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Evaluation of anal cytology and dysplasia in women with a history of lower genital tract dysplasia and malignancy

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Abstract

Objective—To compare the prevalence of abnormal anal cytology, high-risk anal HPV and biopsy proven anal dysplasia among women with a history of lower genital tract malignancy compared to those with dysplasia.

Methods—A prospective cohort study was performed from December 2012 to February 2014 at outpatient clinics at an academic medical center. Women with a history of high-grade cervical, vulvar, or vaginal dysplasia, or malignancy were recruited. Anal cytology and HPV genotyping were performed. All women with abnormal anal cytology were referred for high-resolution anoscopy and biopsy.

Results—Sixty-seven women had a lower genital tract malignancy and 123 had a history of genital dysplasia. Average age in the malignancy group was 52.6 years (range 27–86) versus 43.5 years (range 21–81) in the dysplasia group ($p<0.0002$). Similar rates of anal dysplasia were seen in both groups, 12.99% (10 cases) in the malignancy group, versus 12.20% (15) in the dysplasia

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group (p=1.0). Six women in the malignancy group had anal intraepithelial neoplasia (AIN2+) compared to 2 in the dysplasia group (p= 0.03).

Conclusions—We found high rates of abnormal anal cytology and HPV in women with lower genital tract dysplasia and malignancy. We also found high rates of anal dysplasia in both groups with a trend towards increased rate in those women with history of genital malignancy. Since precancerous anal lesions are detectable and treatable, anal cancer screening may be potentially useful in both of these higher risk groups.

Introduction

Anal cancer, like cervical, is caused by high-risk subtypes of the human papilloma virus (HPV) in 90% of cases [1]. The anal transformation zone, the junction between the stratified squamous epithelium of the anus and the columnar epithelium of the rectum, is morphologically analogous to the transformation zone of the cervix. The squamous cells of the transformation zone are highly reactive, making them most susceptible to infection with high risk HPV.. A recent study followed 75 women (mean age 23.5 years) who tested positive for anal HPV for 5 years. They demonstrated that about 85% of women cleared low risk HPV and non-16 high-risk HPV types by the end of 3 years. The clearance rate of HPV-16 was slower that in cervical HPV infection, with only 75% having cleared at 3 years. [2] Knowing that anal cancer is caused by HPV in a similar way to cervical disease is helpful, but there is a lack of data guiding anal cancer screening recommendations. Most experts recommend anal screening for HIV+ men and women as well as men who have sex with men [3], and the American Cancer Society suggests that those at increased risk of anal intraepithelial neoplasia (AIN) may benefit from screening, including women who have had cervical or vulvar cancer [4]. A recent study by Slama, et al examined 172 high-risk women with cervical intraepithelial neoplasia 2 or greater (CIN2+) compared to 100 women with non-neoplastic gynecologic disease [5]. They found that concurrent cervical and anal HPV infection was found in 42% of the high-risk women vs. 8% of controls. This group with concurrent infections had a high percentage of women with CIN3+ and HPV16. The authors advocate that all women with cervical HPV16 and history of anal intercourse should have anal pap screening. Similarly, Calore, et al. demonstrated that there was a high prevalence (59.2%) of anal squamous intraepithelial lesions among those with cervical dysplasia. They found no significant correlation between anal intercourse and prevalence of anal cytologic abnormalities [6]. In an attempt to better delineate who should be included as high risk for anal cancer screening, Saleem, et al recently reviewed data from the National Cancer Institute’s Surveillance, Epidemiology and End Results program and in assessing 189,206 cases of in situ or invasive genital neoplasia, found the subsequent development of 255 cases of anal cancer, with incidence ratio of 13.6 compared rates expected based on age, race, and calendar year rates in an unaffected population [7]. They found the highest rates of anal cancer in women with history of in situ and invasive vulvar cancer with incidence ratios of 22.2 and 17.4 respectively, compared to incidence ratios to 16.4 and 6.2 for those with cervical dysplasia and invasive cervical cancer respectively. Based on their data, they recommended that women with HPV related gynecologic neoplasms might benefit from early anal cancer screening.

