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Prevalence of high-grade anal dysplasia among women with high-grade lower genital tract dysplasia or cancer: Results of a pilot study☆

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HIGHLIGHTS

- There is limited evidence to guide anal cancer screening in women with lower genital tract dysplasia or cancer.
- The high prevalence of anal HSIL in this high-risk group supports its inclusion into anal screening guidelines.
- Anal cytology, anal HPV16/18 and high resolution anoscopy should be considered for anal cancer screening.
- Further study is needed to determine what screening strategy is suited to this population.

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ABSTRACT

Objective. To estimate the prevalence of high-grade anal dysplasia in women with high-grade dysplasia or carcinoma of the cervix, vagina or vulva.

Methods. In this cross-sectional study, participants underwent anal cytology, anal HPV testing with Cervista HPV16/18 and high-resolution anoscopy (HRA). Patients with HSIL (high-grade squamous cell intraepithelial lesion) or greater on anal cytology or anal biopsy were referred to a colorectal surgery specialist for further evaluation.

Results. Seventy-five women were enrolled in the study, including 47 with cervical (cervix group), 10 with vaginal (vagina group), 15 with vulvar (vulva group), 1 with cervical and vaginal, and 2 with vulvar and vaginal disease. The median age in the cervix group (40 years (range 26–69)) was substantially younger than in the vagina (60 years (38–69)) and the vulva (59 years (36–75)) groups. Anal HSIL based on composite endpoints of the most severe cytology or histology result was diagnosed in 6 patients (8.0%). Anal cytology revealed HSIL in 2 (2.7%), atypical squamous cells of undetermined significance (ASCUS) in 12 (16.0%), low-grade squamous cell intraepithelial lesion (LSIL) in 2 (2.7%), and was normal in 59 (78.7%) patients. Anal HPV16/18 test was positive in 15 (20.0%), negative in 48 (64.0%) and insufficient in 12 (16.0%) patients. Of the 6 women with high-grade anal dysplasia, three (50%) had a positive anal HPV16/18 test. No case of anal cancer was observed.

Conclusion. Our results suggest that the prevalence of anal HSIL is elevated among women with HPV-related lower genital tract dysplasia or cancer. To further support the inclusion of this high-risk group into screening guidelines for anal dysplasia, further studies are necessary to determine what screening strategy is suited to this population.

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1. Introduction

Persistent high-risk human papillomavirus (hrHPV) infection is the primary cause of cervical cancer, and has also been linked to the occurrence of vulvar and vaginal cancers [1,2]. Similarly, hrHPV infection is a necessary risk factor for anal precancerous lesions and has been observed in 80 to 90% of anal cancer cases [2–4]. There is a growing body of evidence suggesting that the natural history of HPV-induced anal cancer is close to that of cervical cancer [5]. Typically, HPV is sexually transmitted through direct contact of epithelial lining of a person's sex partners' genitals. While primary anal HPV infection may occur with ano-receptive intercourse, pooling in the posterior vagina, and front-to-back dabbing and wiping behavior can facilitate virus extension to the anus in women [1,3].

Despite etiopathogenic similarities between lower genital tract and anal dysplasia and cancer, there is a lack of data to guide anal cancer screening guidelines. Based on experts opinion and considering the success of widespread cervical cancer screening programs in reducing the burden of cervical cancer in high-income countries, anal cancer screening is now recommended by major scholarly societies in the US, including the American Cancer Society, the Association of the Infectious Diseases Society of America, and the American society of colon and rectal surgeons [6–8]. However, evidence-based anal cancer recommendations for this high-risk group are unknown. Previous studies have reported a substantially higher prevalence of anal HPV infection, anal cytological abnormalities and histologically proven anal dysplasia or cancer in women with HPV-related genital neoplasia [9–13]. However, interpretation of results from these studies was limited by the fact that (i) the rates of insufficient specimens for anal cytology were as high as 10% [10], (ii) anoscopy was indicated only for women with abnormal anal cytology [12,13], and (iii) only 40% of women referred for anoscopy actually underwent the procedure [12,13].

