A Comparison of Uterine Cervical Cytology and Biopsy Results: Indications and Outcomes for Colposcopy

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Background. There is some debate in the literature over the proper approach to the patient with a mildly abnormal cervical cytologic finding. One current approach for handling low-grade cytologic abnormalities is to perform colposcopy and biopsy if atypia, human papillomavirus (HPV) changes, or mild dysplasia is noted on cytologic examination. If a Papanicolaou (Pap) smear shows inflammation without atypia, the test is repeated after 3 months, and if inflammation does not clear, colposcopy is performed. This study was undertaken to determine whether the above recommendations are appropriate.

Methods. In a 1-year period, 125 patients underwent colposcopy and biopsy. Results were reviewed and compared.

Results. Of 47 patients with smears showing human papillomavirus (HPV) changes, 68% had a higher grade abnormality (dysplasia) on biopsy; 15% had moderate or severe dysplasia. Of eight patients with atypia, 63% had dysplasia on biopsy. Of 41 patients with mild dysplasia on Pap smear, 37% had moderate dysplasia or higher grade disease on biopsy. Of nine patients with persistent inflammation on cytologic examination, biopsy showed 56% with inflammation, 33% with mild dysplasia, and 11% normal.

Conclusions. Patients who presented with minimal Pap smear abnormalities such as HPV changes or atypia are likely to have a worse histologic diagnosis, with approximately two thirds showing dysplasia. Patients with persistent inflammation are less likely to have dysplasia. The results support our aggressive approach toward minimally abnormal smears and our consideration of inflammation without atypia as a separate and lower risk category.

Key words. Colposcopy; papilloma; cervix dysplasia; vaginal smears. (*J Fam Pract 1994; 38:40–44*)

Most authorities agree that patients with significant abnormalities on Papanicolaou (Pap) smear, such as cervical intraepithelial neoplasia (CIN) or dysplasia, need colposcopic evaluation and biopsy. This is especially true for high-grade cytologic abnormalities such as CIN 2 or CIN 3 (moderate or severe dysplasia). However, there are varying opinions in the literature regarding recommendations for the follow-up of minimally abnormal Pap smears.

The British tend to be more conservative than American authors, typically advocating a repeat smear as follow-up for cytologic atypia. Some recommend cytologic follow-up rather than biopsy for patients with dyskaryotic (dysplastic) cytologic findings. Kirby et al[1] followed 500 women with abnormal smears with mild or moderate dyskaryosis. After a median follow-up of 7 years, 60% had smears reverting to normal or inflammation. Thirty-seven percent, of which 19% were CIN 3 or worse, had undergone biopsy, but the authors recommended conservative management of patients with abnormal smears. Giles et al[2] followed women with mild dyskaryosis by repeat smear. When colposcopy was performed after a single dyskaryotic smear, 31% had a negative biopsy; if two abnormal smear results preceded biopsy, only 10% were negative. Repeat cytologic examination was associated with a 24% false-negative rate, but the authors considered the missed lesions to be of low grade.

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Most authors in the United States focus on the high false-negative rate inherent in cytologic follow-up. Since a patient needs three negative smears to be considered truly negative, there is not only a modest cost inherent in cytologic follow-up with multiple return visits and smears, but also a measurable danger of overlooking a significant lesion. Tabbara et al[3] found that high-grade abnormalities on cytologic examination were predictive of high-grade lesions histologically, but that low-grade cytologic lesions had poor predictive value for either low-grade histologic findings or "low-risk" human papillomavirus (HPV) types. Maggi et al[4] followed patients with CIN 1 with repeat Pap smear and biopsy. The abnormal smear was found to identify a group at increased risk of CIN but could not be relied on to determine disease severity. They found that 20% of patients with a negative repeat smear had CIN at biopsy, and 18% of those with a mildly abnormal smear had a high-grade lesion. They therefore recommended biopsy in management of all patients with a mildly abnormal smear.

Morrison et al[5] studied patients with atypia without dyskaryosis on smear. Of those with atypia, 25% showed CIN on biopsy. All degrees of atypia were found to have a significant association with CIN, and the degree of cytologic atypia could not be used to exclude colposcopic evaluation. The routine use of colposcopy was endorsed for patients with atypical cells either immediately or after a single repeat smear.

Noumoff[6] reviewed a series of patients with smears reported as atypical and divided them into categories of inflammatory atypia, squamous atypia, and endocervical atypia. Those in the latter two groups and those with persistent inflammation underwent colposcopy and biopsy. Twenty-nine percent of the patients were found to have CIN. Of those, in one third the dysplasia was worse than CIN 1, with no statistically significant difference between the three groups as to the incidence of underlying CIN.

