Published in final edited form as:

Obstet Gynecol. 2017 December ; 130(6): 1218–1225. doi:10.1097/AOG.0000000000002330.

Diagnosis of Cervical Precancers by Endocervical Curettage at Colposcopy of Women With Abnormal Cervical Cytology

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Abstract

Objective—To evaluate the performance of routine endocervical curettage (ECC) for diagnosing high-grade cervical intraepithelial neoplasia (CIN)2⁺ and additional precancers not otherwise detected by ectocervical biopsies.

Methods—In a secondary analysis of the Biopsy Study, a cross-sectional study conducted between 2009 and 2012 at the University of Oklahoma Health and Sciences Center that found incremental increase in detection of cervical precancers by multiple biopsies at colposcopy, ECC was performed in most women aged 30 years or older. Cervical intraepithelial neoplasia 2⁺ yield by ECC alone was evaluated in analyses stratified by cervical cytology (ASC-US or LSIL vs. ASC-H or HSIL⁺), colposcopic impression (<high-grade vs. high-grade), HPV16 infection status, whether the examination was satisfactory, and by ECC indications per the current guidelines for cervical cancer screening. The diagnostic value of ECC for detecting additional disease was evaluated by the number of lesion-directed ectocervical biopsies.

Results—Of the 204 women 30 years old, 181 (88.7%) underwent ECC. Overall ECC detected 14.4% CIN2⁺ (95% CI: 10.0–20.2%). Endocervical curettage was more likely to find disease in the endocervix among women with high-grade cytology, positive HPV16 infection, or high-grade colposcopic impressions (respective p-values < 0.05). Among women with ASC-US or LSIL cytology, those with an unsatisfactory examination had a 13.0% CIN2⁺ yield on ECC (95% CI: 6.1–25.7); when colposcopic examination was normal or satisfactory with visible abnormal lesions, ECC detected <5% CIN2⁺ in the endocervix. An ASC-H or HSIL⁺ cytology was associated with a CIN2⁺ yield of 25.8% by ECC (95% CI: 16.6–37.9%). However, ECC found only 3.9% (95% CI: 1.9–7.8%) additional CIN2⁺ beyond the cumulative disease detected by up to

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Financial Disclosure

The authors did not report any potential conflicts of interest.

Each author has indicated that he or she has met the journal's requirements for *authorship*.

Clinical Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00339989), NCT00339989.

four biopsies of visible acetowhite ectocervical lesions. Additional CIN2⁺ yield by ECC increased when fewer lesion-directed biopsies were taken (p-value < 0.05).

Conclusion—The additional yield of CIN2⁺ by ECC in a colposcopy with up to four ectocervical biopsies was low. Based on our findings, we recommend routine ECC be performed in women aged 45 years old with HPV16 infection and in any woman 30 years old with HSIL⁺ or ASC-H cytology, high-grade colposcopic impression, or ASC-US or LSIL cytology and unsatisfactory examination.

Introduction

Endocervical curettage (ECC) has been increasingly incorporated in the colposcopy-biopsy examination for a subset of approximately 3 million women undergoing colposcopic evaluation each year in the U.S.^{1–3} for abnormal screening cytology. Cervical colposcopy has limitations related to the reproducibility of colposcopic impression and biopsy placement.^{4–5} Some studies have suggested that colposcopic biopsy can fail to detect 30–50% of prevalent high-grade cervical precancers^{6–7}. To improve the accuracy of the overall cervical colposcopy-biopsy examination, taking multiple lesion-directed biopsies and ECC have both been proposed^{6,8–10}.

However, the specific indications for ECC remain debated¹¹. Besides the clear contraindication in pregnancy, there is wide agreement on the greater benefits of performing ECC in older women, in whom the squamo-columnar junction (SCJ) is more difficult to visualize entirely⁸. Yet the age cut-off to begin performing ECC differs between or is not stated in various management guidelines¹². The evidence for identifying women most likely to benefit from endocervical sampling based on cytology and colposcopic abnormalities has also been inconclusive due to biased selection of women undergoing the procedure^{8, 13–16}. Studies on routine ECC are heterogeneous in methodologies and designs and report a wide range of CIN2⁺ yield from 1.0% to 15%,^{3,11,17–19}.