In order to provide more accurate data to inform anal cancer screening recommendations in these high-risk women, we performed a study to determine the prevalence of high-grade anal dysplasia and/or cancer in women with known high-grade dysplasia or carcinoma of the cervix, vagina, or vulva.

2. Material and methods

This cross-sectional study was performed at the University of Texas MD Anderson Cancer Center (MD Anderson) and the Lyndon Baines Johnson General Hospital (LBJ), both located in Houston, Texas. Institutional Review Board (IRB) approval was obtained from both facilities.

Women were enrolled at the time of their visit related to cervical, vaginal or vulvar dysplasia and/or cancer at participating sites. Eligible women were approached by a clinician or research assistant and offered study entry, at which point an informed consent was signed in either English or Spanish. Demographics and relevant medical and surgical history were obtained from medical records and through participants' interviews. Data collected included age at enrolment, age at diagnosis of any dysplastic or cancerous lesion of the cervix, vagina, or vulva; race/ethnicity; menopausal status; human immunodeficiency virus (HIV) status; and previous HPV vaccination. Pathology reports and medical records were reviewed for pathologic information including histology, stage and grade.

Women were included in this study if they were at least 21 years of age; had histologically confirmed cervical, vaginal or vulvar high-grade dysplasia or invasive carcinoma; or if cervical cytology showed high-grade intraepithelial lesion (HSIL). Women were excluded if they had previously documented perianal squamous cell dysplasia or invasive squamous cell carcinoma of the anus. Patients undergoing radiation therapy for advanced cervical, vaginal, or vulvar squamous cell carcinoma, as well as those who received prior pelvic radiation therapy were also excluded from the study.

In addition to the standard of care tests related to their cervical, vaginal or vulvar dysplasia or cancer, all patients underwent anal cytology testing, anal HPV16/18 testing, and high-resolution anoscopy (HRA) with targeted biopsy. Two anal swabs per participant (one for anal cytology and one for anal HPV16/18 testing) were separately obtained using a plastic cotton swab soaked in normal saline then gently inserted until resistance from the wall of the rectum was met (approximately 4.5 cm). The swabs were withdrawn with lateral pressure, using a spiral motion, and applied to sample the entire circumference of the anal canal. The swabs were processed using the SurePath (Becton Dickinson and Company, Franklin Lakes, NJ) technique. Next, high-resolution anoscopic examination was performed by inserting a plastic disposable anoscope into the anus and 3% acetic acid was sprayed into the mucosa [14]. A cotton swab soaked in 3% acetic acid was then applied evenly to the deeper anal canal before visualization. Anoscopic examination with 16× magnification was performed. Any abnormalities (acetowhite changes, raised lesions, discolorations) were biopsied. A local anesthetic (lidocaine 1% without epinephrine) was injected before biopsy of lesion distal to the dentate line. Digital vaginal and rectal examinations were also performed. Anal swab collection and HRA were performed by a gynecologic oncologist and a general gynecologist in participating facilities, who completed the American Society of Colposcopy and Cervical Pathology (ASCCP) HRA course and were mentored by a colorectal surgeon with expertise in HRA prior to the start and at the beginning of the study.

Cytology samples from both facilities were examined in the Department of Pathology at MD Anderson by a trained cyto-pathologist and anal cytology results were classified according to the Bethesda System terminology as: negative for intraepithelial neoplasia, atypical squamous cells of undetermined significance (ASCUS), low grade squamous cell intraepithelial lesion (LSIL), high grade squamous cell intraepithelial lesion (HSIL), and invasive anal carcinoma [15]. Anal HPV testing was also performed on all samples from both facilities in the Department of Pathology at MD Anderson, using the Cervista HPV 16/18 Assay (Hologic, Inc., Madison, W), an *in vitro* diagnostic test for the qualitative detection of DNA from HPV type 16 and/or 18 in cervical or anal specimens [16]. This assay uses a signal amplification method for the detection of specific nucleic acid sequences with two types of isothermal reactions: a primary reaction that occurs on the targeted DNA sequence and a secondary reaction that produces a fluorescent signal. Anal biopsy results were classified into four categories: negative for intraepithelial lesion, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and anal carcinoma [15]. Patients with high grade anal dysplasia (HSIL or greater on anal cytology and/or anal biopsy) were referred to a colorectal surgery specialist for further evaluation and treatment per standard of care.

