A Cross-Sectional Study of the Prevalence of Anal Dysplasia among Women with High-Grade Cervical, Vaginal, and Vulvar Dysplasia or Cancer: The PANDA Study

Samantha Batman[1], Craig A. Messick[1], Andrea Milbourne[1], Ming Guo[1], Mark F. Munsell[1], Joel Fokom-Domgue[1], Mila Salcedo[1], Ashish Deshmukh[2], Kristina R. Dahlstrom[3], Mallory Ogburn[4], Anthony Price[1], Nicole D. Fleming[1], Jolyn Taylor[1], Aaron Shafer[1], Lauren Cobb[1], Keith Sigel[5], Erich M. Sturgis[3], Elizabeth Y. Chiao[1], and Kathleen M. Schmeler[1]

ABSTRACT

Background: High-risk human papillomavirus (HR-HPV) infection is a risk factor for anal cancer, yet no anal cancer screening guidelines exist for women with lower genital tract HPV-related disease. We sought to describe the prevalence of anal HR-HPV or cytologic abnormalities in such women.

Methods: This cross-sectional study was performed between October 2018 and December 2021. Inclusion criteria were ≥21 years of age and a prior diagnosis of high-grade dysplasia/cancer of the cervix, vagina, or vulva. Participants underwent anal cytology and anal/cervicovaginal HR-HPV testing. Women with abnormal anal cytology were referred for high-resolution anoscopy (HRA).

Results: 324 evaluable women were enrolled. Primary diagnosis was high-grade dysplasia/cancer of the cervix (77%), vagina (9%), and vulva (14%). Anal HR-HPV was detected in 92 patients (28%) and included HPV-16 in 24 (26%), HPV-18 in 6 (7%), and other HR-HPV types in 72 (78%) patients. Anal cytology was abnormal in 70 patients (23%) and included atypical squamous cells of undetermined significance (80%), low-grade squamous intraepithelial lesion (9%), high-grade intraepithelial lesion (HSIL; 1%), and atypical squamous cells-cannot rule out HSIL (10%). Of these patients, 55 (79%) underwent HRA. Anal biopsies were performed in 14 patients: 2 patients had anal intraepithelial neoplasia (AIN) 2/3, 1 patient had AIN 1, and 11 patients had negative biopsies. Both patients with AIN 2/3 had a history of cervical dysplasia.

Conclusions: Our results suggest an elevated risk of anal HR-HPV infection and cytologic abnormalities in women with lower genital tract dysplasia/cancer.

Impact: These results add to the growing body of evidence suggesting the need for evaluation of screening methods for anal dysplasia/cancer in this patient population to inform evidence-based screening recommendations.

Introduction

The incidence of anal squamous cell cancer has been increasing in high-income countries over the past four decades, with marked increases (3%–6%/year) among women (1, 2). In the United States in 2021, there were an estimated 9,090 new cases of anal cancer, of which 67% occurred in women (3). Persistent high-risk human papillomavirus (HR-HPV) infection is responsible for nearly 90% of squamous cell carcinoma of the anus (SCCA; ref. 4). Notably, women with preexisting HPV-related lower genital tract dysplasia and cancer are at elevated risk for developing SCCA (5–9).

Despite known evidence of higher anal cancer incidence in women with prior HPV-related disease, there are no guidelines for screening this population (10). The current guidelines from the Centers for Disease Control and Prevention state that the current data are "insufficient to recommend routine anal cancer screening with anal cytology among populations at risk for anal cancer" (11), highlighting the need for more research in this area. While several professional organizations, including the American Cancer Society, the Infectious Diseases Society of America, and the American Society of Colon and Rectal Surgeons recommend SCCA screening for persons living with human immunodeficiency virus (HIV), current recommendations are largely based on expert opinion (12). For instance, the American Cancer Society suggests anal cytology may be used as a screening tool for all high-risk groups, including persons living with HIV, but also notes that it has not been studied well enough to know how often it should be done or if it impacts outcomes (10). The New York State Department of Health guidelines include women with lower genital tract dysplasia or cancer, but only for those living with HIV (13), as persons living with HIV have disproportionately elevated anal dysplasia/cancer risk (14, 15).

Understanding the prevalence and risk of anal HPV and high-grade intraepithelial lesions (HSIL) among women with prior HPV-related gynecologic dysplasia/cancer is essential to evaluate and inform optimal use of screening; we therefore sought to estimate the prevalence of anal abnormalities in women with HPV-related lower genital tract dysplasia.

Materials and Methods

This was a cross-sectional study performed between October 2018 and December 2021 at The University of Texas MD Anderson Cancer

[1]The University of Texas MD Anderson Cancer Center, Houston, Texas. [2]The University of Texas Health Science Center, Houston, Texas. [3]Baylor College of Medicine, Houston, Texas. [4]The University of Texas Rio Grande Valley, Edinburg, Texas. [5]The Mount Sinai Hospital, New York, New York.

