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Quantifying the Risk of Cervical Intraepithelial Neoplasia in Women with Unsatisfactory Colposcopy Results

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■ **Abstract**

Objective. To define the risk of high-grade cervical intraepithelial neoplasia (CIN 2,3) among women with unsatisfactory colposcopy results who underwent a loop electrosurgical excision procedure.

Methods. Loop electrosurgical excision procedures were performed for clinical indications by residents supervised by attending obstetrician-gynecologists at an urban public hospital referral clinic. Specimens obtained between July 1, 1996, and April 30, 2002, were retrieved retrospectively after grading and recording in an institutional database. The endpoint of interest was high-grade cervical disease, a composite of CIN 2, CIN 3, and cancer, in excision specimens.

Results. Of 169 evaluable patients, five (3%) had cancer. High-grade disease was found in 6 of 21 patients (29%) without a colposcopic lesion, in 13 of 33 patients (36%) with only koilocytosis on colposcopic biopsy, in 15 of 55 patients (27%) with CIN 1, in 13 of 25 patients (54%) with CIN 2, and in 26 of 35 patients (74%) with CIN 3 ($p < 0.001$). High-grade disease was associated with the grade of referral cytologic results, cytologic analysis repeated at colposcopy, and colposcopic biopsy ($p < 0.001$ for all). Limiting excision to women with cytologic results at the time of colposcopy read as atypical squamous cells of undetermined significance or worse yielded a high-grade disease prevalence of 12%, with a sensitivity of 92%, specificity 46%, negative predictive value 88%, and positive predictive value 56%. Referral cytologic results, colposcopic biopsy, age, and endocervical curettage results did not seem to identify women at low risk for high-grade disease.

Conclusions. Women with negative cytologic results at the time of colposcopy have a low risk for high-grade disease and may avoid a loop electrosurgical excision procedure despite unsatisfactory colposcopy. ■

Key Words: loop electrosurgical excision procedure, colposcopy, unsatisfactory, cervical intraepithelial neoplasia

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Colposcopic evaluation is the first diagnostic step for most women with abnormal cervical cytologic results [1]. However, colposcopy only excludes cancer if the entire area of the cervix at risk for neoplasia is visible [2]. Thus, a critical component of colposcopy is the determination of the visibility of the cervical transformation zone, including the squamocolumnar junction. When visualization is unsatisfactory, the clinician can assess the cervical canal through conization, a minor procedure that nevertheless carries risks of bleeding, cervical stenosis, and diminished fertility [3–5], risks that may be less with a loop electrosurgical

excision procedure than with cold-knife or laser conization [6–8].

For women with higher grades of cervical intraepithelial neoplasia (CIN), conization can be both diagnostic and therapeutic, eradicating preinvasive disease while evaluating the endocervix. Current management guidelines suggest observation for women with CIN 1 when more advanced disease has been excluded [2, 3]. Recent consensus guidelines developed by the American Society for Colposcopy and Cervical Pathology recommend conization for women with CIN 1 and unsatisfactory colposcopy, but data to support this recommendation are scant [9]. Using a large case series of women referred for loop electrosurgical excision procedure at an urban public hospital, we reviewed excision results among women with unsatisfactory colposcopy to define their risk for high-grade cervical disease and to determine whether excision could be performed selectively according to preoperative cytologic results, colposcopic biopsy, results of endocervical curettage (ECC), or age.

MATERIALS AND METHODS

Methods used to develop the database for the study have been described previously [10]. Briefly, colposcopy was performed and data were gathered prospectively for women attending the Cook County Hospital Dysplasia Clinic, a colposcopy referral center for indigent women in metropolitan Chicago. All patients were examined colposcopically using 5% acetic acid after Pap smear collection. Directed biopsies were taken by residents under the supervision of attending physicians who were board certified in obstetrics and gynecology. Any ECC procedures were performed at the discretion of the attending physician. Loop electrosurgical excision procedure was performed for nonpregnant women with CIN 2 or 3, persistent CIN 1, discordant biopsy, cytologic findings including CIN 1 after a smear read as high-grade squamous intraepithelial lesion (HSIL), suspicion of microinvasive cancer, and unsatisfactory colposcopy after cytologic HSIL. Procedures were performed between July 1, 1996, and April 30, 2002, and were carried out using an electrosurgical generator (Utah Medical, Midvale, UT); loop sizes and number, current, and depth of passes were individualized. Histologic findings were graded as benign, condyloma or human papillomavirus (HPV), CIN 1, CIN 2, CIN 3, or cancer. When a range was given or multiple findings were reported, the highest-grade result was recorded. All specimens obtained at the time of colposcopy were assigned a grade of CIN using common criteria by attending staff in the Cook County Hospital Department of Pathology who were board certified in anatomic pathology [11], and results were entered into an institutional database; slide review was not performed.

