The Colposcopic Feature Ridge Sign Is Associated With the Presence of Cervical Intraepithelial Neoplasia 2/3 and Human Papillomavirus 16 in Young Women

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■ **Abstract**

Objective. Interobserver and intraobserver correlation between the colposcopic phenomenon ridge sign and its association with cervical intraepithelial neoplasia (CIN) 2 or 3, with a specific human papillomavirus (HPV) type, and with the age of the patient.

Study Design. Colpophotographs, cervical smears, and histologic results of punch or cone biopsies of 592 patients were evaluated. Colpophotographs were analyzed retrospectively for the presence or absence of an opaque acetowhite ridge at the squamocolumnar junction (ridge sign) by 3 gynecologists of different experience.

Results. Interobserver reliability for colposcopic grading of CIN was between 18.2% and 82.3%. Concerning the ridge sign, interobserver agreement varied between 25.3% and 49.4% according to the observers' experience, and intraobserver reliability varied between 56.4% and 67.5% (Cohen κ = 0.310–0.469). In 83 (14.0%) of 592 patients, a ridge sign was diagnosed by the most experienced investigator. Cervical intraepithelial neoplasia 2 or 3 was confirmed histologically in 53 of these 83 women (63.8%). Sensitivity of ridge sign for detection of CIN 2 or 3 was 33.1%; specificity was 93.1%. Women with ridge sign were significantly younger than women with no ridge sign ($p < .001$). Ridge sign was associated with the presence of HPV 16 ($p < .001$).

Conclusion. Ridge sign is a highly specific marker for CIN 2 or 3 and associated with HPV 16 and young age. ■

Key Words: colposcopy, grading, CIN, human papillomavirus

Colposcopy with directed biopsy is the standard for evaluation of all grades of epithelial abnormality of the uterine cervix and an essential follow-up modality for women with abnormal triage findings [1, 2]. Colposcopy is an investigative technique that allows to estimate the presence and grade of cervical disease [3], to evaluate the extent of the lesion [4], and to identify the most advanced morphologic changes to take guided biopsies [5]. Nevertheless, its use is controversially discussed because the squamocolumnar junction is not always completely visible [6]; colposcopic accuracy depends on the severity of the lesion [7] and the skill and experience of the colposcopist [8, 9]. We determined the interobserver and intraobserver variability to identify the colposcopic finding ridge sign in our cohort of patients and evaluated its association with cervical

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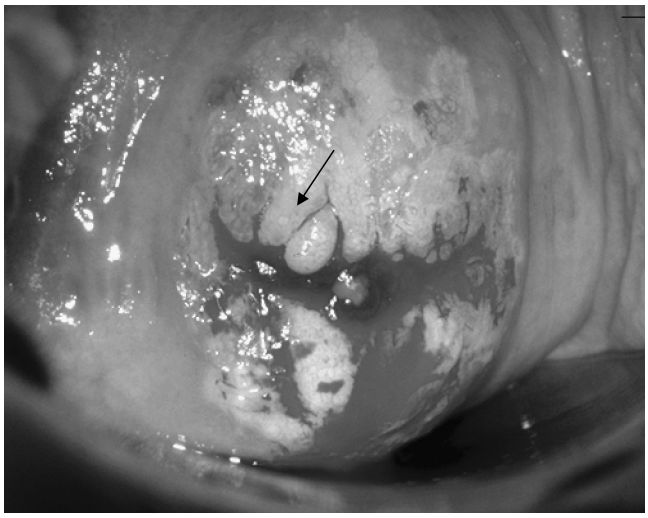

Figure 1. Colpophotograph of a 32-year-old patient with ridge sign (see arrows) after application of 5% acetic acid. A cervical smear was positive for HPV 16 and punch biopsy was diagnosed as CIN 3 by histology.

intraepithelial neoplasia (CIN) 2 or 3, with a specific human papillomavirus (HPV) type, and with the age of the patient.

PROCEDURE

Study Design

Colpophotographs, cervical smears, and histologic results of punch or cone biopsies of 592 patients were evaluated. Colpophotographs were analyzed retrospectively for the presence or absence of an opaque acetowhite ridge at the squamocolumnar junction ("ridge sign") by 3 gynecologists of different experience.

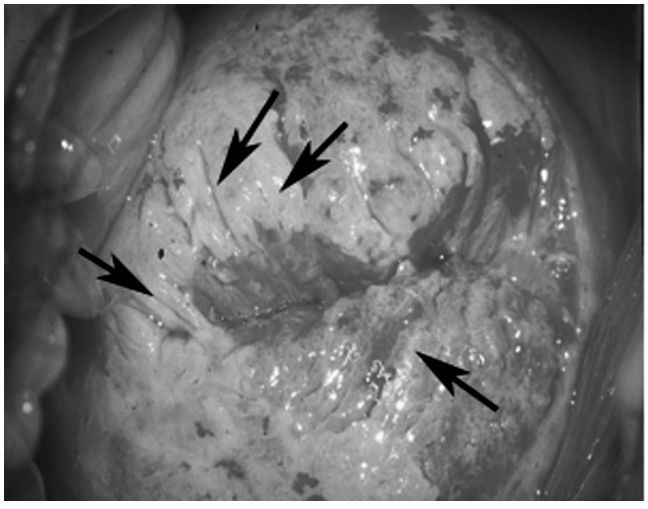

Figure 2. Colpophotograph of a 28-year-old patient with ridge sign (see arrows) after application of 5% acetic acid. A cervical smear was positive for HPV 16, and punch biopsy was diagnosed as CIN 3 by histology.

