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Risk of cervical and vaginal dysplasia after surgery for vulvar intraepithelial neoplasia or cancer: A 6 year follow-up study

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HIGHLIGHTS

- Patients surgically treated for high-grade vulvar dysplasia or cancer are at risk for abnormal cervical/vaginal cytology.
- Prior hysterectomy does not mitigate the risk (8%) for at least high-grade cervical/vaginal neoplasia in these patients.
- Non-white race, immunosuppression, prior abnormal cytology, not prior hysterectomy, are correlates for abnormal cytology.

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ABSTRACT

Objectives. To estimate the frequency of abnormal surveillance cytology leading to high-grade dysplasia after surgical management for high-grade vulvar intraepithelial neoplasia (VIN) and vulvar cancer and to determine whether prior hysterectomy reduces this risk.

Methods. Women who underwent surgery for high-grade VIN or vulvar cancer between 2006 and 2014 were identified retrospectively. Patients who underwent prior hysterectomy for any indication were included. Univariate and multivariate logistic regression analyses were used to identify clinical correlates of abnormal cytology after surgical treatment for VIN and vulvar cancer.

Results. During a median follow-up for 72 months, 302 women underwent surveillance with cytologic screening after vulvar surgery including 99 (33%) women with prior hysterectomy. 75 (25%) women had abnormal cytology results. Of those, 47 (63%) were low-grade and 28 (37%) were high-grade, including 2 (3%) cases of invasive cancer. The rates of high-grade vaginal intraepithelial neoplasia (VAIN), cervical intraepithelial neoplasia (CIN), or cancer were not significantly different despite prior hysterectomy (9% VAIN 2+, 7% CIN 2+). Multivariate analysis showed that correlates of high-grade cytology following treatment for VIN or vulvar cancer included non-white race [odds radio (OR) 3.6, 95% confidence interval (CI) 1.7–7.8], prior abnormal cytology (OR 3.5, 95% CI 1.6–7.6), and immunodeficiency (OR 3.4, 95% CI 1.3–8.8). Prior hysterectomy did not significantly decrease risk of high-grade cytology (OR 0.87, 95% CI 0.5–1.6).

Conclusions. Women treated surgically for VIN/vulvar cancer have an 8% risk of at least high-grade dysplasia from surveillance screening and prior hysterectomy does not mitigate the risk. Extrapolating from current guidelines, we recommend surveillance cytology screening at least 6–12 months after treatment.

1. Introduction

Over 24,000 women in the United States were diagnosed with cancer caused by the human papillomavirus (HPV) in 2018 [1]. High-risk HPV subtypes are especially prevalent in lower genital tract disease. The cervix is most commonly affected, but HPV is also related to VIN, VAIN, as well as invasive cancer [2–6]. Although indications for cytologic screening are well established by consensus guidelines put forth by the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Cancer Society, and the United States Preventative Services Task Force (USPSTF), for patients with and without prior hysterectomy, it remains unclear whether there is a role for cytology screening for women treated surgically for VIN or vulvar cancer. Prior work defining the risk for subsequent cervical or vaginal dysplasia after VIN or vulvar

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cancer treatment does not allow for conclusions to be drawn regarding best management [2,3,6]. Therefore, current guidelines for women who have been treated for VIN recommend follow up with visual inspection of the vulva in 6 and 12 months, but do not specifically define the role of cervical cytologic screening [7].

The subsequent risks of other HPV-related neoplasias and cancers are not well defined after a diagnosis of VIN or vulvar cancer. This is especially true when vulvar disease develops after prior hysterectomy, since risk for VAIN is low in the general population and cervical cancer risk is essentially non-existent if the cervix has been removed. This study builds upon our previous work which suggested that the risk for high-grade cervical and vaginal disease was greater than expected at 8% and 11%, respectively, among women surgically treated for VIN or vulvar cancer [8]. Due to limitations in sample size and short interval follow-up, we were unable to draw conclusions whether or not hysterectomy conferred any protective effects against VAIN 2+. Therefore, we set out to expand our sample size and follow-up period in order to best estimate the risk of cervical and vaginal dysplasia or cancer among women treated surgically for VIN or vulvar cancer and determine if hysterectomy mitigates this risk.