Corresponding Author: Kathleen M. Schmeler, Department of Gynecologic Oncology and Reproductive Medicine, Unit 1362, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-745-3518; E-mail: kschmele@mdanderson.org

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Center (MD Anderson) and the Lyndon Baines Johnson General Hospital (LBJ) located in Houston, Texas. Institutional Review Board approval was obtained at both facilities (protocol 2014–0021). The study was registered with Clinicaltrials.gov (NCT02140021).

Women were included if they were 21 years of age or older and had histologically confirmed cervical, vaginal, or vulvar high-grade dysplasia or cancer or a diagnosis of HSIL on cervical cytology. Women were excluded from the study if they had a history of perianal squamous cell dysplasia or SCCA or had previously documented HPV-related oropharyngeal cancer. Patients were recruited from the colposcopy clinics at both MD Anderson and LBJ Hospital. Any patient that was either scheduled for a colposcopy, scheduled for a new visit for newly diagnosed dysplasia/cancer, presented for a surveillance pelvic exam, or presented for follow-up and met the eligibility criteria was approached for enrollment.

Informed consent was obtained in either English or Spanish. Demographic information and relevant medical history were obtained through patient interviews and from review of medical records. Data collected included race/ethnicity; age at diagnosis of any dysplastic lesion of the cervix, vagina, and vulva; HIV status; and previous HPV vaccination status. Data collected regarding race and ethnicity was determined from patient reported information in their medical records and was included given the racial/ethnic disparities often seen in cervical dysplasia/cancer. Medical records and pathology reports were reviewed to determine histology, stage, and grade of previous dysplasia or cancer.

At the time of their visit, participants underwent anal cytology testing, anal HPV testing, and cervicovaginal HPV testing. Anal cytology specimens were collected using a single plastic Dacron swab that was gently inserted until resistance was noted from the wall of the rectum (approximately 4.5 cm) and withdrawn with lateral pressure in a spiral motion so as to adequately sample the entire circumference of the anal canal. Patients with abnormal anal cytology results were subsequently referred for further evaluation with high-resolution anoscopy (HRA). This was performed by either a colon and rectal surgeon, gynecologic oncologist, or a general gynecologist, all of whom completed the American Society of Colposcopy and Cervical Pathology (ASCCP) HRA course. The course is similar to the ASCCP comprehensive colposcopy courses and is offered to providers already familiar with colposcopy techniques. HRA was performed by applying 5% acetic acid to the anal canal and observing for acetowhite changes. Anal biopsy was performed on any suspicious lesions. Patients found to have high-grade anal dysplasia were then referred to a colon and rectal surgeon for further evaluation and treatment. Patients were not followed longitudinally as this was a cross-sectional study.

Cytology and HPV specimens from both participating facilities were processed by the Department of Pathology at MD Anderson using SurePath (Becton Dickinson and Company, Franklin Lakes, NJ). Cytology results were classified according to the Bethesda System terminology (16). Anal HPV testing was performed using the Cervista HPV 16/18 Assay and HR-HPV assays (Hologic, Inc, Madison, WI) prior to December 2018, and the Cobas HPV testing platform (Roche Molecular Diagnostics, Indianapolis, IN) thereafter, due to an institutional change in HPV testing platforms.

Study data were collected and managed using a secure web-based application for data capture, REDCap (Research Electronic Data Capture; refs. 17, 18), hosted at MD Anderson. Descriptive statistics were used to summarize the demographic and clinical characteristics of patients. Age was summarized with median and interquartile range (IQR), while categorical variables were summarized with counts and frequencies. Patients were grouped by disease site (cervix, vagina, vulva). The Kruskal–Wallis test was used to compare groups with respect to age, and either Fisher exact test or the χ^2 test was used to compare groups with respect to categorical variables.

Results

A total of 327 women were enrolled in the study. Three patients were enrolled but did not undergo sample collection and were therefore not considered evaluable and are excluded from the analyses. The final evaluable group comprised 324 women. There were 250 (77%) women in the cervix group, 28 (9%) women in the vagina group, and 46 (14%) in the vulva group (**Table 1**). Of those in the cervix group, 229 (92%) had preinvasive disease with a diagnosis of cervical intraepithelial neoplasia (CIN) 2/3, HSIL, or adenocarcinoma *in situ* (AIS) and 21 (8%) had a diagnosis of invasive cervical cancer. Of those in the vagina group, all participants had preinvasive disease and a diagnosis of vaginal intraepithelial neoplasia (VAIN) 2/3 or HSIL on prior cytology. Of those in the vulva group, 41 (89%) had vulvar intraepithelial neoplasia (VIN) 2/3 and 5 (11%) had squamous cell carcinoma. Two patients had a diagnosis of both CIN 2/3 and VAIN 2/3. The distribution of dysplasia and cancer diagnoses by group is shown in Supplementary Table S1. The median age of the study population was 45 years (IQR, 36–57). The women in the cervix group tended to be younger (median = 41; IQR, 34–52) than the women in the vagina (median = 56.5; IQR, 48–61.5) or vulva (median = 60.5; IQR, 51–65) groups. In terms of race, 2% of our patient population identified as Asian, 11% as Black or African American, and 83% as White (3% selected "race unknown"). With respect to ethnicity, 46% identified as Hispanic or Latino. The proportion of Hispanic women was highest in the cervix group ($n = 142$, 57%). Five patients (2%) were HIV positive —3 in the cervix group, and 1 each in the vagina and vulva groups. Only 2% of our study population reported previous HPV vaccination.