Reiter[7] found persistent atypia unassociated with inflammation to be a significant risk for development of CIN (79%). Jones et al[8] investigated patients with atypical but not dysplastic smears with repeat Pap smear, colposcopy, and biopsy. Twenty-five percent had CIN, but repeat Pap smear identified only 17% of the patients with CIN, 20% of whom had high-grade lesions. One half of those with CIN 2 or CIN 3 had a negative repeat Pap smear. Davis et al[9] investigated patients with atypical squamous cells with colposcopy, biopsy, and repeat smear. Eighteen percent had CIN on biopsy, 10% of whom had negative smears. Bolger and Lewis[10] support colposcopy and biopsy for dysplastic smears or smears with HPV changes, citing findings of 39% with histologic changes of CIN 2 or worse when biopsied 8 weeks later. Soutter et al[11] recommended that patients with any degree of dysplasia or persistent atypia at the time a 3-month repeat smear was performed should be referred for colposcopy. In evaluating the conservative approach to mild dysplasia, Campion et al[12] found that 26% of patients with CIN 1 progressed to CIN 3 in 19 months.

For this study, we examined the results of all colposcopic biopsies. The majority of these were performed on the basis of a smear showing a low-grade abnormality.

Methods

In our family medicine residency program and outpatient center, nearly 1000 Pap smears are performed annually. In a 6-month sampling of cytology results, the findings on 14% of smears were reported as something other than negative (excluding nonsignificant comments, such as squamous metaplasia without atypia or atrophy in postmenopausal women) and therefore needed follow-up. Using the protocol previously described for nonpregnant patients, 7.5% of the abnormal smears would definitely need colposcopy and biopsy (dysplasias and HPV changes). The smears with inflammation or reactive nuclei might be followed, but a percentage of these may eventually need to be investigated if changes persist. Overall, approximately 10% of patients screened cytologically may eventually need colposcopic evaluation.

One hundred twenty-five nonpregnant patients referred to our colposcopy service during the year June 1991 to July 1992 were reviewed. All patients had undergone colposcopic examination and colposcopically guided biopsy. All but five, who were examined because of the presence of external condyloma or leukoplakia, had abnormal cervical cytologic findings.

Patients were referred from a variety of sources (family medicine clinic, county health department, university health services), but two cytology laboratories were responsible for reading all smears. Both laboratories use a narrative reporting system; neither has adopted the Bethesda System to standardize reporting. Patients entered this study if a referral for colposcopy was made and a biopsy performed. The few patients who were referred but not biopsied because of lack of indication, eg, metaplasia detected on Pap smear or pregnancy, were not included in this study. Patient cytologic results were compared with results on colposcopically directed biopsies. The patients were grouped on the basis of their cervical cytologic findings, and the concordance of biopsy and Pap smear result was determined. Repeat cytologic examination was not performed for several reasons: the majority (approximately 60%) of cytology reports

originated within our institution; a negative repeat smear might represent a false negative, and at the time of our study, the turnaround on cytology results was up to 10 weeks.

Patients were grouped according to their presenting Pap smear. Group 1 consisted of 47 patients whose smears indicated condyloma changes, HPV, or koilocytosis. Group 2 consisted of 8 patients who had atypia but no mention of HPV, inflammation, or infection. Group 3 consisted of 41 patients with mild dysplasia. Group 4 consisted of 9 patients with moderate dysplasia. Group 5 consisted of the 2 patients who were referred for severe dysplasia. Group 6 consisted of 9 patients who were referred for persistent inflammation without nuclear atypia.

Of the 125 studied, there were 5 patients with normal cervical cytologic results and external condyloma or leukoplakia on examination, 2 with record retrieval problems, and 2 with initial Pap smears reported in a manner that could not be classified ("abnormal Pap," "Class II Pap"). Since roughly 75% of patients were referrals, prior history and treatment records were incomplete. In the case of patients referred for persistent inflammation, for example, the referring information may or may not have included prior testing, treatment, or previous cytology results. The referral diagnosis of "persistent inflammation" was defined by the referring facility.

Results

These results are summarized in the Figure and the Table. When multiple biopsy specimens were taken, the result reported is the most severe lesion found. Of 47 patients whose Pap smears showed condyloma, HPV, or koilocytosis, only 14 had colposcopically directed biopsies that concurred. Of these, 26 patients had higher grade biopsy results such as mild dysplasia. Six showed moderate or severe dysplasia.

