Prospective Evaluation of Colposcopic Features in Predicting Cervical Intraepithelial Neoplasia: Degree of Acetowhite Change Most Important

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■ **Abstract:**

Objective. To prospectively evaluate the contribution of three colposcopic features—degree of acetowhite change, blood vessel pattern, and lesion margin—to the diagnosis of cervical intraepithelial neoplasia.

Materials and Methods. A total of 301 women, who participated in two randomized controlled trials and a cross-sectional study of human papillomavirus testing and who were referred to a regional colposcopy center, were studied. Women were examined by colposcopists, who prospectively scored all abnormal transformation zones using three features. The site with the highest score (the most abnormal site) was biopsied and histology reviewed by two pathologists.

Results. In multivariate analysis, degree of acetowhite change was the only feature significantly associated with cervical intraepithelial neoplasia.

Conclusions. Grading lesion severity using degree of acetowhite change alone gave comparable results to grading using the three combined features. ■

Key Words: colposcopy, cervix neoplasms, sensitivity and specificity

Colposcopy with directed biopsy of abnormalities is the reference standard for the evaluation of women with abnormal cervical screening cytology. After the application of acetic acid to the cervix, colposcopists use several visual characteristics of the abnormal transformation zone, such as degree of acetowhite change, lesion border, and blood vessel pattern, to select the biopsy site. Comparing the presence of high-grade cervical intraepithelial neoplasia (CIN) lesions on histology with colposcopic examination, the sensitivity and specificity of colposcopy ranged from 87.0% to 99.0% and 23.0% to 87.0% respectively in a recent meta-analysis [1]. Using colposcopic photographs or videos, interobserver agreement on lesion characteristics and severity is moderate at best, with kappas ranging from 0.13 to 0.63 [2–4].

In an effort to improve the accuracy and increase the reproducibility of colposcopic findings, several indices for colposcopic assessment have been developed to guide clinicians in their evaluation of lesions [5–8]. These indices may be particularly useful in more complex lesions to identify the most significant area for biopsy. Reid and Scalzi's [5] index is the only quantitative scoring system for acetowhite lesions, allowing the graded contribution of several colposcopic features: degree of acetowhite change, lesion border, blood vessel

pattern, and Lugol's iodine staining. None of these indices have been prospectively validated to determine their true performance in clinical practice.

To prospectively examine the contribution of acetowhite change, lesion margin, and blood vessel pattern to the diagnosis of CIN, we compared these colposcopic features to cervical histology in women referred to our colposcopy clinic.

MATERIAL AND METHODS

Sample Description

Participants were consecutive, premenopausal women at least 17 years of age who participated in two randomized controlled trials of human papillomavirus (HPV) testing, and consecutive women aged 18 or older who participated in a cross-sectional study of HPV testing [9–10].

Women in the three studies were recruited from community family practices and a university student health clinic in Ontario, Canada, between May 1995 and October 1998. The women in the two trials were invited to participate after attending their physician for routine cytologic screening and receiving an abnormal Pap smear. Women in the cross-sectional study were consecutive new referrals to the McMaster University Colposcopy Clinic with at least atypical squamous cells of undetermined significance on cytologic screening. The endpoint for women in all three studies was colposcopy and directed biopsy at the McMaster University Colposcopy Clinic. All participants gave written informed consent, and the studies were approved by the Hamilton Health Sciences Corporation Research Ethics Board.

Colposcopy Assessment

Women were examined by 1 of 11 experienced colposcopists who were clinical teaching faculty at McMaster University. After application of 5% acetic acid, colposcopists used a standard form to record their findings. Three features of the abnormal transformation zone were evaluated: degree of acetowhite change, lesion margin, and blood vessel pattern (Table 1). Each feature was scored using a three-point scale, a total score was calculated, and the most abnormal site was biopsied. If more than one site was identified and biopsied in the same woman, the lesion with the highest overall score was used for analysis.

Laboratory Methods

Cytologists and pathologists were blinded to all of the clinical data. One expert gynecologic pathologist re-examined all of the histology that had been read by the routine hospital pathology service. When the diagnosis differed from that of the hospital pathologist, a second expert pathologist read the slides. Discordant diagnoses were resolved by discussion between the two experts.

