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High-grade cervical dysplasia after negative loop electrosurgical excision procedure

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Abstract

Objectives—To describe the prevalence and correlates of high-grade cervical intraepithelial neoplasia (CIN2+) after a negative loop electrosurgical excision procedure (LEEP), performed for high-grade squamous intraepithelial lesion (HSIL) cervical cytology.

Methods—106 women from our university-based colposcopy clinic underwent LEEP between 2007 and 2014. Negative LEEP was defined as CIN1. Persistence/recurrence estimates were calculated by treatment (see-and-treat vs. 3-step conventional strategy—cervical cytology, colposcopic biopsy, LEEP) and LEEP results (negative vs. positive) using the Kaplan-Meier method. Predictors of CIN2+ after a negative LEEP were examined by multivariate Cox proportional-hazard model.

Results—Overall, the prevalence of CIN2+ after a negative LEEP for HSIL was 14%. Persistence/recurrence of CIN2+ was similar between women with a negative and positive see-and-treat LEEP (25% vs. 15%), and those with a negative or positive 3-step conventional LEEP (7% vs. 22%) (log-rank $p=0.58$). Positive LEEP margin was more common among women with a positive LEEP (53.7% see-and-treat vs. 42.6% conventional) compared to a negative result (0% see-and-treat vs. 3.7% conventional, $p<0.0001$). The risk of CIN2+ after a negative LEEP did not differ by management strategy (log-rank $p=0.85$) or LEEP result (log-rank $p=0.58$). In multivariate analysis, correlates of persistent/recurrent CIN2+ included older age [adjusted OR (aOR) 1.09, $p=0.0003$], history of prior LEEP (aOR 8.99, $p<0.0001$), and positive LEEP margin (aOR 13.56, $p=0.0005$).

Conclusions—A negative LEEP does not allow less stringent surveillance, as CIN2+ risk is similar to that after CIN2+ is found in the LEEP specimen, whether the specimen was obtained by see-and-treat or conventional 3-step approach.

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Précis

Margin status at LEEP after high grade cytology should not alter surveillance, as risk for persistent/recurrent CIN2+ is unaffected.

Keywords

Negative see-and-treat LEEP; recurrent CIN2+; HSIL cytology

Introduction

Sixty percent of women with high-grade squamous intraepithelial lesion (HSIL) are diagnosed with cervical intraepithelial neoplasia grade 2 or worse (CIN2+) at the time of colposcopy [1–3] and the 5-year cervical cancer risk among women 30 years of age and older is 8% [4]. Due to these substantial risks, the 2012 Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors [1] state that non-pregnant women older than 24 years of age with HSIL may be managed by immediate excision [ie, “see-and-treat” loop electrosurgical excision procedure (LEEP)], and this approach is specifically recommended when colposcopic examination is inadequate. As we and others have shown, compared to a 3-step conventional strategy (e.g. cervical cytology, colposcopic biopsy, LEEP), see-and-treat LEEP is cost-effective [5], reduces clinic visits, improves patient compliance, reduces patient anxiety [6], and has similar rates of overtreatment [4, 5, 7].

Most LEEP specimens correlate with the original biopsy diagnosis, but in some cases the LEEP specimen will fail to reveal residual high-grade disease. Historically, these LEEPs have been labeled overtreatment, and risk for overtreatment has been cited as a reason for avoiding see-and-treat LEEP. However, we recently conducted a prospective analysis of women with HSIL cytology from our university-based colposcopy clinic and reported negligible differences in overtreatment rates between see-and-treat and 3-step conventional strategy (20% vs 23%, $p=0.403$) [7]. Potential reasons for discrepancy between HSIL cytology and negative LEEP include diagnostic error, complete excision of the dysplastic focus by biopsy, spontaneous regression of the lesion, immune boosting by exposure of intraepithelial human papillomavirus (HPV) to stroma by biopsy, or secondary destruction of the dysplasia by post-biopsy inflammation [8].

Despite a growing body of literature that endorses see-and-treat LEEP within the United States and abroad in low resource countries, there are no published reports to date regarding CIN2+ recurrence risk after negative see-and-treat LEEP. At best we can extrapolate from few studies that have evaluated the clinical significance of a negative 3-step conventional LEEP strategy for HSIL cytology. Consistently, women with a negative LEEP have a recurrence rate of high-grade dysplasia similar to those with a positive LEEP result [8–11]. As such, it has been recommended that both populations should be observed closely with follow-up exams.

