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## Gaps and Opportunities to Improve Prevention of Human Papillomavirus-Related Cancers

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### Abstract

Human papillomavirus (HPV) infections cause more than 35,900 cancers annually in the United States. Although cervical cancer is the most prevalent HPV-related malignancy in women, the virus is also responsible for a significant percentage of anal, vaginal, and vulvar cancers. A comprehensive approach to mitigating cervical cancer includes HPV vaccination (primary prevention), screening and treatment of precancerous lesions (secondary prevention), and diagnosis and treatment of invasive cancer (tertiary prevention). Although a successful strategy, there are opportunities to innovate and increase access that can also be adapted to address the unique clinical care gaps that exist with the other anogenital cancers. The Society for Women's Health Research held a series of interdisciplinary meetings and events, during which expert researchers, clinicians, patient advocates, and health care policy leaders evaluated the current landscape of HPV-related cancers and their effects on women's health. This report summarizes the discussions of this working group and areas it identified in which to address gaps in primary and secondary prevention approaches to improve access and health outcomes for women with HPV-related anogenital cancers.

**Keywords:** anal cancer, cancer screening, cervical cancer, HPV vaccine, stigma, vaginal cancer, vulvar cancer

### Introduction

**H**UMAN PAPILOMAVIRUS (HPV) is one of the most common sexually transmitted infections in the United States. The U.S. Centers for Disease Control and Prevention

(CDC) estimate that more than 80% of people in the country will acquire HPV by the age of 45.<sup>1</sup> These viral infections of mucosal surfaces, including the reproductive tract, anus, and oropharyngeal cavity, are typically asymptomatic and, for younger adults, are often suppressed by the body's immune

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system within 2 years. However, there are over 100 types of HPV—14 of which have been identified as “high risk” because persistent infections of these types are linked to HPV-related diseases such as cervical cancer.<sup>2,3</sup>

HPV infections cause more than 35,900 cancers annually in the United States, occurring more often in women than in men—21,100 versus 14,800 cases, respectively.<sup>4</sup> HPV is widely understood to cause nearly all cervical cancers; however, the virus is also responsible for an estimated 75% of vaginal cancers, 69% of vulvar cancers, and 63% of penile cancers. Two-thirds of the 91% of anal cancers caused by HPV occur in women.<sup>5</sup> High-risk HPV types from which DNA has been detected in these anogenital cancers are shown in Table 1.<sup>4</sup>

Cervical cancer once had the highest cancer mortality rate among women in the United States. Overall incidence and mortality rates have declined significantly thanks to vaccination and screening efforts.<sup>6,7</sup> Although cervical cancer is a highly studied HPV-related disease with well-developed guidelines for its prevention, diagnosis, and treatment, it is still the fourth most commonly occurring cancer in women globally.<sup>8</sup> Moreover, limited research, surveillance, and trial participation for HPV-related anal, vulvar, and vaginal diseases make it challenging for these less common anogenital cancers to get needed attention,<sup>9</sup> further enhancing the disparities in health care and outcomes for affected women.

The Society for Women’s Health Research (SWHR) held a roundtable meeting to address barriers to care related to HPV-related disease prevention, diagnosis, and treatment. Researchers and clinicians with expertise in HPV, women’s health, and anogenital cancers, as well as HPV-related cancer patients and advocates, discussed key updates in literature, research, clinical practice, and public health data. During a subsequent public forum, a panel led by an expert gynecologic oncologist and adviser in emerging practices facilitated

discussions about innovations in clinical education and screening. This report summarizes the discussions, focusing on themes that arose from the events as they relate to opportunities for advancement and innovation in the prevention and early detection of HPV-related anogenital cancers to improve women’s health care and quality of life.

**Primary Prevention through HPV Vaccination**

HPV vaccination has been available in the United States since 2006 and is currently the most effective method of preventing infection.<sup>10,11</sup> The latest nonavalent vaccine targets seven of the high-risk types detected in ~90% of HPV-related cancers (Table 1).<sup>4,12</sup> While vaccine-type HPV infection rates in both women and men have decreased since the initial introduction of the vaccine, vaccine implementation in the United States remains relatively low and inconsistent across genders, ages, regions, and racial and ethnic subgroups.<sup>13</sup> Current guidelines recommend vaccinations for everyone through age 26, yet, in 2020, only 58.6% of adolescents were up-to-date on their HPV vaccination, despite CDC’s recent reiteration of its previous guidelines recommending girls and boys ages 11 and 12 receive the vaccine.<sup>14–16</sup>

