

Evaluation of Atypical and Low-Grade Cervical Cytology in Private Practice

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Objective: To evaluate the adequacy of cytology alone for diagnosis of grade of cervical intraepithelial neoplasia (CIN) and to study performance of cytology, human papillomavirus (HPV) testing, and colposcopy in the evaluation of cytologic findings suggesting low-grade squamous intraepithelial lesions (SIL), or atypical squamous (ASCUS) or atypical glandular (AGCUS) cells of undetermined significance.

Methods: Standard gynecologic and cytologic evaluation and colposcopic inspection as an additional screening approach were performed on women with no prior hysterectomies screened in a private practice between January 1, 1993, and August 1, 1995. Among these 7651 women, 367 had ASCUS, AGCUS, or SIL cytology or clinically or colposcopically visible cervical lesions. Sensitivity, specificity, and relative risk of CIN in the 367 women were compared by colposcopic, cytologic, histologic and virologic diagnoses.

Results: The sensitivity of all non-negative Papanicolaou smears for CIN 2-3 and cancer was 92%, combined cytologic categories of high- and low-grade SIL were 59%, and high-grade SIL alone was 22%. Colposcopy was performed in all 367 patients, and positive findings led to biopsies in 48%. Colposcopy of patients with ASCUS increased detection of CIN 2-3 by 32% and CIN 1 by 48%. Cervical cytology was false negative in 8% of patients with CIN 2-3 and in 14% of those with CIN 1. These cases of CIN were detected by screening colposcopic inspection. High-risk HPV DNA was positive in 41% of women with CIN 2-3, and in 25% of those with CIN 1. The positive predictive value of ASCUS cytology increased from 5% to 42% for CIN 2-3 and from 30% to 85% for all grades of CIN in patients carrying high-risk HPV DNA. Virologic studies did not add to an increase in the sensitivity for CIN 2-3 among women in the low- and high-grade SIL cytology groups.

Conclusion: Because of the limited sensitivity of the high-grade SIL cytologic category for CIN 2-3, we recommend

that all women with ASCUS, AGCUS, low- or high-grade SIL cytology be recalled for colposcopy, with biopsy only when indicated by colposcopic findings. (Obstet Gynecol 1998;92:601-7. © 1998 by The American College of Obstetricians and Gynecologists.)

Cervical cancer remains the second most frequent cause of death in women across the world. This mortality has been extensively reduced in North America and Western Europe through recognition and treatment of precancerous lesions, made possible by cytologic screening. It has been estimated that about 50 million American women have an annual Papanicolaou smear¹ and that 5% to 10% of these require some type of follow-up. There is general agreement that cytologic or clinical findings suggesting cancer or high-grade cervical intraepithelial neoplasia (CIN) require biopsy for accurate diagnosis. However, questions remain about the consistency of associations between cytologic findings and histologic diagnoses. The ideal management of patients with atypical squamous cells of undetermined significance (ASCUS) or atypical glandular cells of undetermined significance (AGCUS), or with cytologic findings suggesting low-grade squamous intraepithelial lesions (SIL) is yet to be determined.² We estimate that decisions about workup and management of such patients must be made 2-4 million times each year in the United States alone. The frequency of such findings adds a considerable burden to health expenditures and might create conflicts between optimal management and cost.

This investigation was designed to evaluate the adequacy of cytology alone for the diagnosis of CIN grade and the performance of cytology, human papillomavirus (HPV) testing, and colposcopy in evaluation of ASCUS, AGCUS and low-grade SIL cytology in a private practice.

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Materials and Methods

The study population included all patients with clinical, cytologic, or colposcopic lesions suspect for cervical neoplasia between January 1, 1993, and August 1, 1995, in the authors' private practice. The 367 patients represented 4.8% of 7651 women, who underwent breast and pelvic examinations and screening colposcopic inspections of the cervix. The mean age of the 367 women was 43 years (median = 44, mode = 50, range 13–83 years). The ethnic group distribution was 342 (92.3%) whites, 8 (2.2%) blacks, 11 (3%) Hispanics, 2 (0.5%) native Americans, and 4 (1%) women of Asian descent. Sixty-one percent of the patients were multiparas and 39% were nulliparas. With two exceptions, all patients were from middle or upper socioeconomic classes and none had active sexually transmitted diseases. Ten patients were referred by other physicians, eight because of abnormal Papanicolaou smears (five ASCUS, two low-grade SIL, one high-grade SIL), and two because of visible cervical lesions. All other women were either established in the authors' practice, or were referred for other than cervical problems.