Table 1. Validity of Ridge Sign as a Marker for CIN 2/3 (in %)

	Colposcopist		
	A	B	C
	25 years of experience	4 years of experience	No experience
Sensitivity	33.1	25.0	15.6
Specificity	92.5	96.5	97.0
Positive predictive value	63.9	74.1	67.6
Negative predictive value	77.6	76.3	74.2

CIN, cervical intraepithelial neoplasia.

Patients and Methods

A total of 592 women with atypical or abnormal cytology results and/or suspicious colposcopic findings and/or positivity for high-risk HPV referred to our Colposcopy Clinic were evaluated. The mean age was 33 years (range, 16–75 years). All patients were examined colposcopically using 5% acetic acid and Schiller test and were photodocumented. Colposcopy-directed biopsies were taken from the area with the most severe lesion. In 67 patients, a cone biopsy was performed because of severe cytologic results without preceding verification. For all specimens, the severity of CIN was assessed by a certified pathologist using common criteria. In addition, 90% of the punch biopsies were reevaluated by 2 independent pathologists. The prevailing diagnosis was accepted as the final result. Before biopsy, a cervical smear was taken for HPV DNA detection. Human papillomavirus DNA detection and typing was performed using GP5+/bioGP6+ polymerase chain reaction–enzyme immunoassay according to Jacobs et al. [10].

Three colposcopists of different experience [(A) 25 years of experience; (B) 4 years of experience; (C) basic

Table 2. Correlation Between Ridge Sign With and Without Reference to CIN 2 or 3 and Patients' Age (Median Age in Years)

	All histologic diagnosis	CIN 2 or 3
Ridge sign	28.0	28.0
No ridge sign	33.0	33.5
	$p < .001$	$p = .004$

CIN, cervical intraepithelial neoplasia.

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Table 3. Association of Ridge Sign With HPV 16 (in %)

	HPV 16 (+)	HPV 16 (−)/HR-HPV (+)	HR-HPV (−)
Ridge sign	58.5	29.3	12.2
No ridge sign	9.9	33.7	56.4

HPV, human papillomavirus; HR-HPV, high-risk HPV.

knowledge, no experience) reviewed all colpophotographs twice in an interval of 4 months and were blinded to clinical data, histomorphologic findings, and HPV results. Colposcopic impressions were graded as benign, CIN 1, CIN 2 or 3, or cancer. In addition, they decided on the presence or absence of an opaque acetowhite ridge at the squamocolumnar junction (ridge sign), which is prominent as an iodine-negative tongue after Schiller test (Figures 1 and 2).

RESULTS

The prevalence of CIN 2 or 3 according to the histologic diagnosis was 27.0% (160/592). Interobserver agreement for the colposcopic grading of CIN varied between 18.2% and 82.3%. Concerning the ridge sign, interobserver agreement varied between 25.3% and 49.4% according to the observers' experience (Cohen κ = 0.288–0.487). Intraobserver reliability varied between 56.4% and 67.5% (Cohen κ = 0.310–0.469). In 83 (14.0%) of 592 patients, a ridge sign was diagnosed by the most experienced investigator (A), in 55 (9.3%) by investigator B, and in 39 (6.6%) by the beginner without colposcopic experience (investigator C). Cervical intraepithelial neoplasia 2 or 3 was confirmed histologically in 53 (63.8%) of these 83 patients, in 40 (72.7%) of the 55 patients, and 25 (64.1%) of the 39 patients. Sensitivity of ridge sign for detection of CIN 2 or 3 by investigator A was 33.1%, specificity was 92.5%, and a positive predictive value was 64% (Table 1). Women with ridge sign were significantly younger than women with no ridge sign ($p < .001$; Table 2). Ridge sign was associated with the presence of HPV 16 ($p < .001$; Table 3).

DISCUSSION

Already in the early 1980s, Burghardt [11] described thick epithelium growing in the squamocolumnar junction as "ledges" without reference to histologic findings. Every colposcopist has observed these "ledges" or "ridges," which are suspicious for high-grade CIN because of their opaque color and lack of iodine uptake. Other grading criteria such as surface, intercapillary distance, or margin do not apply to this phenomenon because these ridges are not vascularized and are part of a larger lesion, which is closest to the squamocolumnar junction. Thus, despite having been seen by most colposcopists for many years, the question remains if this specific phenomenon is associated with a certain disease and patient characteristics.

Our data show, independent of the investigator's experience, that the colposcopic ridge sign is associated with CIN 2 or 3 in 64% to 74%. This high positive predictive value is very helpful for the novice in colposcopy: a beginner may want to classify most abnormal transformation zones as suspicious for CIN and thus has a positive predictive value of 20%. This will lead to unnecessary biopsies in most patients and can be avoided by colposcopic signs highly associated with high-grade CIN.

Differential colposcopic features and colposcopic scores allow us to estimate the severity of a lesion [6]. So far, the ridge sign has not been integrated in any scores. We believe that the occurrence of the ridge sign can lead to quick and accurate diagnosis of high-grade CIN and helps the colposcopist to direct the biopsy forceps to the most abnormal area for histologic verification.

The ridge sign was found most frequently in women younger than 35 years. By definition, this colposcopic phenomenon appears at the area of the transformation zone, which borders to the squamocolumnar junction. Because the squamocolumnar junction must be visible to see a ridge, the ridge sign is by its definition associated with younger age of the patient: in young women, the squamocolumnar junction is located at the ectocervix more frequently compared with older women [12]. The detection rate decreases with age because the squamocolumnar junction disappears into the cervical canal "taking the ridges along."

In previous studies, no colposcopic sign could be associated with specific HPV types [4]. We found a significant association between the presence of HPV 16 and ridge sign.

Colposcopists can identify the ridge sign even at the beginning of their career. They will find this phenomenon highly associated with the presence of CIN 2 or 3 and HPV 16. Whenever this phenomenon is detected, a biopsy should be taken to prove or exclude high-grade CIN.

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