All data were entered onto a spreadsheet (Excel; Microsoft, Redmond, WA) and tabulated. The endpoint of interest was high-grade cervical disease, a composite of CIN 2, CIN 3, and cancer in loop electrosurgical excision procedure specimens. In calculating indices of accuracy, cases of ungraded dysplasia were excluded. The significance of differences among women with varying preoperative characteristics was determined using χ^2 tests.

RESULTS

In all, 222 women with unsatisfactory colposcopy underwent a loop electrosurgical excision procedure during the study period. We excluded two patients with negative referral cytologic results, 17 whose colposcopic biopsies could not be graded, two whose biopsies were insufficient for diagnosis, and 32 who had no biopsy performed (total exclusions, 53), leaving 169 women for analysis. Their mean age was 40.6 years, and the median was 38 years (range, 20–71 years). The population was largely minority, with 100 (59%) African-American women, 42 (25%) Latina women, 14 (8%) white women, 4 (2%) Asian women, and 9 women (5%) of other or unknown ethnicity. Referral cytologic results were atypical squamous cells of uncertain significance (ASCUS) in 27 women (16%), atypical glandular cells of uncertain significance (AGUS) in 2 women (1%), low-grade squamous intraepithelial lesion (LSIL) in 44 women (26%), HSIL in 78 women (46%), cancer in 10 women (6%), and unknown in 8 women (5%). Results of cytologic analysis repeated at the time of colposcopy were normal in 42 women (25%), ASCUS in 27 women (16%), AGUS in 1 woman (1%), LSIL in 32 women (19%), HSIL in 47 women (28%), cancer in 2 women (1%), and not done in 18 women (11%).

Invasive cancer was found at loop electrosurgical excision procedure in 5 women (3%), and CIN 2 or 3 was found in 72 women (43%). In only 19 women (11%) was no disease found, whereas the remaining patients (43%) had low-grade disease, including CIN 1 and koilocytosis. Correlations between the grade of colposcopic biopsy and loop electrosurgical excision procedure histologic results are shown in Table 1, after excluding women with missing data. The risk of high-grade disease

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Table 1. Histologic Findings in Loop Excision Specimens Among Women with Unsatisfactory Colposcopy and Various Grades of Cervical Abnormality at Colposcopic Biopsy[a]

		Loop excision histological results						
Colposcopic biopsy	Benign	HPV[b]	CIN 1	CIN 2	CIN 3	Ungraded[c]	Cancer	Total
Benign	4 (19)	4 (19)	6 (29)	3 (14)	3 (14)	1 (5)	0	21
HPV	5 (15)	5 (15)	10 (30)	5 (15)	7 (21)	0	1 (3)	33
CIN 1	8 (15)	11 (20)	21 (38)	8 (15)	7 (13)	0	0	55
CIN 2	1 (4)	2 (8)	9 (36)	7 (28)	5 (20)	0	1 (4)	25
CIN 3	0	1 (3)	4 (11)	1 (3)	25 (71)	4 (11)	0	35
Total	18	23	50	24	47	5	2	169

HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia.
[a]Results are n (%). $p < 0.001$ for the difference in likelihood of CIN 2, CIN 3, or cancer for women with benign changes, HPV, or CIN 1 when compared with those with CIN 2 or CIN 3 on biopsy.
[b]Human papillomavirus changes, including koilocytosis and condyloma.
[c]Cervical intraepithelial neoplasia, not graded due to technical factors.

was 29% for women without a lesion, 36% for those with only HPV on colposcopic biopsy, 27% for those with CIN 1, 54% for those with CIN 2, and 74% for those with CIN 3. Women with CIN 2 or CIN 3 on biopsy were more likely than those with less severe or no disease to have CIN 2, CIN 3, or cancer in loop electrosurgical excision procedure specimens ($p < 0.001$). A strategy using CIN 2 as the threshold for excision had a sensitivity for high-grade disease of 53%, a specificity of 81%, a negative predictive value (NPV) of 69%, and a positive predictive value (PPV) of 70%. Using CIN 1 in colposcopic biopsy as the threshold for triage to loop electrosurgical excision procedure yielded a sensitivity of 74%, but with one cancer still missed, with specificity of 37%, NPV of 64%, and PPV of 49%.