This study is a sub-set analysis of our larger study that examined the prevalence of abnormal anal cytology and high-risk HPV among women with a recent history of HPV-related genital neoplasia compared to women without a history of neoplasia. This larger study demonstrated the prevalence of 4.3% for AIN2 or greater among women with a history of genital neoplasia or cancer [8]. This represents a significant risk to these women and supports the need for anal cancer screening. In this current analysis we attempted to further delineate if there was a clear subgroup of women who would benefit from anal pap screening. We examined those women with lower genital tract dysplasia compared to those with lower genital tract malignancy to determine if the malignancy group had higher rates of abnormal anal cytology, high-risk anal HPV or anal dysplasia.

Methods

A prospective cohort study was performed from December 2012 to February 2014 at Women and Infants Hospital, a large academic medical center. After IRB approval was obtained, women ages 18 and older were recruited from outpatient general gynecology and gynecologic oncology clinics. 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 through participant interviews.

Women with a recent history of high-grade cervical cytology, CIN2, CIN3, VIN2, VIN3, VAIN2, or VAIN3 in the prior 2 years, comprised the dysplasia group and women with recent history (also less than 2 years) of biopsy proven vaginal, vulvar or cervical cancer comprised the malignancy group. Women were excluded if they were HIV positive, unable to give informed consent or had a history of anal cancer or AIN.

All women had anal cytologic testing with thin-layer cytology using a swab as previously described in Robison, et al [8]. All cytology samples were evaluated by two trained cytopathologists and the results entered in the electronic record. In the event of an abnormal anal cytology, participants were referred to a colorectal surgeon for high-resolution anoscopy (HRA) regardless of cytologic abnormality. The HRA examinations were performed in the operating room by a single colorectal surgeon comfortable with this procedure. Anal biopsies were performed at the discretion of the colorectal surgeon.

HPV typing was performed at the University of California, San Francisco laboratory using a complex multiplex real time PCR test that simultaneously detected, typed, and quantified all 15 high-risk HPV types known to cause anogenital cancer. HPV 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 Beta-globin gene as an internal control, and this was used to determine the normalized viral load (viral load/cell) to eliminate sample variations. A standard curve was created with the amplified products for each of the 15 high-risk virus templates at the concentration range of 10^0 to 10^7. The crossing point (cp) 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 [9–11]. 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 Chi-square or Fisher's exact test. Continuous variables were compared between groups by Student's T-test or ANOVA. If the continuous data deviated from a normal distribution, then the equivalent nonparametric tests were used. Ninety-five percent confidence intervals (95% CI) were calculated as measures of statistical stability for prevalence estimates. The association between HPV types and abnormal anal cytology and histology are summarized by odds ratios (ORs) and 95% CIs. Multivariate logistic regression was used to adjust the OR estimates for potential confounding by patient characteristics.

This is an ad hoc analysis of our larger study examining differences in anal cytology and HPV types between women with and without lower genital tract neoplasia [8]. Based on calculations for the number of patients included in this analysis, we can detect a 17% difference between our two groups.

Results

A total of 190 women met eligibility criteria. There were 67 women in the malignancy group and 123 women in the dysplasia group. As seen in table 1, the median age in the malignancy group was 52.6 years (range 27–86) versus 43.5 years (range 21–81) in the dysplasia group. Ninety-one percent of women in the malignancy group were white versus 68.3% in the dysplasia group. No difference was observed in smoking history, with 56.1% of the malignancy group versus 64.9% of the dysplasia group having ever smoked. There were no differences in rates of anal intercourse, 26.6% in malignancy group versus 31.8% in dysplasia group.