Overall, 70 patients (23%) had abnormal anal cytology results (**Table 2**), including atypical squamous cells of undetermined significance (ASCUS; $n = 56$, 80%), low-grade squamous intraepithelial lesion (LSIL; $n = 6$, 9%), HSIL ($n = 1$, 1%), and atypical squamous cells-cannot rule out HSIL (ASC-H; $n = 7$, 10%). The rate of abnormal anal cytology was highest in the cervix group ($n = 55$, 23%) and lowest in the vagina group ($n = 6$, 21%), though this did not reach statistical significance ($P > 0.99$). Anal HR-HPV testing was positive in 92 (29%) women with a definitive test result, with a greater proportion ($n = 16$, 37%) testing positive in the vulva group compared with the vagina and cervix groups, though the difference was not statistically significant ($P = 0.532$). Of note, anal cytology was insufficient in 7 (2%) patients who were tested and anal HPV testing was insufficient in 35 (11%) patients who were tested.

All patients with abnormal anal cytology were recommended to undergo HRA. In total, 55 of 70 (79%) patients eligible for HRA underwent the procedure (**Table 3**). Fourteen patients (25%) had lesions noted at the time of HRA with biopsies performed with negative/benign findings in 11 patients (79%), anal intraepithelial neoplasia (AIN) 1 in 1 patient (7%), and AIN 2/3 in two patients (14%). Both women with AIN 2/3 (ages 33 and 44 years) had a history of CIN 3 and were HIV-negative. None of the study participants were found to have SCCA. HRAs were performed by three different individuals: a colon and rectal surgeon ($n = 23$, 42%), a general gynecologist ($n = 26$, 47%), and a gynecologic oncologist ($n = 6$, 11%).

Table 4 describes the eight women with either HSIL or ASC-H on anal cytology. Six of these women were from the cervix group, 1 was from the vagina group, and 1 was from the vulva group. Both cases of AIN 2/3 on anal biopsy were patients with a history of CIN 3; 1 had

Table 1. Demographics.

	Cervix ($N = 250$)	Vagina ($N = 28$)	Vulva ($N = 46$)	Total ($N = 324$)	*P*
Diagnosis, *n* (%)					
Preinvasive disease[a]	229 (92%)	28 (100%)	41 (89%)	298 (92%)	
Cancer	21 (8%)	0 (0%)	5 (11%)	26 (8%)	
Study Center, *n* (%)					< 0.001[b]
MD Anderson Cancer Center	112 (45%)	24 (86%)	42 (91%)	178 (55%)	
LBJ Hospital	138 (55%)	4 (14%)	4 (9%)	146 (45%)	
Age					< 0.001[c]
Median (IQR)	41 (34–52)	56.5 (48–61.5)	60.5 (51–65)	45 (36–57)	
Race, *n* (%)					0.866[b]
Asian	6 (2%)	0 (0%)	0 (0%)	6 (2%)	
Black or African American	27 (11%)	3 (11%)	7 (15%)	37 (11%)	
White	205 (82%)	24 (86%)	39 (85%)	268 (83%)	
American Indian / Alaska Native	1 (0%)	0 (0%)	0 (0%)	1 (0%)	
Subject declined to answer	1 (0%)	0 (0%)	0 (0%)	1 (0%)	
Unknown	10 (4%)	1 (4%)	0 (0%)	11 (3%)	
Ethnicity, *n* (%)					< 0.001[b]
Hispanic or Latina	142 (57%)	4 (14%)	4 (9%)	150 (46%)	
Not Hispanic or Latina	107 (43%)	24 (86%)	42 (91%)	173 (54%)	
Missing	1	0	0	1	
Menopausal status, *n* (%)					< 0.001[2]
Premenopausal	171 (74%)	6 (21%)	12 (27%)	189 (62%)	
Postmenopausal	60 (26%)	22 (79%)	32 (73%)	114 (38%)	
Missing	19	0	2	21	
HIV status, *n* (%)					0.320[b]
Negative	231 (99%)	26 (96%)	41 (98%)	298 (98%)	
Positive	3 (1%)	1 (4%)	1 (2%)	5 (2%)	
Unknown	16	1	4	21	
Previous HPV vaccine? *n* (%)					0.625[b]
No	175 (71%)	22 (81%)	37 (80%)	234 (73%)	
Yes	5 (2%)	0 (0%)	0 (0%)	5 (2%)	
Unknown	67 (27%)	5 (19%)	9 (20%)	81 (25%)	
Missing	3	1	0	4	