All but two patients over 18 years of age reported they had annual gynecologic examinations, including cervical cytology. Three-hundred women (81.7%) had at least one Papanicolaou smear within 14 months prior to entry. Prestudy cytology reports were available for 248 patients. With the exception of one woman treated with radiation for cervical carcinoma in 1960 and another treated for CIN 1 with conization in 1991, no patients had prior therapy for cervical neoplasia.

As part of the annual examination, colposcopic inspection of the cervix (screening colposcopy) was performed without additional charge in each of the 7651 patients who did not have a prior hysterectomy. Colposcopic inspections, before and after application of 5% acetic acid, added only about 5 minutes to each examination, because of the availability of wall- or table-mounted colposcopes in our examining rooms. Papanicolaou smears were collected with a Cervexbrush (Unimar, Inc., Wilton, CT). Cervical cytology and outpatient biopsies were processed and interpreted either at PLA Laboratories (Rockville, MD), or at other laboratories imposed by patient insurance. Inpatient biopsies or conization specimens were ready by pathologists at Sibley Memorial Hospital (Washington, DC). All Papanicolaou smears were reported according to the Bethesda system.³ Original cytology and pathology reports were accepted as final for the purposes of this study.

Patients with ASCUS, AGCUS, low- or high-grade SIL cytology ($n = 311$) and those with colposcopically

detected lesions and normal cytology ($n = 56$), were recalled for repeat colposcopy, endocervical cytology testing using a Cytobrush (Medscand, Hollywood, FL) and testing for HPV DNA. Specimens for HPV were collected from the cervical canals of 319 women. Human papillomavirus tests were omitted in 48 patients because of temporary unavailability of collection material. Human papillomavirus testing was performed at Digene Laboratory (Silver Spring, MD) using the Hybrid Capture test, which demonstrates high-risk HPVs of 16, 18, 31, 33, 35, 45, 51, 52, and 56 types. Details on this test are published elsewhere.⁴ Testing for low-risk HPV DNA (types 6, 11, 42, 43, and 44) was not part of the study protocol. Sterile dacron-tipped applicator and transport medium were provided by Digene laboratory. Colposcopically directed cervical biopsies and endocervical curettage were performed by two of the coauthors (IN, FSB) in patients in whom colposcopy revealed dense acetowhite epithelium, mosaicism, punctations or atypical vessels, and when the squamocolumnar junction could not be clearly seen. Seventeen patients underwent loop electrosurgical excision without prior colposcopic biopsies. Patients without colposcopically determined lesions were considered free of CIN and were scheduled for a 3-month follow-up examination. This study focuses on the results of the initial evaluations.

Statistical analyses included calculation of rates of CIN by grade and cytologic results, as well as calculation of the percentage of cytologic results by HPV DNA status and by histologic diagnoses. The initial results were analyzed by standard contingency table approach using the χ^2 test of independence or using the Fisher exact test for trend across the cells when tables included expected cell sizes at or below ten patients. The analyses then focused on the relative risks (RR) with 95% confidence intervals (CI) of CIN by grade among those HPV DNA positive and negative, using the Epi6 statistical package distributed by the Centers for Disease Control and Prevention (Atlanta, GA). Finally, the sensitivity, specificity, positive and negative predictive values for grade-specific CIN by cytology and HPV DNA results were calculated according to established formulas. All findings were considered statistically significant at $P < .05$ unless otherwise specified.