No differences were observed in rates of abnormal anal cytology (Table 2): 38.8% of the malignancy group compared to 42.5% of the dysplasia group. Ten (15.2%) women in the malignancy group and 28 (23.9%) in the dysplasia group were positive for high risk anal HPV. A minority of women in both groups, 10.6% of women in the malignancy group and 13.7% of the dysplasia group, had both abnormal anal cytology and high risk HPV. The rates of insufficient cytology were similar between groups, 10.5% of malignancy group and 9.2% of dysplasia group, while 30.3 % in malignancy group and 22.2% in the dysplasia group had insufficient HPV results. 4.6% of malignancy group and 4.3% of the dysplasia group had both insufficient cytology and HPV results.

Of the 26 women in the malignancy group referred for anoscopy, 7 (26.9%) did not present for follow up anoscopy while 20 (39.2%) of 51 in the dysplasia group did not follow-up. Of the 19 women in the malignancy group who underwent anoscopy, 11 had biopsies: 1 was normal, 4 had AIN 1, 4 had AIN 2, 1 had AIN 3 and 1 had cancer. Of the 31women in the dysplasia group that had anoscopy, 17 had biopsies: 2 were normal, 13 had AIN 1, 1 had AIN 2, 1 had AIN 3 and there were no diagnoses of cancer. We identified 10 cases (12.99%) of anal dysplasia in the malignancy group and 15 cases (12.20%) were identified in the

dysplasia group (p=1.0.). Of the women who underwent anal biopsies, there were more cases of AIN2+ in the malignancy group, with 6 (54.6%) in the malignancy group and 2 (11.8%) in the dysplasia group (p-0.03)

Of the 6 women diagnosed with AIN2+ in the malignancy group, 3 had a history of vulvar cancer and 3 had a history of cervical cancer. Of the women with a history of vulvar cancer, 1 was diagnosed with anal cancer, one with AIN 2 and the third with AIN3. The woman diagnosed with anal carcinoma had an ASCUS anal pap that was high risk HPV negative. The woman diagnosed with AIN2 also had an ASCUS pap and negative high risk HPV. The third patient with a history of vulvar malignancy, who had AIN3 on biopsy, had an HSIL pap with HPV16. Of the three women with a history of cervical cancer diagnosed with anal dysplasia, all were diagnosed with AIN2. Of these, 2 had LSIL and 1 had HSIL for anal cytology. They all had HPV, but with varying non-HPV 16 or 18 genotypes.

Of the two women in the dysplasia group diagnosed with AIN2+, one had a history of CIN3 and the other had VAIN2. They were both HPV16 positive on anal testing. The woman with a history of CIN3 was found to have AIN3 after ASCUS anal pap and the other woman was found to have AIN2 after HSIL pap. (Table 4)

Discussion

In a prior analysis, we demonstrated that women with a history of lower genital tract neoplasia were more likely to have positive anal cytology and high-risk anal HPV than those without neoplasia [8]. In this study we observed high-rates of abnormal anal cytology, high-risk anal HPV and anal dysplasia among women with a history of cervical, vulvar or vaginal cancer or dysplasia. While we demonstrated similar rates of anal dysplasia in the 2 groups, 12.99% in the malignancy group versus 12.20% in the dysplasia group, we did find higher rates of AIN2+ in the malignancy group. This is likely due to the longer time it takes to develop a HPV related malignancy. Therefore, while we may have expected higher rates of anal dysplasia among women with an HPV related genital cancer, our study suggests even women with a history of lower genital tract dysplasia are at increased risk of anal dysplasia.

Since precancerous anal lesions are detectable and treatable, anal cancer screening may be potentially useful in women with history of genital dysplasia and malignancy. There is some concern about uptake of anal pap smear due to patient willingness to undergo the procedure and follow up testing, however, similar to what we found in our study, a recent study by Ferris, et al. demonstrated in a survey of 370 women that despite limited knowledge about anal cancer and anal cancer screening that if necessary they would be receptive to screening, with only 21% citing embarrassment as main reason for not wanting it done [12]. Anoscopy is performed similarly to colposcopy, and many gynecologists and gynecologic oncologists may be comfortable performing the procedure in the office. ASCCP offers courses in the procedure directed at physicians in the fields of internal medicine, infectious disease, gastroenterology, general surgery, colo-rectal surgery and gynecology to aid in understanding of fundamentals of anoscopy as well as hands on training.