To address selection bias related to cytology and colposcopic findings, we designed an ancillary analysis of the Biopsy Study²⁰ to evaluate detection of cervical precancers by routine endocervical sampling in women 30 years or older. Using a highly-standardized multiple-biopsy colposcopy protocol, we also compared the additional precancer yield by ECC over additional ectocervical biopsies.

Materials and Methods

In a secondary analysis, women 30 years old underwent routine endocervical sampling in the Biopsy Study, a cross-sectional study that evaluated the incremental benefit of multiple biopsies at colposcopy²⁰. Of the 2,270 women referred to the colposcopy clinic at the University of Oklahoma Health Sciences Center (OUHSC) between February 2009 and September 2012 for abnormal cervical screening results or treatment of previously diagnosed disease, 690 of 1,373 (50.3%) eligible women agreed to participate in the study. The remaining 897 women were excluded by history of previous surgery, chemotherapy, or radiation treatment for cervical disease or neoplasia; pregnancy; or known HIV infection²⁰. All women 30 years old enrolled in the Biopsy Study (age range: 18–76, median age: 26

years) were supposed to undergo endocervical sampling to avoid selection biases by cervical cytology or colposcopic findings. Women <30 years old received ECC for the following indications: discrepancy between colposcopic findings and HSIL referral cytology, unsatisfactory examination, or AGC or AIS cytology. Institutional Review Boards at both the OUHSC and the National Cancer Institute approved the study.

Community-based referral for colposcopy was based on the 2007 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines²¹. Each of the six participating colposcopists performed between 60–179 colposcopic examinations in the study. Cervical samples were collected using a Wallach broom and transferred to PreservCyt solution (Hologic, Marlborough, MA, USA) for cytology and HPV testing. After the cervix was assessed with 5% acetic acid application, each distinct area of aceto-white cervical epithelium in the transformation zone was sampled as a lesion-directed biopsy using sharp Tischler or Baby-Tischler biopsy forceps. A single random biopsy of normal-appearing cervical epithelium in any quadrant of the cervix was added if fewer than four lesion-directed biopsies were taken. Cervical specimens were placed into separate labeled containers with 10% buffered formalin. Each biopsy was ranked by the severity of colposcopic impression at the time of examination, stained with hematoxylin and eosin, and evaluated independently by a study pathologist for clinical management. In addition, p16-staining was performed to establish biomarker-adjudicated CIN endpoints for each cervical biopsy (CINtec, Roche mtm Laboratories, Mannheim, Germany)²².

To assess the endocervix, a sharp Kevorkian curette without basket was placed inside the endocervical canal. Gentle pressure was applied at its tip, and the curette was moved back and forth along the length of the endocervix while being rotated in a circular fashion to sample the entire circumference of the canal. The extension of sampling to lesions external to the cervical os was avoided during the procedure to minimize contamination with ectocervical tissue. A rapid spinning motion was exerted when removing the curette from the endocervical canal, trapping all tissue and cellular materials in the curette chamber. To retrieve any remaining curettage material, a Singly or Campion forceps could be introduced into the canal. In women with severe cervical stenosis, a cytobrush (Cervix-Brush) or Wallach broom was used to provide specimens to evaluate the endocervical canal.

Community-based referral cytology was reported using the Bethesda nomenclature²³. Women were referred with one of the following diagnosis - “atypical squamous cells of undermined significance” (ASC-US), “low-grade squamous intraepithelial lesion” (LSIL), “atypical squamous cells, favor high-grade” (ASC-H), “high-grade squamous intraepithelial lesion” (HSIL), “atypical glandular cells” (AGC), “adenocarcinoma in situ” (AIS), and “squamous cell carcinoma” (SCC)²³. HPV genotyping was performed using the Linear Array (LA) HPV Genotyping Test (Roche Molecular Diagnostics, Branchburg, NJ) according to the manufacturer’s instructions, with slight modifications^{24–25}.

Histological endpoints were defined according to the LAST criteria²⁶: All CIN3 and p16-positive CIN2 biopsies were grouped as high-grade cervical precancers. ECC samples did not yield sufficient specimens to perform p16-adjudication. CIN2⁺ on ECC defined the

precancer yield by routine endocervical sampling. Additional precancer yield by ECC was defined as CIN2⁺ not otherwise found on biopsies of ectocervical lesions.

