A Comparison of the Reliability of Repeat Cervical Smears and Colposcopy in Patients with Abnormal Cervical Cytology

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Background. To determine the reliability of repeat cervical smears (Papanicolaou smears) in patients who have had an abnormal initial smear, prospective data were collected on patients being followed up for a previously abnormal cervical smear.

Methods. All 428 patients who were referred for colposcopy because of abnormal cervical smears underwent simultaneous cervical smears and colposcopy with directed biopsy. Patients with colposcopic evidence of invasive carcinoma or a history of prior colposcopy were excluded. Cervical smear results were compared with the histologic findings on colposcopically directed biopsy. The ability of cervical smears to identify cervical intraepithelial neoplasia (CIN) and high-grade lesions (CIN 2 and 3) were also calculated for the repeat cervical smear.

Results. The sensitivity of repeat Papanicolau screening for CIN was 48%. When differentiating high-grade lesions from low-grade and benign biopsies, the sensitivity of the repeat cervical smear was only 25%. Of 110 patients with biopsy-proven high-grade lesions, 68% had low-grade initial cervical smears and 73% had low-grade or benign repeat cervical smear cytology.

Conclusions. This study demonstrates that repeated Pap smears often fail to identify high-grade lesions and that the sensitivity of a repeat cervical smear is very low in patients with low-grade abnormalities found on routine screening examinations. Using follow-up cervical smears to monitor patients who have low-grade squamous intraepithelial lesions (LGSIL) carries unacceptable risks. A more reliable diagnostic test such as colposcopy is indicated.

Key words. Vaginal smear; colposcopy; cervical intraepithelial neoplasia; neoplasms, squamous cell; diagnostic errors. (*J Fam Pract 1995; 40:57-62*)

Routine cervical smear screening (Papanicolaou [Pap] smears) to identify cervical intraepithelial neoplasia (CIN) in the general population has been shown to be cost-effective and to lower the incidence of invasive cervical cancer.[1] It has become common practice in the United States to follow up abnormal cervical smears with colposcopy and directed biopsy to define the level of CIN or to detect the presence of invasive carcinoma.[2,3] Some researchers, however, have demonstrated a high regression rate of cervical low-grade squamous intraepithelial lesions (SILs).[4–9] This finding has led to controversy about whether to treat or to closely follow these lesions. Some authors advocate the use of repeat cervical smears as a follow-up for patients with low-grade SIL found on screening cervical smears.[10,11] Other experts recommend always using colposcopy to provide a tissue diagnosis and to determine the extent of lesions.[2,12–16]

The use of Pap smears to follow patients who have had previously abnormal low-grade cervical smears essentially changes the role of the test from a screening method for detecting the presence of CIN to a diagnostic test for

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identifying high-grade histologic lesions based on cytologic evaluation. The cervical smear is considered to have an adequate, if not good, sensitivity for routine screening for CIN in the general population, but it is generally not considered sensitive enough to be a diagnostic test. Part of the argument in the scientific literature concerning screening intervals for the cervical smear revolves around the necessity for repeated smears to overcome the test's lack of sensitivity. General assumptions concerning the efficacy of the cervical smear as applied to routine screening in the general population may not be accurate when used as a diagnostic test to separate patients with high-grade from those with low-grade or benign histologic lesions. This study examined the accuracy and usefulness of repeat cytologic evaluation by comparing findings from repeat Pap smears with results from simultaneous colposcopically directed biopsies in a series of patients referred for abnormal cervical smears on routine screening.

Methods

Since the inception of the colposcopy program in the Department of Family Practice at Louisiana State University Medical Center in Shreveport, data have been collected for all patients undergoing this procedure. This study was approved by the university institutional review board. The patients referred for colposcopy were from the university's Family Practice Center, the Comprehensive Care Clinic (a large continuity clinic for student teaching), local fee-for-service clinics, and the county health unit. The usual interval between initial cervical smear (initial cytologic evaluation) and follow-up was 1 to 6 months. All patients with a cervical smear showing evidence of SIL, any form of atypia, or a second inflammatory smear result after treatment were routinely referred for colposcopy. Patients found on referral to have colposcopic evidence of invasive cancer were referred to the Gynecology Oncology Service without biopsy or further workup and were excluded from the study. Pregnant patients were also excluded.