Note: Two patients had cervical diagnosis CIN 2/CIN 3 and vaginal diagnosis VAIN2/VAIN3. They are included in the Cervix group.
[a]Diagnoses included for preinvasive disease: cervix = CIN 2/CIN 3/HSIL/AIS, vagina = VAIN 2/VAIN 3/HSIL, vulva = VIN 2/VIN 3.
[b]Fisher Exact *P* value.
[c]Kruskal–Wallis *P* value.

Table 2. Anal cytology and anal HPV testing.

	Cervix ($N = 250$)	Vagina ($N = 28$)	Vulva ($N = 46$)	Total ($N = 324$)	*P*
Anal cytology result, *n* (%)					> 0.99[a]
Normal	177 (77%)	22 (79%)	34 (77%)	233 (77%)	
Abnormal	54 (23%)	6 (21%)	10 (23%)	70 (23%)	
Insufficient	6	0	1	7	
Missing	13	0	1	14	
Abnormal anal cytology result, *n* (%)					0.730[a]
ASCUS	42 (78%)	4 (67%)	9 (90%)	55 (79%)	
LSIL/AIN 1	5 (9%)	1 (17%)	0 (0%)	6 (9%)	
HSIL/AIN 2–3	1 (2%)	0 (0%)	0 (0%)	1 (1%)	
ASC-H	6 (11%)	1 (17%)	1 (10%)	8 (11%)	
Anal HPV testing result, *n* (%)					0.532[a]
Total HR-HPV–positive	70 (32%)	6 (24%)	16 (37%)	92 (32%)	
Total HR-HPV–negative	149 (68%)	19 (76%)	27 (63%)	195 (68%)	
Insufficient	30	3	2	35	
Missing	1	0	1	2	

Note: Percentages may not sum to 100% due to rounding.
[a]Fisher exact *P* value.

Table 3. HRA and anal pathology results.

	Cervix ($N = 44$)	Vagina ($N = 3$)	Vulva ($N = 8$)	Total ($N = 55$)	*P*
Lesions present? *n* (%)					0.852[a]
No	32 (73%)	3 (100%)	6 (75%)	41 (75%)	
Yes	12 (27%)	0 (0%)	2 (25%)	14 (25%)	
Biopsy taken? *n* (%)					
Yes	12 (100%)		2 (100%)	14 (100%)	
Biopsy result, *n* (%)					> 0.99[a]
Negative for intraepithelial neoplasia	9 (75%)		2 (100%)	11 (79%)	
AIN 1	1 (8%)		0 (0%)	1 (7%)	
AIN 2/3	2 (17%)		0 (0%)	2 (14%)	

[a]Fisher Exact *P* value.

ASC-H on anal cytology and the other had HSIL on anal cytology. Anal biopsy was performed in 3 of the women in this subset (37.5%). With the exception of the patient with HSIL on anal cytology, ASC-H was the predominant anal cytologic finding in this subset. All 8 women were HIV-negative. Five women (62.5%) were positive for other anal HR-HPV types, while 1 woman was positive for HPV-18 only, 1 woman was positive for HPV-16 only, and 1 woman was positive for both HPV-16 and other HR-HPV types.

HPV testing results are shown in **Table 5**. Of the 92 women who had a positive anal HPV testing result, 26% ($n = 24$) were positive for HPV-16, 7% ($n = 6$) were positive for HPV-18, and 78% ($n = 72$) were positive for other high-risk types. Ten patients had more than one type of anal HR-HPV. Of the 154 women with a positive cervical/vaginal HPV testing result, 34% ($n = 52$) were positive for HPV-16, 8% ($n = 12$) were positive for HPV-18, and 68% ($n = 104$) were positive for other high-risk types. Fourteen patients had more than one type of cervical/vaginal HR-HPV. Sixty women (36%) had concurrent positive anal and cervical/vaginal HPV testing, while 32 (19%) had positive anal but negative cervical/vaginal HPV testing, and 76 (45%) had negative anal HPV but positive cervical/vaginal HPV testing. HPV testing results by cytology status for each group are shown in Supplementary Table S2.

Discussion

To our knowledge, this study is the largest study of anal HPV testing and anal dysplasia in HIV-negative women with prior HPV-associated lower genital tract disease. The results of the PANDA study demonstrate that women with lower genital tract dysplasia and/or cancer have elevated rates of abnormal anal cytology and positive anal HPV testing. In our group of 324 women, 23% had abnormal anal cytology and 29% tested positive for anal HR-HPV. The most common anal cytologic finding was ASC-H in women with high-grade anal dysplasia on cytology. Ultimately, two cases of AIN 2/3 were diagnosed in this population of relatively young (median age: 45 years) and mainly HIV-negative (98%) women, and both were patients with a prior history of CIN 3.