As previously reported, the main analyses of the Biopsy Study found a 25% increase in detection of precancers between the first and second lesion-directed biopsy (60.6% to 85.6%); and a 10% increase between the second and third lesion-directed biopsy (85.6% to 95.6%). This incremental increase in sensitivity by multiple biopsies was observed in all subgroups of patient characteristics²⁰. In the current analysis, we first evaluated the overall yield of high-grade precancers on ECC, and stratified by age, referral cytology (ASC-US or LSIL vs. ASC-H or HSIL⁺), HPV 16 infection status, adequacy of squamo-columnar junction visualization (satisfactory vs. unsatisfactory colposcopy), or colposcopic impression (< high-grade vs. high-grade). Women missing any of the information were not included in the respective stratified analyses. CIN2⁺ yield by ECC was also estimated based on indications in the current U.S. management guidelines for cervical cancer screening¹¹. Specifically, we assessed the recommendations to perform ECC (1) routinely in non-pregnant women with ASC-H or HSIL⁺ cytology undergoing colposcopy and (2) selectively in women with ASC-US or LSIL cytology, who either had a normal colposcopy, unsatisfactory examination, or a satisfactory examination and visible colposcopic lesions. We evaluated the additional CIN2⁺ yield in ECC by varying the number of ectocervical biopsies (from only one biopsy of the most severe colposcopic lesion, to up to four acetowhite lesions), which changes the cumulative disease found on the ectocervix. All analyses were performed with the statistical programming language R-3.1.2, in the open-source integrated development environment of RStudio.

Results

Of 204 women ≥ 30 years old enrolled in the Biopsy Study, 181 received an endocervical curettage procedure (88.7%). Among 477 women < 30 years old, 100 had ECC (21.0%) for discrepancy between normal colposcopy and HSIL referral cytology, an unsatisfactory colposcopy, or AGC or AIS cytology results (data not shown). We compared characteristics between 23 women ≥ 30 years old who did not receive ECC and the majority of 181 who did. Women without an ECC were more likely to have a satisfactory examination (78.3% vs. 58.0%, χ^2 p-value < 0.05), but did not differ from those who received an ECC by the prevalence of HPV infection and types, cervical cytology, or colposcopic impression. (Table 1) Of the 181 ECC samples, 144 were normal (79.6%, 95% CI: 73.1–84.8%); 5 showed atypical metaplasia (2.8%, 95% CI: 1.2–6.3%); 6 showed CIN1 (3.3%, 95% CI: 1.5–7.0%); 14 showed CIN2 (7.7%, 95% CI: 4.7–12.6%); and 16 showed CIN3⁺ (8.8%, 95% CI: 5.5–13.9%). Seven of the 23 women who met the age criterion but did not receive ECC were diagnosed with CIN2⁺ on ectocervical biopsies.

We evaluated the diagnostic yield of CIN2⁺ based on routine endocervical curettage. Age stratification by 10-year increments showed overall higher CIN2⁺ yield by ECC with increasing age. Of 99 women 20–29 years old who received ECC for specific indications other than age, 10 (10.1%, 95% CI: 5.6–17.6%) showed CIN2⁺ in the endocervix. Routine ECC found 11.9% CIN2⁺ (95% CI: 7.1–19.4%) among 30–39 year-old women, 18.0% among 40–49 year-old women (95% CI: 9.8–30.8%), 14.3% among 50–59 year-old women

(95% CI: 4.0–40.0%), and 25% (95% CI: 9.7–70.0%) among 60–69 year-old women (χ^2 test for trend; p-value = 0.55, Table 2). To avoid selection bias related to cervical cytology and colposcopic examination findings in the youngest age group, further analyses were restricted to the 181 women ≥ 30 years old who met age eligibility for endocervical sampling at colposcopy.

The ECC found CIN2⁺ among 26 of 181 women (14.4%; 95% CI: 10.0–20.2%) ≥ 30 years old. CIN2⁺ yield by ECC was significantly higher among women with an ASC-H or HSIL⁺ (includes AGC, AIS, and SCC) cervical cytology (27.1%) versus 7.3% in women with ASC-US or LSIL cytology (p-value <0.05), positive HPV16 infection (24.4% vs. 11.5% in women without HPV 16 infection, p-value <0.05), or high-grade colposcopic impression (26.8% vs. 8.0% in women with <high-grade impression, p-value <0.05), and non-significantly higher among women with inadequate colposcopies (20.3% of 74 women with unsatisfactory examination vs. 10.5% of 105 women with satisfactory examination, p-value 0.07) (Table 3). Our study population (women who qualified for ECC procedure at colposcopy based on age of ≥ 30 years old) was relatively young; only 22.1% were ≥ 45 years old. Statistical power was limited to detect unique findings in women ≥ 45 years of age, but similar trends among women 30–44 years old held in this age group, except for the association between endocervical involvement and HPV16 positivity (Table 4).