Results

During the study period, 311 of the 367 women had abnormal cytology, and 56 had abnormal colposcopy with abnormal cytology. A grade 2–3 CIN was diagnosed in 37 (10%), with a rate of five in 1000, and CIN 1 in 117 (32%), with a rate of 15/1000 in the total patient

Table 1. Distribution of Cytologic Findings and Final Diagnoses

| Cytology | Vaginal cancer | | CIN 2-3 | | CIN 1 | | No CIN* | | Total | |
|----------|----------------|-------|----------|------|----------|-------|----------|-------|----------|-------|
| | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % |
| ASCUS | — | — | 12 | 32.4 | 56 | 47.9 | 159 | 75.0 | 227 | 61.9 |
| AGCUS | — | — | — | — | 2 | 1.7 | 5 | 2.4 | 7 | 1.9 |
| HGSIL | 1 | 100.0 | 8 | 21.6 | 2 | 1.7 | 2 | 0.9 | 13 | 3.5 |
| LGSIL | — | — | 14 | 37.8 | 41 | 35.0 | 9 | 4.2 | 64 | 17.4 |
| Negative | — | — | 3 | 8.1 | 16 | 13.7 | 37 | 17.5 | 56 | 15.3 |
| Total | 1 | 100.0 | 37 | 99.9 | 117 | 100.0 | 212 | 100.0 | 367 | 100.0 |

CIN = cervical intraepithelial neoplasia; ASCUS = atypical squamous cells of undetermined significance; AGCUS = atypical glandular cells of undetermined significance; HGSIL = high-grade squamous intraepithelial lesion; LGSIL = low-grade squamous intraepithelial lesion; Negative = no epithelial cell abnormalities.

* CIN diagnosis was based on histology. No CIN means benign biopsy result (*n* = 23), or absent colposcopic lesion (*n* = 189).

population (*n* = 7651)(Table 1). The mean age of patients with CIN 2-3 was 29 years (median = 29, mode = 33, range 14-42), and with CIN 1, 32 years (median = 33, mode = 37, range 17-42). Among the 7651 patients, the frequencies of ASCUS, AGCUS, low-grade and high-grade SIL were 3%, 0.09%, 0.8%, and 0.2%, respectively.

Colposcopic inspections revealed dense acetowhite epithelium, mosaicism, punctations or atypical vessels in 178 (49%) of 367 of patients, biopsies were performed in all of these (Table 2). Cancer or CIN was diagnosed in 155 (87%) of 178 of women who underwent biopsies, cervical histology was benign in 23 (13%), but one of the patients with ASCUS cytology had vulvar intraepithelial neoplasia grade 2. Colposcopy was normal or suggestive of benign conditions (cervicitis, polyps or Nabothian cysts in 189 (51%) of 367 patients. These women, as well as those with positive colposcopic findings and benign histologic diagnoses (*n* = 22) were classified as free of CIN. With one exception, a patient with adenocarcinoma in situ and high-grade SIL cytology but no detectable HPV DNA, all patients with CIN had squamous lesions. One patient had invasive squamous cell carcinoma of the vagina, with prior cervical carcinoma treated with radiation elsewhere in 1960. This

patient had high-grade SIL cytology and tested positive for high-risk HPV DNA.

Colposcopy was positive in 100% of women with high-grade SIL, in 87% with low-grade SIL, in 37% with ASCUS, and in 29% with AGCUS cytology. Biopsies were performed on all women who had abnormal colposcopic findings, no biopsies were done in the absence of colposcopic lesions.

Cytologic groups by histologic diagnoses are enumerated in Table 2. In the high-grade SIL cytology group, all but two patients (15%), were diagnosed with CIN or cancer; eight (61%) with CIN 2-3, two (15%) with CIN 1, and one (7.7%) with cancer of the vagina. The relative risk of CIN 2-3 was not modified by high-risk HPV DNA in the high-grade SIL cytology group (RR = 0.96, 95% CI = 0.39, 2.35) (Table 3).

