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RISK OF CIN2+ AMONG WOMEN WITH A HISTORY OF PREVIOUS TREATMENT FOR CERVICAL INTRAEPITHELIAL NEOPLASIA:

ASCUS and LSIL Pap smears post-treatment

Heather R. Burks, MD[1], **Katherine M. Smith, MD**[1], **Nicolas Wentzensen, MD, PhD, MS**[2], **Meaghan Tenney, MD**[1], **S. Terrence Dunn**[1], **Sophia S. Wang**[2], and **Michael A. Gold, MD**[3]

[1] Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma [2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland [3] Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

OBJECTIVE—The objective of the current study is to describe outcomes among women with low grade abnormalities on cervical cytology screening in the setting of previous excisional or ablative treatment for cervical intraepithelial neoplasia (CIN).

METHODS—Study participants were recruited into the "Study to Understand Cervical Cancer Early Endpoints and Determinants" (SUCCEED). At enrollment, the patient's previous cytology results, previous colposcopic biopsy results, and previous cervical procedures were recorded. Study procedures included collection of biospecimens followed by colposcopy and biopsy. From clinical records, additional information was collected regarding prior treatment for CIN.

RESULTS—Two hundred and seventy four women had an ASCUS referral pap and 532 women had a LSIL referral pap. For patients with an ASCUS referral pap, previous treatment was associated with an OR for CIN2+ (45.0% v 28.2% of untreated patients) of 2.08 (95% CI 1.05–4.13; p=0.04). For patients with an LSIL referral pap, 33.3% of those women with previous treatment had CIN2+ compared with 16.7% of those patients enrolled with no prior treatment (OR 2.49, 95% CI 1.12–5.51; p=0.03).

CONCLUSION—Patients with a history of previous treatment for CIN have a twofold risk of CIN2+ at the time of colposcopy referral for ASCUS or LSIL cervical cytology.

Keywords

ASCUS; LSIL; cervical intraepithelial neoplasia; colposcopy; HPV

INTRODUCTION

The American Society for Colposcopy and Cervical Pathology 2006 Consensus Guidelines on the management of low grade cervical cytologic abnormalities are mainly based on data obtained during the ASCUS-LSIL Triage Study (ALTS Trial), a large, multicenter,

Corresponding author: Heather Burks, MD, 920 SL Young Blvd, WP 2410, Oklahoma City, OK 73104, Heather-burks@ouhsc.edu, Work: 405-271-8470, Cell: 615-403-6190, Fax 405-271-2122.

randomized clinical trial designed to compare alternative strategies for the management of atypical squamous cells of uncertain significance (ASCUS) and of low-grade squamous intraepithelial lesion (LSIL) cytology. [1–3] The data obtained from this trial showed that human papillomavirus (HPV) testing is an effective triage tool for ASCUS results, with a comparable sensitivity to immediate colposcopy, but a reduction of colposcopy referrals by about 50%.[3]

Current recommendations for management of ASCUS and LSIL do not routinely account for a history of previous treatment for abnormal cervical cytology. There may be important differences in risk of disease between ASCUS and LSIL cytology results in patients with a new diagnosis versus those with previous intervention for abnormal cervical cytology and biopsy results. Due to the lack of data on risk of CIN2+ in women with ASCUS or LSIL and with a history of previous treatment for cervical intraepithelial neoplasia, it is unclear whether a more aggressive management strategy is warranted in this population. Here, we analyzed the risk of CIN2+ among women with ASCUS or LSIL cytology in relation to prior treatment in a large cross-sectional study.

MATERIALS AND METHODS

The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) is a large cross-sectional study of women referred to the University of Oklahoma colposcopy clinic with abnormal screening results. The study was approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and the National Cancer Institute. A more detailed description of study design and recruitment has been previously published.[5,6] Referral criteria to the dysplasia clinic include two sequential ASCUS pap results, a single ASCUS Pap with a positive HPV result, or an LSIL or greater Pap smear. Patients were referred from various clinics and health departments across the state of Oklahoma. Among subjects enrolled in the original study, only those referred to colposcopy with a cytology result of ASCUS or LSIL were included in the current study.

At enrollment, a research nurse completed the intake form including the patient's previous cytology results, previous colposcopic biopsy results, and previous excisional procedures. The study database included important information on risk factors and clinical data, including (1) the cytology result that prompted referral, (2) the cytologic and histologic results from samples obtained during their dysplasia clinic appointment, (3) HPV genotype(s), and (4) worst colposcopic impression. From clinic records, additional information was obtained including (1) type of prior treatment for CIN, (2) year of the procedure, (3) histologic diagnosis following the procedure if available, (4) intervening cervical cytology results, and (5) time elapsed between the procedure and referral pap. For participants who have undergone multiple procedures, information was obtained for each previous procedure.

