

# Umbilication Is a Strong Predictor of High-Grade Cervical Intraepithelial Neoplasia

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## ■ Abstract

**Objective.** This study aimed to assess the diagnostic value of the colposcopic feature of umbilication for detecting high-grade cervical intraepithelial neoplasia (CIN 2/3).

**Materials and Methods.** Study included 430 randomly selected women who underwent conization for CIN 2 or CIN 3. The control group consisted of 102 patients with biopsy-confirmed CIN 1. Colpophotographs and reports from colposcopy examinations from all patients were retrospectively analyzed by 2 independent colposcopy experts with the aim to assess the presence of umbilication. The occurrence of more than 2 mosaic “tiles” with central punctation was considered to be a positive finding regardless of whether the mosaic pattern was coarse or fine. The prevalence of umbilication in CIN 1 and CIN 2/3 respectively was compared. The diagnostic value of umbilication alone and combination of umbilication and/or ridge sign was assessed.

**Results.** Umbilication was detected in 10% and ridge sign in 10.2% of patients with CIN 2/3. Simultaneous presence of umbilication and ridge sign was rare (1.1%). The umbilication solely reached 12% sensitivity, 100% specificity, and 100% positive predictive value for the detection of underlying CIN 2/3.

**Conclusions.** Umbilication is an age-independent colposcopic feature with very high specificity for predicting CIN 2/3. ■

**Key Words:** CIN, colposcopy, ridge sign, umbilication, mosaic

To predict the real grade of cervical disease within an abnormal transformation zone could be difficult because colposcopic features represent a wide spectrum of changes. Identifying specific colposcopic features may increase the accuracy of colposcopic examination. In light of this, the recently introduced International Federation for Cervical Pathology and Colposcopy 2011 colposcopy terminology of the cervix included 2 new and highly specific colposcopic features associated with acetowhite changes—the ridge sign and the inner border sign [1–3]. Their specificity for the detection of underlying cervical intraepithelial neoplasia 2/3 (CIN 2/3) reached 93.1% and 97%, respectively [2, 3].

Surprisingly, no study to date has assessed whether similar features may be identified also in the category of vascular changes, which are represented by punctation, mosaics, and atypical vessels. If punctation and mosaic patterns are superimposed in 1 area, capillary loops occur in the center of each mosaic “tile,” and this appearance is called umbilication (see Figure 1). We hypothesize that umbilication represents such a feature increasing the specificity for the detection of underlying CIN 2/3. The aim of our study was to assess the diagnostic and predictive value of umbilication and its combination with the ridge sign.

## MATERIALS AND METHODS

From the total number of 4,616 patients referred to colposcopy clinic between January 2009 and October

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**Figure 1.** Colpophotograph of umbilication—mosaic tiles with central punctation are visible at 1 o'clock position and 7 o'clock position. Biopsy-confirmed CIN 3.

2011 with abnormal result of screening Pap smear and/or abnormal colposcopic finding, 532 women were randomly selected. The study group consisted of 430 women who underwent conization for CIN 2 ( $n = 106$ ) or CIN 3 ( $n = 324$ ) and 102 patients with CIN 1 verified by punch biopsy in control group. Colpophotographs and reports from colposcopy examinations in all patients were retrospectively analyzed by 2 independent colposcopy experts. All findings were described using the current International Federation for Cervical Pathology and Colposcopy 2011 terminology of the cervix [1]. The presence of more than 2 mosaic tiles with central punctation was considered as a positive case of umbilication regardless of whether there was a concomitant coarse or fine mosaic pattern. The acetowhite opaque ridge at the squamocolumnar junction was described as the “ridge sign.”

Umbilication and ridge sign were assessed as potential predictors of CIN 2 and CIN 3 (reference category, CIN 1) and as potential predictors of high-grade lesion (HGL) on colposcopy (reference category, low-grade lesion [LGL]). Umbilication and ridge sign were tested separately (“umbilication or ridge sign”) and in combination (“umbilication and ridge sign”). Association with patient age, referral Pap smear, type of transformation zone, variation in acetowhite changes, as well as mosaic and punctation pattern were analyzed. Study was approved by the institutional review board and the local ethical committee.

### Histopathology

All biopsy specimens submitted to histological assessment were routinely examined in their entirety. Sections

from formalin-fixed, paraffin-embedded tissue fragments were stained with hematoxylin-eosin. Histological grading of dysplasia was based on standard CIN 1, CIN 2, and CIN 3 criteria.

