

## Outcome of serviced Papanicolaou smear in women with cancerous lesion of the uterine cervix.

Prasert Trivijitsilp\*  
Dasni Punyashthiti\*

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*The occurrence of false negative Papanicolaou smear in women with cancerous lesions involving the cervix diagnosed histologically at Chulalongkorn University Hospital from 1 January 1992 through 31 December 1992 was studied. During the period of study there were a total of 330 cases of tissue-proven cervical malignancy with only 194 cases having Papanicolaou smears done before or at the same time as the tissue biopsy was taken. Of the 194 cases, 142 cases (73.19%) were abnormal cytologically (Papanicolaou smear class III to V), leaving 52 cases (26.8%) a false negative cases. The majority of the false negative cases (43 cases, 22.11%) represents a sampling error. The remainder of the false negative cases were attributed to screening and interpretation error (9 cases, 4.7%). Causes and the effective ways to reduce the error were discussed.*

**Key words :** *False negative papanicolaou smear, Ca Cervix.*

Reprint request: Trivijitsilp P, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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ทำการศึกษา Papanicolaou smear ย้อนหลังในสตรีที่ได้รับการตรวจวินิจฉัยจากชิ้นเนื้อว่าเป็น มะเร็งปากมดลูกในช่วง 1 มกราคม 2535 ถึง 31 ธันวาคม 2535 ซึ่งมีผู้ป่วยทั้งสิ้น 330 ราย แต่มีการตรวจ Papanicolaou smear เพียง 194 ราย พบว่า 142 จาก 194 รายสามารถให้การวินิจฉัยว่าเป็นมะเร็งปาก มดลูก โดยการตรวจ Papanicolaou smear ส่วนที่เหลือ 52 ราย ไม่สามารถให้การวินิจฉัยได้ คิดเป็นผล ลบลวงร้อยละ 26.81 ซึ่งเป็นผลมาจาก sampling error 43 ราย ที่เหลืออีก 9 ราย เป็นผลจาก screening และ interpretation error.

Since the introduction of cervical cytologic screening by George Papanicolaou in 1943, much has been written about the accuracy, sensitivity, and specificity of the smear. The rate of false negative examination varies from 1.5% to 55.5%,<sup>(1-9)</sup> and this may result from sample errors (lack of diagnostic cells in the specimen obtained) or observer errors (overlooked or misinterpreted by the examiner).<sup>(6,10-12)</sup> However, according to Stafland co-workers, the true false negative rate is difficult to determine since a cervix that is clinically normal and has a negative cytologic smear is usually not examined further.<sup>(13)</sup>

The purpose of this study was to evaluate the occurrence of false negative smears in women with cancerous lesions of the uterine cervix.

### Materials and Methods

All tissue-proven cases of cervical malignancy (carcinoma in situ, microinvasive, and invasive carcinoma) diagnosed at cytological unit, Obstetrics-Gynecological Department, Chulalongkorn Hospital from 1 January 1992 to 31 December 1992 were reviewed. Tissue diagnoses were obtained by biopsy, conization, hysterectomy or a combination of these.

Papanicolaou smears were obtained by staffs, residents and medical students using a circumferential cervical scrape with a Plastic (Ayre) spatula. Slides were immediately fixed in 95% ethanol and stained by the Papanicolaou method. All smears were initially evaluated by cytotechnologists then all "other than normal" smears were re-examined by our-staffs of cytopathological unit. Negative smears were not rescreened, except for 10% selected at random as part of the quality control rescreening procedure. Cytologic reports were classes as follows: class I and II, no or slight abnormalities ; class III, suspicious (correspond with mild to moderate dysplasia); class IV, very suspicious (correspond with severe dysplasia or carcinoma in situ); class V positive (correspond with invasive carcinoma). If the smear contained no endocervical cells or too heavy concentrates of cells obscuring epithelial cells and contents, we classified as unsatisfactory smear.

After obtaining the clinical and pathological data, cytologic materials were obtained from the cytologic files and were reviewed by the authors. To analyse the validity of the smears, cytologic classification was arranged into two categories. The smears of which the reports requested an immediate repeat smear or a histologic examination (class III to V) were considered to be positive and those smears of which the reports recommended follow up yearly or 2-3 months interval (class I and II) were considered to be negative. Unsatisfactory smears were also considered to be negative. False negative cases (incorrectly recognized persons with diseases) were placed in the following causes : sampling error (no malignant or dysplastic cells found on review), screening error (malignant or dysplastic cells present but not marked by cytotechnologist), and interpretation error (malignant or dysplastic cells present but not marked by our staffs).

