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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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HIGHLIGHTS

- AIN is a known precursor lesion for anal carcinoma.
- Women with lower genital tract dysplasia and malignancy had high rates of abnormal anal cytology.
- Identifying who is at high risk for anal dysplasia and warrants screening is important.

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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 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.

1. 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

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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.

2. 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 <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.

3. 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.

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)	