In the low-grade SIL group (*n* = 64), CIN was detected in 55 women (86% of all and 98.2% of the 56 women with abnormal colposcopic findings). Of the 55 cases of CIN, 14 (25%) were CIN 2-4 and 41 (75%) were CIN 1. The presence of high-risk HPV DNA in the low-grade SIL group did not modify the relative risk of CIN 2-3 or of CIN 1 (RR of CIN 2-3 by high risk HPV DNA = 1.2, CI 0.48, 3.05); RR of CIN 1 = 1.1, CI 0.76, 1.59).

Among patients with ASCUS cytology, 68 (30%) of

Table 2. Histologic Diagnoses by Cytologic Findings in Patients With Positive Colposcopy*

| Cytology | Vaginal cancer | | CIN 2-3 | | CIN 1 | | VIN | | Cervicitis | | Polyp | | Total | |
|----------|----------------|-----|----------|------|----------|------|----------|-----|------------|------|----------|-----|----------|-----|
| | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % |
| ASCUS | — | 0 | 12 | 14.5 | 56 | 67.5 | 1 | 1.2 | 13 | 15.7 | 1 | 1.2 | 83 | 100 |
| AGCUS | — | 0 | — | 0 | 2 | 100 | — | 0 | — | 0 | — | 0 | 2 | 100 |
| HGSIL | 1 | 7.7 | 8 | 61.5 | 2 | 15.4 | — | 0 | 1 | 7.7 | 1 | 7.7 | 13 | 100 |
| LGSIL | — | 0 | 14 | 25 | 41 | 73.2 | — | 0 | 1 | 1.8 | — | 0 | 56 | 100 |
| Negative | — | 0 | 3 | 12.5 | 16 | 66.7 | — | 0 | 5 | 20.8 | — | 0 | 24 | 100 |
| Total | 1 | | 37 | | 117 | | 1 | | 20 | | 2 | | 178 | |

Abbreviations as in Table 1; VIN = vulvar intraepithelial neoplasia.

* Biopsies were performed when colposcopy revealed dense acetowhite epithelium, mosaicism, punctations or atypical vessels; no biopsies were performed in cases of normal colposcopy.

Table 3. Number and Percentage of Cytologic Results by Human Papillomavirus DNA Status and Histology

| Cytology groups by HPV screen results | No CIN (<i>n</i> = 170) | CIN 1 (<i>n</i> = 105) | CIN 2-3 (<i>n</i> = 37) |
|---------------------------------------|-----------------------------|----------------------------|-----------------------------|
| Negative (<i>n</i> = 28) | | | |
| HPV positive (%) | 3 (75.0) | 1 (25.0) | 0 |
| HPV negative (%) | 9 (37.5) | 12 (50.0) | 3 (12.5) |
| ASCUS (<i>n</i> = 209) | | | |
| HPV positive (%) | 2 (15.4) | 6 (46.2) | 5 (38.5) |
| HPV negative (%) | 145 (74.0) | 44 (22.5) | 7 (3.6) |
| LGSIL (<i>n</i> = 62) | | | |
| HPV positive (%) | 2 (7.1) | 19 (69.9) | 7 (25.0) |
| HPV negative (%) | 6 (12.6) | 21 (61.8) | 7 (25.0) |
| HGSIL (<i>n</i> = 13) | | | |
| HPV positive (%) | 2* (40.0) | 0 | 3 (60.0) |
| HPV negative (%) | 1 (12.5) | 2 (25.0) | 5 (62.5) |

Abbreviations as in Table 1; HPV = high-risk human papillomavirus DNA.

The total number of HPV screens is 319 but this table excludes the seven patients with AGCUS who had HPV assays.

* Cancer of the vagina *n* = 1.

the 227 patients had CIN; the percentage increased to 82% in those with positive colposcopic findings (*n* = 83). Twelve (5% of all ASCUS, 14.5% of ASCUS and abnormal colposcopy) had CIN 2–3, and 56 (25% of all ASCUS, 67.5% of ASCUS and abnormal colposcopy) had CIN 1 (Table 2). Without colposcopy, the diagnosis of 32% of cases of CIN 2–3 and 48% of cases of CIN 1 prevalent in the ASCUS group would have been delayed or missed. High risk HPV DNA was detected in 13 (6%) of 209 tested patients with ASCUS cytology. The percentage of CIN in women with ASCUS and HPV DNA infection was higher than in women not infected with HPV (84.7% versus 26.1%; Fisher exact test *P* < .001 for CIN 1; *P* = .004 for CIN 2–3). Compared with patients not infected with high-risk HPV, the RR of CIN 2–3 in patients with ASCUS and high-risk HPV DNA was 10.77 (CI 3.96, 29.30), and the RR of all grades of CIN was 3.25 (CI 2.34, 4.53).