Of eight patients whose cytology showed atypia without HPV changes, biopsy results showed that five had dysplasia, either mild or severe. Two had HPV changes as suggested by their smear, and one had just inflammation on biopsy.

Forty-one patients had mild dysplasia on Pap smear. Of these patients, 15 had moderate dysplasia or worse on biopsy. Fifteen of the colposcopically directed biopsies agreed with the Pap smears. Eleven of these patients had biopsies that did not show the dysplasia detected on the presenting smear, with five patients demonstrating HPV; four, inflammation; and two, negative histologic results.

Nine patients had moderate dysplasia on Pap smear.

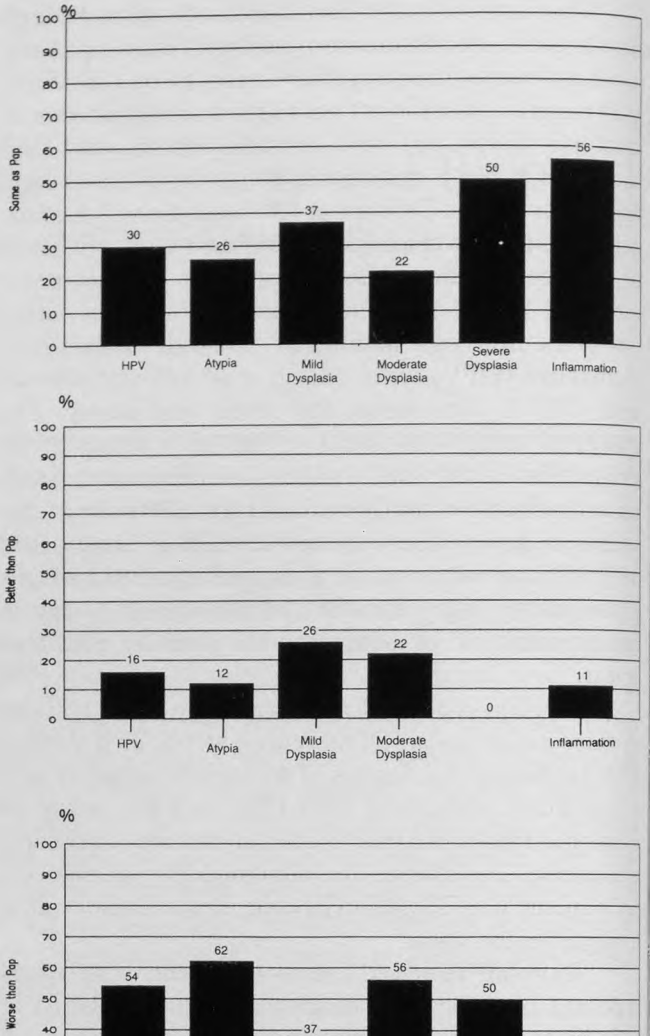

Figure. Outcome of cervical biopsy results as compared with presenting Pap smear.

Of these, five had severe dysplasia on biopsy, two had moderate dysplasia, one had mild dysplasia, and one had HPV. Of the patients presenting with severe dysplasia on cytologic examination, one had severe dysplasia on histologic diagnosis and one had carcinoma in situ (CIS).

Of nine patients presenting with persistent inflammation, five had chronic inflammation, three had mild dysplasia, and one patient had a negative pathologic diagnosis on biopsy.

Using the narrative reports for cervical cytology, this study found that nearly 50% of the time, the biopsy results showed a higher grade lesion than the cytologic findings suggested; fewer than 20% of the biopsy reports

Table. Results of Colposcopically Directed Biopsies Compared with Results of Cervical Cytologic Examinations

Patient Group No./ Cytologic Finding	Colposcopically Directed Biopsy Result							No. (%)
	Negative	Inflammation	HPV	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	CIS	
1/HPV changes	1	6	14	20	5	1	—	47 (38)
2/Atypia	—	1	2	3	—	2	—	8 (6)
3/Mild dysplasia	2	4	5	15	12	2	1	41 (33)
4/Moderate dysplasia	—	—	1	1	2	5	—	9 (7)
5/Severe dysplasia	—	—	—	—	—	1	1	2 (2)
6/Inflammation	3	5	—	1	—	—	—	9 (7)

HPV denotes human papillomavirus; CIS, carcinoma in situ.

showed a less severe lesion. This effect was especially marked for low-grade cytologic abnormalities such as HPV changes or atypia (Figure). The groups with cytologic results most likely to be associated with high-grade lesions on biopsy were those with mild and moderate dysplasia (groups 3 and 4), but because 20% of patients with atypical Pap smear results had severe dysplasia and 10% of those in whom HPV changes were detected had moderate dysplasia, a low-grade smear result did not preclude the presence of a high-grade lesion. Although they would be grouped together under the Bethesda System of reporting, the HPV and mild dysplasia groups seemed to differ. Thirteen percent of HPV patients had a high-grade lesion on biopsy, compared with 30% of patients with mild dysplasia.