2. Methods

After approval by Washington University's Human Research Protection Office, a retrospective cohort study evaluated all patients who underwent surgical excision for VIN and/or vulvar cancer by the Division of Gynecologic Oncology at Washington University School of Medicine sequentially from January 1, 2006, to December 31, 2014. Patients were included in final analysis if they were older than 18 years of age with a histologically confirmed diagnosis of high-grade squamous VIN or invasive vulvar cancer. In addition, at least one liquid-based cytology specimen after vulvar surgery must have been obtained. Patients were excluded if there was no documented follow-up after vulvar surgery. Other exclusion criteria included vulvar excision for low-grade squamous intraepithelial lesion (LSIL) of the vulva or treatment with laser ablation. All cases of vulvar melanoma in situ, invasive melanoma, or Paget disease were excluded as well.

Decisions made regarding cytologic screening, management after abnormal cytology, and performing colposcopy were at the discretion of the treating gynecologic oncologist. Our primary endpoint was high-grade dysplasia from directed colposcopic biopsies of the cervix/vagina and/or endocervical curettage. All specimens underwent centralized review by subspecialized gynecologic pathologists in the Ackerman Laboratory of Surgical Pathology at Barnes-Jewish Hospital/Washington University School of Medicine. Cytology results were read according to the Bethesda system for cervicovaginal cytologic diagnosis as normal, atypical squamous cells of uncertain significance (ASC-US), ASC-US with high risk HPV positivity (ASC-US + HPV), atypical squamous cells, cannot exclude high-grade intraepithelial lesions (ASC-H), LSIL, high-grade squamous intraepithelial lesions (HSIL), and atypical glandular cells (AGC) favor neoplasia [9]. Our endpoint for risk included high-grade cytology which is defined as HSIL, ASC-H, AGC, and cancer. CIN 2 and VAIN 2 or greater were deemed high-grade for histology.

Demographic and clinical characteristics were summarized by descriptive statistics for continuous variables and percentage for categorical variables. The difference between normal and abnormal cytology cases after vulvar therapy was analyzed using Kruskal-Wallis for continuous variables and Fisher's Exact tests for categorical variables. All the tests were two-sided, and the significance level was set at 0.05. Univariate and multivariate logistic regression models were used to examine the association between abnormal cytology results after vulvar therapy and clinical risk factors including age, race, current cigarette smoking, immunosuppression, previous abnormal cervical or vaginal cytology, and previous hysterectomy. Women were deemed immunosuppressed if they had a diagnosis of human immunodeficiency virus (HIV) or were transplant patients taking immunosuppressant medications. Stepwise selection was used in the multivariate logistic regression, where a significance level of 0.3 was required to allow a risk factor into the model, and a significance level of 0.35 was required for a risk factor to stay in the model. The uncertainty of estimates was assessed by confidence intervals. The final model included risk factors with a significance level of 0.05.

3. Results

We identified 587 women treated for vulvar cancer or high-grade VIN between 2006 and 2014. Of these, 302 met inclusion for final analysis with a median surveillance follow-up of 72 months (range 56–237). This included 1167 surveillance liquid-based cytology tests that were performed after vulvar surgical management (median 2 per patient, range 1–21). The mean age at time of vulvar surgery was 53 and the majority of patients were Caucasian (85%). Risk factors for abnormal cytology did not differ between women with normal versus abnormal cytology after vulvar treatment. These included cigarette smoking status, human immunodeficiency virus (HIV) seropositivity or other immunodeficiency, and history of prior cervical dysplasia at the time of presentation. The primary vulvar lesion was VIN 2 in 5% of all patients, VIN 3 in 53%, and invasive cancer of any stage in 42% (Table 1).