Data analyses were performed using the statistical software package STATA 15 (StataCorp LLC, College Station, TX). Women were classified into three groups based on the site of the lower genital tract dysplasia or cancer: 1) cervix, 2) vagina, or 3) vulva. Categorical variables were compared between groups using the Chi-square or Fisher's exact test. Continuous variables were compared between groups using the Student's *t*-test or ANOVA. If the continuous data deviated from a normal distribution, then the equivalent nonparametric tests were used.

3. Results

Between July 2016 and May 2018, 80 patients met the eligibility criteria and were enrolled in the study. Five patients had incomplete data (unavailable anal HPV test results) and were excluded from further analysis, leaving a final sample size of 75 women. There were 48 women in the cervix group (45 with CIN2/3 and three with carcinoma), 13 women in the vagina group (all with VAIN2/3 and none with cancer) and 17 women in the vulva group (16 with VIN2/3 and one with cancer). Of note, one woman with cervical disease and two women with vulvar disease also had vaginal disease, and were included separately

in each study group. As shown in Table 1, the median age of the study population was 46 years (range: (26–75)). Women in the cervix group (median age: 40 years (range 26–69)) were significantly younger than in the vagina group (60 years (38–69)) and the vulva group (59 years (36–75)) ($p < 0.001$). There were a higher proportion of Hispanic women in the cervix group (47.9%) compared to the vagina group (7.7%) and the vulva group (0.0%) ($p < 0.001$). Overall, only one woman (vagina group) was HIV positive, and she did not have anal dysplasia (normal anal cytology, normal anal biopsy) or anal HPV16/18 infection. In addition, only one woman (cervix group) reported having received HPV vaccination (two doses of the quadrivalent vaccine). She had negative cervical and anal HPV testing, and normal anal cytology and normal HRA-guided anal biopsy.

Overall, sixteen women (21.3%) had abnormal anal cytology. The rates of abnormal anal cytology were lower among women in the cervix group (12.5%), compared to those in the vagina group (30.8%) and the vulva group (47.1%) (Table 2). There were no significant differences between groups with respect to anal HPV16/18 positivity with 9 (18.7%) women in the cervix group, one (7.7%) in the vagina group and 6 (35.3%) in the vulva group having positive results. Only 2 (4.2%) women in the cervix group, 1 (7.7%) in the vagina group and 3 (17.6%) in the vulva group had both abnormal anal cytology and positive anal HPV16/18 testing. While samples collected for anal HPV16/18 testing were insufficient in 12 (16.0%) women of the study population, no specimen was reported to be inadequate for anal cytology.

All participants underwent HRA, and the results were abnormal in 29 (38.7%) participants, including 15 (31.2%), 8 (61.5%) and 8 (47.1%) women in the cervix, vagina and vulva groups, respectively (Table 3). Of the 15 women in the cervix group with abnormal HRA findings, one declined biopsy and the other 14 had anal biopsies performed: 10 were normal, 2 had LSIL, and 2 had HSIL. All 8 women with abnormal HRA findings in the vagina group had biopsies: 5 were normal, 1 had LSIL, and 2 had HSIL. Of the 8 women who had anal biopsy following abnormal HRA findings in the vulva group, 6 were normal, 1 had LSIL and 1 had HSIL (Table 3). None of the participants were found to have anal cancer.