Examination of the cytologic makeup of the 37 patients with CIN 2–3 (Table 1) revealed that only eight (22%) had high-grade SIL; 14 (38%) had low-grade SIL, and 12 (32%) had ASCUS cytology. Papanicolaou

smears were normal for SIL in three (8%) of CIN 2–3 and in 16 (14%) of CIN 1 cases. These were detected because of abnormal findings on screening colposcopy. The cytologic composition of CIN 1 included two (2%) high-grade SIL, 41 (35%) low-grade SIL, 56 (48%) ASCUS, and two (2%) AGCUS cases. These findings demonstrate that the grade of cytologic SIL is not equivalent to the grade of histologic CIN.

A test for high-risk HPV DNA was performed in 319 (87%) of 367 of patients, 50 (16%) of whom were HPV DNA positive. CIN was detected in 41 (82%) of 50 infected women. High-risk HPV DNA was found in 15 (41%) of 37 of tested patients with CIN 2–3 and in 26 (25%) of 105 with CIN 1, a difference that was not statistically significant $\chi^2 = 3.56, P < .059$ (Table 3). In women with negative colposcopy, seven (4.5%) were positive for high-risk HPV DNA. No random biopsies were performed on these patients and they were scheduled for a 3-month follow-up.

The relationship between verified prestudy cytology reports and the last in-study cytologic category was available for 248 patients. The mean interval between the prestudy and last in-study Papanicolaou smears was 348.3 days (median 317, mode 210, minimum 103, maximum 362). The prestudy results by last in-study results are outlined in Table 4. No significant difference was found between the prestudy and last in-study cytologic categories ($\chi^2 = 12.88, P = .38$). A prestudy ASCUS report did not increase the RR of CIN 2–3 when compared to the last in-study ASCUS result (Fisher exact test *P* = .35) but it did modestly increase the risk of the combined groups of CIN 1-2-3 (RR 1.64; CI 1.17, 2.31). The RR of CIN 2–3 did not increase significantly when both the last in-study and the prestudy Papanicolaou smear were reported as ASCUS (RR 1.61; CI 0.22, 12.02). Among the 50 patients who had prestudy ASCUS cytology, four were ultimately diagnosed with CIN 2–3 and 22 with CIN 1 during the study. The in-study cytology results of the four cases of CIN 2–3 were high-grade SIL in two, low-grade SIL in one, and ASCUS in one. Among the 22 patients with CIN 1, the

Table 4. Comparison of Prestudy and Last In-Study Cytology

| Prestudy cytology | ASCUS <i>n</i> (%) | AGCUS <i>n</i> (%) | HGSIL <i>n</i> (%) | LGSIL <i>n</i> (%) | Negative <i>n</i> (%) | Total <i>n</i> (%) |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------------------|-----------------------|
| ASCUS | 11 (22) | 0 | 2 (4) | 3 (6) | 34 (68) | 50 (100) |
| HGSIL | 1 (33) | 0 | 0 | 0 | 2 (67) | 3 (100) |
| LGSIL | 8 (53) | 0 | 0 | 2 (13) | 5 (33) | 15 (99) |
| Negative | 58 (32) | 4 (2) | 1 (1) | 14 (8) | 103 (57) | 180 (100) |
| Total | 78 | 4 | 3 | 19 | 144 | 248 |

Abbreviations as in Table 1.

$\chi^2 = 12.88, P = .38$.