The purpose of this study was to evaluate the prevalence of CIN2+ during surveillance follow-up among women with HSIL cervical cytology who had a negative (e.g. CIN1 or less) vs. positive (CIN2+) see-and-treat or 3-step conventional LEEP. We hypothesize that patients with a negative LEEP portend a similar rate of persistent/recurrent CIN2+ as those with a positive result. We also suspect that outcomes of negative LEEP are similar regardless of management strategy (see-and-treat vs. 3-step conventional). Our second aim was to identify risk factors for CIN2+ persistent/recurrences after LEEP.

Methods

We performed a single institution, retrospective cohort study of women aged 25 and older with HSIL cytology who presented to the Colposcopy Clinic at Barnes-Jewish Hospital between January 2007 and December 2014. Our clinic does not have a specific protocol established to recommend see-and-treat LEEP over the 3-step conventional strategy for HSIL cytology. Given that we are an academic medical center, all LEEPs were performed by either a resident or fellow under the supervision of a gynecologic oncology attending. Prior to initiation of our study, all procedures were reviewed and approved on March 9, 2015 by Washington University's Human Research Protection Office (Institutional Review Board, IRB Project #201503011). Abstracted data from patient medical records were de-identified, and due to the retrospective nature of this project, informed consent was waived.

Women aged 25 years or older who presented with HSIL cytology and underwent LEEP were included. This specific age criterion was designated because see-and-treat LEEP is not recommended for women under 25 years unless completed childbearing. We recorded whether women underwent see-and-treat LEEP or 3-step conventional management of HSIL cytology and compared the incidence of CIN1 or less on final LEEP pathology (negative LEEP). The 3-step conventional group (control) comprised women with HSIL cytology who underwent colposcopic biopsies and proceeded to LEEP if those showed CIN2+ or if there was a 2-fold discrepancy between cytology and biopsy results. See-and-treat LEEP was offered unless women came with outside colposcopic biopsies showing CIN2+ or logistics including availability of treatment slots or child care or work responsibilities precluded immediate treatment. Patients were included without regard to whether their LEEP was performed in the outpatient setting under local anesthesia or scheduled as an operative procedure under monitored anesthesia care. We excluded women if they underwent see-and-treat LEEP for abnormal cytology other than HSIL, lacked follow-up data, were under 25 years old, had a positive pregnancy test, or had a history of cervical cancer. Our primary outcome, CIN2+ after LEEP, was diagnosed by either cervical cytology, biopsy, repeat LEEP, or hysterectomy specimen. All specimens underwent centralized review by subspecialized gynecologic pathologists in the Ackerman Laboratory of Surgical Pathology, Barnes-Jewish Hospital/Washington University School of Medicine.

SAS version 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses. Demographic and clinical characteristics were summarized by descriptive statistics and results were presented as means and standard deviations (SDs), or medians and interquartile ranges (IQRs) for continuous variables, and counts and percentages for categorical variables. The group difference among patients having different treatment (see-and-treat vs. 3-step

conventional LEEP) and LEEP results (negative or positive) was examined by Kruskal-Wallis tests for continuous variables and Fisher Exact tests for categorical variables. Any significant p-value represented in Table 1 is a significant difference between at least one cohort and the remaining groups. Recurrence-free survival (RFS) was defined as the time interval (in months) from the date of LEEP diagnosis to the date of recurrent CIN2+, death from any cause, or last follow-up. Kaplan-Meier curves were generated to provide unadjusted RFS estimates by treatment (see-and-treat vs. 3-step conventional LEEP) and/or LEEP results (negative vs. positive). Univariate Cox proportional-hazard models were used to evaluate the relationship between RFS and various risk factors separately. RFS difference between negative and positive LEEPs was examined via multivariate Cox proportional-hazard model adjusting for significant risk factors identified in the univariate analysis. Proportional hazard assumption was examined by Cumulative Martingale residual plots, log of negative log plots, correlations between Schoenfeld residual and rank of survival time, as well as significance tests of time dependent covariates. All analyses were two-sided and p-values ≤ 0.05 were considered statistically significant.