We stratified women based on the indications for ECC in the current U.S. management guideline for cervical cancer screening (Table 5). Among women with ASC-US or LSIL cytology, endocervical sampling is preferred when the colposcopic examination is normal or unsatisfactory, and is acceptable when the examination is satisfactory with visible colposcopic lesions. Among women with ASC-US or LSIL cytology, ECC found CIN2⁺ in 4.3% of normal examinations (95% CI: 0.8–21.0%), 13.0% of unsatisfactory examinations (95% CI: 6.1–25.7%), and 1.9% of satisfactory examinations with positive findings on the ectocervix (95% CI: 0.3–10.0%). The indication for performing ECC in all non-pregnant women with ASC-H or HSIL referral cytology was associated with a 25.8% CIN2⁺ yield in the endocervix (95% CI: 16.6–37.9%). The number of additional CIN2⁺ by ECC not otherwise found on ectocervical biopsies was too few for analyses in these strata (data not shown).

We also evaluated the utility of ECC for diagnosing precancers otherwise missed on ectocervical biopsies. Endocervical sampling showed a CIN2⁺ yield of 14.4% (95% CI: 10.0–20.2%) when no lesion-directed ectocervical biopsies were taken. In the multiple-biopsy colposcopy protocol, cumulative CIN2⁺ yield on the ectocervix increased with the number of lesion-directed biopsies. Sampling the worst-appearing lesion found CIN2⁺ in 21.0% of examinations, and adding one, two, or three additional colposcopic biopsies showed 27.6%, 29.3%, and 29.8% CIN2⁺, respectively. Additional yield of CIN2⁺ by ECC (gain over ectocervical biopsies) decreased from 7.7% to 5.0%, 4.4%, and 3.9% with the incremental increase in detection of precancer by each successive lesion-directed colposcopic biopsy of the ectocervix (χ^2 test for trend; p-value < 0.05, Table 6).

Discussion

Detecting endocervical disease on ECC during colposcopy can increase the sensitivity of colposcopy and biopsy, and inform the method of treatment. However, there is controversy about when endocervical sampling should be performed. In the Biopsy Study²⁰, selecting for the ECC procedure by age alone affirmed previously reported associations between diagnosing cervical precancers on routine ECC and high-grade colposcopic impression and ASC-H or HSIL⁺ cytology. For the first time, we described an association between HPV16 infection and positive ECC among women ≥ 45 years old (Tables 3 and 4). Unconstrained by selection biases, our findings support the following ECC indications in the current cervical cancer screening guidelines – (1) ASC-H or HSIL⁺ cytology; (2) ASC-US or LSIL cytology with unsatisfactory colposcopy. Using a multiple-biopsy colposcopy protocol, we showed that detection of additional CIN2⁺ by ECC substantially decreases with increasing number of ectocervical biopsies (Table 6).

Considerations for the risk of finding precancers in the endocervix differ by age. In contrast to previous research, we showed that ECC did not yield significantly more disease in unsatisfactory examinations in women 30–44 years old. (Table 4). This suggests that for younger women, incomplete visualization of the squamo-columnar junction can be related more to the colposcopist's technique and does not necessarily raise concern for missed disease in the endocervix. Examination technique may attribute less to the incomplete visualization of squamo-columnar junction in older women, which recedes into the endocervix with postmenopausal decrease of estrogen level. However, our finding of 10.1% CIN2⁺ yield on ECC in women 20–29 years old implicates that AGC or AIS cytology, unsatisfactory examination, as well as discrepancy between HSIL cytology and normal examination, remain important considerations for performing endocervical curettage in young women. HPV16 positivity in women ≥ 45 years old should particularly raise concern for persistent oncogenic infection and trigger endocervical sampling at colposcopy. Based on a woman's age, it is important to distinguish the different sets of examination technique and biological factors associated with the risk of endocervical disease.

