Vaginal Neoplasia-A Common Clinical Dilemma: Management of Abnormal Vaginal Cytology and Human Papillomavirus Test Results

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Outline

- Scope of the problem
  - Epidemiology
  - HPV attribution in VaIN and vaginal cancer
- Vaginal tests
  - Cytology
  - High-risk HPV testing
- Management of abnormal vaginal tests: recommendations based on expert opinion

A Common Clinical Dilemma: Management of Abnormal Vaginal Cytology and Human Papillomavirus Test Results

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Objective: Vaginal cancer is an uncommon cancer of the lower genital tract, and standardized screening is not recommended. Risk factors for vaginal cancer include a history of other lower genital tract neoplasia or cancer, smoking, immunosuppression, and exposure to diethylstilbestrol in utero. Although cervical cancer screening after total hysterectomy for benign disease is not recommended, many women inappropriately undergo vaginal cytology and/or human papillomavirus (HPV) tests, and clinicians are faced with managing their abnormal results. Our objectives were to review the literature on vaginal cytology and high-risk HPV (hrHPV) testing and to develop guidance for the management of abnormal vaginal screening tests.

Materials and Methods: An electronic search of the PubMed database through 2015 was performed. Articles describing vaginal cytology or vaginal hrHPV testing were reviewed, and diagnostic accuracy of these tests when available was noted.

Results: The available literature was too limited to develop evidence-based recommendations for managing abnormal vaginal cytology and hrHPV screening tests. However, the data did show that (1) the risk of vaginal cancer in women after hysterectomy is extremely low, justifying the recommendation against routine screening, and (2) in women for whom surveillance is recommended, e.g., women posttreatment for cervical precancer or cancer, hrHPV testing may be useful in identification of vaginal cancer precursors.

Conclusions: Vaginal cancer is rare, and asymptomatic low-risk women should not be screened. An algorithm based on expert opinion is proposed for managing women with abnormal vaginal test results.

Key Words: vaginal cytology, HPV, vaginal cancer, VaIN

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Vaginal cancer is a rare human papillomavirus (HPV)–associated gynecologic disease, accounting for approximately 1% to 4% of cancers of the female genital tract.[1] A recent report from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results Program estimated that 729 cases of vaginal cancer occurred each year from 2004 to 2008, with approximately 500 attributable to HPV.[2] The reported incidence rate of vaginal cancer is 0.4 to 0.6 per 100,000 women; by comparison, the incidence rate for cervical cancer in the United States is 7.7 per 100,000 women.[2,3] Most vaginal cancers are of squamous cell histology; adenocarcinomas and melanomas are seen in smaller numbers.

High-grade squamous intraepithelial lesion (HSIL) or vaginal intraepithelial neoplasia (VaIN) grades 2/3 is a precancerous lesion analogous to HSIL/cervical intraepithelial neoplasia (CIN) grades 2/3.[4–6] Low-grade squamous intraepithelial lesion (LSIL) or VaIN 1 is a benign manifestation of HPV infection. Although natural history data on VaIN are scarce, it is thought that invasive vaginal cancer, such as invasive cervical cancer, is caused by persistent high-risk HPV (hrHPV) infection.[7] Other known risk factors for vaginal cancer include age at first intercourse younger than 17 years, 5 or more lifetime number of sexual partners, immunosuppression, smoking, pelvic radiation therapy, and exposure to diethylstilbestrol in utero.[4,8] Women who have had cervical cancer are also at significantly increased risk of developing vaginal cancer.[7] Age is also a risk factor for precancerous lesions of the vagina: HSIL/VaIN 2/3 was found more often in women older than 50 years compared with LSIL/VaIN 1 (mean age = 45 years).[9] The Centers for Disease Control and Prevention reported that the mean age at diagnosis of vaginal cancer was 69 years, 2 decades later than the mean age of cervical cancer of 48 years.[10]

There are no recent population-based studies that provide an accurate estimation of the incidence of VaIN, but extrapolating from older data, the incidence is thought to be approximately 0.2 to 0.3 per 100,000 women in the United States.[11] Vaginal intraepithelial neoplasia incidence may be rising as a result of increased sexual exposure to hrHPV with changing sexual behavior for the past several decades, as well as with improved detection with widespread sensitive cervical cancer screening tests and colposcopy.[12] The estimated progression rate of VaIN to vaginal cancer ranges from 0% to 9% in 5 different studies. These studies included cases of women with VaIN grades 1–3 who progressed to invasive vaginal cancer. These reported rates of progression are much lower than the demonstrated up to 30% progression rate for CIN 3 to invasive cervical cancer.[1,7–9,13–16]

