

Human Papillomavirus–Related Gynecologic Neoplasms: Screening and Prevention

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The recent recognition of oncogenic human papillomavirus (HPV) as a key component of female lower genital tract malignancies has led to significant changes in many screening and prevention guidelines for cervical cancer, and, combined with the advent of vaccination, will likely have sweeping repercussions on the incidence of cervical, vulvar, and vaginal carcinoma. This article focuses on the specific principles of cancer screening and prevention with an emphasis on HPV-mediated disease.

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Over the past 25 years, the human papillomavirus (HPV) has been identified as the etiologic agent driving much of the neoplasia observed in the lower female reproductive tract (Table 1).¹⁻³ HPV has been implicated in close to 100% of cervical cancers,⁴ up to 70% of squamous cell carcinomas (SCCs)⁵ of the vulva, and 60% of SCCs of the vagina.⁶ Given the high worldwide prevalence of preinvasive and invasive disease, cervical cancer has been the historical focus of extensive screening programs that began with the Papanicolaou test, and now continue with the emergence of vaccines that target the oncogenic strains of HPV known to cause the majority of cervical dysplasia and carcinoma. This recent

Table 1
Prevalence of HPV Infection by Lower Genital Tract
Dysplasia and Malignancy

Disease Site	Number of Studies	Pooled Prevalence of HPV (%)
Cervix		
CIN 1	8	84
CIN 2/3	8	92
Squamous cell carcinoma	8	90
Adenocarcinoma	5	84
Vulva		
VIN 1	2	93
VIN 2/3	2	92
Squamous cell carcinoma	4	65
Vaginal		
VaIN 1	2	100
VaIN 2/3	2	89
Squamous cell carcinoma	1	73

CIN, cervical intraepithelial lesion; HPV, human papillomavirus; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

Data from Insinga RP et al.¹

recognition of oncogenic HPV as a key component of female lower genital tract malignancies has led to significant changes in many screening and prevention guidelines for cervical cancer, and, combined with the advent of vaccination, will likely have sweeping repercussions on the incidence of cervical, vulvar, and vaginal carcinoma.

This article focuses on the specific principles of cancer screening and prevention with an emphasis on HPV-mediated disease. With this background, revamped strategies for cervical cancer screening and prevention are presented, with a focus on the special dysplasia circumstances, the role of the HPV test, and the efficacy of vaccination against HPV. Finally, discussions of the literature linking HPV and vulvar and vaginal cancer

are presented, along with the limitations of screening in these populations, thus expanding the implications of an effective HPV vaccination program.

Principles of Cancer Prevention and Screening

Primary, secondary, and tertiary prevention are the mainstays of cancer prevention strategies. *Primary prevention* refers to environmental adjustments in the healthy population that alter the risk of developing any of a host of cancers. Interventions such as weight loss, smoking cessation, and a high-fiber diet would be considered primary preventive measures. *Secondary prevention* refers to the detection and treatment of preinvasive disease. Screening tests, such as routine colonoscopy or mammog-

raphy, are examples of secondary prevention. *Tertiary prevention* encompasses measures utilized to decrease the burden of established disease and prevent recurrence, such as tamoxifen therapy after breast cancer excision.⁷

Within this model, screening tests form the backbone of secondary cancer prevention and serve as the first line of intervention targeted against specific cancers. The ability of screening tests to detect preinvasive or invasive disease is highly dependent on the specific characteristics of the individual cancer being screened. The prevalence of the disease is perhaps the largest predictor of a given screening test's positive predictive value, making rare cancers with a low incidence practically impossible to screen. In addition to this crucial characteristic, however, are the cancer's physical accessibility, clinical behavior, and treatment options. From a screening standpoint, the ideal cancer would have a high prevalence, a slow growing period of preinvasion, improved treatment options and outcomes if discovered early, and possess an accessible marker that could be feasibly assessed on a population basis.⁸