On composite anal cytology and histology, we identified anal HSIL among 3 women (6.2%) with cervical dysplasia/cancer, two women (15.4%) with vaginal dysplasia, and two women (11.8%) with vulvar dysplasia/cancer ($p = 0.60$). Among women with abnormal HRA findings, rates of HSIL were not significantly different between the vagina group (25.0%), the cervix group (14.3%) and the vulva group (12.5%) ($p = 0.96$) (Table 3). Table 4 describes the 6 women with high-grade anal dysplasia on cytology (2 women) or biopsy (4 women). None had lower genital tract cancer, three (50%) were positive for anal HPV 16/18, and two had insufficient anal HPV result. Both cases of HSIL on anal cytology were from women with vulvar disease (VIN3) and had positive anal HPV16/18. Of the four women with HSIL on anal biopsy, two had high-grade cervical dysplasia (CIN2), one had high-grade vaginal dysplasia (VAIN3), and one had both vaginal (VAIN3) and vulvar (VIN3) dysplasia; on anal cytology, two had ASCUS, one had LSIL and one was normal.

Table 1
Study characteristics by disease site.

	All[a]	Cervix	Vagina	Vulva	p-value
Total	75	48	13	17	
Median age (range), years	46 (26–75)	40 (26–69)	60 (38–69)	59 (36–75)	<0.001
Ethnicity, n (%)					<0.001
Non-Hispanic White	41 (54.7)	16 (33.3)	11 (84.6)	16 (94.1)	
Hispanic	23 (30.7)	23 (47.9)	1 (7.7)	0 (0.0)	
African American	8 (10.6)	6 (12.5)	1 (7.7)	1 (5.9)	
Asian	3 (4.0)	3 (6.2)	0 (0.0)	0 (0.0)	
HIV status, n (%)					0.13
Negative	70 (93.3)	46 (95.8)	12 (92.3)	15 (88.2)	
Positive	1 (1.3)	0 (0.0)	1 (7.7)	0 (0.0)	
Unknown	4 (5.4)	2 (4.2)	0 (0.0)	2 (11.8)	
HPV vaccination, n (%)					0.89
Yes	1 (1.3)	1 (2.1)	0 (0.0)	0 (0.0)	
No	54 (72.0)	35 (72.9)	9 (69.2)	12 (70.6)	
Unknown	20 (26.7)	12 (25.0)	4 (30.8)	5 (29.4)	

[a] One patient with cervical disease and two patients with vulva disease also presented with vaginal disease.

4. Discussion

In this pilot study, we observed high rates of histologically proven high-grade anal dysplasia (5.3%) among women with high-grade cervical, vulvar, or vaginal dysplasia or cancer. These findings are consistent with those of a study by Cronin et al., who reported a 4.2% prevalence of histologically confirmed high-grade anal dysplasia in a population of 190 women with a recent history of lower genital tract dysplasia or cancer [12,13]. In this study, however, anoscopy was performed only in women with abnormal anal cytology and/or positive HPV results, and the rates of compliance to HRA were reportedly low [13]. This suggests that the prevalence of anal dysplasia in this report may have been underestimated. Our study is unique in that HRA (followed by biopsies of suspicious areas) was performed in all eligible women, regardless of anal cytology results. Only one study of the prevalence of anal dysplasia where all women with genital dysplasia underwent HRA was previously reported [17]. However, the study population consisted of 205 heterosexual women with lower genital tract dysplasia regardless of grade (*i.e.* including both low-grade and high-grade cervical, vaginal and vulvar dysplasia), and did not include women with genital cancers (*i.e.* women with histologically proven invasive carcinoma of the cervix, vagina and vulva). The prevalence of high grade-anal dysplasia in this report was 8,3% [17], which is higher than the prevalence obtained in our study. In addition to different inclusion criteria of women with lower genital tract dysplasia/cancer, the higher HIV rate (5%) in this study by *Santoso* et al. compared to ours (1.3%) could explain the difference in high-grade anal dysplasia prevalence observed. Another particularity of the present pilot study is that no specimen collected for anal cytology was found to be insufficient/inadequate, unlike previous reports [10]. This design may have contributed to reduce selection bias, and thus estimates of high-grade anal dysplasia rates from the present study may be more accurate.

