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Colposcopy and additive diagnostic value of biopsies from colposcopy-negative areas to detect cervical dysplasia

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Abstract

Introduction. We evaluated colposcopy in the routine diagnostic workup of women with abnormal cervical cytology, as well as the diagnostic value of endocervical curettage material and biopsies taken from colposcopy-positive and colposcopy-negative quadrants of the cervix. *Material and methods.* This cross-sectional study included 297 nonpregnant women with abnormal cervical cytology and no prior treatment for cervical dysplasia or cancer. All women underwent gynecological examination, colposcopy, endocervical curettage, and had cervical biopsies taken. Colposcopy was considered satisfactory if the squamocolumnar junction was fully visible, and biopsies were taken from all four quadrants of the cervix, regardless of colposcopy results. *Results.* In all, 130 of the women in our study had satisfactory colposcopy results and were diagnosed with cervical intraepithelial neoplasia grade 2 or worse (CIN2+), 61% via a colposcopy-positive biopsy and 39% via a colposcopy-negative biopsy. Eighty-seven of them had positive colposcopy results, but CIN2+ was histologically verified from colposcopy-positive biopsies in 91% ($n = 79$) and from colposcopy-negative biopsies in 9% ($n = 8$). The remaining 43 women with CIN2+ had negative colposcopy findings, so their diagnosis was verified in colposcopy-negative biopsies. The sensitivity of colposcopy alone to detect CIN2+ was 61% (95% CI 52–69). *Conclusions.* In the present study, colposcopy was not a stand-alone diagnostic method. Colposcopy-negative biopsies had a clear additive value, identifying a substantial proportion of women with both positive and negative colposcopy results with treatment-worthy cervical dysplasia. Endocervical curettage material had little diagnostic value in this study.

Abbreviations: ACIS, adenocarcinoma in situ; AGUS, atypical glandular cells of undetermined significance; ASC-H, atypical squamous cellsfavor high-grade; ASC-US, atypical squamous cells of undetermined significance; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Introduction

Colposcopy is the visual inspection of the cervix under magnification and is one of the first steps in the diagnostic workup of women with abnormal cervical cytology. For colposcopy to be deemed satisfactory, the squamocolumnar junction and the transformation zone must be visible. The criteria for positive colposcopy results are well established and include the detection of

blood vessel abnormalities (punctuation, mosaic, and atypical vessels), whitening of the epithelium after the application of acetic acid, color changes after the application of iodine, size, and demarcation. Several scoring systems for colposcopy have been developed (1–3). The purpose of colposcopy is to guide subsequent histological sampling, the result of which governs treatment.

Several studies have reported that colposcopy-directed biopsies are suboptimal and fail to detect cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in 26–57% of cases (4–7). Some authors have found that an increase in the number of biopsies taken from colposcopy-positive areas improves the detection of high-grade dysplasia (4,5,8,9). Others have shown that taking additional biopsies from colposcopy-negative areas increases the detection of CIN2+ (7,10,11). Although the performance of and diagnostic criteria for colposcopy are now standardized, colposcopy-directed tissue sampling seems to be less standardized with regard to the number of samples to take and the sites to be sampled.

In Norway, national guidelines dictate that all women with high-grade cytological abnormalities are to be referred to colposcopy and biopsy. This is also the case for women who are positive for human papillomavirus with persistent low-grade cytological abnormalities at repeat cytology, as well women with persistent high-risk human pappillomavirus and normal cytology (12). The aim of our study was to evaluate colposcopy in the routine diagnostic workup of these women, as well as the diagnostic impact of endocervical curettage material and biopsies taken from colposcopy-positive and colposcopy-negative quadrants of the cervix.

Material and methods

Between November 2010 and June 2012, we recruited women who were referred for colposcopy and biopsy according to Norwegian national guidelines (12) at the Department of Obstetrics and Gynecology, St. Olav's Hospital, Trondheim University Hospital, Norway. Women who were pregnant or had received previous treatment for cervical dysplasia or cancer were not eligible to participate. Written informed consent was obtained from all included women, and the study was approved by the Regional Committee for Ethics in Medical Research, West Region, Norway (2010/420).

Medical history was obtained through interview at the time of examination, and data on smoking habits and lifetime number of sexual partners were collected using a self-administered questionnaire. All women underwent a routine gynecological examination, colposcopy, endocervical curettage, and had cervical biopsies taken. All procedures were performed by the same experienced gynecologist, who was not blinded to the referral cytology.