Results

We reviewed 168 electronic medical records of women who underwent LEEP for HSIL cervical cytology between 2007 and 2014. Of these, 106 (65%) women had follow-up data available and are the basis of our analysis. To evaluate for selection bias, we compared socio-demographic and clinical characteristics between women who were excluded due to no follow-up data (N=62) and women who were compliant with follow-up appointments. There were no significant differences between the two groups (data not shown).

Of the 106 women, 56 underwent see-and-treat LEEP and 50 completed a 3-step conventional management strategy for HSIL cytology with a median follow-up time of 12.7 and 13.1 months respectively ($p=0.84$). Among all women, the mean age at time of LEEP was 33 years, and the majority were non-Caucasian, including 61 African American and 1 Asian. With regards to risk-factors related to HSIL cytology, 58 women reported HPV positivity, 97 had never received the HPV prophylactic vaccine, 47 were cigarette smokers and 10 had previously undergone a LEEP for abnormal cytology (Table 1). Review of sexual and reproductive history revealed that most women were multiparous (median number of pregnancies was 3). Eighteen women denied any form of contraception while the remainder used either a reversible method, had previously undergone permanent sterilization, or were postmenopausal (Table 1).

Table 1 displays the demographic and clinical characteristics of women with HSIL cytology who underwent LEEP stratified by management approach and LEEP result. Over a median follow-up period of 13 months (range 0.8 to 91.7 months), the incidence of a negative LEEP after see-and-treat vs. 3-step conventional LEEP was 14% and 28% respectively ($p=0.08$). Overall, the 4 groups were well-balanced with the exception of positive margin status and reflective of a high-risk population for CIN2+ disease (Table 1). By definition, positive margin status was higher among women with a positive LEEP (54% see-and treat vs. 43% 3-step conventional) compared to those with a negative result (0% see-and-treat vs. 4% 3-step conventional, $p<0.0001$).

Table 2 displays the incidence of low- vs. high-grade dysplasia after LEEP based on LEEP result and subdivided by management strategy. Overall 31 of 106 (30%) women had dysplasia on follow-up exam, including 13 low-grade and 18 high-grade recurrences. Those with a negative LEEP overall experienced similar rates of abnormal cytology at follow-up compared to women with a positive result [negative: 5/22 (23%) vs. positive: 26/84 (31%), $p=0.60$]. Furthermore, there were no significant differences in the proportion of high-grade lesions when stratified by LEEP result [negative: 3/22 (14%) vs. positive: 15/84 (18%), $p=0.76$]. However, among the positive LEEP cohort, women with a positive margin had a significantly higher rate of persistent/recurrent CIN2+ compared to those with negative margins (27% vs. 3%, $p=0.014$) (Table 2). When analyzed by treatment strategy, there were no significant differences between see-and-treat vs. 3-step conventional strategy based on incidence of abnormal cytology at follow-up or recurrent CIN2+ disease (Table 2).

Next, Kaplan-Meier curves were generated to demonstrate differences in time-to-persistent/recurrent CIN2+ based on LEEP result and management strategy (Figure 1 and 2 respectively). Overall, there were no significant differences in time-to-persistent/recurrent CIN2+ based on treatment strategy (see-and-treat vs. 3-step conventional) and LEEP results (negative vs. positive) (log rank p -value = 0.58; Figure 1). The median RFS of CIN2+ was as follows: 6.8 and 4.8 months for negative and positive see-and-treat LEEP respectively compared to 6.6 and 5.0 months for negative and positive 3-step conventional LEEP respectively.

When analyzed by management strategy alone, there still remained no significant differences in RFS. The median RFS of CIN2+ who underwent see-and-treat vs. 3-step conventional LEEP was 4.8 and 5.5 months respectively (log-rank, $p=0.85$, Figure 2).

Lastly, multivariate Cox proportional-hazard model revealed that correlates of CIN2+ recurrence included older age (adjusted hazard ratio, aHR 1.09, $p<0.001$), history of prior LEEP (aHR 8.99, $p<0.0001$), and positive LEEP margin (aHR 13.56, $p<0.001$) (Table 3). After adjusting for these potential confounders, management strategy was not correlated with recurrent CIN2+ after LEEP.