### Results

The study period examined 291 cases of invasive and microinvasive cervical carcinoma and 39 cases of carcinoma in situ. Review of the patient's records and cytologic files disclosed that only 194 cases had documented cytologic smears. The remaining cases may have undergone cytologic evaluation by referring physicians or outside facilities, but the results were not available for review.

For 194 cases, the original and review cytologic diagnosis are given in Table 1. There were 142 smears (73.19%) which could be diagnosed in the original smears (class III to V). The remaining 52 cases (26.81%) were classified as false negative. It was apparent that the majority of errors were due to the sampling method. In 43 cases (82.69% of false negative cases), a review of the smears did not indicate dysplastic or malignant cells. Nine smears (17.31% of false negative cases) were determined to be screening errors. Interpretation errors accounted for three cases (5.77% of false negative cases) in which our cytotechnologist and staffs did not recognize the dysplastic or malignant cells.

**Table 1.** Outcome of Review of 194 Cervical Smears.

Original Cytologic Diagnosis		Cytologic Diagnosis Following Review					Total	
		Unsatisfactory	Class I	Class II	Class III	Class IV		Class V
Unsatisfactory		11 <sup>a</sup>	-	-	-	1 <sup>b,c</sup>	-	12
Class	I	2 <sup>a</sup>	15 <sup>a</sup>	1 <sup>a</sup>	5 <sup>b</sup>	1 <sup>b</sup>	-	24
Class	II	-	-	14 <sup>a</sup>	2 <sup>b,c</sup>	-	-	16
Class	III	-	-	-	97	1	1	99
Class	IV	-	-	-	-	17	-	17
Class	V	-	-	-	-	-	26	26
<b>Total</b>		<b>13</b>	<b>15</b>	<b>15</b>	<b>104</b>	<b>20</b>	<b>27</b>	<b>194</b>

a Sampling error (no malignant or dysplastic cells upon review)

b Screening error (malignant or dysplastic cells present but not marked by cytotechnologist)

c Interpretation error (malignant or dysplastic cells present but not marked by staff)

## Discussion

Cervical cytology has become one of the standard screening procedures in the practice of Obstetrics and Gynecology,<sup>(14,15)</sup> but there is some question about the

accuracy of the Papanicolaou smear for predicting cervical dysplasia or cancer. Therefore, numerous estimates are found in the literature for the false negative rate of Papanicolaou smears (Table 2).

**Table 2.** Reported Estimates of False Negative Rates for Papanicolaou Smears.

Study	False Negative Rate (%)
Richard & Vaillant (1965) <sup>(7)</sup>	6.0
Tuncer et al (1967) <sup>(9)</sup>	14.6
Figge et al (1970) <sup>(3)</sup>	17.6
Coppleson & Brown (1974) <sup>(2)</sup>	20-45
Berkowitz et al (1979) <sup>(1)</sup>	55.5
Gay et al (1985) <sup>(4)</sup>	20
Graaf et al (1987) <sup>(5)</sup>	5-11
Pairwuti (1990) <sup>(6)</sup>	1.5
Soost et al (1991) <sup>(8)</sup>	17.7-18.6
Kristensen et al (1991) <sup>(16)</sup>	13.5-30

To approximately determine false negative cytologic results, several methods may be used.<sup>(8,12)</sup> One is the comparison of all cytologic findings with the data in a complete cancer registry such as exists in only a few countries.<sup>(5)</sup> A second method is the systematic re-examination of a large group of screened women; for example, three months after the first examination.<sup>(3,11)</sup> Another possible method is the retrospective review of previous smears in cases of histologically proven carcinoma or

carcinoma in situ. This last method has been used by several groups<sup>(1,4,6-9,16)</sup> and was used in this study also.

In our study, the false negative rate (26.81%) was not much different from previous studies. It also disclosed that the false negative rate may result from sampling errors (82.69%) and screening-interpretation errors (17.31%). The high sampling error rate can be explained by numerous reasons.<sup>(4,11,12,16,17)</sup> If the clinicians scrape too strong or deep, the epithelial cells or abnormal cells may be hidden

by the numerous white or red blood cells. Otherwise, if it is done too lightly, only surface cells will be procured and only the overlying infection will be diagnosed, not the underlying cancerous or precancerous lesions.<sup>(4,6,18)</sup> Husain et al<sup>(11)</sup> described that 75% of the smears taken from cases of invasive carcinoma have been found to be unsatisfactory due to necrotic tissue preventing exfoliation and numerous red or white blood cells. Other explanations are small or inaccessible lesions, trapped cells on wooden spatulas, and washed or douched vagina by the patients before examination.<sup>(14,18-20)</sup> In order to decrease the sampling error, the endocervical scrape should be fairly strong and a punch or colposcopic biopsy should be performed if a cancerous lesion is clinically suggested.<sup>(6,11,21)</sup>

Effective ways to reduce screening and interpretation errors are good supervision and training of the cytotechnologist staff, a maximum workload of 25 to 30 smears daily, interlaboratory and intralaboratory exchange of slides with abnormalities, descriptive term reports, such as the Bethesda system for cervical cytologic diagnosis, and continuing education.<sup>(6,11,12,19,22)</sup>

In summary, the authors have found a high false negative rate in the Papanicolaou smears of patients with cancerous lesions. This does not mean that Papanicolaou smears should be abandoned. The false negative rate can be reduced by improving the method of taking cytological samples and by using cytological diagnostic procedures as described above.