Because of the rarity of vaginal cancer, there are currently no formal guidelines recommending screening for vaginal cancer in the general population (see Table 1). In fact, research articles and professional society guidelines recommend against vaginal cancer screening in women posthysterectomy for benign disease and in women posthysterectomy for cancers other than cervical cancer.[19–22] However, current cervical cancer screening guidelines do recommend that high-risk groups such as women who have

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Epidemiology: Vaginal Cancer

- Accounts for 1-4% of cancers of the female genital tract
- Incidence 0.4 – 0.6 per 100,000 women
- 729 cases per year
- Mean age at diagnosis: 69 years

MMWR 2012;61:258-61.

Characteristic	Cervical carcinoma			Vulvar SCC			Vaginal SCC			Penile SCC		
	Rate†	(95% CI§)	Average annual no.	Rate	(95% CI)	Average annual no.	Rate	(95% CI)	Average annual no.	Rate	(95% CI)	Average annual no.
Total	7.7	(7.7–7.8)	11,967	1.8	(1.8–1.9)	3,136	0.4	(0.4–0.4)	729	0.8	(0.8–0.8)	1,046
Age group (yrs)												
0–19	0.0	(0.0–0.1)	15	0.0	(0.0–0.0)	0	—¶	—	—	—	—	—
20–29	3.2	(3.1–3.3)	650	0.1	(0.1–0.1)	17	—	—	—	0.0	(0.0–0.0)	5
30–39	12.6	(12.4–12.8)	2,525	0.7	(0.7–0.8)	144	0.1	(0.1–0.1)	21	0.2	(0.1–0.2)	33
40–49	14.2	(14.0–14.4)	3,200	2.0	(1.9–2.1)	461	0.3	(0.3–0.4)	74	0.4	(0.4–0.5)	97
50–59	12.3	(12.1–12.6)	2,411	2.9	(2.8–3.0)	573	0.7	(0.6–0.7)	132	1.0	(0.9–1.0)	182
60–69	12.5	(12.2–12.8)	1,589	4.2	(4.1–4.4)	536	1.2	(1.1–1.3)	147	2.3	(2.2–2.5)	261
70–79	10.8	(10.5–11.1)	975	6.9	(6.6–7.1)	623	1.8	(1.7–2.0)	167	3.7	(3.5–3.9)	262
≥80	8.7	(8.3–9.0)	602	11.1	(10.7–11.4)	781	2.6	(2.5–2.8)	184	5.5	(5.2–5.9)	205
Race												
White (referent)	7.4	(7.3–7.5)	9,278	1.9	(1.9–2.0)	2,788	0.4	(0.4–0.4)	585	0.8	(0.7–0.8)	889
Black	9.9**	(9.7–10.2)	1,867	1.4**	(1.4–1.5)	262	0.7**	(0.6–0.7)	114	0.9**	(0.9–1.0)	112
AI/AN	6.5**	(5.9–7.1)	94	1.1**	(0.9–1.4)	14	0.3	(0.2–0.5)	4	1.0	(0.7–1.4)	9
A/PI	7.1	(6.8–7.4)	510	0.4**	(0.4–0.5)	27	0.3**	(0.2–0.3)	18	0.4**	(0.3–0.5)	21
Ethnicity												
Non-Hispanic	7.4	(7.3–7.4)	10,099	1.9	(1.9–1.9)	2,989	0.4	(0.4–0.4)	673	0.7	(0.7–0.8)	902