Since the prevalence of high-grade anal dysplasia in this study is above the 5-year risk (5%) endorsed by the American Society for Colposcopy and Cervical Pathology (ASCCP) as a threshold for cervical colposcopy [18], our results suggest that screening for anal cancer in this high-risk population should be considered. Indeed, there is evidence supporting that anal cancer may develop from untreated or incompletely treated high-grade anal dysplasia [19,20], similar to cervical cancer [1]. Screening for anal cancer could be modeled on the algorithm for cervical cancer, with primary screening using anal cytology and/or anal HPV testing with follow-up evaluation of the anal canal with HRA and HRA-guided biopsies in case of positive screening, and treatment of high-grade anal dysplasia. Approved treatment options for high-grade anal dysplasia include tricholoroacetic acid (TCA), cryotherapy, infrared clotting, and ablation. Usually applied on anal verge and margin, condylomas and tiny areas of the anal canal with dysplasia every 2 to 3 weeks up to 4 times, TCA is well-tolerated by patients, with high rates of clearance [21]. Cryotherapy uses liquid nitrogen to freeze anal lesions, and the procedure is highly tolerated and can be offered in the office. Another option is ablation of smaller lesions, which can be safely performed in the office without lidocaine, aided by HRA. Infrared clotting is indicated in patients unsuccessfully treated with TCA or cryotherapy, and for wider lesions [22].

Prevalence of high-grade anal dysplasia based on composite endpoints of the most severe cytology or histology was about twice as high in women in the vagina (15.4%) and vulva (11.8%) group, as in those in the cervix group (6.2%), although this difference was not statistically significant ($p = 0.60$). A study of the risk of anal cancer examined

Table 2
Anal cytology and Anal HPV 16/18 testing by disease site.

	All[a]	Cervix	Vagina	Vulva	p-value
Total	75	48	13	17	
Anal cytology results, n (%)					0.01
Normal	59 (78.7)	42 (87.5)	9 (69.2)	9 (52.9)	
Abnormal	16 (21.3)	6 (12.5)	4 (30.8)	8 (47.1)	
Abnormal anal cytology results, n (%)					0.86
ASCUS	12 (75.0)	5 (83.3)	3 (75.0)	5 (62.5)	
LSIL	2 (12.5)	0 (0.0)	1 (25.0)	2 (25.0)	
HSIL	2 (12.5)	1 (16.7)	0 (0.0)	1 (12.5)	
Anal HPV 16/18 testing results, n (%)					0.21
Positive	15 (20.0)	9 (18.7)	1 (7.7)	6 (35.3)	
Negative	48 (64.0)	33 (68.8)	8 (61.5)	8 (47.1)	
Insufficient	12 (16.0)	6 (12.5)	4 (30.8)	3 (17.6)	

ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.
[a] One patient with cervical disease and two patients with vulva disease also presented with vaginal disease.

189,206 cases of *in situ* or invasive lower genital tract neoplasia from the National Cancer Institute (NCI)'s Surveillance, Epidemiology and End Results (SEER) database between 1973 and 2007, and identified 255 incident cases of anal cancer [11]. Authors of this study reported an overall incidence of anal cancer in this high-risk group to be 13.6 times higher than the incidence expected based on age-, race-, and calendar year-specific rates in the non-affected population. They also found that the incidence ratio of anal cancer was lower in women with a history of vaginal dysplasia and cancer (7.6 and 1.8, respectively), compared to those with cervical dysplasia and cancer (16.4 and 6.2, respectively), and those with vulvar dysplasia and cancer (22.2 and 17.4, respectively) [11]. However, this SEER database report is limited by the lack of HIV reporting and the use of a specific terminology that requires a diagnosis of carcinoma *in situ*, not high-grade dysplasia. The lower rates of anal dysplasia in women with cervical dysplasia or cancer in our prospective study could be explained by the younger age of the population in this study group (median age of 40 years in the cervix group), compared to other groups (60 years and 59 years in the vagina and vulva groups, respectively). In the US, the median age for diagnosis of anal cancer (61 years) is over a decade older than that for cervical cancer (49 years) [23]. Therefore, it is possible that many women in the cervix group included in our report were screened for anal dysplasia before the occurrence of these lesions. As a result, if screening for anal cancer is recommended in women with HPV-related genital dysplasia/cancer, it will be critical to determine the adequate age for and interval between screenings. It will also be essential to educate women in this high-risk group about the importance of anal screening, as previous studies have reported women to be reluctant to undergo anal examination [24]. Indeed, it has been shown that HPV infection is a multisite disease as cervical, vaginal, vulvar and anal HPV infections seem to occur simultaneously. HPV infection at any of these anatomical sites may serve as reservoir for HPV infection at the other sites [22,25]. Likewise, anal receptive intercourse was not found to be independently associated with anal HPV infection, dysplasia or cancer in women [26,27].