During colposcopy, the squamocolumnar junction and transformation zone were sought and an assessment was made for each quadrant of the cervix. Then, 3% acetic acid was applied and another assessment was performed. Colposcopy results were recorded according to the Reid Colposcopic Index criteria (margin, color, vessels), with the exception of iodine staining, which was not used (1). Colposcopy was considered satisfactory if the entire squamocolumnar junction was visible. Biopsies were taken from all four quadrants of the cervix for each woman, regardless of colposcopy results. After biopsies were taken, endocervical curettage was performed.

Cervical biopsies and endocervical curettage material were examined and histological results were classified according to the 2003 World Health Organization classification (13). The results were reviewed independently by two pathologists (CV or MV), and final histology for each woman was defined as the most severe pathology detected in all of the samples.

Statistical analyses

Statistical analyses were performed using STATA 12.0 (Stata Corp, College Station, TX, USA). Confidence intervals for proportions were estimated using the exact option for binomial variables in STATA. The sensitivity, specificity, positive predictive value, and negative predictive value of colposcopy vs. histology were calculated with 95% CIs.

Results

In total, 305 women fulfilled the study inclusion criteria and consented to participate. Eight women whose pathology report indicated that no squamocolumnar junction was found in biopsies or endocervical curettage material were excluded, leaving a study sample of 297 women. Ninety-eight per cent of the study sample was Caucasian. Mean age at first sexual intercourse was 17 years (range 13–32 years) and did not differ between age cohorts. In contrast, having more than 10 sexual partners in one's lifetime was less common in older age cohorts, with 36% of women aged 19–49 years reporting more than 10

Key Message

In our study, biopsies from colposcopy-negative quadrants of the cervix increased the detection of cervical intraepithelial neoplasia in women with and without colposcopic lesions.

sexual partners, compared with only 5% of women aged ≥50 years (Table 1).

Cervical cytology was classified according to the Bethesda Classification of 2001 (14). Mean time between referral cytology and colposcopy was 99 days (range 13–485 days), and the most frequent referral cytology diagnosis was atypical squamous cells favor high-grade (ASC-H) (43%), followed by high-grade squamous intraepithelial lesions (HSIL) (33%) and atypical glandular cells of unknown significance (AGUS) (12%) (Table 2). Among women <25 years of age, 91% (95% CI 76–98%) had ASC-H, HSIL, or adenocarcinoma in situ (ACIS); compared with 41% (95% CI 21–64%) among women aged ≥50 years. Moreover, 41% (9/22) of women aged ≥50 years had a referral cytology of AGUS, compared with 10% (28/275) of women <50 years of age (data not shown). An increased proportion of CIN2+ was found with increasing severity of cytology, with CIN2+ diagnosed in 15% of women with ASCUS, 19% of those with AGUS, 36% of those with low-grade squamous intraepithelial lesions (LSIL), 59% of those with ASC-H, and 84% of those with HSIL (Table 2).

The squamocolumnar junction was fully visible in 70% (207) of all study women, partly visible in 20%, and not visible in 10% (Table 3). As expected, visibility of the squamocolumnar junction was related to age: 201 of the 275 women <50 years of age (73%, 95% CI 67–78%) had a fully visible squamocolumnar junction, compared with only six of the 22 women aged ≥50 years (27%, 95% CI 11–50). Colposcopy results were positive (i.e. indicated cervical dysplasia) in 51% (150/297) of the study sample. Acetowhite lesions were the most frequent, present among 85% of the women, followed by punctuation in 68%, and mosaic in 57%.

Table 1. Selected characteristics of the 297 study participants.

Characteristics	Total	
	n	%
Mean age and range, years	35 (19–75)	
Smoker		
Yes	94	32
No	203	68
Parity		
0	103	35
1–2	138	46
3–6	56	19
Lifetime number of sexual partners		
1	20	7
2–4	70	24
5–10	106	36
>10	100	34

Table 2. Histology according to referral cytology.

	Histology					
	Normal		CIN1		CIN2+	
	n	%	*n*	%	*n*	%
Referral cytology						
Persistent HPV infection (*n* = 4)	3	75	0	0	1	25
ASCUS (*n* = 13)	5	39	6	46	2	15
LSIL (*n* = 11)	6	55	1	9	4	36
AGUS (*n* = 37)	24	65	6	16	7	19
ASC-H (*n* = 129)	35	27	18	14	76	59
HSIL (*n* = 98)	10	10	6	6	82	84
ACIS (*n* = 2)	0	0	0	0	2	100
Other[a] (*n* = 3)	1	33	1	33	1	33
Total (*n* = 297)	84	28	38	13	175	59

CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; AGUS, atypical glandular cells of uncertain significance; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ACIS, adenocarcinoma in situ.

