Papanicolaou Smear Discrepancy: Resolution By Review

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Background: **Discrepancy between Papanicolaou smears and colposcopically directed biopsies often creates a treatment dilemma, especially when the cytologic specimen suggests a higher grade lesion than the histologic specimen. A method of side-by-side review using the Bethesda System was evaluated as a means of resolving this discrepancy between cytologic and histologic specimens.**

Methods: **By means of a retrospective chart review, we selected 150 patients undergoing colposcopic evaluation for abnormal cytologic findings. Thirty-eight patients had higher grade lesions on cytologic examination than on histologic examination. Twenty-four of these patients had both cytologic and histologic slides available, and these specimens were evaluated in a blinded review by a single pathologist using the Bethesda System of classification.**

Results: **Reevaluation yielded resolution of discrepancy in 19 of 24 cases, a 79.2 percent resolution.**

Conclusion: **Review of cytologic and histologic specimens by an experienced pathologist using the Bethesda System can resolve many of the cases in which the cervical lesion is considered to be of a higher grade by cytologic examination than by histologic examination. (J Am Board Fam Pract 1994; 7:9-13.)**

A number of studies in the past 50 years have determined that Papanicolaou smears are an effective screening tool for detection of cervical cancer. The Papanicolaou smear is only a screening test, however, and screening errors for precancerous lesions have exceeded 28 percent in some studies.[1] Colposcopic examination and biopsy of the cervix have become the accepted method of evaluating the condition of the cervix when atypia or dysplasia are detected by cytologic examination. When cytologic and histologic specimens show the same degree of atypia or cervical intraepithelial neoplasia, management can proceed based upon the results. In 13 to 50 percent of cases there is discrepancy between cytologic samples and histologic specimens,[2] often necessitating repeat biopsies or conization. An initial review of the results of the first 150 colposcopic examinations at a family practice residency program revealed a level of discrepancy between cytologic and histologic findings similar to that found in previous studies.

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Discrepancy between cytologic and histologic specimens fits into two separate groups: cytologic findings that reveal a higher grade lesion than histologic specimens, or cytologic findings that reveal a lower grade lesion than histologic specimens. In the latter group, treatment can proceed based upon the histologic findings, as the implication is that the Papanicolaou smear (the screening tool) missed the area of the cervix that had the highest grade lesion, but the more directed colposcopic biopsy sampled this area. For the first type of discrepancy, in which the cytologic specimen shows a higher grade lesion than does the histologic specimen, treatment cannot be based upon histologic findings, as the cytologic results imply that the worst lesion on the cervix was missed on colposcopy, and further evaluation is needed.

In the subset of cases for which lesions on cytologic examination were of a higher grade than the findings on histologic examination, a system of decreasing this level of discrepancy by reevaluation of these cases using the Bethesda System[3] is tested and discussed.

Methods

From June 1988 to June 1991, 150 patients were referred to the Anderson Family Practice Center for colposcopy because of abnormalities found on

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Papanicolaou smear (either two smears 3 to 6 months apart with persistent atypia or a single smear with cervical intraepithelial neoplasia [CIN] I, II, or III). Patients were referred from the Anderson County Health Department or from within the practices of family practice faculty and residents at Anderson Memorial Hospital. For health department patients, the initial cervical smears were done by a nurse practitioner and interpreted by an outside cytology laboratory (before 1 June 1989) or by cytologists at Anderson Memorial Hospital (after 1 June 1989). Patients referred from family practice faculty and residents had their cervical smears done by the family practice resident and interpreted by cytologists at Anderson Memorial Hospital. Colposcopies were performed by residents supervised by attending obstetrician-gynecologists or family physicians who had special training in colposcopy, and the biopsy specimens were interpreted by pathologists at Anderson Memorial Hospital.