Discussion

In our population, as in others studied, the concordance between Pap smears and biopsy is poor. Low-grade lesions found on cytologic examination show concordance with biopsy results about one third of the time. One third to two thirds of biopsies are worse than the Pap smear suggested, confirming the impression of Walker et al,[13] who found a poor correlation between mildly atypical cytologic and histologic findings and discouraged reliance on cytologic follow-up. This study also supports the conclusion of Tabarra et al[3] that a high-grade cytologic finding is predictive of a high-grade histologic finding but that a low-grade cytologic finding does not necessarily indicate a low-grade disease. The use of Pap smears alone to follow cervical smear abnormalities or low-grade CIN would result in a gross underestimation of the prevalence and severity of disease and lead to undertreatment or delayed treatment of high-grade lesions in up to 21% of patients. In this study, biopsies confirmed cytologic results one third of the time and exceeded cytologic results in nearly one half of the cases.

In our protocol, a distinction was made between atypia without HPV changes and persistent inflammation. It appears that a cytologic reading of atypia reliably differentiates a group at higher risk than those labeled as inflammation. The majority of patients with persistent inflammation had inflammation on biopsy, suggesting that these patients were indeed different from those whose smears showed atypia, for which the majority showed CIN. Our numbers are relatively small to draw definite conclusions, but our results agree with the findings of Kohan et al,[14] who looked at minimally abnormal smears. They found that of these smears with inflammation, 35% persisted. These underwent colposcopy and biopsy, and 22% of them were found to have CIN on biopsy. If the presenting smear showed squamous atypia, 70% had CIN. Our results support those of Bolger and Lewis,[10] who found that koilocytosis diagnosed on smear was associated with CIN in 62% of cases, and that 48% had high-grade lesions found on biopsy. In the study by Pearlstone et al,[15] atypia was a relatively common finding, ranging from 13% to 29% of smears, and repeat Pap smears for these patients had a relatively low predictive value in regard to underlying CIN. Our experience differs from that of Shepherd and Lynch,[16] who compared Pap and biopsy results in patients with koilocytic changes and found CIN in only 20% and HPV changes in the remainder; we found CIN in 55%. However, the caveat of Shepherd and Lynch about the variability in interpretation of minimally abnormal smears by different cytology laboratories is well taken. Each practitioner's experience with minimally abnormal smears will be affected by the cytology laboratory used.

In reviewing records for the study reported here, the variability of terms used in narrative reporting systems for cervical cytology was a drawback. Although it appears that the clinical decisions made on the basis of the reports seem rational, there is occasionally some question as to what an individual report means when characterized by "reactive nuclei" or other such terms. Strict adoption of the Bethesda System for reporting might help overcome

this difficulty and simplify the process of comparing studies from various centers. Use of the Bethesda System for cytology reports also might change our own and our referring facilities' protocols for handling abnormal smears. HPV and CIN 1 would be combined into a category of low-grade squamous intraepithelial neoplasia, and moderate and severe dysplasia and CIS would be combined into a category of high-grade squamous intraepithelial lesion, with or without additional pathologist comment. Most reports of atypia would be categorized as atypical squamous cells of undetermined significance. For example, while we recognize that HPV and CIN 1 can be indistinguishable cytologically and that severe dysplasia and CIS can be essentially identical histologically, we have retained the categories under which the smears and biopsy results were reported, as there are differential rates of referral of HPV vs mild dysplasia from our referral sources. Under the Bethesda System, HPV and CIN 1 would be combined into a cytology reading of low-grade squamous intraepithelial lesion, although a few HPVs might be classified as atypical squamous cells of undetermined significance. Under the Bethesda System, this aggregate group would not receive differential treatment or referral.

In our patient population, an aggressive approach to patients with mildly atypical smears was supported on retrospective review of patients undergoing colposcopy and biopsy. We therefore continue to recommend that all dysplasia and persistent inflammation and atypia be referred for colposcopy and colposcopically directed biopsy.

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