### Statistical Analysis

Standard robust summary statistics were used to describe primary data as follows: frequency analysis, median and 5th to 95th percentile range. ML- $\chi^2$  test and Fisher exact test were applied to assess mutual associations between categorical or binary variables in contingency tables. The diagnostic power of umbilication and ridge sign as potential predictors of advanced lesions was measured on the basis of sensitivity, specificity, as well as positive and negative predictive values. Estimates of all used diagnostic measures were supported by CIs. A value  $\alpha = 0.05$  was used as the limit of statistical significance in all performed analyses. Statistical package SPSS for Windows (rel 12.0.1, 2003; SPSS, Inc. Chicago, IL) was used.

## RESULTS

The characteristics of study cohort and prevalence of colposcopic features are summarized in Tables 1 and 2. Umbilication was found in 53 patients (10%); subsequent biopsy confirmed high-grade CIN in all cases (CIN 2 and CIN 3 in 8 and 45 cases, respectively). The incidence of umbilication was significantly higher in HGL (14.0%) than in LGL, where no case was detected ( $p < .001$ ). Correspondingly, no case of umbilication was found among patients with biopsy-confirmed CIN 1,

**Table 1. Characteristics of Study Cohort ( $n = 532$ )**

Characteristics	Value
Age, n (%)	34 (24; 55)
$\leq 30$ y	144 (27.1)
31–40, y	270 (50.8)
$>40$ , y	118 (22.2)
Referral reasons, n (%)	
Clinical reasons	36 (6.8)
Abnormal Pap smear finding	496 (93.2)
ASC/AGC	80 (15.0)
LSIL	161 (30.3)
HSIL	255 (47.9)
Disease grade (colposcopy), n (%)	
LGL	153 (28.8)
HGL	379 (71.2)
Disease grade (histology), n (%)	
CIN 1	102 (19.2)
CIN 2	106 (19.9)
CIN 3	324 (60.9)

ASC, atypical squamous cells; AGC, atypical glandular cells; LSIL, low-grade squamous intraepithelial lesion; high-grade squamous intraepithelial lesion; LGL, low-grade lesion; HGL, high-grade lesion; CIN, cervical intraepithelial neoplasia.

**Table 2. Prevalence of Colposcopic Features (n = 532)**

Feature	Value
TZ type, n (%)	
TZ 1	202 (38.0)
TZ 2	219 (41.2)
TZ 3	111 (20.9)
Acetowhite changes, n (%)	
None	8 (1.5)
Transparent, snow white	173 (32.5)
Dense, oyster white	351 (66.0)
Punctuation, n (%)	
None	259 (48.7)
Fine	125 (23.5)
Coarse	148 (27.8)
Mosaic, n (%)	
None	284 (53.4)
Fine	101 (19.0)
Coarse	147 (27.6)
Umbilication, n (%)	
No	479 (90.0)
Yes	53 (10.0)
Ridge sign, n (%)	
No	473 (88.9)
Yes	59 (11.1)

TZ, transformation zone.

whereas umbilication was present in 7.5% cases of CIN 2 and in 13.8% cases of CIN 3. The occurrence of umbilication significantly discriminated between CIN 1 and CIN 2 ( $p = .007$ ) and between CIN 1 and CIN 3

( $p < .001$ ), whereas the difference between CIN 2 and CIN 3 was not significant ( $p = .091$ ). Positive predictive value, negative predictive value, sensitivity, and specificity of umbilication for HGL on colposcopy were 1.00, 0.32, 0.14, and 1.00, respectively. Positive predictive value, negative predictive value, sensitivity, and specificity of umbilication for biopsy result of CIN 2/3 were 1.00, 0.21, 0.12, and 1.00 respectively (see Table 3).

The ridge sign was found in 59 patients (11.1%)—54 cases revealed high-grade CIN (CIN 2 in 7 and CIN 3 in 47 cases), whereas CIN 1 was present in 5 cases. In contrast with umbilication, the discrimination between different grades of CIN based on ridge sign presence was slightly less significant. Nevertheless, ridge sign significantly ( $p = .009$ ) differentiated between LGL (5.2%) and HGL (13.5%) on colposcopy. The ridge sign was more frequent in CIN 3 (14.5%) than in CIN 2 patients (6.6%) ( $p = .041$ ). The occurrence of ridge sign in patients with CIN 3 was significantly different from CIN 1 (4.9%) ( $p = .014$ ); however, the incidence of ridge sign did not distinguish CIN 1 and CIN 2 categories ( $p = .768$ ). Positive predictive value, negative predictive value, sensitivity, and specificity of ridge sign for HGL on colposcopy were 0.86, 0.31, 0.13, and 0.95, respectively. Positive predictive value, negative predictive value, sensitivity, and