A larger body of literature exists for those who are living with HIV, as this is a known risk factor for high-grade anal dysplasia. The prevalence of anal HSIL has been shown to be as high as 27% in women living with HIV in the United States, and the prevalence of anal HR-HPV in this population has been shown to be as high as 85% (15). As a result, more is known about the importance of screening for anal dysplasia in this population. However, there is a lack of research discussing the risks of high-grade anal dysplasia in women with a history of other HPV-related cancers, particularly in the HIV-negative population.

The results from our study showing elevated rates of abnormal anal cytology and positive HPV testing are similar to findings from previously reported studies (5, 19–22). A 2015 study by Robison and colleagues (5) analyzed anal cytology and HPV testing in 190 women with a history of high-grade cervical, vulvar, or vaginal dysplasia or cancer. The authors found that 41.2% of these high-risk women had abnormal anal cytology and 20.8% had anal HR-HPV. They ultimately had five cases of anal HSIL and no cases of cancer reported. The majority of their patient population was non-Hispanic White (76% of the high-risk group) and HIV-positive status was a reason for exclusion from the study. Of note, approximately 10% of anal cytology samples in this study were insufficient. In contrast, 46% of our patient population identified as Hispanic or Latino and 2% of our study

Table 4. Description of patients with high-grade anal dysplasia on cytology (AIN 2/3, ASC-H) or histology (HGAIN).

Age	Diagnosis	Abnormal anal cytology result	Anal HPV testing result	HRA performed?	Lesions present?	Biopsy taken?	Biopsy result
44	CIN 3	ASC-H	Positive other high-risk types	Yes	Yes	Yes	AIN 2/3
39	CIN 2/3	ASC-H	Positive other high-risk types	Yes	Yes	Yes	Negative for intraepithelial neoplasia
52	Cervix HSIL	ASC-H	Positive other high-risk types	Yes	No	.	.
59	Cervix HSIL	ASC-H	Positive other high-risk types / Positive 16	Yes	No	.	.
68	VIN 3	ASC-H	Positive 16	Yes	No	.	.
33	CIN 3	HSIL	Positive other high-risk types	Yes	Yes	Yes	AIN 2/3
59	VAIN 2	ASC-H	Negative	No	.	.	.
52	CIN 2	ASC-H	Positive 18	No	.	.	.
38	CIN 3	ASC-H	Positive other high-risk types	Yes	Yes	Yes	AIN 1

Table 5. Anal and cervical HPV results.

	Cervix ($N = 250$)	Vagina ($N = 28$)	Vulva ($N = 46$)	Total ($N = 324$)	P[a]
Anal HR-HPV testing result, *n* (%)					
Positive 16	18 (26%)	2 (33%)	4 (25%)	24 (26%)	0.914[b]
Positive 18	6 (9%)	0 (0%)	0 (0%)	6 (7%)	0.728[b]
Positive high-risk types	55 (79%)	5 (83%)	12 (75%)	72 (78%)	0.900[b]
Positive high-risk types/Positive 16	8 (11%)	1 (17%)	0 (0%)	9 (10%)	0.260[b]
Positive high-risk types/Positive 18	1 (1%)	0 (0%)	0 (0%)	1 (1%)	> 0.99[b]
Negative	149 (68%)	19 (76%)	27 (63%)	195 (68%)	0.532[c]
Insufficient for diagnosis[d]	30 (12%)	3 (11%)	2 (4%)	35 (11%)	
Missing	1	0	1	2	
Cervical/Vaginal HR-HPV testing result, *n* (%)					
Positive 16	42 (32%)	8 (53%)	2 (29%)	52 (34%)	0.261[b]
Positive 18	12 (9%)	0 (0%)	0 (0%)	12 (8%)	0.783[b]
Positive high-risk types	91 (69%)	8 (53%)	5 (71%)	104 (68%)	0.439[b]
Positive high-risk types/Positive 16	10 (8%)	1 (7%)	0 (0%)	11 (7%)	> 0.99[b]
Positive high-risk types/Positive 18	3 (2%)	0 (0%)	0 (0%)	3 (2%)	> 0.99[b]
Negative	117 (47%)	13 (46%)	39 (85%)	169 (52%)	< 0.001
Missing	1	0	0	1	
HR-HPV results, *n* (%)					< 0.001
Anal HPV + / Cervical HPV +	50 (37%)	4 (27%)	6 (35%)	60 (36%)	
Anal HPV + / Cervical HPV −	20 (15%)	2 (13%)	10 (59%)	32 (19%)	
Anal HPV − / Cervical HPV +	66 (49%)	9 (60%)	1 (6%)	76 (45%)	
Missing	114	13	29	156	