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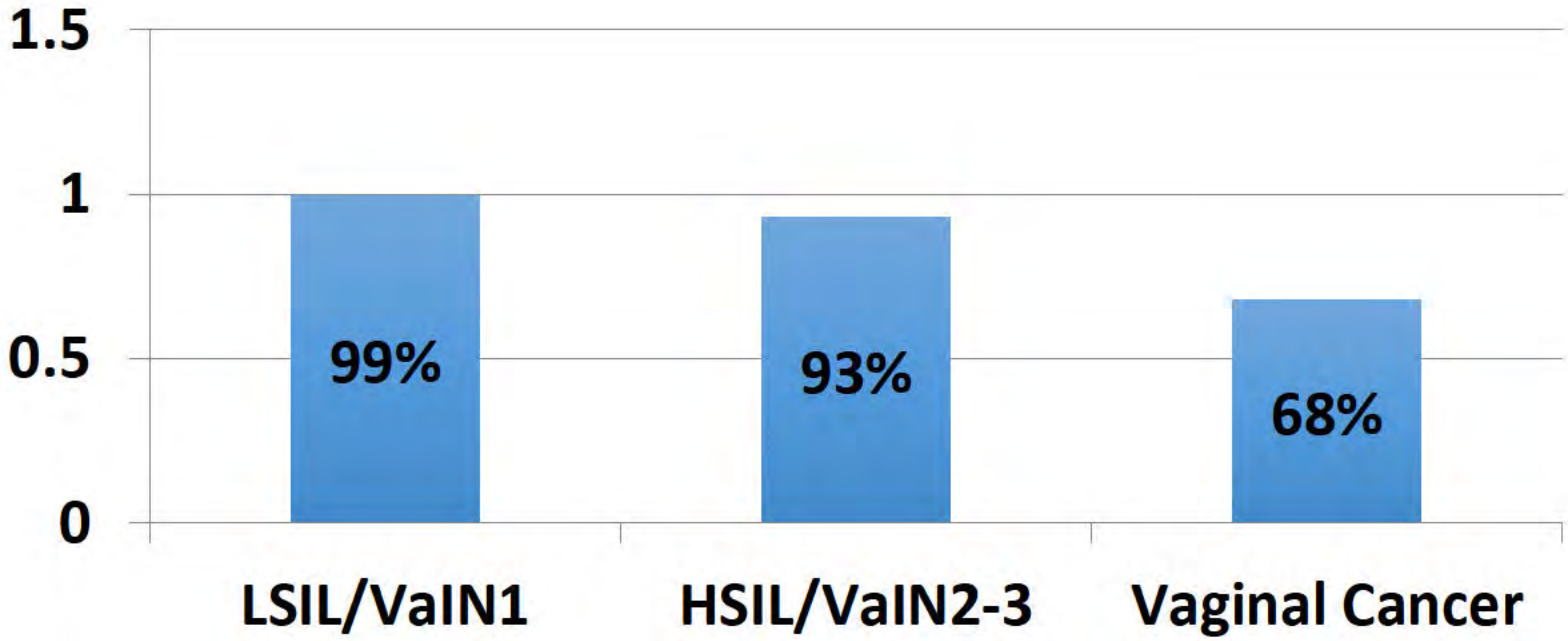
Risk factors for vaginal cancer

Age at 1st intercourse <17 years old
≥ 5 lifetime sexual partners
Immunosuppression
Smoking
Pelvic radiation therapy
Exposure to diethylstilbestrol in utero
History of CIN2/3 or invasive cervical cancer

Progression of Vaginal intraepithelial neoplasia (VaIN) to invasive cancer

Author, Year of Publication	Baseline histology of case(s)	Progression rate
Aho *et al.* 1991	LSIL/VaIN1, HSIL/VaIN3	9%
Sillman *et al.* 1997	HSIL/VaIN3	5%
Dodge *et al.* 2001	LSIL/VaIN1, HSIL/VaIN2	2%
Frega *et al.* 2007	HSIL/VaIN3	5%
So *et al.* 2009	N/A	0%
Gunderson *et al.* 2013	HSIL/VaIN2, HSIL/VaIN3	4%

HPV positivity in VaIN/vaginal cancers



HPV type distribution in VaIN/vaginal cancers

Author Year	Number and type of cases	HPV16+	HPV18+	HPV31+	HPV33+	HPV52+
DeVuyst 2009	107 LSIL/VaIN1, 191 HSIL/VaIN2/3, 136 vaginal cancers	48%	7%	4%	4%	
Smith 2009	39 LSIL/VaIN1, 68 HSIL/VaIN2/3, 87 vaginal cancers	50%	13%	2%	2%	1%
Chao 2011	194 LSIL/VaIN1, 200 HSIL/VaIN2/3	36%	3%	3%	7%	10%
Larsson 2013	69 vaginal cancers	70%	5%	5%	5%	5%
Sinno 2014	60 vaginal cancers	55%	2%		18%	2%

Epidemiology: HPV in the vagina

- In women with a cervix, it is difficult to distinguish between a vaginal and cervical infection when hrHPV+

- Castle *et al.* 2004 – hrHPV prevalence in Costa Rican cohort
  - 569 women s/p hysterectomy: 9.5%
  - 6,098 women with intact uterus: 9.3%