Patients' charts were located by patient schedules, and all 150 records were reviewed for results of Papanicolaou smears and colposcopically directed biopsies. The subgroup of patient specimens with cytologic findings revealing a higher grade lesion than that determined by histologic examination was selected for intensified review, and these specimens were retrieved by pathologic specimen number. A single pathologist, blinded to the previous interpretation of these specimens, as well as patient identity, reviewed each of the specimens using the Bethesda System of classification. The results were then compared.

To provide a control group, specimens from an equal number of patients with equivalent cytologic and histologic findings were also selected and resubmitted to the same pathologist for review using the Bethesda System, thus providing information on intraobserver reliability.

Results

From a total of 150 patients, the histologic and cytologic samples were of equivalent grade in 76 (50.7 percent). In 36 (24.0 percent) the histologic sample showed a higher grade lesion than the cytologic sample, while in 38 (25.3 percent) the cytologic sample revealed a higher grade lesion than the histologic sample (Table 1). The specimens from the latter group of patients were selected for further evaluation because of the implication that the colposcopically directed biopsy had missed the highest grade area on the cervix that had been detected by cytologic examination.

Table 1. Comparison of Initial Cytologic and Histologic Findings on Cervical Specimens for 150 Patients.

Result	Number (Percent)
Histologic and cytologic findings equivalent	76 (50.7)
Histologic finding of higher grade than cytologic specimen	36 (24.0)
Histologic finding of lower grade than cytologic specimen	38 (25.3)

Of these 38 patients, 24 had both the cytologic and histologic specimens available for review in Anderson (14 patients had their cervical smears evaluated by an out-of-state laboratory before June 1989). On blinded review of the cytologic and histologic specimens of these 24 patients using the Bethesda System, 19 of 24 had cytologic and histologic specimens that were equivalent, thus resolving the discrepancy (Tables 2 and 3). In the remaining five cases the discrepancy was not resolved by further review. Thus, review by a single pathologist using the Bethesda System resolved 19 of 24 cases (79.2 percent) in which the cytologic examination had previously revealed a higher grade lesion than the histologic examination.

In the control group of 24 patients with an equivalent grade of cytologic and histologic findings, blinded review by the same pathologist yielded 23 equivalent specimens with 1 specimen having discrepancy on review (Table 4), for a 4.2 percent rate of variation by the reviewing pathologist on previously equivalent samples.

Discussion

Discrepancy between cervical smear samples and biopsy samples is common; in fact, strict agree-

Table 2. Reinterpretation of 38 Cases with Histologic Findings of Lower Grade than Cytologic Findings.

Result	Number
Cytologic specimens unavailable*	14
Histologic and cytologic specimens available	24
Discrepancy resolved by review	19
Discrepancy unresolved	5

*Specimens taken before June 1989 were unavailable.

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Table 3. Original Findings and Review Cytologic and Histologic Results of Patients Whose Cervical Specimens Were Discrepant.

Patient	Original Cytology	Original Histology	Review Cytology	Review Histology
1	CIN II	CIN I	SIL low	SIL low
2	CIN II	CIN I	SIL low	SIL low
3*	CIN I	Atypia	SIL low	Atypia
4	CIN I	KA	SIL low	SIL low
5	CIN I	KA	SIL low	SIL low
6	CIN I	KA	SIL low	SIL low
7*	KA	Neg	SIL low	Neg
	KA	Neg	SIL low	Neg
8	CIN II	CIN I	SIL low	SIL low
9	CIN I	KA	SIL low	SIL low
10	CIN II	CIN I	SIL low	SIL low
11*	CIN I	Neg	SIL low	Neg
12	CIN II	CIN I	SIL low	SIL low
13†	CIN I	Atypia	SIL low	Neg
	CIN I	KA	SIL low	SIL low
14	CIN I	KA	SIL low	SIL low
15*	CIN I	KA	SIL low	SIL low
	CIN I	Neg	SIL low	Neg
16	CIN I	KA	SIL low	SIL low
17*	CIN II	CIN I	SIL high	SIL low
18	KA	Inflam	Inflam	Inflam
19	CIN I	KA	SIL low	SIL low
20	CIN I	KA	SIL low	SIL low
21	CIN I	KA	SIL low	SIL low
22	CIN II	CIN I	SIL low	SIL low
23	CIN II	KA	SIL low	SIL low
24	Atypia	Inflam	Inflam	Inflam