[a]Includes one women with LSIL where HSIL cannot be excluded, one adenocarcinoma and one where adenocarcinoma cannot be excluded.

Table 3. Colposcopy results by visibility of the squamocolumnar junction (SCJ) irrespective of histology.

	All women (*n* = 297)				
	Negative colposcopy results		Positive colposcopy results		Total
	n	%	*n*	%	*n*
Visibility of SCJ					
SCJ not visible	29	94	2	6	31
SCJ partly visible	26	44	33	56	59
SCJ fully visible	92	44	115	56	207

Twenty-eight per cent of our study women had normal histology, 13% had CIN1, and the remaining 175 women had CIN2+ (13% CIN2, 45% CIN3), and five (1%) ACIS, including four with coexisting CIN3. Invasive cancer was not found in any of the biopsies or endocervical curettage material. The proportion of women with CIN2+ was considerably higher among women <50 years of age (62%, 95% CI 56–68%) compared with women aged ≥50 years (18%, 95% CI 5–40%).

Among the 175 women with CIN2+, the lesion was found only in biopsies in 135 (77%). The lesion was found in both biopsies and endocervical curettage material in 39 (22%) women, and one woman had the lesion

in endocervical curettage material only. The proportion of women with CIN2+ detected in endocervical curettage material increased with the severity of dysplasia: 5% among the 37 women with CIN2 compared with 28% of the 138 with CIN3 and/or ACIS. However, it should be noted that the amount of endocervical curettage material was found to be unsatisfactory in 21% of women.

The relation between histology and colposcopy in the entire study sample showed crude sensitivity and specificity of 65 and 70%, respectively, of colposcopy to detect CIN2+, with corresponding positive and negative predictive values of 75% and 58% (Table 4). Specificity tended to be lower (64%), and sensitivity only improved slightly to 67%, when the analysis was restricted to women with a fully visible squamocolumnar junction (Table 4).

Focusing on the 207 women with satisfactory colposcopy, 130 women had CIN2+ (Table 4). Forty-three (33%) of the women with histologically-confirmed CIN2+ had negative colposcopy results. Among women with CIN2+ and positive colposcopy results, eight (6%) had CIN2+ located only in colposcopy-negative biopsies, leaving 79 "true-positive" women who had their dysplasia identified from a colposcopy-positive biopsy (Table 5), rendering a sensitivity of 61% for colposcopy to detect CIN2+ lesions in this subsample (95% CI 52–69%). When looking at subcategories of dysplasia, we observed trends of increased positive colposcopy results with increasing severity of dysplasia. Indeed, 48% of women with CIN2 had negative colposcopy results, compared with only 29% of women with CIN3 and/or ACIS. Also, the proportions of women with dysplasia detected in colposcopy-positive biopsies increased from 45% in CIN2 to 65% in CIN3 and/or ACIS. Among the 79 women with CIN2+ detected in colposcopy-positive biopsies, 51 (65%) also had dysplasia detected in colposcopy-negative biopsies.

In the 43 CIN2+ women with fully visible squamocolumnar junction and negative colposcopy results, on average two of the four biopsies taken contained CIN2+.

Discussion

In our setting of current clinical practice, we found more severe referral cytology in young women. As expected, this correlated with a higher yield of significant dysplasia (CIN2+) in these women. This probably reflects a high threshold for cytological sampling and colposcopy referral in younger women, particularly those who are too young to participate in the screening program (which starts at 25 years in Norway), as opposed to a low threshold for colposcopy referral of women aged >50 years with cytological abnormalities. The substantially higher proportion of AGUS cytology in older women also contributes to this difference.

We took ectocervical biopsies from all four quadrants and endocervical curettage material from all study women. As the severity of dysplasia increased, dysplasia was more often observed in both biopsies and curettage material, whereas we found only one women with dysplasia detected in the curettage material only. This woman had CIN3 and was a 53-year-old postmenopausal woman with a partly visible transformation zone. This result is in agreement with the majority of previous studies, which have led to the discussion if endocervical curettage should only be performed in women with invisible transformation zones (5,8,9,15). However, at least two studies have recommended endocervical curettage in all women above 25 years (7,15). Our own conclusion on this point should be cautious due to small numbers and a high proportion of suboptimal endocervical specimens.

Table 4. Colposcopy results by histology in all women and in women with the squamocolumnar junction fully visible.