Table 5. Sensitivity, Specificity, and Positive and Negative Predictive Values of Selected Tests

| Tests | Grade 2-3 CIN | | | | Grade 1-2-3 CIN | | | |
|----------------------------|---------------|-------------|-----|-----|-----------------|-------------|-----|-----|
| | Sensitivity | Specificity | PPV | NPV | Sensitivity | Specificity | PPV | NPV |
| Colposcopy | 100 | 57 | 21 | 100 | 100 | 89 | 87 | 100 |
| HGSIL, LGSIL, ASCUS, AGCUS | 92 | 16 | 11 | 95 | 88 | 17 | 44 | 66 |
| HGSIL, LGSIL | 59 | 83 | 29 | 95 | 42 | 94 | 84 | 69 |
| HGSIL | 22 | 98 | 62 | 92 | 6 | 99 | 77 | 99 |
| HGSIL, HPV positive | 17 | 100 | 100 | 100 | 2 | 100 | 100 | 100 |
| LGSIL | 38 | 85 | 22 | 92 | 36 | 96 | 56 | 67 |
| LGSIL, HPV positive | 19 | 93 | 25 | 90 | 18 | 99 | 93 | 59 |
| ASCUS | 32 | 35 | 5 | 82 | 44 | 25 | 30 | 38 |
| ASCUS, HPV positive | 14 | 98 | 42 | 90 | 10 | 99 | 85 | 64 |
| High-risk HPV alone | 41 | 88 | 30 | 88 | 28 | 95 | 82 | 62 |

Abbreviations as in Table 1; PPV = Positive predictive value; NPV = Negative predictive value.

in-study cytology was ASCUS in 15, high-grade SIL in two and low-grade SIL in five cases.

Calculation of sensitivity, specificity and predictive values revealed that the all-inclusive ASCUS, AGCUS, low-grade and high-grade SIL cytology group had the highest sensitivity (92%) for CIN 2-3 as well as for all grades of CIN (88%) (Table 5). The sensitivities of high-grade SIL cytology and low-grade SIL cytology combined were lower for CIN 2-3 at 59% and for all grades of CIN at 42%. The sensitivities of each individual cytologic group were lower than those of the combined groups, and among these, low-grade SIL cytology had the highest sensitivity for CIN 2-3 and ASCUS cytology had the highest sensitivity for CIN 1-2-3. The sensitivities of HPV DNA positive ASCUS findings for CIN 2-3 and of HPV DNA positive high-grade SIL cytology findings for CIN 1-2-3 were the lowest. The positive predictive value of ASCUS cytology increased from 5% to 42% for CIN 2-3 and from 30% to 85% for CIN 1-2-3 in women infected by high-risk HPV DNA. Presence of HPV DNA also increased the specificity of ASCUS cytology from 35% to 98% for CIN 2-3, and from 25% to 99% for all grades of CIN. The positive predictive value of high-grade SIL cytology increased from 62% to 100% in the presence of HPV DNA. High-risk HPV DNA, independent of cytology, had a sensitivity of 41% for CIN 2-3 and 28% for all grades of CIN.

Colposcopy had a 100% sensitivity in this study; however, false negative results would not have been detected in patients with normal cytology and normal colposcopy. Normal colposcopic findings on the screening examination detected three cases of CIN 2-3 and 16 cases of CIN 1 from patients who had negative cytology. The specificity, positive predictive value and negative predictive value of colposcopy for CIN 1-2-3 were 89%, 87%, and 100%, respectively, and for CIN 2-3 57%, 21%, and 100%, respectively.

The number of patients with AGCUS was too small

($n = 7$) for any conclusion. Two of these patients had CIN 1 and none had histologic glandular cell disease or detectable high-risk HPV DNA. All patients with AGCUS underwent additional tests, including endometrial biopsies.

Discussion

In this office-based private patients population, the high-grade SIL cytologic category contributed only 22% to the diagnosis of CIN 2-3, and cytologic categories were not consistently associated with the histologic diagnoses. Similar findings were reported by others who detected CIN 2-3 in up to 39% of those with low-grade SIL cytology, and in 5% to 10% of patients with ASCUS cytology.⁴⁻¹⁰ These findings reconfirm that cytology is dependable detecting most cases of CIN, but tends to underestimate final histologic diagnoses. Therefore, the evaluation of ASCUS and all grades of SIL cytology is necessary to diagnose high-grade CIN in a timely manner. We believe the best and most cost-effective method is colposcopy, rather than repeating cytology.

