predictive values. We used the Pap smear together with speculscopy to screen each patient in this study and the results showed a lower false negative rate than that of Pap screening alone.

The data suggests that LGSILs are more difficult to detect by Pap smear alone than HGSILs. In this study 21 out of 26 patients (80.8%) with LGSILs were not found by Pap smears. However, Pap smears alone can detect 87.5% of HGSILs, 14 out of 16 in this study, showing similar results as previous studies [6, 10]. The theory of shedder and non-shedder in cervical intraepithelial

lesions may be one reason for the impaired detection rate of the Pap smear in respect to LGSIL detection [11, 12]. Adhesion molecules in cervical intraepithelial neoplasias have different forms of expression, some resulting in lesions not easily detected by the Pap smear [12-14]. Theoretically, these lesions would be clearly visible in a visual examination. However, the sensitivity of speculscopy is higher in premenopausal women than postmenopausal (data not shown). These results may be due to inversion of the transformation zone into the cervical canal in postmenopausal women.

This study confirms the findings of previous studies that the Pap smear alone can typically find only half or less of cervical disease that is detectable by colposcopy [6, 10]. If a Pap smear is combined with speculscopy, the sensitivity increases dramatically, but so does the false-positive detection rate. Using PapSure, four-fifths of the patients found positive for lesions turned out to be negative when checked by colposcopy and biopsy in this study. This means the difference between missing 17 patients with disease, including two HGSILs, if screened by Pap smear alone, or unnecessarily sending 181 disease-free patients (10.8% total disease-free patients) to colposcopy if screened by PapSure. Thus, the false-positive rate is quite high when evaluating cervical cancer screening by PapSure in comparison to the Pap smear. The answer to the question "Is the high false-positive rate in PapSure acceptable for screening purposes?" may vary based on different philosophies and points of view.

The data indicates that the addition of speculscopy results in a significant increase in sensitivity but causes a decrease in specificity. In considering whether the increase of false-positive rates (from 0.7% to 10.6%), and the increase of LGSIL detection rates (from 0.3% to 1.5%) (Table 2), allow for a cost-effective screening program,

consideration should also be given to the goals of the screening program in question. Epidemiological studies have revealed that LGSILs had 34-60% regression and 30-55% persistence, but still a relatively high rate of 10-15% progress to HGSILs or worse [15-18]. Early studies revealed that more than 50% of LGSIL cases developed CIN3 within five years. [19] Earlier detection of disease may help patients adhere to proper follow-up with less chance of rapid disease progression. We agree with Edward *et al.*'s opinion that selecting the risk population could allow for the treatment of persistent or progressive lesions, resulting in both a treatment-oriented and prevention-oriented screening program [10]. However, early detection may cause panic in the patient and result in over-treatment. Thus, a healthy policy to take is that of proper patient education to understand the nature of the disease as well as regular follow-ups on the part of the patient.

Cost-effectiveness analysis is an important issue in evaluating screening tools and making strategies for public health. Considering the goal of identifying 90.5% of all SILs, the cost per case of finding a SIL lesion in a Pap smear alone protocol would be \$3,870 compared to \$2,482 with use of a PapSure protocol. The estimated cost shows the direct and indirect cost savings to be approximately 17.2 million US dollars when adding speculscopy to Pap smear screening in comparison to a Pap smear alone in order to achieve a 90.5% of SIL detection rate for the female population. Taiwans aged 30 years or older are estimated to be approximately 5.6 million.

Proper visual inspection is one of the most important methods for a practitioner to determine the nature of a patient's condition. It is generally agreed that a practitioner should strive to make visual assessments of potentially diseased areas whenever feasible. While the Pap smear has extracted significant benefit from in vitro examination, cervical screening has always lacked a proper in vivo component, because visual inspection of the cervix has traditionally been inconvenient and/or expensive. The recent development of tools, such as the speculite, has made visual inspection of the cervix much easier. Thus physicians should consider it their duty to combine in vitro and in vivo methods of examination, as in the PapSure procedure or colposcopy, when dealing with the uterine cervix rather than simply taking a smear.

## Conclusion

To objectively test the sensitivity and specificity of the conventional Pap smear and speculscopy, colposcopy was used as the gold standard and applied to every case in this study. The combination of Pap smear and speculscopy (PapSure) in cervical cancer screening can reach a much higher sensitivity than either screening alone. However, PapSure screening loses in specificity when compared to the Pap smear. The results of the study show that a single high sensitivity PapSure test can achieve a 90.5% detection rate, similar to that of a 4-consecutive Pap smear protocol. This means that patients can receive accurate results in fewer visits when obtaining a PapSure exam than with the Pap smear alone. As well, the cost

savings of the combination of a Pap smear and visual inspection means that medical resources could be directed to patients with early cervical lesions in order to prevent progression of the disease.

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