	Histology					
	<CIN2		CIN2		CIN3/ACIS	
	n	%	*n*	%	*n*	%
All women						
Colposcopy results						
Negative	85	70	19	51	43	31
Positive	37	30	18	49	95	69
Total (%)	122	100	37	100	138	100
Women with the squamocolumnar junction fully visible						
Colposcopy results						
Negative	49	64	13	48	30	29
Positive	28	36	14	52	73	71
Total	77	100	27	100	103	100

CIN, cervical intraepithelial neoplasia; ACIS, adenocarsinoma in situ.

Table 5. The distribution of diagnostic biopsies according to colposcopy results in women with histologically confirmed high-grade dysplasia and fully visible squamocolumnar junction (n = 130).

	Histology					
	CIN2		CIN3/ACIS		CIN2+	
	n	%	*n*	%	*n*	%
Source of diagnostic biopsy						
Colposcopy-negative women	13	48	30	29	43	33
Colposcopy-positive women						
Biopsy outside lesion	2	7	6	6	8	6
Biopsy inside lesion	12	45	67	65	79	61
Total	27	100	103	100	130	100

CIN, cervical intraepithelial neoplasia; ACIS, adenocarsinoma in situ.

The proportion of women with a visible squamocolumnar junction decreased with age, which was as expected. Of the 297 women in our study sample, 150 had positive colposcopy results, and, as expected, most of these had a fully or partly visible squamocolumnar junction. Only two women (6%) with a non-visible squamocolumnar junction had a positive colposcopy result. From a practical point of view, and in light of the relative insensitivity of colposcopy even in optimal conditions, we would argue that interpretation and conclusions should not be based on colposcopy in women without a visible squamocolumnar junction.

In the subcategory of women with CIN2+ and a visible squamocolumnar junction, the sensitivity of colposcopy was 67%, which is similar to that reported in previous studies (4,7,9,16). Although we observed a better sensitivity for colposcopy to detect CIN2+ among women with satisfactory colposcopy, this was not the case for specificity, which was lower (64%) in this subgroup than in the entire study sample (70%). Consequently, a see-and-treat policy based solely on colposcopy would imply a significant amount of both under- and overtreatment.

Due to the inherent problem of inferior sensitivity, several studies have evaluated the diagnostic impact of taking additional biopsies to compensate for this problem. Pretorius et al. reported an additional CIN2+ yield of 37.4% by taking biopsies from both colposcopy-negative and colposcopy-positive quadrants (7). Our results among women with satisfactory colposcopy are similar, as we found an additional yield of CIN2+ of 39% from colposcopy-negative quadrants. Pretorius et al. did not specify the colposcopy status of the women in their study who were diagnosed from colposcopy-negative biopsies. Our data showed that the majority of dysplasia in colposcopy-negative biopsies came from women with negative colposcopy results, but a significant minority (6% with CIN3/ACIS) was detected in the colposcopy-negative biopsies of women with positive colposcopy results. In the ATHENA trial, one colposcopy-negative biopsy obtained from women with negative colposcopy detected 21% of CIN2+ (11). In comparison, we detected 39% of CIN2+ among women with negative colposcopy results. A possible explanation for our higher yield could be that we took four biopsies, one from each quadrant, in all study women, including those with negative colposcopy results.

Two studies have reported a substantial diagnostic gain from taking more biopsies from colposcopy lesions, whereas random biopsies outside these lesions rendered only a minor additional gain (8,9). In both studies, colposcopy was comprehensive, with biopsies taken from the most to the least severe of the lesions. In the study by Nakamura et al., the findings were graded 1–3 and random biopsies were only taken in 29% of the patients (8). In the Biopsy Study, only 4.3% of the patients had negative colposcopy results (9).

In our design we put relatively less impact on colposcopy by taking biopsies from all four quadrants of the cervix: targeted biopsies were taken in quadrants with obvious findings, but all quadrants were sampled regardless of colposcopy results. We believe that these results are not contradictory, but rather reflect an inherent inferior sensitivity of colposcopy. Performing intensified colposcopy according to the above studies (8,9), or performing more limited colposcopy compensated by random biopsies similar to our design, could be expected to perform similarly with regard to CIN2+ detection. However, the second option offers ease of performance and practicality. Although the results of these studies are not directly comparable due to different designs, all studies point in the same direction that the inferior sensitivity of colposcopy can be compensated for by taking additional biopsies, which is also in accordance with the conclusion in the colposcopy part of the FUTURE vaccine studies (4).

The ALTS study by Gage et al. is also relevant to this discussion, as it showed that when nurse practitioners and general gynecologists took more biopsies from colposcopy-positive areas than their expert gynecological oncologist counterparts, an equal sensitivity was obtained (5).