**Table 3. Diagnostic Power of Umbilication and Ridge Sign**

Diagnostic marker	Predicted categories (95% CI)			
	Reference category, LGL	Reference category, CIN 1		
		HGL	CIN 2	CIN 3
<b>Umbilication</b>				
Overall accuracy	0.39	0.53	0.35	0.29
Sensitivity	0.14 (0.11–0.18)	0.08 (0.03–0.14)	0.14 (0.11–0.18)	0.12 (0.09–0.16)
Specificity	1.00 (0.98–1.00)	1.00 (0.96–1.00)	1.00 (0.96–1.00)	1.00 (0.96–1.00)
PPV	1.00 (0.93–1.00)	1.00 (0.59–1.00)	1.00 (0.92–1.00)	1.00 (0.93–1.00)
NPV	0.32 (0.28–0.36)	0.51 (0.44–0.58)	0.27 (0.22–0.32)	0.21 (0.18–0.25)
<b>Ridge sign</b>				
Overall accuracy	0.37	0.50	0.34	0.28
Sensitivity	0.13 (0.10–0.17)	0.07 (0.03–0.13)	0.15 (0.11–0.19)	0.13 (0.10–0.16)
Specificity	0.95 (0.90–0.98)	0.95 (0.89–0.98)	0.95 (0.89–0.98)	0.95 (0.89–0.98)
PPV	0.86 (0.75–0.94)	0.58 (0.28–0.85)	0.90 (0.79–0.97)	0.92 (0.81–0.97)
NPV	0.31 (0.27–0.35)	0.50 (0.42–0.57)	0.26 (0.22–0.31)	0.21 (0.17–0.24)
<b>Umbilication and ridge sign</b>				
Overall accuracy	0.30	0.50	0.25	0.20
Sensitivity	0.02 (0.01–0.03)	0.01 (0.00–0.05)	0.02 (0.01–0.04)	0.01 (0.01–0.03)
Specificity	1.00 (0.98–1.00)	1.00 (0.96–1.00)	1.00 (0.96–1.00)	1.00 (0.96–1.00)
PPV	1.00 (0.54–1.00)	1.00 (0.50–1.00)	1.00 (0.48–1.00)	1.00 (0.54–1.00)
NPV	0.29 (0.25–0.33)	0.49 (0.42–0.56)	0.24 (0.20–0.29)	0.19 (0.16–0.23)
<b>Umbilication or ridge sign</b>				
Overall accuracy	0.46	0.53	0.43	0.37
Sensitivity	0.26 (0.22–0.31)	0.13 (0.07–0.21)	0.27 (0.22–0.32)	0.24 (0.20–0.28)
Specificity	0.95 (0.90–0.98)	0.95 (0.89–0.98)	0.95 (0.89–0.98)	0.95 (0.89–0.98)
PPV	0.93 (0.86–0.97)	0.74 (0.49–0.91)	0.95 (0.88–0.98)	0.95 (0.89–0.99)
NPV	0.34 (0.30–0.39)	0.51 (0.44–0.59)	0.29 (0.24–0.34)	0.23 (0.19–0.27)

LGL, low-grade lesion; CIN, cervical intraepithelial neoplasia; HGL, high-grade lesion; PPV, positive predictive value; NPV, negative predictive value.

specificity of ridge sign for CIN 2/3 were 0.92, 0.21, 0.13, and 0.95, respectively (see Table 3).

The combination of umbilication and ridge sign did not contribute significantly to the discrimination of results, neither colposcopic nor CIN grade, mostly owing to its low incidence (1.1%, 6/530). The opposite outcome was detected in case of the disjunction of both features, which was substantially more frequent (19.9%). Umbilication and ridge sign, if evaluated separately, highly specifically indicated HGL and consequently reached high positive predictive value. Umbilication in particular reached 100% specificity because no case of tiles with umbilication was found in patients with CIN 1. On the other hand, the sensitivity of both features for the detection of CIN 2/3 was low (ranging from 0.07 to 0.15), which was due to the low incidence thereof.