- Castle *et al.* 2006 – hrHPV prevalence in Kaiser Portland cohort
  - 573 women s/p hysterectomy: 4.5%
  - 581 women with intact uterus: 6.5%

Guidelines for screening for vaginal cancer

Population	Recommended screening method
Healthy asymptomatic women with a cervix undergoing annual gynecologic exam; no prior history of cervical dysplasia	None; Cervical cancer screening per ASCCP/ASCP/ACS and USPSTF guidelines
Healthy asymptomatic women post-hysterectomy for benign disease undergoing annual gynecologic exam; no prior history of cervical dysplasia	None
Women with history of cervical precancer (CIN2, CIN2/3, or CIN3) with a cervix	Cervical cancer screening per ASCCP 2013 management guidelines
Women with history of cervical precancer or cervical cancer post-hysterectomy	Per ASCCP 2013 and NCCN management guidelines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Vaginal Tests

Vaginal Cytology

- Positivity rates dependent on site/study
  - Pearce *et al*. 1996
    - 9,610 vaginal cytology samples in post-hysterectomy women over a 3-year period
      - 104 (1.1%) abnormal
        - 0.5% ASC-US, 0.5% LSIL, 0.1% HSIL, 0.02% SCC
      - 6 cases of VaIN1/2, no VaIN3/cancer
  - Castle *et al.* 2006
    - 0/573 women s/p hysterectomy had abnormal vaginal cytology
  - Bansal *et al.* 2011
    - 2,892 vaginal cytology samples in post-hysterectomy women over a 4-year period
      - 1,320 (45.6%) abnormal
      - 85% ASC-US, 5.1% LSIL, 3% ASC-H, 1% HSIL
      - In women with LSIL, 41 cases of LSIL/VaIN1 and 7 HSIL/VaIN2/3

Vaginal Cytology (2)

- Frega *et al.* 2007: prospective study of 830 women
  - 44 cases of VaIN: 14 LSIL/VaIN1, 24 HSIL/VaIN2, 6 HSIL/VaIN3
    - 83% of HSIL positive by cytology
    - 2 cases of HSIL/VaIN3 progressed to cancer over 3-year follow-up, both were positive by cytology
- Sensitivity: 83%-100% for HSIL/vaginal cancer
- Positive Predictive Value: 0 – 14% for HSIL/vaginal cancer