After surgical treatment for high-grade VIN or vulvar cancer, 75 (24.8%) had abnormal cervical/vaginal cytology. Forty-seven (56%) were low-grade (ASCUS and LSIL), and 28 (37%) high-grade (ASC-H, HSIL, AGC). These resulted in 58 women who underwent colposcopic evaluation with the following final pathology: benign [26 (45%)], CIN/VAIN 1 [13 (22%)], CIN/VAIN 2 [4 (7%)] and CIN/VAIN 3 [16 (28%)]. There were 46 patients who had no known follow up. Excluding these patients, the cumulative incidence of CIN/VIN 2+ diagnosed after excision for VIN/cancer was 8% (Table 2).

Two patients (1%) were found to have invasive cancer. One woman, aged 82 was diagnosed initially with stage III squamous cell carcinoma of the vulva and underwent radical vulvectomy followed by adjuvant radiation. Over 3 years after treatment, she presented with postmenopausal bleeding and was found to have grade 1 endometrial adenocarcinoma on endometrial biopsy. The other, aged 66 with an initial diagnosis of VIN 3, was diagnosed after treatment for suspected CIN 3 on colposcopic biopsy and found to have invasive cervical cancer on final pathology evaluation after surgical management. Only this patient was included for final analysis when comparing rates of at least high-grade dysplasia stratified by history of hysterectomy. Neither patient had a history of hysterectomy.

Overall, 99 (33%) women had undergone hysterectomy, 34 (11%) for benign indications, 22 (7%) for cervical dysplasia, 5 (2%) for cervical cancer, and 36 (12%) for unknown indications. None of the patients who underwent hysterectomy for benign indications had a history of high-grade cytology or CIN 2+ prior to treatment for vulvar disease. There was no significant difference in rates of high-grade preinvasive disease or cancer between women who had undergone a prior hysterectomy versus those who had an intact cervix [9% (9/99) vs. 7% (15/203), $p = 0.59$]. Univariate analysis demonstrated that non-white race [odds ratio (OR) 4.57, 95% confidence interval (CI) 2.36–8.83], immunosuppression (OR 3.96, 95% CI 1.79–8.80) and prior abnormal cytology (OR 4.4, 95% CI 2.11–9.34) were associated with at least high-grade cytology (Table 3). In our multivariate logistic regression model, after adjusting for age, race, smoking status, prior abnormal cytology, and prior hysterectomy, these factors remained significantly associated with the development of abnormal cytology after vulvar surgery for high-grade VIN or vulvar cancer (adjusted OR 3.69, 95% CI 1.26–10.83).

4. Discussion

Women treated for high-grade VIN and/or vulvar cancer are at high risk for synchronous or metachronous cervical or vaginal HPV-related lesions. In our cohort, we found an overall risk of 25% for abnormal

Table 1
Patient characteristics and history before presentation for vulvar surgery.

	Total $n = 302$	Cytology results after vulvar therapy	
		Normal $n = 227$ (%)	Abnormal $n = 75$ (%)
Age (years, mean ± SD)	53.2 ± 15.6	53.2 ± 15.4	53.2 ± 16.2
Primary vulvar lesion			
VIN2	14 (4.6)	12 (5.2)	2 (2.7)
VIN3	159 (52.7)	119 (52.4)	40 (53.3)
Cancer – any stage	125 (41.4)	92 (40.5)	33 (44.0)
Race			
White	256 (84.8)	195 (85.9)	61 (81.3)
Non-white	46 (15.2)	32 (14.1)	14 (18.7)
Current cigarette smoker	134 (44.4)	103 (45.4)	31 (41.3)
Human immunodeficiency virus	14 (4.6)	8 (3.5)	6 (8.0)
Other immunosuppression	28 (9.3)	22 (9.7)	6 (8.1)
Prior hysterectomy	99 (32.8)	77 (33.9)	22 (29.3)
Prior treatment for cervical disease	75 (24.8)	53 (23.4)	22 (29.3)
Cervical/vaginal cytology prior to diagnosis of VIN/vulvar cancer			
Negative	150 (49.7)	116 (51.1)	34 (45.3)
ASCUS HPV positive	7 (2.3)	5 (2.2)	2 (2.7)
ASCUS HPV negative	5 (1.7)	1 (0.4)	4 (5.3)
ASCUS HPV unknown	4 (1.3)	4 (1.8)	0 (0)
ASC-H	4 (1.3)	4 (1.8)	0 (0)
LSIL	28 (9.3)	20 (8.8)	8 (10.7)
HSIL	19 (6.3)	11 (4.9)	8 (10.7)
Cancer	1 (0.3)	1 (0.4)	0 (0)
Unknown	84 (27.8)	65 (28.6)	19 (25.3)