Statistical Methods

Univariate logistic regression analyses between each colposcopic feature and the reference standards of cervical histology were performed by calculating crude odds ratios and 95.0% CI for categories of each variable. The score of zero was used as a reference category for each colposcopic feature. Unconditional and stepwise multivariate logistic regression analyses were performed in case any strong correlations existed among the three colposcopic features tested. In stepwise multivariate analyses, forward and backward selection pro-

Table 1. Colposcopic Index[a]

Colposcopic sign	Score[b]		
	Zero points (0)	One point (1)	Two points (2)
Lesion margin	Condylomatous or micropapillary contour Indistinct acetowhitening Flocculated or feathered margins Angular, jagged lesions Satellite lesions and acetowhitening that extends beyond transformation zone	Regular lesions with smooth, straight outlines	Rolled, peeling edges Internal demarcations between areas of differing appearance
Degree of acetowhite change	Shiny, snow-white color Indistinct acetowhitening	Intermediate shade (shiny gray)	Dull, oyster-white
Blood vessels	Fine-caliber vessels, poorly formed patterns Condylomatous or micropapillary lesions	Absent vessels	Definite punctuation or mosaic Individual vessels dilated, arranged in sharply demarcated well-defined patterns

[a]Adapted from Reid and Scalzi's index [5].
[b]Total score can range from 0–6 points.

cedures based on the likelihood ratio test were used to iteratively select the colposcopic features that were significantly associated with any CIN and CIN 2 or 3. When no lesion was identified during colposcopy assessment, the case was excluded from the analyses. The results of endocervical curettage pathology were not used in the analyses, because only observable cervical sites were relevant to a visual scoring system.

The diagnostic performance of each colposcopic feature was assessed via calculation of sensitivity, specificity, predictive values, and positive likelihood ratios using several different cut-off points. Data analysis was performed with SPSS (version 6.1.1, SPSS Inc., Chicago, IL), and the probability of a type I error (alpha) was chosen to be 0.05 (two-tailed).

RESULTS

Data were available for analysis from 425 women from these three studies. A total of 124 women had what were considered normal transformation zones, and were not biopsied. They were excluded from the analysis. A total of 301 women had a colposcopic lesion score recorded and biopsy results available for analyses comparing the relative contribution of each colposcopic feature to histology. The average age of the 301 women with abnormal transformation zones on colposcopy was 30.9 (SD = 9.1). The majority (80.3% [242/301]) had high-school education, 49.3% (148/301) were married/common law, 45.3% (146/301) were current smokers, and 42.9% (129/301) were currently taking an oral contraceptive. The median number of lifetime sexual partners was 4.0, and the average age at first intercourse was 17.3 (SD = 2.9). Referral cytology reported atypical cells of undetermined significance or low-grade intraepithelial lesion in 81.0% (230/284) and high-grade intraepithelial lesion in 19.0% (54/284) of women. Cytology data were missing for 17 cases. Cervical biopsy results were normal in 162 (53.8%), CIN 1 in 43 (14.3%), and CIN 2 or 3 in 96 (31.9 %) women.

All three colposcopic features were significantly associated with the presence of any grade of CIN and CIN 2 or 3 in the univariate logistic regression analysis (Tables 2 and 3). Both the unconditional and stepwise multivariate regression analyses revealed that the degree of acetowhite change was the only feature significantly associated with any CIN (Table 2) and CIN 2 or 3 (Table 3) after adjustment for other colposcopic features.

The degree of acetowhite change performed similarly

Table 2. Estimated Odds Ratios (95% CI) of Any CIN Before and After Adjusting for the Effects of Other Colposcopic Features (N = 301)

Colposcopic feature	N	Any CIN % (n)	Crude OR (95% CI)	Adjusted OR (95% CI)
Lesion margin[b]				
Zero points (0)	66	31.8 (21)	1.0[a]	1.0[a]
One point (1)	212	46.7 (99)	1.9 (1.0–3.4)	1.2 (0.6–2.3)
Two points (2)	23	82.6 (19)	10.2 (3.1–33.7)	2.7 (0.7–10.5)
Acetowhite change				
Zero points (0)	129	31.0 (40)	1.0[a]	1.0[a]
One point (1)	140	50.7 (71)	2.3 (1.4–3.8)	1.9 (1.1–3.2)
Two points (2)	32	87.5 (28)	15.5 (5.1–47.3)	10.1 (3.1–32.8)
Blood vessels				
Zero points (0)	96	44.8 (43)	1.0[a]	1.0[a]
One point (1)	160	40.6 (65)	0.84 (0.51–1.41)	1.0 (0.6–1.7)
Two points (2)	45	68.9 (31)	2.73 (1.3–5.8)	2.0 (0.9–4.5)

[a]Reference category.
[b]See Table 1 for the scoring scheme.

to the three features combined in terms of sensitivity, specificity, positive and negative predictive values, and positive likelihood ratio for any CIN or CIN 2 or 3 (Table 4).

DISCUSSION

A simplified approach to colposcopic assessment, which classifies only the degree of acetowhite change, performed as well as using all three features combined in our sample of women. Although a degree of acetowhite change classified as ≥2 has a low sensitivity for high-grade CIN (28.0%), this improves to 81.0% when a score of ≥1 is used. This finding emphasizes the importance of obtaining a biopsy in the presence of any degree of acetowhite change in the abnormal transformation zone.