The clinical and cost effectiveness of the nonavalent HPV vaccine as a public health tool has helped mitigate the barriers of individual patient costs and insurance coverage toward reaching national vaccine uptake goals.<sup>17</sup> Federal assistance programs like Vaccines for Children have also been instrumental in improving access and reducing socioeconomic disparities seen for vaccinations against HPV, as it has for other vaccines such as diphtheria–tetanus–acellular pertussis and measles–mumps–rubella.<sup>13,18</sup> Health departments charged with managing local program implementation should collaborate with recognized leaders of professional and community organizations to build public awareness and educate their constituents about vaccine safety and access.<sup>19</sup> Altogether, they can combine efforts to ensure that health care providers, such as primary care physicians and pediatricians, are registered to participate in such programs, especially in underserved areas. Barring systemic challenges of costs and access, individuals must still choose to receive the HPV vaccine as a preventive measure for their health.

HPV is a sexually transmitted infection that bears disease-associated stigma, which continues to limit the successful impact of vaccination and screening recommendations.<sup>20,21</sup> For individuals considering HPV vaccination, this association with sexual activity (particularly early sexual activity for recommended preteen recipients) raises issues around societal norms and faith-based beliefs. Increasing uptake of the HPV vaccine will require destigmatization among individuals of all genders and age groups. Women, as the primary health care decision-makers for their families,<sup>22</sup> are often tasked with making informed decisions for their children, as well as themselves, to ensure the best chance of mitigating preventable HPV-related disease. Messaging must be sensitive to these factors to reduce stigma and improve education about HPV-related disease prevention.

To further address the stigma around HPV and related diseases, as well as public perception and understanding of its need, it is essential that health care providers reframe the

TABLE 1. HIGH-RISK HUMAN PAPILLOMAVIRUS TYPES DETECTED IN ANOGENITAL CANCERS

HPV type	Nonavalent vaccine <sup>a</sup>	HPV-related cancer				
		Cervical	Anal	Vulvar	Vaginal	Penile
16	+	◆	◆	◆	◆	◆
18	+	◆	◆	◆	◆	◆
31	+	◆	◆	◆	◆	◆
33	+	◆	◆	◆	◆	◆
35			◆		◆	◆
39						
45	+	◆			◆	◆
51			◆	◆	◆	◆
52	+	◆	◆	◆	◆	◆
56				◆		
58	+	◆	◆		◆	◆
59						◆
66						
68			◆	◆		

Data source.<sup>4</sup>

<sup>a</sup>HPV types targeted in the nonavalent vaccine, not including low-risk HPV 6 and 11 strains associated with genital warts.

<sup>+</sup>Indicates the HPV types targeted by the nonavalent vaccine.

◆Indicates the HPV types detected in the given cancers.

HPV, human papillomavirus.

conversation about HPV vaccination as a necessary public health measure for cancer prevention. While the benefits of HPV vaccination for prevention of cervical cancer are widely recognized, awareness should expand to include the other anogenital cancers.<sup>4</sup> Educational materials should reflect gender diversity to encourage all individuals to participate in this much-needed preventive measure, recognizing that men are at risk for HPV-related anal, oropharyngeal, and penile cancers. Such efforts also combat inequitable care and feminization of HPV vaccination and related diseases, which ultimately slow attempts to reach herd immunity.<sup>23</sup>

HPV vaccine endorsement (or hesitancy) by an individual's health care provider is a major factor influencing patient acceptance or resistance of this preventive measure.<sup>24,25</sup> Providers should discuss the risks of HPV transmission, the benefits of HPV vaccination and routine screening, and overall sexual health during annual and specialized women's and men's health appointments. However, a lack of preparedness and consistency among health care providers to have these conversations is a barrier to addressing patient concerns.<sup>26,27</sup> Fortunately, providers have expressed a desire for training on how to counsel parents and adolescents through the decision-making process, as well as a willingness to take web-based trainings if offered the opportunity.<sup>28</sup>

While vaccination is an important primary prevention strategy to eliminate HPV-related cancers, screening to detect early signs of disease is an indispensable measure to ensure success of this public health issue.

### Early Detection for the Preventive Care of HPV-Related Cancer

#### *Cervical cancer*

Cervical cancer is a slow-developing malignancy, providing opportunities for early detection and treatment of abnormal cervical tissue in precancerous stages. Although most frequently diagnosed in women, ages 35 to 65 years, cervical cancer is rarely found in women who have maintained consistent screening tests.<sup>29</sup> In fact, over half of new cases occur in women who have rarely or never been screened, and this likelihood is highest among women who are uninsured or do not have a primary care physician.<sup>30,31</sup> There is a need to develop and implement innovative screening methods that are more accessible to broader populations of women.