Cervical carcinoma possesses a high worldwide prevalence as the second most common cancer in women; a slow growing period of preinvasion, dysplasia, that can take up to 10 years to progress to carcinoma; and abundant shed transitional zone cells that can be easily sampled in the office. In addition, if identified early, cervical cancer has improved therapeutic options and outcomes. Cervical cancer satisfies all the criteria for a cancer amenable to screening. It is therefore not surprising that in countries with ubiquitous Papanicolaou testing, such as the United States, cervical cancer has experienced a 75% drop in prevalence that can be directly attributed to screening alone.^{9,10} It is now known that these clinical characteristics of

cervical cancer reflect the nature of HPV infection in the cervix, leading to the hypothesis that all HPV-related lower female genital tract neoplasms may be amenable to screening strategies. Given the extremely low prevalence of SCC of the vulva and vagina, in addition to the incomplete association with HPV, it seems unlikely that

with therapeutic guidelines based on cytologic and pathologic findings to determine patients who needed colposcopy or definitive treatment.¹² In the setting of a clear high-grade squamous intraepithelial lesion (HSIL), further investigation is always warranted with either colposcopy or even an excisional procedure. However, the

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any population screening test will be feasible or effective.

Screening for Cervical Cancer

Numerous trials have evaluated the use of cytology and pathology to recommend screening and treatment algorithms for providers to utilize in screening for and treating cervical dysplasia and carcinoma in what has been considered by many cancer experts to be the single most successful cancer prevention strategy in history.⁹ Even in the era of modern liquid cytology and automation, Papanicolaou testing has a broad range of sensitivity and specificity to predict high-grade (cervical intraepithelial neoplasia [CIN] 2/3) pathologic lesions, mostly in the 50% to 60% and 80% to 100% ranges, respectively. Given the indolent nature of this carcinogenesis, yearly screening could reliably pick up abnormalities that needed further sampling with colposcopy over the course of several years.⁹ Treatment of these high-grade lesions after colposcopic-directed biopsy with either ablative or excisional techniques has been shown to have similar efficacy in removing CIN and reducing the risk of developing cervical cancer.¹¹

In 2001, the Bethesda criteria and classifications of Papanicolaou test results were introduced to standardize terminology across the United States,

diagnosis of lower grade Papanicolaou test results, encompassed by the atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells—cannot exclude HSIL (ASC-H), and low-grade squamous intraepithelial lesion (LSIL) categories, provide more of a clinical dilemma that has been evaluated extensively because only a fraction of these cytologic results will be harbingers of a high-grade pathologic lesion. Although up to 90% of these low-grade lesions will spontaneously regress,^{13,14} numerous investigators have demonstrated that these lesions carried up to a 33% risk of harboring at least a CIN 2 lesion, suggesting an improved triage tool was needed to understand which women could be observed, and

via a variety of assays has a high sensitivity and specificity to predict CIN 2 lesions after an ASC Papanicolaou test result.¹⁵ In 2004,¹⁸ and again in 2007, these guidelines were reassessed in light of the prominent role that oncogenic strains or high-risk HPV serotypes play in the development of high-grade dysplasia (CIN 2/3).^{11,19} The fundamental recognition that high-grade dysplasia or invasive cervical cancer cannot manifest without evidence of oncogenic HPV has led to testing expansion that includes triage of ASCUS Papanicolaou test results, follow-up of therapeutic outcome after colposcopy or therapy for CIN 2/3 lesions, and primary screening in women older than 30 years coupled with cytology.^{9,20}

The most recent guidelines for cervical cancer screening identify several populations in whom differing HPV profiles can guide management through the use of HPV testing that evaluates for the presence of 13 high-risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The adolescent population, defined as under 21 years, has been shown to have a high prevalence (80%–90%) of high-risk HPV infection,²¹ but a low risk of invasive cancer as most of these infections clear spontaneously.²² In this setting, an HPV test has limited