Note: There were 92 women with a positive anal HR-HPV testing result: 70 (Cervix), 6 (Vagina), and 16 (Vulva); Women may have had more than 1 positive anal HR-HPV testing result: 9 (Cervix), 1 (Vagina); There were 154 women with a positive cervical/vaginal HR-HPV testing result: 132 (Cervix), 15 (Vagina), and 7 (Vulva); Women may have had more than 1 positive cervical/vaginal HR-HPV testing result: 13 (Cervix), 1 (Vagina).
[a]Fisher exact test *P* value.
[b]Compared with other positive results.
[c]Compared with any positive result.
[d]Percentage of women in group.

population tested positive for HIV. Only 2% of our anal cytology samples were insufficient.

Similarly, a 2016 study by Cronin and colleagues (19) performed anal cytology and anal HPV genotyping in women with a history of high-grade cervical, vulvar, or vaginal dysplasia or cancer and compared the dysplasia group with the malignancy group. The authors found that the rates of abnormal anal cytology did not differ significantly between the two groups. One case of anal cancer and three cases of anal HSIL were diagnosed in their cohort. Approximately 10% of cytology samples were insufficient in this study. While all patients with abnormal cytology were referred for HRA and biopsy, the authors note that 39% of patients did not follow up. In our study, 22% of the women with abnormal anal cytology did not return for HRA as recommended.

A database study by Saleem and colleagues (22) assessed the risk of anal cancer among women with a history of HPV-related gynecologic neoplasms, but did not separately address the burden of abnormal anal cytology or abnormal anal HPV testing. The authors ultimately concluded that women with a history of HPV-related gynecologic neoplasms were at higher risk for developing anal cancer than the general population. Slama and colleagues (20) in 2015 studied the risk factors associated with concurrent cervical and anal HPV infections, which were detected in 42.4% of their study group. Given the higher rate of concurrent anal and cervical HPV infection compared with their control group, the authors concluded that anal cytology and HPV testing should be done in all women with severe cervical lesions and a history of anal sexual contact, smoking, and/or multiple lifetime sexual partners. In our study, 36% of those with a positive cervical or anal HR-HPV result had concurrent anal and cervical HR-HPV infections.

The strengths of our study are the evaluation of a large group of 324 women. Furthermore, our patient population was racially and ethnically diverse, with 46% of patients identified as Hispanic/Latino. Therefore, our results may be more generalizable to this population that is known to have a higher incidence of cervical dysplasia/cancer as compared with non-Hispanic whites (23). In addition, we had a relatively lower rate of insufficient anal cytology and HR-HPV samples. Of note, our rates of insufficient anal HR-HPV samples were higher than the rate of insufficient anal cytology, and we surmise that this may be due either inadequate sample collected at time of patient visit or due to sequential processing in which the anal HPV testing was performed on the residual from the anal cytology specimen.

A limitation of our study is that patients were not followed longitudinally, and as such our results reflect a point prevalence. Our study is therefore unable to assess the persistence of anal HPV, which could be further elucidated with more longitudinal data in this area. The optimal age of screening for anal cancer in this population remains unknown, though it is understood that cervical dysplasia/cancer tends to affect women at an earlier age than anal dysplasia/cancer and that anal HPV infections may persist longer or occur later in a woman's life (24) Thus, our data are further limited by the wide age range of our study population which may have biased our results towards lower rates of abnormalities as our population was relatively young (median age = 45). This age distribution may have also differed on the basis of a patient's initial diagnosis of precancerous or cancerous lesions, though our sample size did not allow for such stratification (Supplementary Table S3). Furthermore, our patients were followed in colposcopy clinic but their time from diagnosis of cervical, vaginal, or vulvar

dysplasia and/or cancer to enrollment in the study varied. We are also limited by the lack of a control group to better understand the baseline risk for anal cytologic abnormalities and HPV infection among women who do not have cervical, vaginal, or vulvar dysplasia/cancer, though prior studies have found anal HR-HPV infection rates of 4% to 76% and rates of anal cytologic abnormalities of 4% to 90% (25).

Lastly, our study is also limited by the variability in anoscopy practice. HRAs were performed by three different individuals: a colon and rectal surgeon, a general gynecologist, and a gynecologic oncologist. Biopsies were not required at the time of HRA and were based on clinical impression. As a result, only 25% of patients who had HRA underwent anal biopsy, which may have resulted in undiagnosed cases of anal dysplasia. While it is known that random biopsies during satisfactory colposcopy can increase detection of cervical HSIL (26), further research is needed to elucidate if this is the case for HRA as well. A prior study by Silvera and colleagues (27) demonstrated that random biopsy after adequate HRA increased detection of high-grade lesions, though the majority of the patient cohort was living with HIV. It would be important to assess the value of random biopsy in our select patient population.