All cervical smears were obtained with the Unimar Cervex Brush (Unimar Inc, Wilton, Conn) using the standard collection protocol recommended by the manufacturer in the product's package insert, and were placed on a single slide for analysis. All Pap smears performed at the time of colposcopy (repeat cytologic testing) were interpreted by the staff of the university's pathology department. Smears were first examined by cytotechnologists. All abnormal smears, all normal smears in patients with a previously abnormal smear, and one in 10 of all smears previously examined were reinterpreted by a pathologist. This protocol meets criteria for cervical smear quality control as defined by the Centers for Disease Control and the American Society of Cytology.[2,17] All cervical smears were reported using the Bethesda System.[18,19]

In the study institution's Department of Family Practice, colposcopy is always performed either by colposcopically trained faculty or by second- and third-year medical residents under the direct supervision of faculty using video colposcopy. Each examination in this study included a visual inspection of the perineum, vagina, and cervix, and any necessary wet preparations and cultures. The cervix was then examined for leukoplakia, and a cervical smear was obtained. Acetic acid 5% was applied, and all acetowhite lesions were noted. Lugol's solution was sometimes applied to further define abnormalities. After the entire transformation zone had been adequately examined, an endocervical curettage was performed, and directed biopsies were taken from the most abnormal-appearing areas of all lesions.

All patients referred for colposcopy to the university's Family Practice Center between August 1989 and June 1993 were considered for this study. Only patients with single, first-time colposcopies who were referred because of abnormal cytologic smears were included. Eleven patients with colposcopic findings of invasive carcinoma or inadequate colposcopies also were excluded, leaving a study population of 453 patients who had been referred for colposcopy for the first time for an abnormal cervical smear.

The results of the initial and the repeat cytologic evaluations were compared. Findings on repeat cytologic evaluation were compared with the colposcopically directed cervical biopsy results (colpopathologic findings). Sensitivity, specificity, and predictive values were calculated using methods described by Campion and Reid[1] and Soost et al.[20] Correlation coefficients were calculated between the initial and repeat cytologic findings and the colposcopic biopsy results.

To evaluate the reliability of using repeat cervical smears to separate patients with high-grade SIL (HGSIL) from those with low-grade SIL (LGSIL), calculations were repeated, with both repeat cytologic and biopsy LGSIL results included in the "negative" group. This arbitrary classification was necessary to calculate the cervical smear's ability to identify patients with high-grade lesions and to test this unconventional use of cervical cytologic smears. This approach is consistent with recommendations that the grade of cytologic abnormality be used to guide patient management decisions; ie, use repeat cervical smear to follow LGSIL and use colposcopy with biopsy for HGSIL.[11]

In an attempt to establish the types of errors asso

Table 1. Results of Initial and Repeat Cervical Smears

Cytologic Finding	All Patients		Patients with Biopsy-Proven High-Grade Cervical Lesions		
	Initial Smear n (%)	Repeat Smear n (%)	Initial Smear n (%)	Repeat Smear n (%)	Repeat Smear with Low-Grade Initial Cytologic Finding,* n (%)
Normal	0 (0)	184 (41)	0 (0)	26 (24)	17 (23)
Inflammation	17 (4)	92 (20)	5 (5)	18 (16)	14 (19)
Atypical	17 (4)	6 (1)	3 (3)	1 (1)	1 (1)
LGSIL	337 (74)	122 (27)	67 (61)	38 (35)	33 (44)
HGSIL	82 (18)	47 (10)	35 (32)	27 (25)	10 (13)

**Repeat cytologic evaluation was conducted for patients with low-grade squamous intraepithelial lesion, atypia, or persistent inflammation found on initial cytologic examination. LGSIL denotes low-grade squamous intraepithelial lesion; HGSIL, high-grade squamous intraepithelial lesion.*

ated with cervical smears in this selected population, repeat cervical cytologic smear slides of all biopsy-proven high-grade lesions were reviewed by one of the authors, a pathologist who regularly reads cytologic smears at the study institution. Any questionable smears were read by two additional pathologists, who were blinded to patient identity. Any one of the pathologists may have read some of the slides previously. The percentage of cytologic interpretation errors and sampling limitation errors was calculated. Statistics were performed using Microsoft *Excel*, Version 4, and SAS, Version 6.04.

Results

The study included a total of 453 patients with a mean age of 26 years (range, 15 to 73 years). Most (77%) of the women were aged 30 years or younger. Two patients had inadequate repeat cervical smears, and their follow-up smears were not available. Seven patients had inadequate colposcopies that required referral for further follow-up, and the records of 16 other patients could not be obtained, leaving 428 participants for reliability calculations. Results of both the initial and repeat cervical cytologic smears and the cytologic results for the 110 patients with biopsy-proven high-grade lesions are shown in Table 1.