Given acetowhitening is highly sensitive for the detection of cervical precancers²⁷, the additional yield of CIN2⁺ by ECC was $< 10\%$ in our study even when the worst-appearing colposcopic lesion was the only ectocervical biopsy taken. The detection of additional precancers by ECC may appear greater in studies that used biopsy protocols targeting less-sensitive lesion characteristics such as mosaicism or punctation. This relationship of ECC yield to biopsy protocols may in part explain the heterogeneity of previous findings regarding yield of ECC in different studies.

Furthermore, presence of endocervical disease may be important in guiding the decision between ablation and excisional treatment. The current U.S. management guideline recommends against ablation in women with significant endocervical disease¹². Our results showed that an unsatisfactory examination in women with low-grade or equivocal cytology warrants endocervical sampling, which may indicate excision rather than ablation therapy in approximately one out of every 7 or 8 women. A high-grade cytology is associated with

endocervical disease in approximately one out of every 4 women and also supports performing ECC.

Given the relatively young colposcopy population, the number of women 30 years old was small and limited the statistical power of some of our stratified analyses. The prevalence of HPV18 infection was low, preventing analyses of the association between HPV 18 infection and endocervical involvement of cervical precancers (data not shown). HPV genotyping was performed as part of the research protocol at colposcopy and further analysis of population screened by cytology-HPV contesting is necessary for evaluating ECC in women with normal cytology and high-risk HPV types. Since women younger than 30 years old had to have specific indications for ECC, we were not able to fully evaluate clinical predictors for performing endocervical sampling in this age group. A larger sample size would be needed to calculate more accurately the number needed to treat (NNT). Prospective concordance analyses between the histology of excision treatment specimen and ECC performed at colposcopy will better assess the accuracy of the endocervical sampling technique used in this study.

Our study addresses important questions about the role of ECC in colposcopic diagnosis and treatment of cervical precancers. Importantly, not every woman benefited from the ECC procedure equally. By refining the selection of women for ECC, young women with unsatisfactory examination may be spared a painful procedure, high-risk women with positive ECC will receive appropriate excision treatment to confirm the margin status and minimize missed disease or recurrence, and obstetric complication can be avoided in women with low-grade cytology and intermediate risk of precancers in the endocervix.

Acknowledgments

Supported by the Intramural Research Program of the National Cancer Institute.

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Table 1

Characteristics of women who met age eligibility for endocervical curettage

30 years old (row%)				
	Total	ECC Taken	No ECC Taken	P-value
Colposcopic Impression				
Normal or Acetowhitening	49	46 (93.9)	3 (6.1)	0.11
Low or High-grade	152	133 (87.5)	19 (12.5)	
Cervical Cytology				
ASC-US or LSIL	126	110 (83.3)	16 (12.1)	0.36
ASC-H or HSIL ⁺	68	62 (91.2)	6 (8.8)	
HPV Status				
HPV Negative	31	27 (87.1)	4 (12.9)	0.44
HPV16+	46	41 (89.1)	5 (10.9)	
HPV18+	16	15 (93.8)	1 (6.3)	
Oncogenic HPV+ (non 16/18 types)	113	100 (88.5)	13 (11.5)	
% SCJ Visualized				
Complete (Satisfactory Colposcopy)	123	105 (85.4)	18 (14.6)	<0.05
Partial or Not Visualized (Unsatisfactory Colposcopy)	79	74 (93.7)	5 (6.3)	
Total (row%)	204	181 (88.7)	23 (11.3)	

ASC-US: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, favor high-grade; HSIL: High-grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in situ; SCC = squamous cell carcinoma. HSIL⁺ includes HSIL, AGC, and SCC cytology. HPV: Human papillomavirus. SCJ: Squamo-columnar junction.

Table 2Age and CIN2⁺ yield by ECC

Age Group	N	ECC Diagnosis (row %)		P-value
		< CIN2 ⁺	CIN2 ⁺	
20–29 yro	99	89 (89.9)	10 (10.1)	0.55
30–39 yro	109	96 (88.1)	13 (11.9)	
40–49 yro	50	41 (82.0)	9 (18.0)	
50–59 yro	14	12 (85.7)	2 (14.3)	
60–69 yro	8	6 (75.0)	2 (25.0)	

ECC: endocervical curettage. Chi-square (χ^2) analyses for trend was conducted.

