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Review Article

A common clinical dilemma: Management of abnormal vaginal cytology and human papillomavirus test results☆

Michelle J. Khan [a,*], L. Stewart Massad [b], Walter Kinney [c], Michael A. Gold [d], E.J. Mayeaux Jr [e], Teresa M. Darragh [f], Philip E. Castle [g], David Chelmow [h], Herschel W. Lawson [i], Warner K. Huh [j]

[a] Division of Women's Reproductive Healthcare, Department of Obstetrics and Gynecology, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, USA
[c] Department of Women's Health, The Permanente Medical Group, Sacramento, CA, USA
[d] Tulsa Cancer Institute, University of Oklahoma, School of Community Medicine, Tulsa, OK, USA
[e] Department of Family and Preventive Medicine, Department of Obstetrics and Gynecology, University of South Carolina School of Medicine, Columbia, SC, USA
[f] Department of Clinical Pathology, University of California, San Francisco, CA, USA
[g] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
[h] Department of Obstetrics and Gynecology, Virginia Commonwealth University, Richmond, VA, USA
[i] Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA, USA
[j] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA

HIGHLIGHTS

- After hysterectomy, HSIL and cancer of the vagina are rare.
- Vaginal cancer screening is not recommended, yet women receive vaginal testing requiring clinical management.
- We propose a conservative approach to management of abnormal vaginal cytology and/or high-risk HPV tests.

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ABSTRACT

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 (hrHPV) tests, and clinicians are faced with managing their abnormal results. Our objective is to review the literature on vaginal cytology and hrHPV testing and to develop guidance for the management of abnormal vaginal screening tests.

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 post-treatment for cervical precancer or cancer, hrHPV testing may be useful in identification of vaginal cancer precursors.

Conclusion. 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.

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* Corresponding author at: University of Alabama at Birmingham, 1700 6th Ave. South WIC 10261, Birmingham, AL, 35249, USA.
E-mail address: mjkhan@uabmc.edu (M.J. Khan).

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1. Introduction

Vaginal cancer is a rare human papillomavirus (HPV) — associated gynecologic disease, accounting for approximately 1–4% 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 0.4–0.6 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]. The majority of 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 VaIN1, is a benign manifestation of HPV infection. Although natural history data on VaIN are scarce, it is thought that invasive vaginal cancer, like invasive cervical cancer, is caused by persistent high-risk HPV infection [7]. Other known risk factors for vaginal cancer include age at first intercourse <17 years old, ≥5 lifetime number of sexual partners, immunosuppression, smoking, pelvic radiation therapy, and exposure to diethylstilbestrol (DES) *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/VaIN2/3 was found more often in women >50 years old compared to LSIL/VaIN1 (mean age of 45 years) [9]. The Centers for Disease Control and Prevention reported the mean age at diagnosis of vaginal cancer was 69 years, two 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 0.2–0.3 per 100,000 women in the United States [11]. VaIN incidence may be rising as a result of increased sexual exposure to hrHPV with changing sexual behavior over 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, 2, and 3 who progressed to invasive vaginal cancer. These reported rates of progression are much lower than the demonstrated up to 30% progression rate for CIN3 to invasive cervical cancer [1,7–9,13–16].

Due to the rarity of vaginal cancer, there are currently no formal guidelines recommending screening for vaginal cancer in the general population (Table 1). In fact, research articles and professional society guidelines recommend against vaginal cancer screening in women post-hysterectomy for benign disease and in women post-hysterectomy for cancers other than cervical cancer [17–20]. However, current cervical cancer screening guidelines do recommend that high-risk groups such as women who have had cervical precancer (HSIL/CIN2/3) or invasive cervical cancer undergo continued surveillance testing for at least 20 years after treatment [17]. By this definition, women with a history of cervical precancer who subsequently undergo hysterectomy will still require vaginal cytology screening for at least 20 years after their treatment for cervical precancer.

Despite guidelines recommending against vaginal cancer screening for women post-hysterectomy for benign conditions and NO history of precancer (Table 1), many such women have cytology and/or cotesting (cytology + hrHPV testing) performed [17,21]. This leaves clinicians with the dilemma of how to manage these abnormal vaginal screening tests. The objective of this article is to review the literature on vaginal cytology and hrHPV testing and their accuracy in prediction of VaIN/cancer, and to provide guidance on how to best manage women who were screened inappropriately after hysterectomy, as well as women undergoing surveillance after treatment for cervical HSIL/cancer. For women screened inappropriately, we aim to provide guidance for discontinuation of further testing.

Unlike the consensus management guidelines for abnormal cervical cancer screening results and diagnosed cervical precancer published by the ASCCP, this guidance is based expressly on expert opinion, because there are no large clinical trials or rigorous epidemiologic studies of vaginal cancer screening on which to base our recommendations.

2. Methods

We performed a search of the PubMed database through June 2015 using the keywords “vaginal intraepithelial neoplasia, vaginal dysplasia, HPV DNA testing, hysterectomy, vaginal cancer, and HPV/human papillomavirus.” We also searched the references of retrieved articles. Articles were reviewed if they reported on vaginal screening tests and reviewed at least 20 histologically-confirmed cases of vaginal cancer and/or VaIN. Studies were excluded if they did not distinguish between

Table 1
Current screening guidelines 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 [17,20]
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 [38]
Women with history of cervical precancer or cervical cancer post-hysterectomy	Per ASCCP 2013 and NCCN management guidelines [38,39]