The findings from our study and others suggest that women with preexisting lower genital tract dysplasia and cancer should be considered a high-risk group with respect to the development of anal dysplasia. Despite this elevated risk, there are not yet screening guidelines for anal dysplasia in this population. While the progression rate and predictors of anal dysplasia to SCCA, as well as the clinical performance of screening measures, is uncertain in this group, existing literature does suggest that prior anal cytology screening is associated with a decreased risk of progression, though this was studied in male patients living with HIV (28, 29).

More recently, the Anal Cancer/HSIL Outcomes Research study was halted early due to the finding that treating precursor anal cancer lesions significantly reduces the risk of progression to anal cancer (30). These data were from a randomized phase III clinical trial of men, women, and transgender people living with HIV with a history of biopsy-proven anal HSIL. The primary objective of the trial was to determine whether treating anal HSIL is effective at reducing the anal cancer incidence in this population (30). The final results of this study are pending and may help guide further study in other high-risk groups, such as our group of women with a history of lower genital tract dysplasia or cancer.

Continuing research efforts in this realm are especially relevant as the SCCA incidence continues to increase over 5% per year among women aged 50 years and older, with the incidence even surpassing cervical cancer incidence in White women aged 65 to 74 and 75 years or older (31). Thus, further research should be targeted towards the development of these guidelines, specifically the timing and frequency of anal cytology and HPV testing. In collaboration with The Mt. Sinai Hospital in New York, our research group is performing a follow-up study evaluating anal dysplasia in 300 HIV uninfected women with prior lower genital tract HPV-related disease (NCT05217940). All patients in this cohort will undergo HRA using a standardized protocol and will be followed longitudinally with three study visits over 2 years. This study will also assess the utility of self-collected anal HPV testing.

In summary, the results of the PANDA study show that anal cytologic abnormalities and positive anal HPV testing are increased in women with a history of cervical, vaginal, or vulvar dysplasia or cancer. These results add to the growing body of evidence suggesting the need for evaluation of screening methods for anal dysplasia/cancer in this patient population to inform evidence-based screening recommendations. Further research is needed to determine the optimal age, timing, and frequency of anal cytology and HPV testing (particularly in women undergoing continued surveillance for other lower genital tract disease), as well as the role of random biopsies at time of HRA in this population. In the interim, providers should remain vigilant and aware of this elevated risk of anal abnormalities when treating women with a history of lower genital tract dysplasia or cancer.

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Authors' Contributions

S. Batman: Data curation, formal analysis, writing–original draft. **C.A. Messick:** Conceptualization, data curation, writing–review and editing. **A. Milbourne:** Resources, data curation, writing–review and editing. **M. Guo:** Resources, data curation, writing–review and editing. **M.F. Munsell:** Software, formal analysis, methodology, writing–review and editing. **J. Fokom-Domgue:** Writing–review and editing. **M. Salcedo:** Writing–review and editing. **A. Deshmukh:** Writing–review and editing. **K.R. Dahlstrom:** Writing–review and editing. **M. Ogburn:** Resources, data curation, writing–review and editing. **A. Price:** Resources, data curation, writing–review and editing. **N.D. Fleming:** Data curation, writing–review and editing. **J. Taylor:** Data curation, writing–review and editing. **A. Shafer:** Data curation, writing–review and editing. **L. Cobb:** Data curation, writing–review and editing. **K. Sigel:** Writing–review and editing. **E.M. Sturgis:** Writing–review and editing. **E.Y. Chiao:** Conceptualization, supervision, writing–review and editing. **K.M. Schmeler:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, methodology, writing–original draft, writing–review and editing.