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which ones needed to move on to more invasive and costly colposcopic-directed biopsy.¹⁵

The potential role of an HPV test as a crucial cervical cancer screening tool has been solidified after the ASCUS-LSIL Triage Study (ALTS),^{16,17} as well as a meta-analysis of over 20 smaller studies confirming that screening for high-risk HPV strains

performance as a triage tool, and the recommendation for low-grade cytology (ASC, LSIL) in this population is repeated cytology with only HSIL being referred for colposcopy. In the population older than 30 years, however, high-risk HPV has been shown to have a 5% to 10% prevalence,^{21,23} prompting the use of an HPV test in the triage of LSIL in postmenopausal

women, and is acceptable upfront screening for women older than 30 years in concert with cytologic screening. In fact, numerous European studies have documented that HPV testing is 97% to 98% specific, and 93% to 95% specific for the detection of high-grade dysplasia, a significant improvement over liquid-based cytology.²⁴⁻²⁷ Although an HPV test alone has been shown to have a greater sensitivity and specificity to predict CIN 2 or greater, combining an HPV test with conventional cytology further improves the test characteristics in the population older than 30 years (Table 2).^{24,28,29} Because of the near 100% negative predictive value of combined upfront screening, experts recommend that women older than 30 years with negative HPV and cytology results need reassessment only after 3 years.^{9,15} Given these strong test characteristics of HPV testing in the population older than 30 years, investigators have suggested that the general HPV test could be utilized as the

upfront screen, with reflex cytology only in those patients demonstrating existence of high-risk HPV.^{9,30} This strategy would decrease the need for expensive and often imprecise cytology while preserving almost the same predictive values. When examining the follow-up strategies for women after colposcopy and excisional procedures, investigators continued to note that high-risk HPV testing had a superior profile compared to cytology, leading to the recommendation that the HPV test can be used exclusively for follow-up in women older than 20 years.^{31,32}

Although a general high-risk HPV test that encompasses multiple strains is becoming more integrated into the fabric of cervical cancer screening, further investigation into the invasive profiles of specific high-risk HPV serotypes has demonstrated that HPV 16 and 18 are associated with significantly more CIN 2 or higher lesions than other high-risk types.³³ The US Food and Drug Administration (FDA)

has yet to approve genotyping assays for specific HPV subtypes, but future triage strategies will likely employ these tests to better understand a patient's risk of manifesting a high-grade lesion that requires an excisional procedure. Refined HPV testing could have an important role in overcoming the poor sensitivity of cytology alone, as many women present with normal Papanicolaou test results and HPV-positive status. Defining the risk profile of the specific HPV type manifested could aid in determining which patients require more invasive testing, and which require 1-year follow-up.³³

Although these secondary prevention strategies of HPV-mediated cervical cancer have been crucial to decrease the incidence of disease in wealthy developed countries, nearly 250,000 women die worldwide, making it the second most common, second most deadly cancer affecting women.³⁴ To address this global concern, primary prevention strategies with vaccines exploiting the capsular L1 proteins hold the promise of significantly reducing the incidence of cervical cancer, as well as other cancers mediated by HPV. The use of the FDA-approved quadrivalent (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ) or experimental bivalent (Cervarix™, GlaxoSmithKline, Philadelphia, PA) HPV vaccine to immunize women against the 2 most common high-risk HPV serotypes 16 and 18 has demonstrated near 100% efficacy in preventing the development of HPV 16/18 related CIN 2+ lesion or adenocarcinoma in situ (AIS) in women aged 16 to 26 years who were naive to HPV infection. Four international, double-blind, randomized trials evaluating the quadrivalent HPV vaccine³⁵⁻³⁹ with an approximately 3-year follow-up demonstrated a pooled efficacy of 99% in preventing CIN 2+ lesions due to vaccine serotypes in the populations