High-risk HPV testing in the vagina

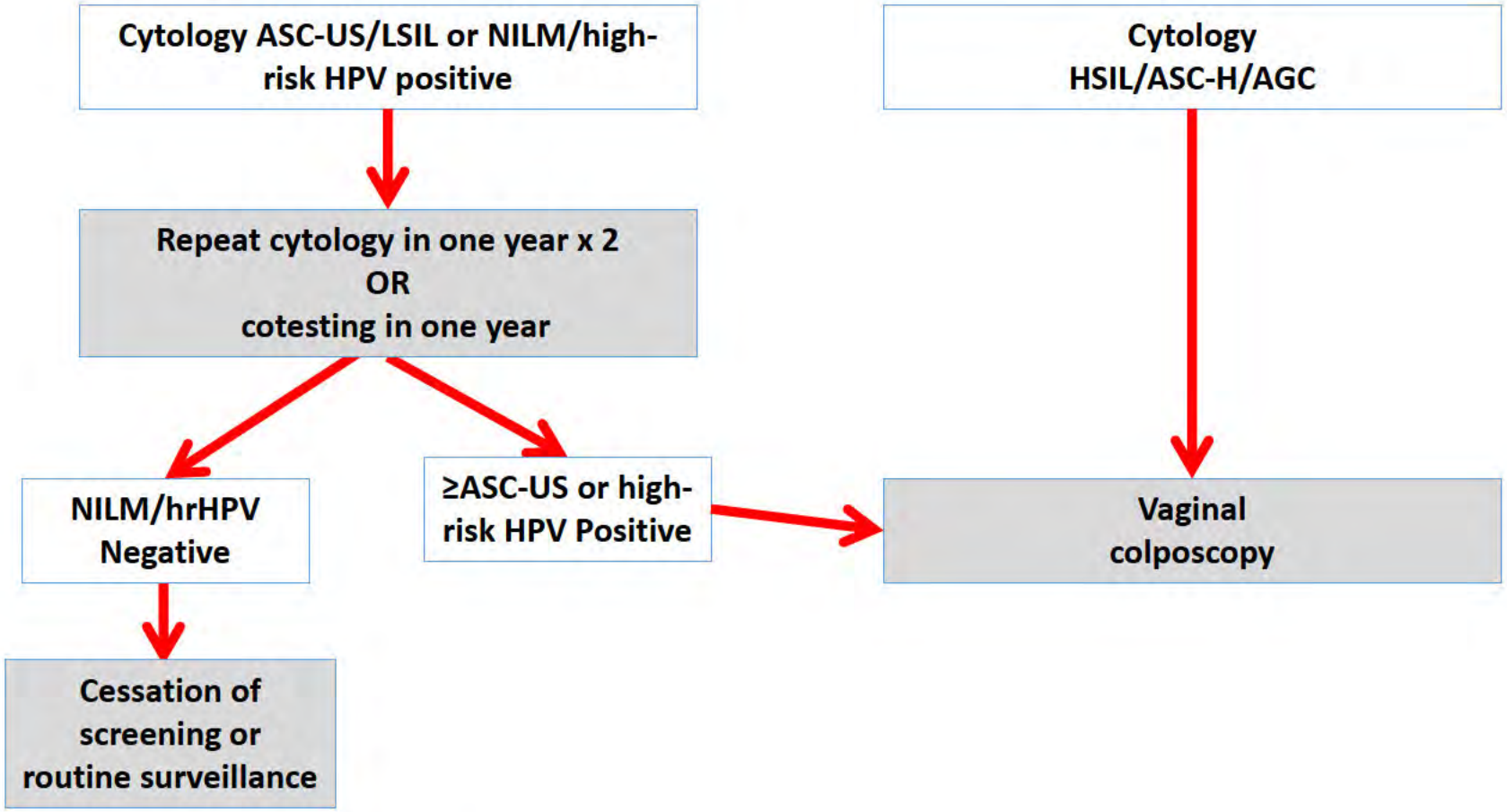
- **Not FDA-approved for the vagina**
- Frega *et al.* 2007: prospective study of 830 women
  - 44 cases of VaIN: 14 LSIL/VaIN1, 24 HSIL/VaIN2, 6 HSIL/VaIN3
    - 100% hrHPV+
  - 2 cases of HSIL/VaIN3 progressed to cancer over 3-year follow-up
- So *et al.* 2009:
  - 48 cases of VaIN, followed for up to 6 years
  - 74% of LSIL/VaIN1, 86% of HSIL/VaIN2, and 100% of HSIL/VaIN3 hrHPV+
  - hrHPV+ and HPV viral load were predictive of disease persistence

High-risk HPV testing in the vagina (2)

- Sensitivity: 92-100% for HSIL/cancer
- Sensitivity: 82 – 90% for VaIN persistence/progression
- Positive predictive value: 15% for HSIL/cancer
- Positive predictive value: 75% for persistence/progression

Recommended management of abnormal vaginal screening tests

- **Expert opinion-based**
- Vaginal cancer is rare
- Progression rates are lower than for the cervix
- Many tests are inappropriately sent


Cytology ASC-US/LSIL or NILM/high-risk HPV positive
Cytology HSIL/ASC-H/AGC
Repeat cytology in one year x 2
OR
cotesting in one year
NILM/hrHPV Negative
≥ASC-US or high-risk HPV Positive
Vaginal colposcopy
Cessation of screening or routine surveillance

Proposed subsequent management of histopathologic VaIN/vaginal cancer

Biopsy result	Management	Comments
LSIL	Vaginal cotesting in one year; repeat colposcopy if abnormal results	For bulky warty disease can consider cosmetic treatment.
HSIL	Treatment per current best practice	May vary by site and could include laser ablation, excision/vaginectomy, topical treatment. Referral to gynecologic oncologist for large or complex lesions.
Invasive carcinoma	Treatment per current best practice	Referral to gynecologic oncologist.

Conclusions

- Vaginal cancer is a rare HPV-associated cancer

- General screening for vaginal cancer is NOT recommended
  - Women post-hysterectomy for benign disease should not be screened
  - Women post-treatment for cervical HSIL/cancer should undergo surveillance per national screening guidelines

Conclusions (2)

- Women with HSIL/ASC-H/AGC vaginal cytology should undergo vaginal colposcopy
- Women with persistent ASC-US/LSIL/hrHPV+ for ≥1 year should undergo vaginal colposcopy
- HSIL/VaIN2/3 should be treated
- Future studies should examine outcomes after abnormal vaginal cytology and/or hrHPV testing

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QUESTIONS?