AIN can be treated with multiple different modalities, including tricholoroacetic acid 85% (TCA), cryotherapy, infrared coagulation and ablation in the office. TCA is applied with a cotton swab to small warts or areas with AIN every 2 to 3 weeks up to 4 treatments and is generally well tolerated by patients. Studies have demonstrated high rates of clearance of AIN 2–3. [13] Cryotherapy can similarly be performed and is well tolerated in the office, with liquid nitrogen being applied directly to lesions for 3 freeze-thaw cycles for 3 to 4 treatments done 2 weeks apart. Office based ablation can be performed in conjunction with high resolution anoscopy, but does require injection of lidocaine. Infrared coagulation is useful for larger lesions or those not responding to TCA or cryotherapy. Small studies have shown good efficacy, but some patients with persistent HSIL require retreatment.[14]

Many authors have attempted to identify prevalence of AIN in high-risk groups, and others have tried to best delineate who constitutes these high-risk groups [15–20]. The majority of these studies only examined women with history of dysplasia, not malignancy. Santoso, et al evaluated women with history of genital neoplasia (cervix, vulva, vaginal) with anal pap and anoscopy and observed a 12.2% prevalence of AIN among women with history genital neoplasia [19]. Similarly, ElNaggar et al. sought to identify risk factors for AIN in heterosexual women. Among a cohort of 327 women with genital dysplasia, of the 137 who had a biopsy, 64 (46.7%) were found to have AIN, with a prevalence of 19.6% in the study population. In addition to immunosuppression, greater than 4 sexual partners, smoking, and history of anal sex, a history of vulvar dysplasia was identified as a risk factor for AIN. Having a combination of two out of three of vulvar dysplasia, immunosuppression and history of anal intercourse predicted 38.8% of AIN lesions [20]. These findings suggest that genital dysplasia increases risk for anal dysplasia. Our research further supports this finding as well as demonstrates that history genital malignancy may further increase this risk.

While we know that HPV infection is often multifocal [15, 21], not all anal cancers are HPV related. In our study, two women with a history of vulvar cancer were diagnosed with anal carcinoma and AIN2. Both of these women had negative anal HPV tests, suggesting their vulvar cancers were likely not HPV related. As discussed previously, ElNaggar et al. demonstrated that vulvar dysplasia was a risk factor for development of anal dysplasia, based on our findings of HPV negative anal dysplasia and cancer, it is clear that the role vulvar cancer, whether HPV mediated or not, plays in this process is important to further delineate. There are at least two potential explanations for the findings. First, there may be local factors such as close proximity of the vulvar neoplastic process playing a role in the pathophysiology of anal dysplasia in the setting of non-HPV mediated malignancies. Second, there may be direct spread of high risk HPV from the vulva to the anus causing disease. Regardless our findings suggest that in this group of high-risk women, anal screening with either anal cytology and/or high-resolution anoscopy is warranted.

Our study has several limitations. First, only women with abnormal anal cytology were referred for high resolution anoscopy and not those women with high-risk anal HPV. Second, we had a low rate of compliance with high resolution anoscopy, so we are unable to determine the sensitivity and specificity of anal cytology or HPV testing. Third, we reported high rates of insufficient cytology, (10.5% of malignancy group and 9.2% of dysplasia group) and insufficient HPV specimens (30.3 % in malignancy group and 22.2% in the

dysplasia group), which have been reported by others in the literature [19]. However, when examining co-testing for cytology and HPV, only 4.6% of malignancy group and 4.3% of the dysplasia group had insufficient results for both tests. Further studies evaluating the utility of HPV testing women with history of genital tract dysplasia and malignancy are warranted.