The Papanicolaou test (Pap test) is a liquid-based cytology test for screening early changes in the cervix,<sup>32,33</sup> which is followed by colposcopy and biopsy to confirm diagnosis. Cytologic abnormalities can present as low-grade squamous intraepithelial lesions that are often transient. Without intervention, these lesions will regress on their own in 90% of young women, particularly if they are caused by a low-risk HPV type.<sup>34</sup> In contrast, the presence of persistent high-grade lesions is predictive of precancer and warrants additional medical attention.

HPV-based testing that assays the presence of DNA or RNA from high-risk HPV types is more likely to detect cervical precancer or cancer and is more efficient than the Pap test in predicting risk for developing cervical cancer.<sup>10,35</sup> The American Cancer Society recommends the HPV test as the preferred primary screening method for cervical cancer for

women 25 to 65 years of age.<sup>36</sup> Alternatively, individuals can be screened simultaneously with both the HPV and Pap tests (cotesting). Screening using HPV tests can be conducted less frequently than Pap tests (*i.e.*, every 5 years instead of three), decreasing the number of procedures and potential harm, including vaginal bleeding, pain, infections, and distress, throughout the lifetime of a patient.<sup>6,32,36</sup>

Implementation of cotesting is increasing; however, historical reliance on Pap tests continues to slow uptake of this advancement in the field.<sup>37</sup> Primary HPV testing is not available and accessible everywhere due to variability in funding, laboratory equipment, and provider training. The COVID-19 pandemic has also caused disruptions to non-emergency procedures, including cervical cancer screening.<sup>38</sup> Moreover, access to providers who offer HPV testing is a significant obstacle for women in low-resource settings.

At-home self-sampling is an innovative extension of in-office screening that has been implemented in some western European and sub-Saharan countries.<sup>39</sup> Adoption of this approach across the United States would be particularly advantageous for women who have limited access to a provider or have access with hesitancy about the internal exam needed for screening.<sup>40</sup> Regulatory considerations and implementation plans would be needed to balance the benefits of accessibility with the risks of improper handling and sample collection. Providing instructions that are simple, image-based, and at a functional literacy level would enhance conduciveness, especially among the most vulnerable populations of women.

#### *Anal cancer*

The American Cancer Society estimated 9,090 new cases of anal cancer in the United States in 2020, with approximately two-thirds of these cases occurring in women.<sup>41</sup> Although anal cancer is considered relatively rare, incidence continues to rise at 2% to 3% per year, and mortality rates are also increasing 2.9% annually.<sup>42</sup> In the United States, almost 80% of anal cancer cases are associated with high-risk HPV types 16 and 18.<sup>4</sup> Furthermore, certain groups of women are observed to have a particularly high risk, including women living with human immunodeficiency virus and women with a history of genital warts or prior genital tract neoplasia.<sup>43,44</sup> If the latest trends continue, anal cancer is predicted to become the leading HPV-related cancer affecting elderly women between 2030 and 2050.<sup>42</sup>

The concept of anal cancer screening is complex in comparison to cervical cancer screening. Well-defined and effective algorithms to prevent cervical cancer guide health care providers to perform cervical cytology or HPV testing and triage patients at highest risk for cervical high grade squamous intraepithelial lesion (HSIL). Anal cytology and/or anal HPV testing could be used to screen individuals, and although they are used in clinic, these methods are not currently approved by the U.S. Food and Drug Administration for the anus.<sup>45</sup> Furthermore, without sufficient evidence demonstrating that treatment of anal HSIL prevents cancer, screening for anal cancer is not commonly recommended in annual health screenings.

Digital anal rectal examination (DARE), however, is a universally available, cost-effective screening tool for detecting early-stage abnormal growths or masses, particularly

in high-risk populations. Recent studies have attempted to identify women who may be at greatest risk and might benefit from screening, including women with a history of lower genital tract neoplasia.<sup>46,47</sup> Practice guidelines have been outlined for DARE, but the procedure is underutilized due to a lack of clinical training, experience, and public health advocacy.<sup>48,49</sup>

High-resolution anoscopy (HRA)—the analogous procedure to colposcopy—is the best tool to manage and treat HSIL and may also detect early cancers.<sup>50</sup> However, implementation requires providers who are expertly trained and experienced in HRA, and even in highly resourced settings, the demand for HRA can quickly exceed the capacity.<sup>51</sup> Studies have correlated provider experience to accurate identification of HSIL in patients, reporting an increase from 18% incidence verification to 30% after 5 additional years of clinical practice.<sup>50,52</sup> Primary care physicians, gynecologists, and gastroenterologists are likely the providers that patients will initially consult about worrisome symptoms. Expanded training in DARE and HRA would better equip these providers with the knowledge and skills to recognize and evaluate anal cancer, potentially improving outcomes for early detection and decreasing the likelihood of over-treating symptoms and undertreating disease.

