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Anal Cytology and Human Papillomavirus Genotyping in Women With a History of Lower Genital Tract Neoplasia Compared With Low-Risk Women

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Abstract

OBJECTIVE—To compare the prevalence of abnormal anal cytology and high-risk human papillomavirus (HPV) among women with a history of HPV-related genital neoplasia with women without a history of HPV-related genital neoplasia.

METHODS—A cross-sectional cohort study was performed from December 2012 to February 2014. Women were recruited from outpatient clinics at an academic medical center. Women with a history of high-grade cervical, vulvar, or vaginal cytology, dysplasia, or cancer were considered the high-risk group. Women with no history of high-grade anogenital dysplasia or cancer were considered the low-risk group. Human immunodeficiency virus–positive women were excluded. Anal cytology and HPV genotyping were performed. Women with abnormal anal cytology were referred for high-resolution anoscopy.

RESULTS—There were 190 women in the high-risk group and 83 in the low-risk group. The high-risk group was slightly older: 57 years compared with 47 years ($P=.045$); 21.7% of low-risk women had abnormal anal cytology compared with 41.2% of high-risk women ($P=.006$). High-risk HPV was detected in the anal canal of 1.2% of the low-risk group compared with 20.8% of the high-risk group ($P<.001$). Among women who underwent anoscopy, no anal dysplasia was detected in the low-risk group, whereas 13.4% in the high-risk group had anal dysplasia with 4.2% having anal intraepithelial neoplasia 2 or greater ($P<.001$).

CONCLUSION—Human immunodeficiency virus–negative women with a history of lower genital tract neoplasia are more likely to have positive anal cytology, anal high-risk HPV, and anal intraepithelial neoplasia. Anal cancer screening should be considered for these high-risk women.

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LEVEL OF EVIDENCE: II

Human papillomavirus (HPV) has been associated with cancers of the cervix, vagina, vulva, anus, and oropharynx.^{1,2} It is a multifocal process affecting the anal and genital tract often simultaneously regardless of risk factors.³⁻⁵ Women with a history of cervical or vulvar dysplasia have an increased risk of developing anal cancer.⁶⁻⁸ Although screening for cervical cancer has long been considered the standard of care, little is known about anal cancer screening despite the growing number of new cases per year, the majority of these among women.⁹

Anal cancer and cervical cancer share biologic similarities leading to an interest in the use of cytology for anal cancer screening.¹⁰⁻¹³ Although women with a history of HPV-related genital neoplasia are at risk for anal dysplasia and cancers, the role of screening remains unclear.^{4,7,8,14} The American Cancer Society released an anal cancer screening statement: "People at increased risk for anal intraepithelial neoplasia and cancer may benefit from screening. This includes...women who have had cervical cancer or vulvar cancer...."¹⁵

In a recent study, Lammé and colleagues¹⁶ found high-risk cervical HPV was associated with high-risk anal HPV and abnormal anal cytology, but they did not include women with a history of HPV-related genital cancers or vulvar dysplasia. The primary objective of this study was to assess the prevalence of abnormal anal cytology and high-risk anal HPV among women with a recent history of HPV-related genital neoplasia compared with women without a history of anogenital neoplasia.

MATERIALS AND METHODS

A cross-sectional cohort study was conducted at a large academic medical center in the Northeast. Women ages 18 years and older were recruited at the colposcopy clinic, gynecologic oncology office, and at routine gynecologic annual examination visits. Eligible participants were approached by a research assistant or clinician and offered entry into the study. To be considered eligible, participants had to be able to give informed consent in English or Spanish with interpreter assistance, as needed. Participants who opted for enrollment signed an informed consent in either English or Spanish. At study entry, participants were given a 10-question survey regarding their sexual behavior and risk factors for anal cancer. Demographics as well as relevant medical and surgical history were obtained from electronic medical charts. The study was approved by the Women & Infants Hospital institutional review board.