Conclusion

Women with lower genital tract dysplasia and malignancy are at increased risk of anal dysplasia and malignancy. Given that cervical dysplasia is easily treated with excision prior to developing into invasive disease, anal dysplasia can be treated by similar methods. Defining what patients constitute a high-risk group that necessitates screening and then the appropriate screening methods is important to enable anal dysplasia to be treated before it becomes invasive disease.

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Highlights

- AIN is a precursor lesion for anal carcinoma; identifying who is high risk and warrants screening is important.
- Women with lower genital tract dysplasia and malignancy both had high rates of anal cytology and HRHPV.

TABLE 1

Characteristics by diagnosis group

	Cancer	Dysplasia	p-value
Total	67	123	
Median age (range)	52.6 (27–86)	43.5 (21–81)	0.0002
Age groups			
<30	4 (6.0)	28 (22.8)	0.004
30–65	54 (80.6)	87 (70.7)	
65+	9 (13.4)	8 (6.5)	
Ethnicity			
Non-Hispanic White	61 (91.0)	84 (68.3)	0.002
African American	1 (1.5)	17 (13.8)	
Hispanic	4 (6.0)	19 (15.5)	
Asian	1 (1.5)	1 (0.8)	
Other	0	1 (0.8)	
Unknown	0	1 (0.8)	
History of Smoking			
No	29 (43.9)	40 (35.1)	0.3
Yes	37 (56.1)	74 (64.9)	
Ever had anal intercourse			
No	47 (73.4)	75 (68.2)	0.5
Yes	17 (26.6)	35 (31.8)	

TABLE 2

Anal cytology by diagnosis group

	Cancer	Dysplasia	p-value
Total	67	123	
Anal Cytology Results		(n=120)	
Normal	34 (50.8)	58 (48.3)	0.9
Abnormal	26 (38.8)	51 (42.5)	
Insufficient	7 (10.5)	11 (9.2)	
Abnormal anal cytology			
ASCUS	13 (50.0)	25 (49.0)	0.8
LSIL	9 (34.6)	21 (41.2)	
ASCUS or LSIL cannot r/o HSIL	2 (7.7)	2 (3.9)	
HSIL	2 (7.7)	3 (5.9)	
High-risk HPV Anal	(n=66)	(n=117)	
Positive	10 (15.2)	28 (23.9)	0.3
Negative	36 (54.6)	63 (53.9)	
Insufficient	20 (30.3)	26 (22.2)	
Anal HPV positive and abnormal anal cytology	(n=66) 7 (10.6)	(n=117) 16 (13.7)	0.6
Anal cytology insufficient and anal HPV insufficient	(n=66) 3 (4.6)	(n=117) 5 (4.3)	1.0

TABLE 3

Anoscopy results by diagnosis group

	Cancer	Dysplasia	p-value
Total	11	17	
Anal Dysplasia			
Normal	1 (9.1)	2 (11.8)	
AIN 1	4 (36.4)	13 (76.5)	0.08
AIN 2	4 (36.4)	1 (5.9)	
AIN 3	1 (9.1)	1 (5.9)	
Cancer	1 (9.1)	0	
HSIL or cannot r/o HSIL	(n=2)	(n=1)	
No anal dysplasia	0	0	
AIN 1	0	0	--
AIN 2	1 (50.0)	1 (100)	
AIN 3	1 (50.0)	0	
Cancer	0	0	

TABLE 4

Breakdown of patients with diagnosis of AIN2, AIN3, or anal carcinoma

Diagnosis	Anal Pap	Anal HPV	HPV genotype	Anal Biopsy
CIN3	ASCUS	Positive	16	AIN3
VAIN 2	HSIL	Positive	16	AIN2
Vulvar Cancer	HSIL	Positive	16	AIN3
Vulvar Cancer	ASCUS	Negative	-	Anal carcinoma
Vulvar Cancer	ASCUS	Negative	-	AIN2
Cervical Cancer	LSIL	Positive	32/42	AIN2
Cervical Cancer	LSIL	Positive	70	AIN2
Cervical Cancer	HSIL	Positive	6/11/51	AIN2