We attempted to determine whether referral cytologic results might be used to identify a group of women with unsatisfactory colposcopy whose risk for CIN2,3 or cancer was low enough to allow observation rather than excision. As shown in Table 2, after excluding women with missing data or ungraded histologic results, the risk of high-grade disease rose progressively from 7 of 27 women (22%) among those with ASCUS referral cytologic analysis, to 14 of 44 women (32%) among those with LSIL, to 43 of 78 women (55%) among those with HSIL, and to 8 of 10 women (80%) among those with malignant cytologic results. After eliminating the few women with AGUS cytologic results and combining women with HSIL and malignant cytologic results, these differences were significant ($p < 0.001$). Using HSIL as a triage threshold yielded a sensitivity for high-grade disease of 71%, a specificity of 58%, NPV of 70%, and PPV of 59%. Lowering the threshold to LSIL improved sensitivity to 90%, although one woman with cancer still would have been missed, whereas specificity dropped to 23%, with NPV of 73% and PPV of 50%.

Results were different when women were classified according to cytologic results obtained at the time of colposcopy (Table 3). The risk of CIN 2,3 or cancer was 4 of 42 women (12%) among those with benign repeat cytologic results, 15 of 27 women (56%) among those

Table 2. Histologic Findings in Loop Excision Specimens Among Women with Unsatisfactory Colposcopy and Various Grades of Abnormality in Referral Cytologic Analysis[a]

		Loop excision histologic results						
Referral cytologic analysis	Benign	HPV[b]	CIN 1	CIN 2	CIN 3	Ungraded[c]	Cancer	Total
ASCUS	7 (26)	4 (15)	8 (30)	3 (11)	3 (11)	1 (4)	1 (4)	27
AGUS	1 (50)	0	1 (50)	0	0	0	0	2
LSIL	4 (9)	6 (14)	19 (43)	11 (25)	3 (7)	1 (2)	0	44
HSIL	5 (6)	13 (17)	16 (21)	10 (13)	32 (41)	1 (1)	1 (1)	78
Cancer	0	0	1 (10)	0	8 (80)	1 (10)	0	10
Total	17	23	45	24	46	4	2	161

HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; AGUS, atypical glandular cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.
[a]Data are n (%). $p < 0.001$ for the difference in likelihood of finding CIN 2, CIN 3, or cancer in loop excision specimens among women with ASCUS vs. LSIL vs. HSIL/caner cytologic results. Because of missing data, eight women were excluded from analysis.
[b]Human papillomavirus changes, including koilocytosis and condyloma.
[c]CIN not otherwise graded for technical reasons.

Table 3. Histologic Findings in Loop Excision Specimens Among Women with Unsatisfactory Colposcopy and Various Grades of Cytologic abnormality at Colposcopy[a]

		Loop excision histologic results						
Repeat cytologic results	Benign	HPV	CIN 1	CIN 2	CIN 3	Ungraded[b]	Cancer	Total
Benign	9 (21)	7 (17)	21 (50)	4 (10)	1 (2)	0	0	42
ASCUS	2 (7)	2 (7)	8 (30)	3 (11)	12 (44)	0	0	27
AGUS	0	1 (100)	0	0	0	0	0	1
LSIL	3 (9)	10 (31)	13 (41)	3 (9)	3 (9)	0	0	32
HSIL	2 (4)	1 (2)	5 (11)	10 (21)	24 (51)	4 (9)	1 (2)	47
Cancer	0	0	0	0	1 (50)	1 (50)	0	2
Total	16	21	47	20	41	4	2	151

HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; AGUS, atypical glandular cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.
[a]Data are n (%). $p < 0.001$ for the difference in likelihood of finding CIN 2, CIN 3, or cancer in loop excision specimens among women with benign vs. ASCUS vs. LSIL vs. HSIL/cancer cytologic results. Because of missing data, 18 women were excluded from analysis.
[b]CIN not otherwise graded for technical reasons.

with ASCUS repeat cytologic results, 6 of 32 women (19%) among those with LSIL results, 35 of 47 women (74%) among those with HSIL results, and 2 of 2 women (100%) among those with malignant cytologic results. Again, after eliminating women with AGUS smears and combining those with HSIL and cancer on cytologic results, these differences were significant ($p < 0.001$). Using a triage threshold of LSIL led to a sensitivity for high-grade disease of 68%, a specificity of 59%, NPV of 71%, and PPV of 56%. With a threshold of ASCUS on repeat cytologic analysis, sensitivity rose to 92% but specificity fell to 46%, with NPV of 88% and PPV of 56%. Neither strategy would have resulted in missed cancer, because cancers were only found in excision specimens from women with HSIL or cancer on repeat smear.

Among women younger than 40 years of age, the risk of high-grade disease was 45 of 90 women (50%). The likelihood of high-grade disease was only 26 of 79 women (33%) among those at least 40 years of age, but all cancers were found in the older group.