There was a significant association between umbilication and transformation zone type 1, coarse mosaic pattern, and absence of dense acetowhite epithelium ( $p < .01$ ). The presence of umbilication and ridge sign in combination did not reveal any significant association with any of the colposcopic features. Positive predictive value, negative predictive value, sensitivity, and specificity of umbilication and ridge sign for colposcopic finding of HGL were 1.00, 0.29, 0.02, and 1.00, respectively. Positive predictive value, negative predictive value, sensitivity, and specificity of umbilication and ridge sign for biopsy result of CIN 2/3 were 0.95, 0.23, 0.24, and 0.95, respectively (see Table 3).

## DISCUSSION

The aim of colposcopy is to rule out invasive carcinoma, triage abnormal results of screening, assess the extent and topography of pathological lesion and to perform directed biopsy from the most advanced morphological changes [2–4]. Colposcopic accuracy depends on the severity of the lesion and the skill and experience of the colposcopist [2]. Owing to the centripetal spread of CIN, the most significant changes are usually localized close to the squamocolumnar junction. Despite that, it may be sometimes difficult to identify the most suitable biopsy site. To increase the accuracy of colposcopy, it is therefore crucial to identify such features, which specifically predict areas with underlying high-grade CIN.

Acetowhite epithelium is the dominant feature associated with the presence of CIN, whereas vascular changes are found less frequently. In a series of 736 patients with CIN 2/3, Hellberg and Nilsson [4] found acetowhite epithelium in 42.2% to 52.2% of the patients, puncta-

tion in 20.3% to 36.8%, mosaic in 16.6% to 17.0%, and atypical vessels in 2.7% to 3.1% of patients. Vessels having larger caliber and larger intercapillary distances form coarse punctation and coarse mosaic, which tend to occur in more severe neoplastic lesions [5, 6]. However, the distinction between coarse vascular pattern and the corresponding fine changes may be blurred. The identification of 2 or more tiles with umbilication proved to be more accurate than the subjective differentiation between coarse and fine mosaic pattern in our cohort. Umbilication alone showed 12% sensitivity and 100% specificity for subsequent confirmation of CIN 2/3. Umbilication thus reached a higher specificity for underlying CIN 2/3 compared with results published for ridge sign (specificity, 93.1%) or inner border sign (specificity, 97%) [2, 3]. Moreover, the umbilication is easy to recognize and can be helpful sign especially for beginners in colposcopy.

Umbilication was more frequently associated with transformation zone type 1, which is common particularly in younger women. Despite that, the prevalence of umbilication showed no difference between the younger and older group of patients ( $p = .059$ ). Furthermore, there was no difference in the prevalence of umbilication depending on the variation of acetowhite color. That is important especially in older patients where acetowhite changes associated with CIN are less conspicuous than in younger patients. As many as 38% to 55% of CIN 2/3 cases could be therefore missed in the group of older women [7]. The same conclusion was confirmed in studies assessing the prevalence of ridge sign and inner border sign. The possibility to fully visualize squamocolumnar junction is a prerequisite for identifying both features; yet, such visualization is difficult to achieve in older women, that being the main reason why the features were significantly more often found in women younger than 35 years ( $p < .001$ ) [2, 3].

Reid Colposcopic Index (RCI) is often used in the diagnostic process. Overall, predictive accuracy of RCI as described by the authors is greater than 95% [5, 6]. Recently published articles, however, indicated that sensitivity of a modified RCI with its component scores of color, margin, and vessels is less reliable and accurate [8, 9]. For example, only 54.8% of women with a final diagnosis of CIN 3 referred to the immediate colposcopy arm of large atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study had a positive colposcopic biopsy result at enrollment [8]. One of the causes was a high interobserver variability due to the absence of highly specific

colposcopic features in RCI. Introducing umbilication and ridge sign in the scoring system could improve its diagnostic value. Moreover, because dynamic changes occur during colposcopy examination, umbilication can be observed independently from epithelial changes including ridge sign. Both umbilication and ridge sign, if evaluated separately, indicated HGLs with high specificity and consequently reached high positive predictive value of 95% and 100%, respectively. The disjunction of umbilication and ridge sign yielded slightly better results than umbilication or ridge sign alone, particularly in predicting CIN 3.

### SUMMARY

Umbilication is an age-independent colposcopic feature, which highly specifically predicts underlying CIN 2/3. Targeted identification of umbilication and ridge sign significantly increases the specificity of colposcopy for the determination of relevant biopsy site.

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