Table 2
Pooled Accuracy for Detection of CIN 2+

Test	Number of Studies	Pooled Sensitivity % and 95% CI	Pooled Specificity % and 95% CI
Cytology ASCUS	18	72.7 (63.9-81.5)	91.9 (90.2-93.6)
Cytology ASCUS > 30 years	7	73.8 (62.9-84.7)	95.8 (94.2-97.3)
Cytology LSIL	12	61.6 (48.0-75.2)	96.0 (94.8-97.2)
Cytology LSIL > 30 years	3	75.2 (70.5-79.9)	95.6 (91.7-99.4)
HC1	3	71.7 (66.8-76.6)	92.5 (91.3-93.8)
HC2	15	90.0 (86.4-93.7)	86.5 (83.1-89.8)
HC2 > 30 years	6	94.8 (90.9-98.7)	86.0 (81.9-90)
PCR	6	80.9 (70.0-91.7)	94.7 (92.5-96.9)

ASCUS, atypical squamous cells of undetermined significance; 95% CI, 95% confidence interval; CIN, cervical intraepithelial neoplasia; HC, hybrid capture; LSIL, low-grade squamous intraepithelial lesion; PCR, polymerase chain reaction.

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with no prevaccine evidence of HPV 16 or 18, which contrasts the more modest, but nonetheless striking 44% reduction observed in the intention-to-treat analysis that included the 20% of subjects with serologic evidence of HPV 16/18 prior to vaccination.³⁹ No differences in serious adverse events, pregnancy rate, or pregnancy outcome occurred between vaccine and placebo groups, although there was an increased rate of injection site events, including pain and erythema.³⁶

The largest randomized trial to date vaccinated 18,000 women with the bivalent vaccine⁴⁰ using the hepatitis A vaccine as the control injection. In addition to only encompassing HPV 16 and 18, and not the nononcogenic strains 6 and 11, the bivalent vaccine is formulated with AS04, an immunogenic compound proposed by the manufacturer to induce a more potent and durable response.⁴¹ The 2007 interim analysis after 15 months follow-up indicated a 100% vaccine efficacy against CIN 2+ lesions due to HPV 16 and 18, and a 90% reduction in CIN 2+ was reported for all the women enrolled in the study. A novel feature of this study involved 2 correlative analyses. The first examined antibody levels by age, demonstrating that younger women tended to mount a stronger immune response than older women.⁴¹ The second conducted extensive molecular serotyping experiments of 5 additional high-risk HPV subtypes (45, 31, 33, 52, 58) to determine if the vaccine provided any cross-serotype coverage. The authors reported a 62%, 46%, and 45% reduction in HPV 45, 33, and 52, respectively, suggesting a moderate degree of cross protection from other oncogenic HPV strains.⁴² Previous phase II studies with the bivalent HPV vaccine with 4 to 5 years of follow-up data also demonstrated high efficacy against HPV 16 and 18, in addition to

a durable cross-protection against other oncogenic HPV strains. The authors reported that the efficacy of the bivalent vaccine to prevent CIN 2+ lesions from HPV of any kind in all women aged 16 to 26 years was 68%.^{43,44}

The long-term implications of these highly effective HPV vaccines have

associated with gynecologic and obstetric complications, including cervical stenosis, preterm labor, low birth-weight, premature preterm rupture of membranes, cervical incompetence, and cesarean delivery.⁴⁵⁻⁴⁷

Cost analyses have demonstrated that in populations with prevalent disease, universal prophylactic ad-

The long-term implications of these highly effective HPV vaccines have yet to be understood, but many researchers hypothesize that vaccination has the potential to reduce cervical cancer by 70%.