SD = standard deviation, ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; HSIL, high-grade intraepithelial lesion.
Numbers are reported as column percentage with the denominator excluding missing values.
No significant differences among the groupings in any characteristic listed.

cytology during surveillance exams, of whom 37% had high-grade cytology (10% overall). This translated to an 8% overall risk for CIN 2+/VAIN 2+ on final colposcopic assessment. When controlling for HPV-related clinical and demographic risk factors, we found that women with history of abnormal cytology, non-white race, and immunosuppression are independent correlates of abnormal cytology despite history of hysterectomy.

Our data support the concept that HPV-related disease can manifest throughout the anogenital region rather than being confined to one particular organ. Prior studies have shown that VIN and vulvar cancers are associated with HPV subtypes that are similarly oncogenic in cervical and vaginal disease [4,10]. It is also well established that HPV-related dysplasias share common risk factors for acquisition and progression like age of sexual debut, number of sexual partners, cigarette smoking, non-white race, and immunocompromise [2,11–13]. Further evidence to support HPV manifestation along the continuum of the lower genital tract, Balamurugan et al. demonstrated a markedly elevated risk of vaginal and vulvar cancers among cervical cancer index cases in the Surveillance, Epidemiology, and End Results database [14]. Gonzalez-Bosquet et al. have shown in a large, prospective study that multicentric HPV lesions mostly involve the cervix and either the vagina or vulva. In that study, HPV infection and immunodeficiency were significantly correlated with multicentric disease and those women faced an increased risk of recurrence or progression to cancer [15].

Despite this body of literature there is a lack of recommendations for surveillance cytology among women surgically treated for high-grade VIN or vulvar cancer. Current guidelines set forth by the American Cancer Society and ASCCP for cervical or vaginal cytology after hysterectomy do not specifically include a decision matrix based on history of vulvar disease despite their elevated risk (9%) for VAIN2+ as demonstrated in our study. For women without a cervix and who have no history of CIN2+, no further cytologic screening is recommended due to the low potential detection rate and incidence of vaginal cancer [16–18]. Other studies have also investigated the utility of cytology screening based on individualized risk assessments. Smeltzer et al. concluded that vaginal cytology should be indicated in women with HIV after hysterectomy. In that study, 30% of HIV-infected women with no abnormal cytology prior to hysterectomy had abnormal vaginal cytology and 29% had VAIN 2+ [19].

Our study is a single-institution retrospective cohort study, limited by the inherent nature of missing data, lack of standardized management practices, and inconsistent patient follow-up. We also acknowledge the lack of information on why certain patients were selected for cytology screening, such as physical exam findings or patient symptoms. Therefore, the possibility for inherent selection bias exists. However, our patient population is relatively diverse and frequently co-managed with community providers, which could represent a more realistic management experience than the study type would suggest. Furthermore, our comparison groups were very well-matched with respect to patient characteristics and risk factors for abnormal cytology, minimizing bias that is inherent to retrospective studies.

Table 2
Distribution of worst abnormal cytology test results after vulvar therapy and colposcopic examination.