Table 3. Estimated Odds Ratios (95% CI) of CIN 2 or 3 Before and After Adjusting for the Effects of Other Colposcopic Features (N = 301)

Colposcopic feature	N	CIN 2/3 % (n)	Crude OR (95% CI)	Adjusted OR (95% CI)
Lesion margin[b]				
Zero points (0)	66	13.6 (9)	1.0[a]	1.0[a]
One point (1)	212	33.5 (71)	3.2 (1.5–6.8)	1.8 (0.8–4.0)
Two points (2)	23	69.6 (16)	14.5 (4.7–45.0)	2.4 (0.6–9.6)
Acetowhite Change				
Zero points (0)	129	14.0 (18)	1.0[a]	1.0[a]
One point (1)	140	36.4 (51)	3.5 (1.9–6.5)	2.6 (1.4–5.1)
Two points (2)	32	84.4 (27)	33.3 (11.4–97.7)	22.10 (6.9–70.4)
Blood vessels				
Zero points (0)	96	30.2 (29)	1.0[a]	1.0[a]
One point (1)	160	26.3 (42)	0.8 (0.5–1.4)	1.0 (0.6–1.9)
Two points (2)	45	55.6 (25)	2.89 (1.4–6.0)	2.11 (0.9–4.8)

[a]Reference category.
[b]See Table 1 for the scoring scheme.

Table 4. The Performance of the Total Index Score and Degree of Acetowhite Change with Respect to the Detection of High-Grade or Any CIN (N = 301)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	+LR (95% CI)
Any CIN					
Total index ≥3[a]	58.0 (49.0–66.0)	71.0 (63.0–78.0)	63.0 (54.0–71.0)	66.0 (59.0–73.0)	2.0 (1.5–2.6)
Acetowhite change ≥1	71.0 (63.0–79.0)	55.0 (47.0–63.0)	58.0 (50.0–65.0)	69.0 (60.0–77.0)	1.6 (1.3–1.9)
High-grade CIN 2,3					
Total index ≥5	18.0 (11.0–27.0)	99.0 (96.0–100.0)	85.0 (62.0–97.0)	72.0 (66.0–77.0)	12.1 (3.6–40.3)
Acetowhite change ≥1	81.0 (72.0–88.0)	54.0 (47.0–61.0)	45.0 (38.0–53.0)	86.0 (79.0–92.0)	1.8 (1.5–2.1)
Acetowhite change ≥2	28.0 (19.0–38.0)	98.0 (94.0–99.0)	84.0 (67.0–95.0)	74.0 (69.0–79.0)	11.5 (4.6–29.0)

[a]See Table 1 for the scoring scheme.

Reid and Scalzi's index is the only other quantitative scoring system currently available. It was originally derived retrospectively, using 72 women with abnormal transformation zones [5]. Reid and Scalzi's original paper and one additional retrospective evaluation of Reid's index in 134 women, reported accuracy rates only and could not be directly compared with data from this study [5, 6]. Both previous studies used small convenience samples and included only women who had positive biopsy results. Because our study has prospectively evaluated a larger number of consecutive patients with abnormal cervical cytology, and included women with negative biopsy results, the spectrum of disease should reflect more closely what is usually encountered in a colposcopy service, thus rendering our results more readily generalizable.

The association of the degree of acetowhite change with CIN was similar to findings in two previous studies that specifically examined the predictive value of colposcopic features. A retrospective study using a single colposcopist and a prospective study involving multiple colposcopists with varied expertise both found that the degree of acetowhite epithelium was the most predictive colposcopic feature of CIN [8, 11].

The ability of the degree of acetowhite change alone to identify CIN also supports findings from two primary screening studies of simple visual inspection with acetic acid in Zimbabwe and China, where acetowhite changes with 5.0% acetic acid wash had sensitivities for detection of high-grade CIN of 76.7% and 71.0%, respectively, and specificities of 64.1% and 74.0% [12, 13].

Our study was limited by the failure to examine interobserver reliability among colposcopists; however, the involvement of multiple colposcopists may improve the generalizabilty of our results. It is possible that smaller CIN 2 or 3 lesions were missed in some of these women, because a recent study showed that the sensitivity of colposcopy and directed biopsy was only 64.0% for CIN 2 or 3 when only one cervical quadrant was involved compared with 100% when two or more quadrants were involved [13]. Estimate of the lesion size was not recorded in our study.

Our findings have implications for teaching and using colposcopy, supporting greater emphasis on learning how to recognize and classify degrees of acetowhite change. A simpler index may be particularly useful in settings where allied health professionals are trained in colposcopy because of the limited availability of medical specialty services. Other colposcopic features such as atypical or abnormal vascularity should continue to be taught and evaluated, because the most important goal of colposcopic assessment is to rule out invasive cancer. Further research should prospectively validate the predictive value of the degree of acetowhite change in different settings and populations.

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