Table 2 shows the association between results of the repeat cervical smear and simultaneous colposcopy. The calculated sensitivity, specificity, positive predictive value, and negative predictive value of the repeat cervical smear, when using the test to screen for all CIN and to detect high-grade lesions, are shown in Table 3. The calculated sensitivity for this population was 45% when screening for all CIN. When differentiating high-grade from low-grade and benign lesions, the sensitivity of the repeat cervical smear (as measured against the reference standard of histologic evaluation of directed biopsy) was only 25%. The specificity of the repeat cervical smear was found to be 80% when the test was used to screen for CIN and 94% when it was used to detect high-grade lesions. The positive predictive value of the repeat cervical smear in delineating high-grade lesions was only 60%; the negative predictive value was 78%.

Of the 428 patients, high-grade lesions were found by colposcopically directed cervical biopsy in 110 patients (Table 1). Of these 110 biopsy-proven high-grade lesions, 75 patients (68%) had low-grade initial cervical smears and 83 (75%) had low-grade or benign repeat cervical smears. Of the 75 patients with biopsy-proven high-grade lesions and low-grade initial smears, only 10 (13%) had high-grade repeat cervical smears, whereas 65 (87%) had low-grade or benign repeat cervical cytologic findings at the time of colposcopy.

Of the 83 patients who had biopsy-proven high-grade lesions with low-grade or benign repeat cervical

Table 2. Results of Repeat Cervical Smear Cytologic Examination and Colposcopic Cervical Biopsy, Both Performed at the Time of Colposcopy

Cervical Smear Cytologic Finding	Biopsy Results, No.						
	Normal	Inflammation	Condyloma	CIN 1	CIN 2	CIN 3	Total
Normal	26	32	43	44	16	10	171
Inflammation	11	10	19	30	13	5	88
Atypical	1	0	1	3	0	1	6
LGSIL	6	10	32	32	22	16	118
HGSIL	2	1	5	10	15	12	45
Total	46	53	100	119	66	44	428

CIN denotes cervical intraepithelial neoplasm; LGSIL, low-grade squamous intraepithelial lesion; HGSIL, high-grade squamous intraepithelial lesion.

Table 3. Sensitivities, Specificities, and Predictive Values of Repeat Cervical Smears Using Colposcopy-Directed Biopsy as the Standard

Value	Repeat Cervical Smears (N=428) To Screen for All CIN, %	To Detect High-Grade Lesions, %
False-negative	42	19*
True-negative	18	70*
True-positive	35	6
False-positive	5	4
Sensitivity=TP/(TP+FN)	45	25
Specificity=TP/(TP+FP)	80	94
PPV=TP/(TP+FP)	88	60
NPV=TN/(FN+TN)	31	78

**Low-grade squamous intraepithelial lesions are not technically negative smears, but for the purpose of calculations to assess using cervical smears to detect high-grade lesions, they are included as negatives here.*
CIN denotes cervical intraepithelial neoplasia; TP, true-positive; FN, false-negative; FP, false-positive; TN, true-negative; PPV, positive predictive value; NPV, negative predictive value.

smears, repeat cervical smear slides were available for 66 patients. Following review of these slides by a pathologist, five (8%) were marked as possible high-grade lesions. These slides were then reviewed by two additional pathologists, who determined that the lesions should have been classified as HGSIL. These misinterpretations were termed reading errors. The other 61 (92%) of the cervical smears were found to have been appropriately interpreted.

Discussion

The low sensitivity and predictive values of repeat Pap smears found in this study raise serious questions about using this test alone to follow up patients with previous low-grade cervical lesions. The findings are compatible with those of previous smaller studies which demonstrate that the sensitivity of the cervical smear when screening for CIN after a previously abnormal cervical smear is lower than when used for routine screening in a general population.[15,21] Of the patients in this study with biopsy-proven CIN 2 or 3, 68% had been referred for low-grade, atypical, or persistent inflammatory cytologic findings on their initial routine cervical smears. When a cervical smear was repeated on the patients with high-grade lesions, 87% still did not have high-grade cytologic results, and 23% of these repeat cervical smears were normal. If these patients had been followed with only repeat cervical smears instead of colposcopy, it would have appeared that 23% of the lesions had regressed, and most of the others would have been erroneously classified as having low-grade lesions. This approach would have caused an unacceptable treatment delay in these patients. The diagnostic test (colposcopy) is a much better choice for the management o these patients.