Table 3

CIN2⁺ detected by endocervical curettage among women aged 30 years or older

ECC Diagnosis (row%)				
	Total	< CIN2 ⁺	CIN2 ⁺	P-value
Overall	181	155 (85.6)	26 (14.4)	
Cervical Cytology	ASC-US or LSIL	110	102 (92.7)	8 (7.3)
	ASC-H or HSIL ⁺	62	46 (74.2)	16 (25.8)
				<0.05
HPV 16 Status	HPV 16 Negative	139	123 (88.5)	16 (11.5)
	HPV 16 Positive	41	31 (75.6)	10 (24.4)
				<0.05
% SCJ Visualized	Complete	105	94 (89.5)	11 (10.5)
	Partial or Not Visualized	74	59 (79.7)	15 (20.3)
				0.07
Colposcopic Impression	< High-grade	121	111 (91.7)	10 (8.3)
	High-grade	58	42 (72.4)	16 (27.6)
				< 0.05

Women missing information of cervical cytology, colposcopic impression, or the adequacy of colposcopic examination were not included in the respective χ^2 hypothesis tests. NA = not applicable, SCJ = squamo-columnar junction. ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in situ; SCC = squamous cell carcinoma. HSIL⁺ includes HSIL, AGC, and SCC cytology. No study participant had AIS cytology.

Table 4

CIN2+ detected by endocervical curettage among women aged 30-44 years

ECC Diagnosis (row %)				
	Total	< CIN2+	CIN2+	P-value
Overall	141	122 (86.5)	19 (13.5)	
Cervical Cytology	ASC-US or LSIL	88	82 (93.2)	6 (6.8)
	ASC-H or HSIL +	48	36 (75.0)	12 (25.0)
				<0.05
HPV 16 Status	HPV 16 Negative	109	96 (88.1)	13 (11.9)
	HPV 16 Positive	31	25 (80.6)	6 (19.4)
				0.22
% SCJ Visualized	Complete	94	84 (89.4)	10 (10.6)
	Partial or not visualized	45	36 (80.0)	9 (20.0)
				0.13
Colposcopic Impression	< High-grade	93	85 (91.4)	8 (8.6)
	High-grade	46	35 (76.1)	11 (23.9)
				< 0.05

ASC-US: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, favor high-grade; HSIL: High-grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in situ; SCC = squamous cell carcinoma. HSIL + includes HSIL, AGC, and SCC cytology. HPV: Human papillomavirus. SCJ: Squamo-columnar junction.

Table 5

CIN2⁺ yield by ECC when performed according to indications in the current cervical cancer screening and management guidelines¹¹

Indication		N	CIN2 ⁺ Yield by ECC (n;%)
Cervical Cytology	Colposcopic Impression/% SCJ Visualized		
ASCUS or LSIL	No lesion identified on colposcopy (preferred)	23	1 (4.3)
	Unsatisfactory colposcopy (preferred)	46	6 (13.0)
	Satisfactory colposcopy and lesion identified (acceptable)	53	1 (1.9)
ASC-H or HSIL ⁺	All non-pregnant women of screening age	62	16 (25.8)

ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in situ; SCC = squamous cell carcinoma. HSIL⁺ includes HSIL, AGC, and SCC cytology. SCJ = squamo-columnar junction.

Table 6Additional CIN2⁺ by ECC, given the number of lesion-directed ectocervical biopsies

Number of Lesion-Directed Ectocervical Biopsies	CIN2 ⁺ on Ectocervical Biopsy (n;% n/N)	Additional CIN2 ⁺ on ECC (n;% n/N)	P-value
Overall N = 181			
0	0 (0.0)	26 (14.4)	<0.05
1	38 (21.0)	14 (7.7)	
2	50 (27.6)	9 (5.0)	
3	53 (29.3)	8 (4.4)	
4	54 (29.8)	7 (3.9)	

Note that examinations with more than one lesion-directed ectocervical biopsy are represented more than once in this table; hence the total column count for the cumulative CIN2⁺ detected on lesion-directed ectocervical biopsies exceeds the number of total examinations (N > 181). Additional CIN2⁺ on ECC when the number of lesion-directed ectocervical biopsy was 0 is equivalent to the overall CIN2⁺ yield on ECC, as previously presented in Table 2. Chi-Square (X²) analysis for trend was conducted and does not include the aggregate rate of 26/181 in the first row.