Women were considered to be high risk if they had: 1) a history within the prior 2 years of: atypical squamous cells of undetermined significance (ASC-US) cannot rule out high grade, low-grade squamous intraepithelial lesion cannot rule out high grade, or high-grade squamous intraepithelial lesion (HSIL) cervical cytology; 2) biopsy-proven cervical cancer or cervical intraepithelial lesion 2 or 3; 3) biopsy-proven vulvar cancer or vulvar intraepithelial lesion 2 or 3; or 4) biopsy-proven vaginal cancer or vaginal intraepithelial neoplasia 2 or 3. Women were considered low risk if they: 1) had a history of normal cervical cytology for the past 5 years; 2) never had cervical cancer or cervical intraepithelial lesion 2 or 3; 3) never had vulvar cancer or vulvar intraepithelial neoplasia 2 or 3; and 4) never had vaginal cancer or vaginal intraepithelial neoplasia 2 or 3 and were able to give

informed consent with interpreter assistance as needed. Women were excluded if they were human immunodeficiency virus (HIV)–positive, were unable to give informed consent, or had a history of anal cancer or anal intraepithelial neoplasia.

All women had anal cytologic testing with thin-layer cytology. Specimens for anal cytopathologic examination were collected using a swab moistened with tap water and inserted 3–5 cm into the anus to the approximate depth of the squamocolumnar junction and then rotated while applying outward pressure and placed into a ThinPrep vial.¹¹ All clinicians performing anal cytology had training consisting of a 15-minute PowerPoint presentation on anal cytology collection. A scheduled interim analysis one fourth of the way through recruitment was performed and we detected an abnormally high number of insufficient HPV results. At that time, it was noted that the swabs being used for anal cytopathologic examination were not Dacron but were cotton. All swabs were then switched to Dacron. All cytology samples were evaluated by two separate pathologists and the results entered in the electronic medical record. In the event of an abnormal anal cytology, participants were referred to a colorectal surgeon for high-resolution anoscopy regardless of cytologic abnormality. Anal biopsies were performed at the discretion of the colorectal surgeon.

Human papillomavirus typing was performed at the University of California, San Francisco laboratory using a complex multiplex real-time polymerase chain reaction test that simultaneously detects, types, and quantifies all 15 high-risk HPV types known to cause anogenital cancer. Human papillomavirus typing was run on the residual ThinPrep vial. The high-risk HPV subtypes tested were: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. The test also detected and quantified the β -globin gene as an internal control, and this was used to determine the normalized viral load (viral load per cell) to eliminate sample variations. A standard curve was made with the amplified products for each of the 15 high-risk virus templates at the concentration range of 10^0 – 10^7 . The crossing point fluorescence levels were plotted against the known standard concentration. Viral loads were determined based on the linear regression analysis of the standard curve. Multiple prior studies have shown this technique to have high reproducibility, sensitivity, and specificity.^{17–19} Anal HPV genotypes were collected for research purposes only.

Data analyses were performed using the statistical software package SAS 9.3. Categorical variables were compared by χ^2 or Fisher's exact test. Continuous variables were compared by Student's *t* test or the nonparametric Wilcoxon rank-sum test. The Shapiro-Wilks test used to test for deviations from a normal distribution. Binomial 95% confidence intervals (CIs) were calculated for the prevalence of abnormal anal cytology and high-risk anal HPV. Crude and adjusted odds ratios (ORs) and 95% CIs were estimated by logistic regression. Variables that differed significantly between the high- and low-risk groups were included in the adjusted models. All *P* values presented were two-tailed with *P* < .05 considered statistically significant.

A sample size estimate was performed based on the primary outcome of abnormal anal cytology with a set power of 80% and an α (two-sided) of 5%. Assuming a prevalence of abnormal anal cytology in the high-risk group of 10%, based on prior studies and a very low

prevalence of abnormal anal cytology in the general population, we determined an 8% difference would be clinically significant.⁷ This means we anticipated the low-risk group would have a 2% prevalence of abnormal anal cytology. To detect an absolute 8% difference, we determined that 348 women were needed in the high-risk group and 116 in the low-risk group.