*Discrepancy not resolved by review.
†Discrepancy resolved by review on repeat cytologic and histologic specimens.
CIN = cervical intraepithelial neoplasia, SIL = squamous intraepithelial lesion, KA = koilocytotic atypia, Neg = negative, Inflam = inflammation (no cause determined).

ment between cytologic and histologic specimens occurs less than one-half the time (Table 5).[4-7] In our study strict agreement occurred in 50.7 percent of patients. When discrepancy occurs, it leaves the physician with the task of deciding on management based upon two differing test results: the screening cervical smear and the more directed colposcopic biopsy.

When the histologic specimen reveals a higher grade lesion than the cytologic specimen, the choice is clear: because the Papanicolaou smear is a random sampling of the entire cervical surface, and cytologic examination is subject to sampling errors often exceeding 28 percent, the more exacting colposcopically directed biopsy specimen should be used as the basis for treatment.

When the cytologic specimen reveals a higher grade lesion than the biopsy specimen, however, the question must be asked, "Did the colposcopist fail to biopsy the worst lesion on the cervix?" Previous investigators have evaluated this discrepancy with repeat Papanicolaou smear and colposcopy, using conization if the discrepancy failed to be resolved and the initial cytologic finding was CIN II or worse.[2]

Although discrepancy can certainly arise based upon sampling error both with Papanicolaou testing and colposcopic biopsy, the next area to consider is at the point of interpretation: could discrepancy between the two specimens be due to variations in evaluation by the cytologist and the pathologist? If so, then side-by-side review using a single pathologist (or referee) could be used to help clarify the situation, as was done in this study. An advantage of this intermediate step is that it could preclude the need for further clinical testing of the patient, potentially saving patient discomfort and time, as well as health care dollars.

In evaluating any discrepancy, the classification of the pathologic specimens must also be considered. Papanicolaou devised a system with 5 classes that was widely adopted in the United States, though its usage varied from one laboratory to another. Additional descriptive terms were added to this classification scheme, such as dysplasia and carcinoma in situ. In the early 1970s, Richart[8] introduced the concept of "cervical intraepithelial neoplasia" (CIN) to replace the former spectrum of classifications of precancerous cervical lesions. There were still variations among different laboratories, and the consensus adopted in Bethesda, Maryland, in December 1988 (the Bethesda System) was created to add uniformity to the procedure of Papanicolaou smear classification. Essentially, it simplified the spectrum of atypia, CIN I, II, and III to atypia, squamous intraepithelial neoplasia (SIL) (low-grade), and SIL (high-grade) for cytologic specimens revealing some epithelial abnormality other than inflammation or carcinoma. This decrease from four categories to three would be expected to decrease the chance of discrepancy by about 25 percent.

Nevertheless, in the language of the Bethesda report, "The cytology report is a medical

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Table 4. Control Group: Original Findings and Review Results of Patients Whose Cervical Specimens Were Not Discrepant.