In this study, colposcopy of patients who had ASCUS or low-grade SIL cytology increased detected cases of CIN 2-3 by 70% and of CIN 1 by 83%. The advantage of prompt colposcopic inspections over repeat smears is not only early diagnoses, but opportunity for the gynecologists to assess the state of the cervix independently from laboratories. Furthermore, colposcopic inspection with reassuring findings reduced the biopsy rate by 63% in patients with ASCUS, and by 13% in patients with low-grade SIL cytology, and allowed prompt diagnosis in all women with potential CIN.

Repeating Papanicolaou smears, an approach recommended for patients with ASCUS and low-grade SIL cytology,^{2,10} carries risk of false negative findings in repeat smears and potential loss of patients who fail to

comply with follow-up instructions. In one study, repeat smears taken immediately prior to biopsies were false negative in 22% of CIN 2–3 as well as in two of six invasive cervical carcinomas.¹¹ Our findings show the importance of initial cytologic results, the value of follow-up smears and the lack of consistency between initial and follow-up cytologic results in previously abnormal and current Papanicolaou smears. In recent times, when managed care may force some patients to change providers, definitive diagnostic evaluation can also be delayed, because wide differences of opinions prevail on the timing of colposcopy. Complacency about the necessity of prompt diagnosis may exist because of reports on regression or lack of progression of low-grade lesions.¹² Since no current test appears able to predict the natural evolution of CIN, the timely establishment of a histologic diagnosis, if not treatment, is important.

The current clinical role of HPV DNA testing for triage of cytologic atypia and SIL is not finalized. In this study, 38% of high-grade SIL, 43% of low-grade SIL, 6% of the ASCUS, and 14% of normal cytology groups were HPV DNA positive, and only 41% of patients diagnosed with CIN 2–3 and 25% with CIN 1 had evidence of HPV infection. Although frequencies differ, our finding of inconsistent association between histologic CIN and HPV DNA agrees with others.^{4,7,13} Perhaps because of the small numbers in the cells of our tables, we could not demonstrate a significant difference ($P < .059$) between grade of CIN and presence of high-risk HPV DNA.

From the clinical standpoint, we believe that the absence of HPV DNA is not a reliable indicator to omit colposcopy in women with abnormal cytology. If we had relied on HPV testing alone, we would have missed two-thirds of cases of CIN. The presence of high-risk HPV DNA does increase the specificity and the positive predictive value of ASCUS cytology (99% specificity and 85% positive predictive value for CIN 1-2-3 and 98% and 42%, respectively, for CIN 2–3). Therefore, testing might be useful, particularly when screening is not performed by gynecologists and colposcopy is not readily available. The sensitivity of HPV DNA alone for CIN 2–3 was 41% in this study compared to 63%, 64% and 86% in three earlier studies, respectively, with similar profiles of HPV DNA assays.^{4,13,14}

We performed colposcopic inspection of the cervix at each screening examination without charges. This approach compensated for 19 false negative Papanicolaou smears that occurred in cases of CIN. We realize that screening colposcopy may be technically difficult in offices without wall- or table-mounted instruments in several examining rooms, and that the initial expense of

several colposcopes might be significant. Our data suggest that colposcopic screening might be an important adjunct to cytologic screening. We believe that when a colposcope is readily available it becomes cost-effective because of the minimal amount of time required for its use in screening.

We recognize certain limitations of this study, including the lack of a second reader of the pathology slides, the reliance upon pathology laboratories carried by the patient's insurer instead of a standard pathology laboratory for all specimens, the use of the original Papanicolaou smear results rather than a repeat smear, and our decision not to include low-grade HPV DNA testing in our series. These limitations show the practical problems encountered in a private practice setting. Cell sizes in our tables were small, but were similar to numbers in tables of others.^{4,13,14} It might be useful to replicate such a study in larger private patient populations.

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