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Note

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References

1. Lum C, Prenen H, Body A, Lam M, Segelov E. A 2020 update of anal cancer: the increasing problem in women and expanding treatment landscape. Expert Rev Gastroenterol Hepatol 2020;14:665–80.
2. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. Int J Epidemiol 2017;46:924–38.
3. American Cancer Society. Cancer facts and figures, 2021. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf.
4. Schiffman M, Doorbar J, Wentzensen N, De Sanjosé S, Fakhry C, Monk BJ, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Prim 2016;2:16086.
5. Robison K, Cronin B, Bregar A, Luis C, Disilvestro P, Schechter S, et al. Anal cytology and human papillomavirus genotyping in women with a history of lower genital tract neoplasia compared with low-risk women. Obstet Gynecol 2015;126:1294–300.
6. Suk R, Mahale P, Sonawane K, Sikora AG, Chhatwal J, Schmeler KM, et al. Trends in risks for second primary cancers associated with index human papillomavirus—associated cancers. JAMA Netw Open 2018;1:e181999.
7. Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, et al. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. Int J Cancer 2021;148:38–47.
8. Sand FL, Munk C, Jensen SM, Svahn MF, Frederiksen K, Kjær SK. Long-term risk for noncervical anogenital cancer in women with previously diagnosed high-grade cervical intraepithelial neoplasia: a Danish nationwide cohort study. Cancer Epidemiol Biomarkers Prev 2016;25:1090–7.
9. Edgren G, Sparén P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol 2007;8:311–6.
10. American Cancer Society. Can anal cancer be found early?. Available from: https://www.cancer.org/content/cancer/en/cancer/anal-cancer/detection-diagnosis-staging/detection/.
11. Centers for Disease Control & Prevention. Sexually transmitted infections treatment guidelines: HPV-associated cancers and precancers. Available from: https://www.cdc.gov/std/treatment-guidelines/hpv-cancer.htm.
12. Domgue JF, Messick C, Milbourne A, Guo M, Salcedo M, Dahlstrom KR, et al. Prevalence of high-grade anal dysplasia among women with high-grade lower genital tract dysplasia or cancer: Results of a pilot study. 2019;153:266–70.
13. National AIDS Treatment Advocacy Project. NYS Guidelines recommendations on anal pap smears. Available from: https://www.natap.org/2010/HIV/032510_01.htm.
14. Chiao EY, Lensing SY, Wiley DJ, Deshmukh AA, Lee J, Darragh TM, et al. Screening strategies for the detection of anal high-grade squamous intraepithelial lesions in women living with HIV. AIDS 2020;34:2249–58.
15. Stier EA, Lensing SY, Darragh TM, Deshmukh AA, Einstein MH, Palefsky JM, et al. Prevalence of and risk factors for anal high-grade squamous intraepithelial lesions in women living with human immunodeficiency virus. Clin Infect Dis 2020;70:1701–7.
16. Solomon D, Davey D, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. J Am Med Assoc 2002;287:2114–9.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
18. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
19. Cronin B, Bregar A, Luis C, Schechter S, Disilvestro P, Pisharodi L, et al. Evaluation of anal cytology and dysplasia in women with a history of lower genital tract dysplasia and malignancy. Gynecol Oncol 2016;141:492–6.
20. Slama J, Sehnal B, Dusek L, Zima T, Cibula D. Impact of risk factors on prevalence of anal HPV infection in women with simultaneous cervical lesion. Neoplasma 2015;62:308–14.
21. Calore E, Giaccio CMS, Nadal S. Prevalence of anal cytological abnormalities in women with positive cervical cytology. Diagn Cytopathol 2011;39:323–7.
22. Saleem AM, Paulus JK, Shapter AP, Baxter NN, Roberts PL, Ricciardi R. Risk of anal cancer in a cohort with human papillomavirus–related gynecologic neoplasm. Obstet Gynecol 2011;117:643–9.
23. American Cancer Society. Cancer facts & figures for Hispanic/Latino people 2021–2023. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-hispanics-and-latinos/hispanic-latino-2021-2023-cancer-facts-and-figures.pdf.
24. Wei F, Xia N, Ocampo R, Goodman MT, Hessol NA, Grinsztejn B, et al. Age-specific prevalence of anal and cervical human papillomavirus infection and high-grade lesions in 11,177 women by human immunodeficiency virus status: a collaborative pooled analysis of 26 studies. J Infect Dis 2022.
25. Stier EA, Sebring MC, Mendez AE, Ba FS, Trimble DD, Chiao EY. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am J Obstet Gynecol 2015;213:278–309.
26. Nam K, Chung S, Kwak J, Cha S, Kim J, Jeon S, et al. Random biopsy after colposcopy-directed biopsy improves the diagnosis of cervical intraepithelial neoplasia grade 2 or worse. J Low Genit Tract Dis 2010;14:346–51.
27. Silvera R, Gaisa MM, Goldstone SE. Random biopsy during high-resolution anoscopy increases diagnosis of anal high-grade squamous intraepithelial lesions. J Acquir Immune Defic Syndr 2014;65:65–71.
28. Arens Y, Gaisa M, Goldstone SE, Liu Y, Wisnivesky J, Sigel CS, et al. Risk of invasive anal cancer in HIV-infected patients with high-grade anal dysplasia: a population-based cohort study. Dis Colon Rectum 2019;62:934–40.
29. Revollo B, Videla S, Llibre JM, Paredes R, Piñol M, García-Cuyàs F, et al. Routine screening of anal cytology in persons with human immunodeficiency virus and the impact on invasive anal cancer: a prospective cohort study. Clin Infect Dis 2020;71:390–9.
30. University of California San Francisco. Treating anal cancer precursor lesions reduces cancer risk for people living with HIV. Available from: https://anchorstudy.org/.
31. Deshmukh AA, Suk R, Shiels MS, Damgacioglu H, Lin YY, Stier EA, et al. Incidence trends and burden of human papillomavirus–associated cancers among women in the United States, 2001–2017. J Natl Cancer Inst 2021;113:792–6.