Discussion

A negative LEEP after HSIL cytology requires diligent surveillance, as our results show that CIN2+ recurrence risk is similar to that after LEEP with CIN2+. The presence of CIN1 or less at LEEP is not an uncommon finding and furthermore the recurrence rate of CIN2+ following a negative LEEP is similar regardless of management strategy (see-and-treat vs. 3-step conventional strategy), LEEP outcome (CIN1 or less vs. CIN2+), or LEEP margin status (negative vs. positive). Without 3-step conventional strategy conferring an advantage of RFS, see-and-treat should be favored for HSIL cytology especially when providing outreach services to indigent women who have limited access to healthcare and compliance is questionable. We accept a higher rate of negative LEEP in our university-based colposcopy clinic due to our poor compliance and a default rate of 23% for scheduled LEEP appointments.

Our findings provide insight for see-and-treat LEEP, but overall reflect slightly higher rates of negative LEEP and persistent/recurrent CIN2+ compared with other studies that have evaluated outcomes after negative 3-step conventional LEEP [8–10]. Overall, the majority of reported CIN2+ recurrence rates after a negative LEEP fall between 0.6% and 13% [8, 9]. We previously studied a larger cohort of 178 women with HSIL cytology (including the 106 women presented here), and have shown that see-and-treat LEEP does not carry a higher risk for overtreatment (CIN1 or less) compared with the 3-step conventional strategy (20% vs. 25%, respectively, $P=0.403$). There were no differences in location of procedure (operating room under monitored anesthesia care vs. outpatient clinic), LEEP specimen size, number of top hat excision procedures, positive margin status, or complications [7]. Most similar to our results, Livsay et al [10] found that patients with a negative LEEP had a recurrence rate of CIN2+ similar to patients with positive LEEPs (13% vs. 17%) with negligible differences in time-to-recurrence ($p=0.63$, log rank test). Taken together with our findings, a negative LEEP is not a reassuring finding and these patients should receive the same follow-up as those with a positive LEEP.

We also identified independent risk factors associated with recurrent CIN2+ disease including older age, history or prior LEEP and positive margin status. It is well established that incomplete excision of dysplasia is associated with LEEP failure rates [11–16]. However, considering these 3 risk factors altogether may enhance the post-test probability of recurrent CIN2+ and assist physicians in counseling women about their individualized risk and personalized management, including re-excision and even hysterectomy. Supportive of this, Dietrich and colleagues performed a retrospective study of 298 women who underwent 3-step conventional LEEP and evaluated risk factors for early cytologic abnormalities post excision procedure [11]. Twenty-nine percent of women had histologic features including positive ectocervical and/or endocervical margin or glandular involvement with dysplasia, but none were found to be independent risk factors for early cytologic abnormalities. However, when these risk factors were analyzed cumulatively, the abnormal cytology rate increased from 24% with no risk factors to 67% with all 3 present ($p=0.037$).

Strengths of our study are highlighted in our methodology which allowed for clinically meaningful and cross-study comparisons with prior publications. Including the 3-step conventional group as a control not only allowed us to study the clinical significance of a negative vs. positive LEEP, but it also enabled us to evaluate the impact of treatment strategy on long-term outcomes. Another key strength was our definition of negative LEEP (e.g.

CIN1). Despite lack of consensual agreement on the definition of negative LEEP, we choose our cutoff criteria based on American Society for Colposcopy and Cervical Pathology (ASCCP) management algorithms which allow women with HSIL cytology and CIN1 on cervical biopsy (with adequate colposcopy and negative endocervical sampling) to undergo co-testing at 12 and 24 months as an alternative to a diagnostic excision procedure.

Some limitations of our study are inherent to our retrospective study design, such as lack of randomization, limited sample size, and incomplete follow-up. However, socio-demographic and clinical characteristics displayed in Table 1 show that our 2 treatment groups were overall well-balanced with the exception of margin status. We also addressed the possibility of selection bias by comparing baseline characteristics between women who were excluded

and included based on availability of follow-up data, and no statistically significant differences were detected. With regards to our sample size, we worked under the constraints of our colposcopy clinic referral volume and included all patients who met eligibility criteria with follow-up data. We acknowledge the lack of power calculation to demonstrate a significant difference between negative and positive LEEP results. However, considering the feasibility of an adequate sample size with appropriate length of follow-up, as a compromise, we believe the consistency of our see-and-treat LEEP results with those previously published on 3-step conventional LEEP has clinical significance.