Our study had a few limitations. First, the HPV assay used (Cervista HPV16/18) in this study could only detect two HPV genotypes [16,18], and thus, we were not able to establish correlation of anal HPV testing of participants with their previous high-risk HPV results. Second, we had a high rate of insufficient HPV specimens (16%), although samples for anal cytology and anal HPV testing were collected separately. While this measure may have contributed to the lower rate (16%) of insufficient HPV results in our study compared to the 25.1% rate reported in another study [12], repeating anal sampling for HPV testing could be useful in patients with insufficient HPV results.

Based on findings from this pilot study, we are performing a larger study to better determine which screening tools (anal HPV testing, anal cytology or both), and what age range and screening intervals are optimal for anal screening in this high-risk population. In addition, a more comprehensive HPV genotyping analysis of anal specimens would allow for a better understanding of HPV strains that are found in women with anal dysplasia or cancer.

5. Conclusion

Our results suggest that women with high-grade HPV-related lower genital tract dysplasia or cancer have high prevalence of high-grade anal dysplasia. To support the inclusion of this high-risk group of women into screening guidelines for anal dysplasia, further studies are necessary to determine what screening strategy is suited to this population.

Conflicts of interest

Each author has disclosed.

Role of the funding source

The funding source had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Table 3
High-resolution anoscopy and anal pathology results by disease site.

	All[a]	Cervix	Vagina	Vulva	p-value
Total	75	48	13	17	
High-resolution anoscopy results, n (%)					0.11
Normal	46 (61.3)	33 (68.8)	5 (38.5)	9 (52.9)	
Abnormal	29 (38.7)	15 (31.2)	8 (61.5)	8 (47.1)	
Anal pathology results, n (%)[b]					0.96
Negative	20 (71.4)	10 (71.4)	5 (62.5)	6 (75.0)	
LSIL	4 (14.3)	2 (14.3)	1 (12.5)	1 (12.5)	
HSIL	4 (14.3)	2 (14.3)	2 (25.0)	1 (12.5)	

LSIL: low-grade anal intraepithelial neoplasia; HSIL: high-grade anal intraepithelial neoplasia.
[a] One patient with cervical disease and two patients with vulva disease also presented with vaginal disease.
[b] One patient with abnormal anoscopy declined anal biopsy.

Table 4
Description of patients with high-grade anal dysplasia on cytology (HSIL) or histology (HGAIN).

Patient number	Age (years)	Inclusion criteria	Anal biopsy	Anal cytology	Anal HPV16/18
1	51	VAIN3	HSIL	ASCUS	Negative
2	45	CIN2	HSIL	Normal	Positive
3	67	CIN2	HSIL	ASCUS	Insufficient
4	63	VAIN3 and VIN3	HSIL	LSIL	Insufficient
5	59	VIN3	LSIL	HSIL	Positive
6	69	VIN3	LSIL	HSIL	Positive

CIN: cervical intraepithelial neoplasia; VAIN: vaginal intraepithelial neoplasia.
VIN: vulvar intraepithelial neoplasia.
ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

Authors' contribution

KMS, CAM, AM, MG and EMS conceived the study, and supervised the data collection. JFD, KRD, AD, and KMS designed the data analysis plan and analyzed the data. JFD, CAM, MPS, and KMS drafted the initial version of the manuscript. AD, EYC, KRD, MPS, CAM, EMS, and KMS critically revised subsequent drafts and provided significant inputs in every section of the manuscript. All authors approved the final version of the manuscript. KMS is the guarantor of the paper.

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