RESULTS

Interim analyses were performed at 25%, 50%, and 75% recruitment. At the final interim analysis, the prevalence of abnormal anal cytology and the difference between groups was much larger than expected, so the research team stopped enrollment at that time. Three hundred three women were eligible and approached, 215 in the high-risk group and 88 in the low-risk group. Ninety percent of women approached consented to participate in the study, 190 women in the high-risk and 83 women in the low-risk group. Three women in the high-risk group were consented but did not have anal cytology or anal HPV testing performed and were excluded from the analyses.

As shown in Table 1, the median age was 47 years in the high-risk group and 57 years in the low-risk group ($P<.001$). The difference in age was in the younger than 30-year-old group; the low-risk group had fewer women younger than the age of 30 years. There was no difference by ethnicity between the two groups with the majority of women in both groups being non-Hispanic white. Women in the high-risk group were more likely to be current smokers (30.0%) than women in the low-risk group (12.1%) ($P=.002$), but there was no difference in having ever smoked between the two groups ($P=.2$). Twenty-seven percent of women in the high-risk group compared with 19% in the low-risk group had ever participated in anal intercourse ($P=.3$). There was no difference in the percent of women currently participating in anal intercourse between the two groups ($P=.3$). Among the high-risk group, 73.1% of women had a history of cervical cancer or dysplasia, 21.1% vulvar cancer or dysplasia, and 5.8% vaginal cancer or dysplasia (Table 1).

As shown in Table 2, 41.2% of women in the high-risk group had an abnormal anal cytology result compared with 21.7% in the low-risk group ($P=.006$). Approximately 10% of all samples were insufficient. The higher odds of abnormal anal cytology (compared with normal or insufficient) for the high-risk group (crude OR 2.50, 95% CI 1.37–4.56) remained statistically significant after adjustment for age and current smoking (adjusted OR 2.58, 95% CI 1.39–4.79). Nine women in the high-risk group had high-grade (HSIL or cannot rule out HSIL) cytology results compared with zero women in the low-risk group. Thirty-eight women (20.8%) in the high-risk group had high-risk HPV detected in the anal canal compared with only one woman (1.2%) in the low-risk group (crude OR 21.22, 95% CI 2.86–157.44, $P<.001$). Forty-six women (25.1%) in the high-risk group had insufficient high-risk HPV results compared with 28 (34.2%) in the low-risk group. Twenty-three women (12.6%) in the high-risk group had both an abnormal anal cytology result and high-risk HPV compared with zero women in the low-risk group ($P<.001$). In the high-risk group, of the 77 women with abnormal anal cytology, 38 tested negative for anal HPV, 15 had insufficient HPV results, and one was not completed. In the low-risk group, of the 18 women with abnormal anal cytology, 12 tested negative for HPV, five had insufficient HPV results,

and one was not completed. Only eight women in the high-risk group and five women in the low-risk group had insufficient anal cytology and anal HPV testing.

All women with an abnormal anal cytology result were referred to anoscopy and 60.0% had anoscopy performed (64.9% in the high-risk group and 38.9% in the low-risk group). In the high-risk group, 28 (56.0%) women had biopsies performed at the time of anoscopy. Of these, three (10.7%) had normal anal biopsies and 25 (89.3%) had abnormal biopsies at the time of anoscopy. In the low-risk group, three (42.9%) had biopsies performed and none had dysplasia. The specific anal cytology and HPV results had no association with who went for anoscopy.

In the high-risk group, among those biopsied, 25 women had anal dysplasia or cancer identified compared with zero in the low-risk group ($P=.03$). Seventeen women in the high-risk group had anal intraepithelial neoplasia 1, five women had anal intraepithelial neoplasia 2, two women had anal intra-epithelial neoplasia 3, and one cancer was identified. Eight women total had high-grade anal dysplasia (anal intraepithelial neoplasia 2 or 3) or cancer. Among these women, all had an abnormal anal cytology result and six also had high-risk positive HPV detected in the anal canal. The two women with negative anal high-risk HPV both had vulvar cancers. The anal cytology results varied among these eight women ranging from ASC-US to HSIL (three ASC-US, two low-grade squamous intraepithelial lesions, three HSIL). The one woman diagnosed with anal cancer had a history of vulvar cancer and an ASC-US anal cytology with negative anal high-risk HPV. Of the remaining seven women, two women had a history of vulvar cancer, one vulvar dysplasia, three cervical cancers, and one cervical high-grade dysplasia.