Conclusions

Women with HSIL cytology followed by a negative see-and-treat LEEP portend a similar rate of CIN2+ persistence/recurrence as women with a positive LEEP result. The impact of management strategy, (see-and-treat LEEP vs. 3-step conventional strategy), and margin status also resulted in negligible differences in follow-up outcomes. We identified predictors of post-LEEP CIN2+, including older age, history or prior LEEP and positive margin status, all which should be used to individualize patient counseling regarding risks for persistent/recurrent CIN2+ disease. However, our findings align with ASCCP consensus guidelines that evidence is insufficient to recommend a different surveillance protocol based on LEEP results and management strategy for HSIL cytology. Under current circumstances, ultimately it is left to physician discretion which strategy to implement. Such decision-making should not only take into account short-term considerations like feasibility, cost-effectiveness and overtreatment rates, but equally important, it should regard follow-up outcomes of recurrent CIN2+ disease.

Future efforts should evaluate the impact of HPV vaccination on long-term outcomes after see-and-treat LEEP for HSIL cytology. Given the recent introduction of the nonavalent prophylactic HPV vaccine, a decline in these specific HPV subtypes may not only increase the incidence of negative LEEP results (i.e. increase the risk for overtreatment), but it may also reduce the risk of CIN2+ recurrence at follow-up. However, until more robust studies are performed showing a difference in CIN2+ recurrence rates after a negative vs. positive see-and-treat LEEP, close surveillance follow-up is equally warranted in both situations.

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List of abbreviations and Acronyms

CIN	cervical intraepithelial neoplasia
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LEEP	loop electrosurgical excision procedure
HSIL	high-grade squamous intraepithelial lesion
HPV	human papillomavirus
RFS	recurrence-free survival
ASCCP	American Society for Colposcopy and Cervical Pathology
IRB	Institutional Review Board
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health

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Figure 1. Kaplan-Meier plot of CIN2+ recurrence-free survival by treatment strategy and LEEP results

Legend: The curves for all 4 groups appear similar and demonstrate that most recurrences occurred early in the course of follow-up. A statistically significant difference in time-to-recurrent CIN2+ between negative and positive LEEP for both see-and-treat and 3-step conventional strategy was not detected (log rank $p = 0.58$).

Figure 2. Kaplan-Meier plot of CIN2+ recurrence-free survival by treatment strategy

Legend: The curves for see-and-treat LEEP and 3-step conventional strategy appear similar without a statistically significant difference in time-to-recurrent CIN2+ (see-and-treat 16% vs. 3-step conventional LEEP 18%, log-rank $p=0.85$).

Socio-demographic and clinical characteristics of patients who underwent LEEP for HSIL cervical cytology^a**Table 1**

Characteristics	Total N=106	See-and-Treat N=56		3-step conventional N=50	
		Negative n=8	Positive n=48	Negative n=14	Positive n=36
Age (years), Mean $\pm$ SD	33 $\pm$ 10.5	42 $\pm$ 15.2	35 $\pm$ 10.3	38 $\pm$ 12.3	31 $\pm$ 10.6
Cotiarche (years), Mean $\pm$ SD	16 $\pm$ 2.3	17 $\pm$ 1.3	16 $\pm$ 2.4	17 $\pm$ 3.4	16 $\pm$ 2.1
Gravidity, Median (IQR)	3(2)	4(2)	3(3)	4(3)	2(2)
Lifetime sexual partners, Median (IQR)	6(6)	6(5)	6(6)	6(7)	6(6)
Race (%) ^b					
Caucasian	44	5 (11)	21 (48)	5 (12)	13 (30)
Non-Caucasian	62	3 (5)	27 (44)	9 (15)	23 (37)
High-risk HPV					
No	16	1 (6)	8 (50)	1 (6)	6 (38)
Yes	58	4 (7)	29 (50)	8 (14)	17 (29)
HPV vaccine					
No	97	5 (5)	45 (46)	14 (14)	33 (34)
Yes	2	0 (0)	1 (50)	0 (0)	1 (50)
HIV					
No	90	5 (6)	41 (46)	11 (12.2)	33 (37)
Yes	7	0 (0)	3 (43)	2 (28.6)	2 (29)
Cigarette smokers					
No	55	3 (6)	23 (42)	8 (14.5)	21 (38)
Yes	47	5 (11)	23 (49)	5 (10.6)	14 (30)
Prior LEEP					
No	96	8 (8)	45 (47)	13 (13.5)	30 (31)
Yes	10	0 (0)	3 (30)	1 (10)	6 (60)
Contraception					
None	18	1 (6)	11 (61)	3 (17)	3 (17)