A strength of our study was the prospective design including consecutive patients referred according to well-defined national guidelines leading to a low risk of selection bias. Furthermore, patient evaluation including colposcopy and histological sampling was uniformly structured. As all histology was revised, the risk of misclassification and random error were probably low.

A limitation could be that one gynecologist performed all the colposcopies, preventing us from assessing interobserver reliability. As colposcopic findings depend upon the skills of the colposcopist, the results may not be generalizable. On the other hand, this led to an equal and standardized examination of all the participants. The colposcopist was not blinded to referral cytology. This may have led to information bias, as a high-grade dysplasia in referral cytology might influence the colposcopic impression and interpretation. According to institutional tradition and policy, we did not use Lugols's iodine staining. This might have reduced the sensitivity of colposcopy, as iodine staining has been reported to be an independent predictor of high-grade lesions (3,6).

In conclusion, our results, which are in agreement with most recent studies, show that in a practical clinical setting, colposcopy is not a stand-alone diagnostic method. A significant proportion of relevant histological lesions were

detected in women with negative colposcopy results and a fully visible squamocolumnar junction, reflecting the low sensitivity of colposcopy. Even when colposcopy results were positive, we found that a significant number of cases would have been missed if biopsies had been restricted to colposcopy-positive quadrants. The most important clinical implications of our findings are to recommend that, in addition to biopsies from colposcopy-positive areas, biopsies should be taken from colposcopy-negative quadrants of the cervix in women with abnormal cytology.

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References

1. Reid R, Scalzi P. Genital warts and cervical cancer. VII. An improved colposcopic index for differentiating benign papillomaviral infections from high-grade cervical intraepithelial neoplasia. Am J Obstet Gynecol. 1985;153:611–8.
2. Bornstein J, Bentley J, Bosze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012;120:166–72.
3. Strander B, Ellstrom-Andersson A, Franzen S, Milsom I, Radberg T. The performance of a new scoring system for colposcopy in detecting high-grade dysplasia in the uterine cervix. Acta Obstet Gynecol Scand. 2005;84:1013–7.
4. Stoler MH, Vichnin MD, Ferenczy A, Ferris DG, Perez G, Paavonen J, et al. The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials. Int J Cancer. 2011;128:1354–62.
5. Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al. Number of cervical biopsies and sensitivity of colposcopy. Obstet Gynecol. 2006;108:264–72.
6. Zuchna C, Hager M, Tringler B, Georgoulopoulos A, Ciresa-Koenig A, Volgger B, et al. Diagnostic accuracy of guided cervical biopsies: a prospective multicenter study comparing the histopathology of simultaneous biopsy and cone specimen. Am J Obstet Gynecol. 2010;203:321.e1–6.
7. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004;191:430–4.
8. Nakamura Y, Matsumoto K, Satoh T, Nishide K, Nozue A, Shimabukuro K, et al. Optimizing biopsy procedures during colposcopy for women with abnormal cervical cancer screening results: a multicenter prospective study. Int J Clin Oncol. 2015;20:579–85.
9. Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. Multiple biopsies and detection of cervical cancer precursors at colposcopy. J Clin Oncol. 2015;33:83–9.
10. Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. J Low Genit Tract Dis. 2011;15:180–8.
11. Huh WK, Sideri M, Stoler M, Zhang G, Feldman R, Behrens CM. Relevance of random biopsy at the transformation zone when colposcopy is negative. Obstet Gynecol. 2014;124:670–8.
12. Norsk gynekologisk forening. Veileder i gynekologisk onkologi 2009: Premaligne lidelser i cervix: Norsk gynekologisk forening [Coaching in gynecological oncology 2009: Premalign disorders of the cervix: Norwegian gynecological association]. 2009. Available online at: http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/veileder-i-gynekologisk-onkologi-2009/premaligne-lidelser-i-cervix/ (accessed January 15, 2015).
13. Tavassoli FA, Devile P. Pathology and genetics of tumours of the breast and female genital organs (World Health Organization classification of tumours; 5). Lyon: IARC Press, 2003.
14. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114–9.
15. Gage JC, Duggan MA, Nation JG, Gao S, Castle PE. Detection of cervical cancer and its precursors by endocervical curettage in 13,115 colposcopically guided biopsy examinations. Am J Obstet Gynecol. 2010;203:481.e1–9.
16. Massad LS, Collins YC. Strength of correlations between colposcopic impression and biopsy histology. Gynecol Oncol. 2003;89:424–8.