## References

1. Berkowitz RS, Ehrmann RL, Lavizzo-Mourey R, Knapp RC. Invasive cervical carcinoma in young women. *Gynecol Oncol* 1979 Dec;8(3):311-6
2. Coppleson LW, Brown B. Estimation of the screening error rate from the Observed detection rates in repeated cervical cytology. *Am J Obstet Gynecol* 1974 Aug; 119(7):953-8
3. Figge DC, Bennington JL, Schweid AZ. Cervical cancer after initial negative and atypical vaginal cytology. *Am J Obstet Gynecol* 1970 Oct;108(3):422-8
4. Gary JD, Donaldson LD, Goellner JR. False negative results in cervical cytologic studies. *Acta Cytologica* 1985 Nov-Dec; 29(6):1043-6.
5. Van der Graaf Y, Vooijs GP. False negative rate in cervical cytology. *J Clin Pathol* 1987 Apr;40(4):438-42
6. Pairwuti S. False negative papanicolaou smears from women with cancerous and precancerous lesions of the uterine cervix. *Acta Cytologica* 1991 Jan-Feb;35(1):40-46
7. Richart RM, Vaillant HW. Influence of cell collection techniques upon cytological diagnosis. *Cancer* 1965 Nov;18:1474-8
8. Soost HJ, Lange HJ, Lechmacher W and Ruffing-Kullmann B. The validation of cervical cytology: sensitivity, specificity and predictive values. *Acta Cytologica* 1991 Jan-Feb;35(1):8-14
9. Tuncer M, Graham R, Graham J. Diagnostic efficiency in invasive cervical cancer. *New York J Med* 1967 Sep 1;67(17):2317-9
10. Gay D, Danos LM, Goellner JR. Analysis of false negative cervical cytology at the Mayo Clinic during a four-year period. *Acta Cytologica* 1985 Nov-Dec;29(6):652
11. Husain OAN, Butler EB, Evans DMD, Macgregor JE, Yule R. Quality control in cervical cytology. *J Clin Pathol* 1974 Dec; 27(12): 935-44
12. Lundberg G.D. Quality assurance in cervical cytology the papanicolaou smear. *JAMA* 1989 Sep 22;262(12):1672-9
13. Stafil A, Friedrich Jr EG, Matting RF. Detection of cervical neoplasia : reducing the risk of error. *CA* 1974;24(1):22-30
14. Morell ND, Taylor JR, Snyder RN, Ziel HK, Saltza A, Willie S. False Negative cytology rates in patients in whom invasive cervical cancer subsequently developed. *Obstet Gynecol* 1982 Jul;60(1):41-45
15. Reagan JW, Scott RB. The detection of cancer of the uterine cervix by cytological study. *Am J Obstet Gynecol* 1951 Dec;62(6):1347-52
16. Kristensen GB, Skyggebjerg KD, Holund B, Holm K, Hansen MK. Analysis of cervical smears obtained within three years of the diagnosis of invasive cervical cancer. *Acta Cytologica* 1991 Jan-Feb;35(1):47-50
17. Frost JK. Diagnostic accuracy of cervical smears. *Obstet Gynecol Surv* 1969 Jul;24(7pt2):893-908
18. Rubio CA. False negative in cervical cytology. Can They be avoided? *Acta Cytologica* 1981 Mar-Apr;25(2):199-202
19. Vander GY, Vooijs GP, Gaillard HLJ, Go DMP. Screening errors in cervical cytologic screening. *Acta cytologica* 1987 Jul-Aug;31(4):434-8
20. Rubio CA. The false negative smear. *Am J Obstet Gynecol* 1974 May 15;119(2):273
21. Cecchini S, Palli D, Casini A. Cervical intraepithelial neoplasia III: an estimate of screening error rates and optimal screening intervals. *Acta Cytologica* 1985 May-Jun; 29(3):329-33
22. Gad C, Koch F. The limitation of screening effects. A review of cervical disorders in previously screened women. *Acta Cytologica* 1977 Nov-Dec;21(6):719-22