yet to be understood, but many researchers hypothesize that vaccination has the potential to reduce cervical cancer by 70%.⁴⁴ Although the outcome measure in all these vaccine trials is high-grade preinvasive disease (waiting for test populations to develop cancer would be unethical), the natural history of cervical cancer as one that progresses over years from dysplasia makes this surrogate measure a reasonable predictor of cancer prevention. A major unresolved question will be the length of time the various vaccines maintain this high efficacy, making further follow-up of these patients crucial to determining if re-immunization will be required later in life. It is clear, however, that

ministration of vaccine to women aged 12 to 26 years is an effective strategy to decrease the health care costs associated with multiple tests and potential morbidity.⁴⁸⁻⁵¹ The research clearly supports that the most benefit will be observed in those women aged 12 to 26 years who undergo vaccination prior to the onset of sexual activity, but given the clear benefits of vaccination for all women regardless of prior HPV exposure, most experts recommend that all women in this age range be vaccinated.^{52,53} Investigators hypothesize that in an age of universal HPV vaccination, routine screening can likely begin at a later age and be a less frequent event, further decreasing

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in the more than 40,000 women participating in these vaccine trials, investigators consistently observed decreased numbers of CIN 2+ lesions and abnormal Papanicolaou test results, leading to decreased colposcopy referrals for biopsies, and, ultimately, fewer excisional procedures that are

potential screening and prevention costs, although most agree the models are limited by the unknown durability of HPV vaccination.⁵⁴ Authors also agree that in an age of universal HPV vaccination, the prevalence of high-risk HPV will decline and markedly decrease the positive predictive value

of the current screening guidelines; this will mandate more sensitive, likely molecular screening techniques addressing specific high-risk strains to screen vaccinated women.^{44,55}

HPV in Vulvar and Vaginal Cancer

Human papillomavirus plays a significant role in the pathogenesis of vulvar and vaginal cancer. In contrast to cervical cancer, oncogenic HPV has been implicated in only a proportion of vulvar and vaginal SCCs, leading researchers to speculate that other unknown etiologies, possibly chronic inflammation or molecular changes, may contribute to the development of these malignancies.^{6,56-58} What has been clearly established, however, is that higher proportions of both vaginal intraepithelial neoplasia (VaIN) and vulvar intraepithelial neoplasia (VIN) are associated with oncogenic HPV, suggesting true commonality with cervical dysplasia (CIN).⁵⁹ In the United States, approximately 3400 new cases of vulvar cancer (90% SCC) and 1100 cases of vaginal cancer (85% SCC) are diagnosed each year,⁶⁰ and because of the low prevalence of these diseases, population-wide screening programs are not currently recommended. Although secondary

prevention strategies are not indicated for vulvar or vaginal cancer, primary prevention of these HPV-related diseases will likely be effective in light of the recent reports demonstrating that the quadrivalent HPV vaccine is 100% effective against both nononcogenic condylomatous disease and oncogenic VIN 2/3 and VaIN 2/3 if administered prior to HPV exposure.^{35,61}

Although the rate of invasive vulvar SCC appears to be only slightly increasing, epidemiologic data have suggested that high-grade preinvasive disease, especially that of the vulva, is on the rise in younger women.⁶² Multiple investigations have demonstrated that HPV is associated with 38% to 75% of SCC of the vulva.^{1,5} Genotypic analysis has shown that SCC of the vulva in women younger than 70 years, as well as VIN 3, was almost exclusively HPV related⁶³ and that the majority of serotypes represented were HPV 16 (80%-90%), 18 (5%-10%), and 33 (5%-10%).^{1,5} Further investigation into HPV serotypes in the setting of VIN demonstrated a near 100% association with HPV infection with all VIN, but noted that HPV 16 was far more prevalent in VIN 3 compared with VIN 1.⁵⁹ This HPV type-specific behavior may also help

to resolve the controversy that exists over whether VIN 3 progresses to invasive SCC, as only 10% to 50% of SCC of the vulva appear to arise from VIN 3.⁶⁴ Although less is understood regarding vaginal dysplasia and SCC, investigations have observed that oncogenic HPV affects 90% to 100% of VaIN and 60% to 70% of vaginal SCC.^{1,59} In addition, research suggests HPV 16 is more prevalent in VaIN 3/SCC lesions (50%-60%), compared with VaIN 1 (5%-21%).⁶ The preponderance of the cervical, vulvar, and vaginal data seem to confirm that the presence of HPV 16 may predispose to a more aggressive phenotype making HPV serotyping a potential modality for screening and prevention of HPV-related neoplasms, especially in light of universal HPV vaccination.

