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

Michelle J. Khan, MD, MPH
Assistant Professor
Department of Obstetrics and Gynecology
Division of Women's Reproductive Healthcare
University of Alabama
Birmingham, AL
Disclosures

• Travel reimbursement from Cepheid for an Investigator’s Meeting in August 2015.

• No other conflicts of interest.
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

Michelle J. Khan, MD, MPH,1 L. Stewart Munsat, MD,2 Walter Klinsey, MD,3 Michael A. Gold, MD,4 El Mejias Jr., MD,4 Teresa M. Dormigh, MD,5 Philip E. Castle, PhD, MPH,6 David Chelmow, MD,6 Herschel L. Lawson, MD,1 and Warner K. Huh, MD*6

Objective: Vaginal cancer is an uncommon cancer of the lower genital tract, and the need for accurate screening is uncertain. 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 are appropriately undergoing vaginal cytology and/or human papillomavirus (HPV) testing, and clinicians are faced with managing their abnormal results. Our objective was 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.

Methods: A systematic review 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 postmenopausal 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; VaN


Gynecol Oncol 2016; epub ahead of print.
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
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cervical carcinoma</th>
<th>Vulvar SCC</th>
<th>Vaginal SCC</th>
<th>Penile SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (95% CI)</td>
<td></td>
<td>Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average annual no.</td>
<td></td>
<td>Average annual no.</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7.7 (7.7-7.8)</td>
<td>1.8 (1.8-1.9)</td>
<td>0.4 (0.4-0.4)</td>
<td>0.8 (0.8-0.8)</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>0.0 (0.0-0.1)</td>
<td>0.0 (0.0-0.0)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>20-29</td>
<td>3.2 (3.1-3.3)</td>
<td>0.1 (0.1-0.1)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>30-39</td>
<td>12.6 (12.4-12.8)</td>
<td>0.7 (0.7-0.8)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>40-49</td>
<td>14.2 (14.0-14.4)</td>
<td>2.0 (1.9-2.1)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>50-59</td>
<td>12.3 (12.1-12.6)</td>
<td>2.9 (2.8-3.0)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>60-69</td>
<td>12.5 (12.2-12.8)</td>
<td>4.2 (4.1-4.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>70-79</td>
<td>10.8 (10.5-11.1)</td>
<td>6.9 (6.6-7.1)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>≥80</td>
<td>8.7 (8.3-9.0)</td>
<td>11.1 (10.7-11.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (referent)</td>
<td>7.4 (7.3-7.5)</td>
<td>1.9 (1.9-2.0)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Black</td>
<td>9.9** (9.7-10.2)</td>
<td>1.4** (1.4-1.5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AI/AN</td>
<td>6.5** (5.9-7.1)</td>
<td>1.1** (0.9-1.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>A/PI</td>
<td>7.1 (6.8-7.4)</td>
<td>0.4** (0.4-0.5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>7.4 (7.3-7.4)</td>
<td>1.9 (1.9-1.9)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

MMWR 2012;61:258-61.
## Risk factors for vaginal cancer

- Age at 1\textsuperscript{st} intercourse < 17 years old
- $\geq 5$ 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

<table>
<thead>
<tr>
<th>Author, Year of Publication</th>
<th>Baseline histology of case(s)</th>
<th>Progression rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aho et al. 1991</td>
<td>LSIL/VaIN1, HSIL/VaIN3</td>
<td>9%</td>
</tr>
<tr>
<td>Sillman et al. 1997</td>
<td>HSIL/VaIN3</td>
<td>5%</td>
</tr>
<tr>
<td>Dodge et al. 2001</td>
<td>LSIL/VaIN1, HSIL/VaIN2</td>
<td>2%</td>
</tr>
<tr>
<td>Frega et al. 2007</td>
<td>HSIL/VaIN3</td>
<td>5%</td>
</tr>
<tr>
<td>So et al. 2009</td>
<td>N/A</td>
<td>0%</td>
</tr>
<tr>
<td>Gunderson et al. 2013</td>
<td>HSIL/VaIN2, HSIL/VaIN3</td>
<td>4%</td>
</tr>
</tbody>
</table>
HPV positivity in VaIN/vaginal cancers

- LSIL/VaIN1: 99%
- HSIL/VaIN2-3: 93%
- Vaginal Cancer: 68%
## HPV type distribution in VaIN/vaginal cancers

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommended screening method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy asymptomatic women with a cervix undergoing annual gynecologic exam; no prior history of cervical dysplasia</td>
<td>None; Cervical cancer screening per ASCCP/ASCP/ACS and USPSTF guidelines</td>
</tr>
<tr>
<td>Healthy asymptomatic women post-hysterectomy for benign disease undergoing annual gynecologic exam; no prior history of cervical dysplasia</td>
<td>None</td>
</tr>
<tr>
<td>Women with history of cervical precancer (CIN2, CIN2/3, or CIN3) with a cervix</td>
<td>Cervical cancer screening per ASCCP 2013 management guidelines</td>
</tr>
<tr>
<td>Women with history of cervical precancer or cervical cancer post-hysterectomy</td>
<td>Per ASCCP 2013 and NCCCN management guidelines</td>
</tr>
</tbody>
</table>
Just as I thought. You have bones.
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

Repeat cytology in one year x 2
OR
cotesting in one year

NILM/hrHPV Negative

Cessation of screening or routine surveillance

≥ASC-US or high-risk HPV Positive

Cytology HSIL/ASC-H/AGC

Vaginal colposcopy
**Proposed subsequent management of histopathologic VaIN/vaginal cancer**

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


References (2)


QUESTIONS?