		See-and-Treat N=56		3-step conventional N=50	
Characteristics	Total N=106	Negative n=8	Positive n=48	Negative n=14	Positive n=36
Reversible	57	2 (4)	23 (40)	7 (12)	25 (44)
Permanent	22	2 (9)	11 (50)	3 (14)	6 (27)
Postmenopausal	7	3 (43)	2 (29)	1 (14)	1 (14)
LEEP positive margins [*]					
Negative	52	8 (15)	19 (37)	12 (23)	13 (25)
Positive	54	0 (0)	29 (54)	2 (4)	23 (43)

SD = standard deviation; IQR = Interquartile Range; HPV = human papillomavirus; HIV = human immunodeficiency virus; LEEP = loop electrosurgical excision procedure; reversible contraception = pills, patch, ring, depo provera, intrauterine device; permanent contraception = bilateral tubal ligation, hysteroscopic tubal ligation.

^aFisher's exact test for categorical variable; Kruskal-Wallis test for continuous variable.

^bDenominator for percentages is the sum across negative/positive LEEP in the See-and-Treat or 3-step group, excluding missing values.

^{*}for p<0.05

Table 2Persistent/recurrent cervical disease after LEEP for HSIL cytology (N =106)^{a,b}

	No Recurrence	Low-grade Recurrence	High-grade Recurrence
Negative LEEP (n=22)	17 (77)	2 (9)	3 (14)
See-and-treat (n=8)	6 (75)	0 (0)	2 (25)
3-step conventional (n=14)	11 (79)	2 (14)	1 (7)
Positive LEEP (n=84)	58 (69)	11 (13)	15 (18)
See-and-treat (n =48)	32 (67)	9 (19)	7 (15)
3-step conventional (n=36)	26 (72)	2 (6)	8 (22)
Positive LEEP (n=84) *	58 (69)	11 (13)	15 (18)
Negative margin (n=32)	25 (78)	6 (19)	1 (3)
Positive margin (n=52)	33 (63)	5 (10)	14 (27)

^aData are n (%) unless otherwise specified^bFisher's exact test

Recurrence = Recurrence of dysplasia (both low- and high-grade); Low-grade = atypical squamous cells of undetermined significance (ASCUS), ASCUS with high-risk HPV positive, low-grade squamous intraepithelial lesion, CIN1; High-grade = atypical squamous cells cannot rule out high-grade (ASC-H), high-grade squamous intraepithelial lesion, CIN2+, atypical glandular cells of undetermined significance, atypical glandular cells, adenocarcinoma in situ, carcinoma

* for p<0.05

Table 3

Cox univariate and multivariate analyses of risk factors for recurrent CIN2+ diagnosed after LEEP for HSIL cervical cytology

	Univariate	Multivariate
Characteristics	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Age (years)	1.06 (1.02–1.1) **	1.09 (1.04–1.13) ***
Age at first intercourse (years)	0.92 (0.72–1.18)	
Gravidity	1.1 (0.86–1.41)	
Lifetime number of sexual partners	1.02 (0.94–1.11)	
Race		
Caucasian	1.31 (0.51–3.31)	
Non-Caucasian	1.0	
High-risk HPV		
No	1.63 (0.42–6.32)	
Yes	1.0	
HIV		
No	1.0	
Yes	2.36 (0.53–10.55)	
Cigarette smokers		
No	1.0	
Yes	1.68 (0.63–4.52)	
History of prior LEEP		
No	1.0	1.0
Yes	6.63 (2.47–17.78) ***	8.99 (3.08–26.24) ***
LEEP management strategy		
3-step conventional	1.0	
See-and-treat	0.91 (0.36–2.3)	
LEEP Results		
Negative	1.0	1.0
Positive	1.43 (0.41–4.93)	0.44 (0.09–2.05)
Positive LEEP margin		
Negative	1.0	1.0
Positive	4.52 (1.49–13.74) **	13.56 (3.1–59.34) ***

HPV = human papillomavirus; HIV = human immunodeficiency virus; LEEP = loop electrosurgical excision procedure

* for $p < 0.05$,

** for $p < 0.01$, and

*** for $p < 0.001$