DISCUSSION

Women with a history of HPV-related genital neoplasia are at increased risk for anal dysplasia and cancers, but the role of anal cancer screening remains unclear.^{20,21} We found a high percent of abnormal anal cytology and high-risk anal HPV among women with a history of genital neoplasia compared with women without a history of genital neoplasia. More importantly, of the high-risk women who underwent anoscopy, 4.2% had anal intraepithelial neoplasia 2 or worse detected, supporting the need for anal cancer screening in this population.

Women with a history of a genital neoplasia are at increased risk of developing anal cancer and may benefit from anal cancer screening. Similar to Ogunbiyi et al,¹⁴ we found a high rate of abnormal anal cytology (41.2%) among high-risk HIV-negative women compared with low-risk women (21.7%). Park et al and Lammé et al reported only 9% and 17.6% abnormal anal cytology, respectively, among women with high-grade lower genital tract intraepithelial neoplasia or cancer, but they both had lower risk populations.^{8,20} In addition, consistent with the literature, we found among our high-risk women who underwent high resolution anoscopy, 13.4% had anal dysplasia and eight (4.2%) had anal intraepithelial neoplasia 2 or greater.^{3,21,22} Although this is lower than that reported for other high-risk populations, it is similar to the 5% 5-year risk proposed by the American Society for

Colposcopy and Cervical Pathology as a cutoff for referral to immediate cervical colposcopy.²³

Human papillomavirus testing has been U.S. Food and Drug Administration–approved for primary screening in cervical cancer but has had limited use in anal cancer screening as a result of the high prevalence of HPV among at-risk populations.^{24–26} Recently, a systematic review reported the prevalence of anal high-risk HPV infection among HIV-negative women ranged from 4% to 36%.⁵ In our study, 20.8% of high-risk women had high-risk anal HPV detected compared with only 1.2% of low-risk women. Although 9.6% and 25.5% of our high-risk group had insufficient anal cytology and HPV testing, respectively, only 4.4% of women in this group had both insufficient anal cytology and HPV. Among those diagnosed with anal intraepithelial neoplasia 2 or worse, only two had negative high-risk HPV and both had vulvar cancers that were likely not HPV-related, suggesting a different method of screening among select women with vulvar cancer may be warranted. These findings suggest high-risk HPV testing plus anal cytology followed by referral to high-resolution anoscopy for all abnormal cytology results may be a useful anal cancer screening method. We are unable to determine the utility of referring women with a positive high-risk HPV test result and normal or insufficient anal cytology because we did not perform high-resolution anoscopy on these women in our study.

Anal cancer incidence among HIV-negative women has been increasing possibly as a result of increases in high-risk behaviors.^{27–29} However, similar to others, we found no difference in anal intercourse between groups supporting the HPV field effect concept.^{7,30} Other sexual behaviors including digital–anal sex have been associated with decreased anal HPV clearance rates and may not be captured in our study.^{26,27}

There were a number of study limitations. First, our study was an observational cohort study, and we cannot determine the sensitivity and specificity of anal cytology because only women with abnormal anal cytology were referred to anoscopy. Additionally, only 60% of those referred kept their appointment, leading to a selection bias. Second, we had a limited number of women younger the age of 30 years and this may be a lower risk group skewing the results.⁷ Another limitation was the high number of insufficient anal cytology and HPV results, which did not change with Dacron swabs. Although high numbers of insufficient anal cytology results were seen in other studies suggesting women may require repeat testing more frequently than with cervical cytology,^{10,11} our high number of insufficient HPV results is possibly the result of performing HPV genotyping off of the Thin-Prep vial cytology was performed on, so future studies may be improved by collecting separate samples. Finally, our study was conducted at a single institution, which limits the generalizability.