	ASCUS + HR HPV	LSIL	ASC-H	HSIL	AGC	Total, n (% of colposcopic biopsies)
Abnormal cytology	8	39	2	25	1	75
Underwent colposcopy	6	25	1	25	1	58
Benign	5	12	1	7	1	26 (44.8)
CIN1	1	5	0	2	0	8 (13.8)
VAIN1	0	3	0	2	0	5 (8.6)
CIN2	0	2	0	2	0	4 (6.9)
VAIN1	0	3	0	2	0	5 (8.6)
CIN3	0	2	0	9	0	11 (19.0)
VAIN3	0	0	0	5	0	5 (8.6)

CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; HR HPV, high-risk human papillomavirus; LSIL, low-grade intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; HSIL, high-grade intraepithelial lesion, AGC, atypical glandular cells.
Total cohort excluding 46 with unknown follow up ($n = 256$).

Table 3
Univariate and multivariate analyses assessing correlates of high-grade cytology after surgical treatment for vulvar intraepithelial neoplasia or cancer (N = 302).

Clinical factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-Value	Odds ratio (95% CI)	p-Value
Age (years)	0.98 (0.962–0.998)	**0.03**		
Race (non-white vs white)	4.57 (2.359–8.834)	<**0.0001**	3.60 (1.657–7.819)	**0.001**
Cigarette smoking[a]	1.03 (0.600–1.767)	0.92		
Immunosuppression[b]	3.96 (1.785–8.801)	**0.001**	3.36 (1.280–8.830)	**0.01**
Prior abnormal Pap[c]	4.44 (2.109–9.340)	<**0.0001**	3.54 (1.637–7.634)	**0.001**
Prior hysterectomy	0.87 (0.487–1.554)	0.64		

Bold data indicates significance at $p < 0.05$.
[a] Current smokers only.
[b] Immunosuppression was defined as patients with human immunodeficiency virus or who were on immunosuppressive medications; 1 missing.
[c] Data available on 232 out of 302 patients.

Most importantly, our study fills a gap in the existing literature to provide recommendations on cervical/vaginal cytology screening among women who undergo surgical excision for high-grade VIN and/or vulvar cancer. Expanding on our prior work [8] by adding nearly twice the number of patients and longer follow up, we show that prior hysterectomy does not negate the risk of high-grade cervical/vaginal dysplasia in this population. This is based on the principle of "similar management for similar risk" as described in the 2012 ASCCP guidelines, which recommend cytologic evaluation and subsequent colposcopy when the 5-year risk for high-grade neoplasia is at least 5% [20]. Our data exceed that risk threshold with greater median follow-up. Therefore, we recommend yearly cervical or vaginal cytologic screening starting 6–12 months after surgical treatment for VIN3 or vulvar cancer and abnormal results evaluated by colposcopy.

Author contributions

1. Tommy Buchanan, M.D.: Lead author who performed the majority of data collection and entry, and assisted with manuscript writing.
2. Abigail Zamorano, M.D.: Performed data collection and entry, as well as assisted with manuscript writing and revisions.
3. Jingxia Liu, PhD: Assisted with statistical analysis and approval of final submitted version.
4. Premal H. Thaker, M.D., M.S.: Assisted with manuscript revisions and approval of final submitted version.
5. L. Stewart Massad, M.D.: Involved with conception and study design. Assisted with manuscript revisions and approval of final submitted version.
6. Matthew A. Powell, M.D.: Assisted with manuscript revisions and approval of final submitted version.
7. David G. Mutch, M.D.: Assisted with manuscript revisions and approval of final submitted version.
8. Lindsay M. Kuroki, M.D., M.S.C.I.: Senior author who helped with initial design, IRB submission, data entry, and manuscript writing.

Declaration of Competing Interest

Dr. Thaker reports personal fees from Celsion, personal fees from Stryker, grants and personal fees from Tesaro, grants and personal fees from Merck, personal fees from Abbvie, personal fees from Clovis, outside the submitted work. Dr. Powell reports personal fees from Merck, personal fees from Tesaro, personal fees from Clovis Oncology, personal fees from AstraZeneca, personal fees from Roche/Genentech, personal fees from GOG Foundation, outside the submitted work. Dr. Kuroki reports grants from Washington University Institute of Clinical and Translational Sciences (R25 STRENGTH), grants from Washington University Institute of Clinical and Translational Sciences (KL2), during the conduct of the study. All other authors declare no potential conflict of interest.

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