Because HPV mediates most dysplasia and a large proportion of SCC of the vulva and vagina, it is not surprising that HPV vaccination has been shown to decrease the incidence of vulvar and vaginal dysplasia. With an average of 3 years of follow-up, the quadrivalent HPV vaccine was shown to be 100% effective in preventing all VIN and VaIN lesions secondary to HPV 6, 11, 16, and 18 in women aged 16 to 24 years with no evidence of previous HPV exposure. In the total

Main Points

- Over the past 25 years, the human papillomavirus (HPV) has been identified as the etiologic agent driving much of the neoplasia observed in the lower female reproductive tract.
- Cervical cancer satisfies all the criteria for a cancer amenable to screening. It is not surprising that in countries with ubiquitous Papanicolaou testing, cervical cancer has experienced a 75% drop in prevalence that can be directly attributed to screening alone.
- The recognition that high-grade dysplasia or invasive cervical cancer cannot manifest without evidence of oncogenic HPV has led to testing expansion that includes triage of ASCUS Papanicolaou test results, follow-up of therapeutic outcome after colposcopy or therapy for cervical intraepithelial neoplasia (CIN) grade 2/3 lesions, and primary screening in women older than 30 years coupled with cytology.
- Although an HPV test alone has been shown to have greater sensitivity and specificity to predict CIN 2 or greater, combining an HPV test with conventional cytology further improves the test characteristics in the population older than 30 years.
- Higher proportions of both vaginal intraepithelial neoplasia and vulvar intraepithelial neoplasia are associated with oncogenic HPV, suggesting true commonality with cervical dysplasia.

cohort that included women with prior exposure (17% of cohort), the HPV vaccine was 62% effective in preventing VaIN 3 or VIN 3 lesions.³⁵ Data from this trial were pooled with 2 additional trials in a recent meta-analysis of 3 placebo controlled, randomized clinical trials with the quadrivalent HPV vaccine.⁶¹ This report further solidified the role of the HPV vaccine finding a similar 100% prophylactic and 70% overall efficacy against HPV 16/18 associated with VIN 3/VaIN 3. The intention-to-treat analysis of the total 18,174 women represented in these studies documented a 49% efficacy rate regardless of HPV type and prior exposure.⁶¹ These data further reinforce the potential efficacy of HPV to decrease the incidence, morbidity, and cost of HPV-related gynecologic malignancies worldwide.⁶⁵

Conclusions

Human papillomavirus is the acquired condition that for cervical cancer is always a necessary component of neoplasia, and for vulvar/vagina SCC may be a driving factor in a significant subset. For these HPV-related gynecologic neoplasms, polyvalent vaccines against various high-risk HPV strains hold the promise of decreasing the incidence of abnormal Papanicolaou test results, colposcopic examinations with biopsy, and excisional procedures with all their associated gynecologic and obstetric morbidities and cost. For those unaffected or ineligible for vaccination, it is likely that with the advent of individual sample HPV serotyping, clinicians will achieve a heightened insight into prospective clinical behavior of dysplasia and carcinoma samples to better guide counseling and therapy. Although further study will be needed to understand the complex relationships that paired primary (HPV vaccine) and secondary prevention (Papanicolaou and HPV testing) strate-

gies will engender, these new modalities hold the promise that clinicians will be able to detect with greater sensitivity and specificity and/or prevent a growing proportion of HPV-related gynecologic cancers. ■

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