Our study is novel because it is one of the largest to date and included women with a history of cervical, vulvar, and vaginal dysplasia and cancer as well as had a low-risk comparison group. A recent study evaluated the prevalence of abnormal anal cytology and anal high-risk HPV among women with known cervical dysplasia, but this study did not include women with vulvar or vaginal dysplasia or women with a history of genital cancers, which is

important because women with a history of vulvar neoplasia seem to be at highest risk for anal intraepithelial neoplasia 2 or greater.¹⁶

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Table 1**Demographics**

Characteristic	High-Risk	Low-Risk	<i>P</i>
Total	190	83	
Age (y)	47 (21–86)	57 (21–72)	<.001
Age group (y)			
Younger than 30	32 (16.8)	5 (6.0)	.045
30–65	141 (74.2)	70 (84.3)	
65 or older	17 (9.0)	8 (9.6)	
Ethnicity			
Non-Hispanic white	145 (76.3)	69 (83.1)	.1
African American	18 (9.5)	2 (2.4)	
Hispanic	23 (12.1)	8 (9.6)	
Asian	2 (1.1)	1 (1.2)	
Other	1 (0.5)	2 (2.4)	
Unknown	1 (0.5)	1 (1.2)	
Current smoking			
No	123 (64.7)	70 (84.3)	.002
Yes	57 (30.0)	10 (12.1)	
Unknown	10 (5.3)	3 (3.6)	
Ever smoked			
No	69 (36.3)	39 (47.0)	.2
Yes	111 (58.4)	42 (50.6)	
Unknown	10 (5.3)	2 (2.4)	
Ever participated in anal intercourse			
No	122 (64.2)	61 (73.5)	.3
Yes	52 (27.4)	16 (19.3)	
Unknown	16 (8.4)	6 (7.2)	
If yes, current anal intercourse			
No	45 (86.5)	12 (75.0)	.3
Yes	7 (13.5)	4 (25.0)	
Diagnosis in the high-risk group			
Cervical cancer	50 (26.3)		
Cervical dysplasia	51 (26.8)		
CIN 2 or 3	38 (20.0)		
HSIL, ASC-US rules out HSIL, LSIL rules out HSIL			
Vulvar cancer	14 (7.4)		
Vulvar dysplasia	26 (13.7)		
Vaginal cancer	3 (1.6)		
Vaginal dysplasia	8 (4.2)		

CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

Data are n, median (range), or n (%) unless otherwise specified.

Age in years was compared by the Wilcoxon rank-sum test. All categorical variables were compared by χ^2 or Fisher's exact test.

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Table 2**Anal Cytology and Human Papillomavirus Results**

Result	High-Risk	Low-Risk	P
Total	187	83	
Cytology			
Normal	92 (49.2) [41.8–56.6]	56 (67.5) [56.3–77.4]	.006
Abnormal	77 (41.2) [34.1–48.6]	18 (21.7) [13.4–32.1]	
Insufficient	18 (9.6) [5.8–14.8]	9 (10.8) [5.1–19.6]	
Abnormal anal cytology			
ASC-US	38 (49.4) [37.8–61.0]	11 (61.1) [35.8–82.7]	.7
LSIL	30 (39.0) [28.1–50.8]	7 (38.9) [17.3–64.3]	
ASCUS, LSIL rules out HSIL	4 (5.2) [1.4–12.8]	0 (0) [0–4.3]	
HSIL	5 (6.5) [2.1–14.5]	0 [0–4.3]	
High-risk HPV anal	n=183	n=82	
Positive	38 (20.8) [15.1–27.4]	1 (1.2) [0.03–6.6]	<.001
Negative	99 (54.1) [46.6–61.5]	53 (64.6) [53.3–74.9]	
Insufficient	46 (25.1) [19.0–32.1]	28 (34.2) [24.0–45.5]	
Both anal HPV-positive and abnormal anal cytology	23/183 (12.6) [8.1–18.3]	0/82 (0) [0–4.4]	.002

ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus.

Data are n (column percentage) [95% confidence interval for percentage] or n/N (column percentage) [95% confidence interval for percentage] unless otherwise specified.

All variables were compared by χ^2 or Fisher's exact test.