The primary outcome measure for this study is the detection of cervical intraepithelial neoplasia grade 2 (CIN2) or greater in colposcopically directed biopsy performed at the SUCCEED study visit. Inclusion criteria were: referral to colposcopy based on an ASCUS or LSIL Pap result, older than 18, non-pregnant, no history of radiation, chemotherapy or HIV. Analyses were conducted separately based on whether the referral pap result was ASCUS or LSIL. Within each cytologic group, subjects were divided into exposure groups based upon whether previous excisional/ablative treatment for CIN had been performed. Cervical histology at the SUCCEED visit was dichotomized into CIN1 or less and CIN2 or greater (CIN2+). Odds ratios for CIN2+ at the SUCCEED visit were calculated comparing patients with and without previous treatment for ASCUS, LSIL, and combined groups. In addition to crude ORs, a model adjusted for age in quintiles was run. The average time

elapsed between previous treatment and referral pap smear was calculated and compared for each subgroup. Statistical analysis was performed using SAS Statistical Software, Version 9.1.

RESULTS

At the time of this analysis, 2190 women were enrolled in SUCCEED. Among those, 806 met the inclusion criteria for the current analysis. Among all subjects analyzed, 274 had an ASCUS referral pap and 532 had an LSIL referral pap. Women with previous treatment tended to be slightly older and had more sexual partners (Tables 1 and 2). The risk of CIN2 or greater in the entire study population was 22.1% (178 of 806 women). Combining women referred for ASCUS and LSIL, 28 of 70 (40.0%) patients with previous treatment had CIN2 or greater at the time of colposopy compared to 150 of 736 (20.4%) patients without previous treatment (OR 2.59 [95% CI 1.55–4.31; p<0.001]). For patients with an ASCUS referral pap, 18 of 40 (45.0%) previously treated subjects had CIN2 or greater at the time of colposcopy, compared to 66 of 234 (28.2%) untreated subjects (OR 2.08 [95% CI 1.05–4.13; *p*=0.04]) (Table 3). For LSIL referral paps, 10 of 30 (33.3%) women with previous treatment had CIN2 or greater compared to 84 of 502 (16.7%) with no prior treatment (OR 2.49 [95% CI 1.12–5.51; p=0.03]).

After adjusting for age, the OR for CIN2 or greater related to previous treatment in the ASCUS population was 2.04 (95% CI 1.02–4.10) and the age adjusted OR for the LSIL population was 2.35 (95% CI 1.05–5.26).

Among women with ASCUS referral, the mean time elapsed since prior treatment until SUCCEED study visit was 4.9 years for subjects with CIN1 or less and 2.4 years for women with CIN2 or greater (*p*=0.05). We observed a similar finding among women with a LSIL pap smear, however, the mean time elapsed was not significantly different between the two groups (3.9 years versus 2.0 years).

DISCUSSION

We analyzed how previous treatment was related to risk of CIN2+ among women with ASCUS or LSIL cytology enrolled into SUCCEED for colposcopy and biopsy. We found that women with ASCUS or LSIL and a history of excisional or ablative treatment for CIN had at least twofold increased risk of having a prevalent CIN2 or worse. Current ASCCP guidelines on management of women with abnormal cervical cancer screening results do not account for previous therapy[1]; overall, there is limited risk data available for this group of women. Our study provides important information to improve risk estimation in women with ASCUS and LSIL cytology. In agreement with our findings, among women undergoing a LEEP procedure for a two step discrepancy between cytology and histology, women with previous treatment for CIN were more likely to have CIN2+on their LEEP specimen when compared to those who had no previous treatment [7].

Women were enrolled into our study regardless of prior treatment. The SUCCEED population is representative for many dysplasia clinics that see a wide spectrum of disease including women with first time abnormal screening results and women with previous treatment for CIN. The patient population in this study includes a large referral base from both urban and rural areas and spans a heterogeneous socioeconomic group.

Our study is limited by the lack of detailed information about the previous procedure and the participants' histologic diagnosis from previously excised lesions and margin status. Some studies have reported similar recurrence rates among women treated with ablative and excisional procedures[8], suggesting that exact treatment information is less critical for a risk

estimate. However, we assume that the previous histology result is an important predictor of current risk, as demonstrated by a recent meta-analysis on incomplete excision of CIN and risk of treatment failure[9]. While we could not analyze whether disease detected in SUCCEED among women with previous treatment was mainly recurrent rather than new incident disease, the short interval between the previous treatment and the CIN2+ detected at the SUCCEED visit suggests that the majority of cases were related to persistent disease. Also, we only had HPV genotyping information available from the SUCCEED visit, not from the previous visit which could further help discriminating women with persistent disease from women with new incident disease caused by a different genotype.