Patient	Original Cytology	Original Histology	Review Cytology	Review Histology
1	CIN I	CIN I	SIL low	SIL low
2	CIN I	CIN I	SIL low	SIL low
3	CIN I	CIN I	SIL low	SIL low
4	CIN I	CIN I	SIL low	SIL low
5	CIN II	CIN II	SIL low	SIL high
6	CIN II	CIN II	SIL high	SIL high
7	CIN I	CIN I	SIL low	SIL low
8	CIN I	CIN I	SIL low	SIL low
9	CIN I	CIN I	SIL low	SIL low
10	CIN I	CIN I	SIL low	SIL low
11	CIN I	CIN I	SIL low	SIL low
12	CIN I	CIN I	SIL low	SIL low
13	CIN I	CIN I	SIL low	SIL low
14	CIN I	CIN I	SIL low	SIL low
15	CIN I	CIN I	SIL low	SIL low
16	CIN III	CIN III	SIL high	SIL high
17	CIN I	CIN I	SIL low	SIL low
18	CIN I	CIN I	SIL low	SIL low
19	CIN I	CIN I	SIL low	SIL low
20	CIN I	CIN I	SIL low	SIL low
21	CIN III	CIN III	SIL high	SIL high
22	CIN I	CIN I	SIL low	SIL low
23	CIN II	CIN II	SIL high	SIL high
24	Atypia	Atypia	Atypia	Atypia

CIN = intraepithelial neoplasia, SIL = squamous intraepithelial lesion.

consultation," and as with any consultation, there should be communication between the patient's primary caregiver and the consultant. When a single pathologist reviewed our cytologic and histologic samples from the same patient, the discrepancy was resolved in 79.2 percent of the cases, more than would be expected just by the simplification introduced by the Bethesda classification. Only in one-fifth of the patients was further clinical assessment required.

The results of this study are limited by the small number of patients involved, but the percentages of discrepancy found in our first 150 cases are similar to those noted in the data from much larger cohorts (findings reported in Table 5 are based upon strict comparisons of cytologic and histologic results reported by the investigators). Because of these findings, the Department of Pathology at our institution now comments on the side-by-side comparison of all histologic specimens with the patient's most recent cytologic specimen. Although this comparison provides the clinician with all of the information available in terms of choosing proper therapy, it precludes further investigation of discrepancy in a blinded fashion at our institution. Further comparisons with larger numbers of patients at different sites could add support to these results, as well as ascertain prospectively whether side-by-side review could decrease the number of repeat colposcopies and potentially lower costs while maintaining equivalent outcomes (issues that were not addressed in this retrospective study).

A control group was included to address another concern with this type of study: intraobserver reliability. Although large hospitals with many pathologists and cytologists would be expected to have some system for addressing interobserver variations — including spot reviews and inservices — many primary care providers are in a setting where they work with a single pathologist or have the option of requesting a specific pathologist to interpret their biopsies. The 95.8 percent agreement of the review of equivalent cytologic and histologic specimens provides some reassurance that the individual variation in interpreting these samples is small.

Treatment and follow-up were not available for all of the 5 patients with unresolved discrepancy; patients 3 and 11 were treated with cryotherapy and have had negative Papanicolaou tests through 1992. Patients 7 and 17 received cryotherapy and

Table 5. Studies Comparing Grading of Cervical Specimens by Histologic and Cytologic Examination.

Authors and Year	Number of Patients	Histo > Cyto (Percent)	Histo = Cyto (Percent)	Histo < Cyto (Percent)
Fowler, et al., 1980[4]	71	32.3	50.7	16.9
Wetrich, 1986[5]	1607	32.1	47.4	20.5
Chomet, 1987[6]	96	46.9	31.3	20.8
LaPolla, et al., 1988[7]	241	14.1	44.8	41.1
Cline, et al. 1994	150	24.0	50.7	25.3

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did not return for any follow-up. Patient 15 transferred her care to another state before starting any therapy.

With the current epidemic of human papillomavirus and the associated abnormalities that can occur on cervical smears, the number of patients requiring colposcopic evaluation is expected to increase during the next several years.[9] Discrepancy will occur, even with the use of the Bethesda System. This study suggests that by combining use of the Bethesda System with directed side-by-side review of discrepant histologic and cytologic specimens, a portion of the repeat clinical evaluations for test discrepancy could be avoided. At this point, a larger prospective evaluation of this method would clarify its position in current clinical practice.

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