### Vulvar and vaginal cancers

Vulvar and vaginal cancers are also rare (2.6 and 0.7 in 100,000 women diagnosed annually, respectively); however, the incidence of vulvar cancer has increased up to four-fold over the past 50 years and is likely to still be significantly underreported.<sup>53</sup> Both diseases share similar risk factors with cervical cancer—HPV infection, immune suppression, and smoking—as well as increased comorbidity with diseases elsewhere in the anogenital tract.

Vulvar HSIL and cancer can be detected by visual inspection of the external genitalia, which should be done as part of cervical colposcopy. Vulvar disease may present with symptoms of painful sexual intercourse, itching, burning, and visible lesions. Unfortunately, women who report chronic vulvar itching or irritation are often treated with antifungals, steroids, and other topical medications before receiving appropriate diagnostic evaluation with biopsy. Moreover, women with a history of vulvar HSIL remain at increased risk for recurrent disease and cancer throughout their lifetime.<sup>54</sup> Increasing provider awareness and training concerning this rare female cancer could improve early diagnosis and management of vulvar disease.

The American Society for Colposcopy and Cervical Pathology's Risk-Based Management Consensus Guidelines recommend screening for vaginal HSIL using an HPV-based test for women who have had a hysterectomy after or as treatment for cervical HSIL.<sup>10,55</sup> Vaginal HSIL is usually asymptomatic, so it is most often diagnosed by colposcopy only after an abnormal cytology or positive HPV test, but these women are at increased risk for developing vaginal HSIL and cancer, with most recurrence within 2 to 3 years.<sup>56,57</sup> Exposure to diethylstilbestrol *in utero* increases risk for vaginal cancer, and these individuals are also screened regularly.<sup>56,58</sup>

There are no formal algorithms developed to screen for vulvar or vaginal cancers in the general population, and providers are generally advised against screening for vaginal

cancer, except in the cases of cervical cancer history and after hysterectomy for cervical HSIL.<sup>10,55</sup> Despite their low prevalence, without formal screening guidelines for vulvar and vaginal cancers, women without a prior history of genital neoplasia are left vulnerable to remaining undiagnosed. Additional research is needed to ensure that at-risk populations are appropriately identified and ensured access to this important measure of preventive care.

### Conclusion

The challenge posed to SWHR's roundtable participants was to consider how the current state of HPV-related disease management could be improved. A few areas of focus became clear.

First, without widespread uptake of the HPV vaccine in the United States, some women and men will develop HPV precancers and a proportion of those will develop into cancer. Messaging around HPV vaccination and testing should be gender inclusive, destigmatize HPV-related diseases, and address the public health benefit of cancer prevention. Communication with patients should also aim to reduce shame and stigma associated with HPV, so that individuals are empowered to advocate for preventive measures and accurate diagnosis and treatment. Moreover, the implementation of diagnostics to detect HPV-related diseases could also be improved. With physician guidance, at-home HPV testing is one such modality on the horizon that may help increase accessibility and reduce perceived stigma among patients.

Finally, the notable decline in cervical cancer incidence over the last 50 years is largely due to the introduction of Pap and recent HPV testing, adoption of routine screening practices, and more recently, the contributions of prophylactic vaccines.<sup>59</sup> Comparable universal guidelines for the screening and diagnosis of other HPV-related anogenital cancers are needed.

Despite the designation of anal, vulvar, and vaginal cancers as rare, their impacts on a woman's health are quite significant. Investment and priority must be given to garner the evidence necessary to elucidate the impact of screening and surveillance toward reducing cancer incidence, morbidity, and/or mortality, and to define appropriate at-risk populations to screen. Maximizing opportunities to implement HPV vaccination and screening will help improve our ability to mitigate these highly preventable and treatable HPV-related anogenital cancers.

### Authors' Contributions

This article was developed through meetings of the SWHR Human Papillomavirus Working Group. I.O.A.: Supervision, Writing—Original Draft, Review, and Editing. J.M.B.L., P.B., T.F., N.J., K.S.-M., J.M., J.B.M., S.N., R.P., T.R., D.S., C.S., and C.L.T.: Conceptualization, Investigation, Writing—Review and Editing. All authors read and approved the final article.

### Acknowledgments

The authors thank Dr. Mona Saraiya, Michele Longabaugh, Celina Schocken, Dr. Mark Einstein, Kate Weissman, and Dr. Lucy Erickson for their contributions toward

elevating this important topic with SWHR. Appreciation also goes to Dr. Melissa Laitner, Emily Ortman, and Shivani Chinnappan for assistance in preparing the article.

### Author Disclosure Statement

No competing financial interests exist.

### Funding Information

This work was supported by programmatic sponsorship from Inovio.

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