While our finding of a higher risk of high grade CIN in women with previous treatment is not surprising, we present quantification of the risk of a prevalent CIN2+ among women with ASCUS or LSIL cytology and a history of prior treatment. Our findings need to be reproduced in different populations with larger sample size before changes in management of these women can be considered. Our data are in support of the recent efforts to move towards risk based management of cervical disease rather than relying on increasingly complicated clinical algorithms[10]. We demonstrate that a previous history of CIN and related treatment affects risk associated with subsequent screening results and needs to be included in future risk models.

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Table 1

Demographics, risk factors, and risk of CIN2+ by previous treatment status among women referred to colposcopy with an ASCUS Pap result

Variable	Previous treatment	No previous treatment	Chi Square p-value
Age in quintiles			
18–20	4 (10.0)	51 (21.5)	
21–23	9 (22.5)	56 (23.6)	
24–25	6 (15.0)	36 (15.2)	
26–30	12 (30.0)	42 (17.7)	0.07
31–65	9 (22.5)	52 (21.9)	
Total	**40**	**237**	
Race			
White	32 (84.2)	153 (71.2)	
Black	4 (10.5)	35 (16.3)	
Other	2 (5.3)	27 (12.6)	0.2
Total	**38**	**215**	
Sexual partners			
1	0	22 (9.7)	
2–3	5 (13.2)	42 (18.5)	
4–10	24 (63.2)	116 (51.1)	
11+	9 (23.7)	47 (20.7)	0.08
Total	**38**	**227**	
Number of pregnancies			
None	9 (22.5)	66 (27.9)	
1–3	25 (62.5)	135 (57.0)	
4+	6 (15.0)	36 (15.2)	0.3
Total	**40**	**237**	
Smoker			
Never	10 (25.6)	99 (42.3)	
Former	8 (20.5)	29 (12.4)	
Current	21 (53.9)	106 (45.3)	0.1
Total	**39**	**234**	
CIN2+			
Yes	18 (45.0)	66 (28.2)	
No	22 (55.0)	168 (71.8)	0.04
Total	**40**	**234**	

Table 2

Demographics, risk factors, and risk of CIN2+ by previous treatment status among women referred to colposcopy with an LSIL Pap result

Variable	Previous treatment	No previous treatment	Chi Square p-value
Age in quintiles			
18–20	4 (13.3)	123 (24.4)	
21–23	7 (23.3)	158 (31.3)	
24–25	5 (16.7)	73 (14.5)	
26–30	9 (30.0)	82 (16.2)	0.06
31–65	5 (16.7)	69 (13.7)	
Total	**30**	**505**	
Race			
White	22 (84.2)	327 (73.2)	
Black	5 (10.5)	77 (17.2)	
Other	2 (5.3)	43 (9.6)	0.9
Total	**29**	**447**	
Sexual partners			
1	1 (3.9)	53 (10.7)	
2–3	2 (7.7)	104 (21.0)	
4–10	17 (65.4)	255 (51.4)	
11+	6 (23.1)	84 (16.9)	0.04
Total	**26**	**496**	
Number of pregnancies			
None	10 (33.3)	174 (34.5)	
1–3	16 (53.3)	278 (55.1)	
4+	4 (13.3)	53 (10.5)	0.7
Total	**30**	**505**	
Smoker			
Never	12 (40.0)	212 (42.7)	
Former	3 (10.0)	76 (15.3)	
Current	15 (50.0)	208 (41.9)	0.6
Total	**30**	**496**	
CIN2+			
Yes	10 (33.3)	84 (16.7)	
No	20 (66.7)	418 (83.3)	0.03
Total	**30**	**502**	

Table 3

Risk of CIN2+ associated with prior treatment among women referred for colposcopy with ASCUS or LSIL cytology

Referral cytology	Crude OR	95% CI	Age adjusted OR	95% CI
ASCUS	2.08	1.05–4.13	2.04	1.02–4.10
LSIL	2.49	1.12–5.51	2.35	1.05–5.26
ASCUS+LSIL	2.59	1.55–4.31	2.47	1.47–4.14

Adjusted for age in quintiles; 95% Wald confidence intervals (CI)