These results suggest that factors causing the false-negative findings on the initial cytologic test also ma cause the repeat examination to underestimate the sever ity of the lesions. Sampling limitations have been shown to cause the majority of false-negative smear results and were responsible for 93% of the false-negative interpreta tions of repeat smears in this study.[22,23] Sampling prob lems may have occurred for any of several reasons: loca tion of the lesions high in the endocervical canal, low shedding of lesion cells, or obstruction of the lesion sur face by debris. These problems or others that have not yet been defined can produce errors in screening that could be carried over in subsequent smears, making the repeat cervical smear unreliable for follow-up of patients with abnormal cytologic findings.

Our study demonstrated a higher proportion o high-grade lesions on biopsy than have many previous studies. This finding may be because our study populatio consisted of young, sexually active, high-risk patients wh are more likely to develop CIN and to have aggressiv disease. This factor should not lower the estimates o sensitivity in the study, however, since it has been shown that sensitivity increases with increasing CIN severi ty.[20,24,25] The patient population in our study is probabl more representative of urban populations in the United States than are studies involving the populations of Ger many,[20] Jamaica,[26] and Glasgow County, Scotland,[which are often quoted in the scientific literature.

Atypia and inflammation are two cervical smear re sults that elicit strong controversy regarding implication and appropriate management. Although some studie show only a minor association, most authors agree tha there is a significant association between atypical smear and the presence of CIN.[7,16,27–29] The results of th present study underscore this association since 67% o patients with atypical smears were found to have CIN o biopsy. Inflammation, conversely, has been shown t have a lower association with underlying CIN unless it persistent.[16,27] In the present study, more than one half o the 17 patients with inflammatory cervical smears demon strated CIN on biopsy. From repeat cytologic examina tion of 110 patients with biopsy-proven high-grade le sions, inflammation was found in 18. Patients wit persistent inflammation should be considered for colpo copy.

A major problem with the present study is that i does not assess the accuracy of multiple screening tests o the same patient over time. Such a study would be diffi cult, because colposcopy with directed biopsy affects th evolution of the disease. Any biopsies performed coul alter the results of subsequent cervical smears and th

natural progression of the disease.[2,30,31] Studying patients with only cervical smears and no biopsy also would introduce error related to the false-negative rate and lowered sensitivity of the repeat cervical smear, as demonstrated in this study.

Our study does not address the possibility that colposcopically directed biopsy itself may underestimate the severity of some lesions. Buxton et al[32] compared loop-electrical excision procedure (LEEP) biopsies with colposcopically directed punch biopsies in 243 women and found that the punch biopsy underestimated the severity of the lesion 47% of the time. Howe and Vincenti[33] conducted a similar study on 100 women and found that 24% of biopsies underestimated the severity of lesions. This effect may have caused the estimate of high-grade lesions to be lower than it actually was.

The cervical smear has been hailed as "perhaps the only effective screening test for cancer today."[2] The purpose of this screening test as defined by Koss[2] and others[3] is to detect occult small carcinomas and precancerous lesions (CIN) that may lead to invasive cancer. For a screening test to be effective, it must be sufficiently sensitive to detect disease in a stage that can be treated effectively enough to improve prognosis, sufficiently specific to distinguish nonpathological conditions, cost-effective, acceptable to patients, and simple enough to use.[14,24] The cervical smear has been shown to meet all these criteria when screening for occult carcinomas and CIN, provided that the screening interval is frequent enough to overcome the test's relatively low sensitivity.[2,3,24] This study demonstrates that monitoring patients with low-grade cervical smears by using follow-up cervical smears is not advisable and is potentially dangerous because of the unacceptably low (25%) sensitivity of the follow-up cervical smear. The study also supports the contention that, as with all screening tests, a diagnostic test such as colposcopy with appropriate management is necessary.[14]

Conclusions

Although the Pap smear is an effective screening tool to detect CIN in the general population, the results of our study raise concerns about using repeat cervical smears to follow up low-grade cytologic findings. These concerns are even greater when the cervical smear is used to select follow-up based on the presence or absence of high-grade SIL. Because the cervical smear is a screening test with inherent limitations, any degree of CIN warrants performing colposcopy with endocervical curettage and directed biopsy for the purpose of diagnosis. Once the histologic grade of the lesion has been determined using colposcopically directed biopsy, the patient can be appropriately triaged for therapy and follow-up.

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