We evaluated the usefulness of ECC in excluding high-grade disease. Of 110 women with negative ECC results, no lesion or HPV was found in 26 (25%), CIN 1 was found in 37 (34%), CIN 2 was found in 15 (23%), CIN 3 was found in 32 (57%), and cancer was found in none. Similar figures for the 36 women with CIN or cancer at ECC were 11 women (31%) with benign changes or HPV, 8 women (22%) with CIN 1, 6 women (17%) with CIN 2, 10 women (28%) with CIN 3, and 1 woman (3%) with cancer. The remaining 23 patients included 5 with ungraded CIN in loop electrosurgical excision procedure specimens and 18 with an ECC that was insufficient for diagnosis or not done. The predictive value of a negative ECC result in excluding CIN 2, CIN 3, or cancer was only 63 of 110 women (57%).

CONCLUSIONS

Our data show that among women with unsatisfactory colposcopy results who undergo diagnostic loop electrosurgical excision procedures for standard indications, the risk of high-grade cervical disease rises with the grade of both cytologic and colposcopic biopsy results. Of various triage strategies we evaluated, only one limiting excision to women with ASCUS or worse on cytologic analysis performed at the time of colposcopy would have resulted in a sensitivity of better than 90% for high-grade disease and no missed cancers. Although others have suggested that repeating cytologic analysis at the time of colposcopy may be insensitive and cost ineffective [12], we find repeat cytologic analysis to be useful because many patients at our referral center are denied access to smears for cytohistologic correlation, have substantial delays between referral cytologic collection and colposcopy, and may have smears that overcall disease [6]. This strategy should be replicated in other populations before being generally adopted, and Pap tests performed temporally close to the time of colposcopy may serve the same role as repeat testing. Triage using referral cytologic results, colposcopic biopsy results, age, and ECC results did not seem useful in our series.

Recent guidelines prescribing diagnostic excision for women with CIN 1 and unsatisfactory colposcopy results have generated controversy [9]. Our results show that the risk of high-grade disease among these women was 27%. When CIN 1 is present and higher-grade

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disease cannot be excluded because of unsatisfactory colposcopy, diagnostic excision would seem to be required.

This recommendation differs from that of others. Yandell et al. [13] suggested that women with unsatisfactory colposcopy and findings of CIN 2 or less on histologic or cytologic analysis could be followed up safely because of a low risk of invasive cancer. However, this study did not cite the sensitivity of this strategy, and the authors' recommendation has not been widely adopted because of concern about occult CIN 3.

Our data are limited by several factors. This study was retrospective and we did not have access to the treatment indications for all patients. In consequence, we could not determine outcomes for women with unsatisfactory colposcopy who did not undergo excision, and we would expect that such women had clinical features leading to lower risk for high-grade disease. We could not stratify outcomes by indication. As we and others have reported for cold-knife and laser conization [14, 15], histologic findings may vary depending on the reason for loop electrosurgical excision procedure. Confirmation of our results may be helpful in developing generalizable guidelines. We did not have access to any Pap results before the referral test; women with multiple abnormalities may have higher risk for abnormalities, and women known to have a single ASCUS smear result may be at lower risk than we describe. In addition, we did not have access to a specialist gynecologic pathologist to perform the histologic review. Nevertheless, we believe our results are generalizable to most practices, for which generalist pathologists provide diagnostic histologic services. Residents performed biopsies and loop electrosurgical excision procedures, and expert colposcopists may have different results, but all residents were directly supervised by faculty certified by the American Board of Obstetrics and Gynecology, and we believe any deviations were minor. Confirmation of the generalizability of our results will require study in practice sites with fewer uninsured and minority patients, groups known to be at increased risk for cervical disease.

Our findings may be biased by our high-risk population, with HSIL or cancer in referral cytologic analysis in 52% and cancer at loop electrosurgical excision procedure in 3%. Studies from lower-risk populations may define women who may be candidates for observation in the face of unsatisfactory colposcopy. More conservative management also may be more appropriate in populations with lower risk of loss to follow-up, because the likelihood of invasive cancer in our series was only 3% and transition times from CIN to cancer may be long.

Because of relatively small numbers, we could not stratify patients further to explore interactions between cytologic and colposcopic biopsy or other factors such as age to determine those at lowest risk. For example, women with ASCUS or LSIL on referral and repeat smears and colposcopic biopsy showing only CIN 1 may be candidates for observation despite unsatisfactory colposcopy, especially if young. Spitzer et al. [15] found that among women with unsatisfactory colposcopy and low-grade colposcopic biopsy and cytologic findings, only 4 of 43 (9%) had high-grade disease in excision specimens and none had cancer, yet they still concluded that preoperative findings were insufficiently sensitive to allow observation. They also found that age did not identify a low-risk subgroup. Further refinement of triage strategies may require combining databases from multiple sites to identify women at high and low risk of high-grade disease.

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