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REVIEW

Morbidity and mortality of vulvar and vaginal cancers: Impact of 2-, 4-, and 9-valent HPV vaccines

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ABSTRACT

Vaginal and vulvar cancers do not account for a large proportion of gynecologic malignancies but their impact is significant. Both vaginal and vulvar lesions have precursors and display levels of dysplasia before progression to invasive disease. Human Papillomavirus (HPV) is a known causative agent of such dysplasia and can be detected now more readily than ever with adequate recognition techniques and provider awareness. Although HPV vaccination is still lagging compared to other recommended childhood vaccinations, the impact on lower genital tract neoplasia is promising. The bivalent and quadrivalent vaccines have been shown to be efficacious and the newest nonavalent vaccine should add even more of impact on coverage of cancer-causing HPV types. Although it is still early to show true clinical and population-based disease reduction due to low disease incidence and relatively short time of vaccine availability, the potential is noteworthy.

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Introduction

The purpose of this review is to describe the epidemiology, etiology, and clinical implications of vulvar and vaginal cancers related to HPV infection. Then, by examining data on the efficacy of HPV vaccination we can see the potential and realized impact that these vaccinations have on reduction of morbidity and mortality of HPV-associated lesions of the vulva and vagina.

Vulvar cancer

Although still a relatively uncommon gynecologic malignancy, the increase in incidence of vulvar cancer is striking over the last several decades.[1] In the United States, there will be an estimated 5,150 new cases of invasive disease and 1,080 deaths.[2] Since the 1970s, there has been over a 20% increase in invasive cancer rates and a 411% increase in pre-invasive or *in situ* disease.[3] The rate of invasive cancer continues to climb 0.5% per year even with improved screening strategies and greater awareness by practitioners. Despite this increase, a recent study by Akhtar-Danesh et al showed that the two- and five- year excess mortality rates in the United States have decreased overall.[4] This is due to the advancement and paradigm shift that has occurred in recognition of cancer etiology and natural history.

Squamous vulvar carcinoma presents in two different etiologic types. The most common type involves infection with HPV and is associated with high-risk sexual activity, immunosuppression, and tobacco use.[5] Mean age at diagnosis for this type is late fifth or early sixth decade. Infection with the virus and evasion of host immunity results in the progression of cells from their native state to histologic evidence of a precursor lesion and classified as vulvar intraepithelial neoplasia (VIN). Low grade VIN is related to initial viral infection and replication. If infection persists, there can be progression to high grade lesions where the HPV genome is integrated into host chromosomes. Malignant transformation then occurs when viral oncogenes interfere with cell-cycle regulation.

In contrast, other types of vulvar cancer do not have an apparent association to HPV infection. The second most common lesion is also a squamous cell carcinoma but does not show high rates of concurrent VIN, and is commonly found adjacent to chronic dystrophic or inflammatory lesions.[6] These cancers are more likely to occur in postmenopausal women in their mid to late 60s and can be associated with low estrogen, tissue atrophy, and other autoimmune conditions. While the term VIN is still used to describe the precursor lesions, the progression to invasive cancer does not involve viral oncogenes. There are also a small proportion of vulvar cancers histologically classified as melanoma, sarcoma, or basal cell lesions, which combined only account for about 10% of all primary vulvar neoplasms.[1] These cancers tend to be more aggressive and have a poorer prognosis than HPV-related disease.[4,6]

Early on there was some debate as to the causal relationship between the Human Papillomavirus (HPV) and vulvar cancer. Now there is sufficient data to confirm the link. The largest study to date is a meta-analysis which included 93 different sources of data for PCR-identified HPV prevalence in women with urogenital dysplasia. HPV found in young women with suspected VIN caused by HPV was upwards of 90%.[7] The vast majority of these cases were type-specific to HPV 16 which accounted for about 71% of advanced HPV associated VIN.

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Most of the remainder of observed HPV-related advanced pre-malignant lesions is associated with types 11, 18, and 33. Interestingly, low grade VIN is predominantly associated with HPV 6, which is not thought to be related to invasive disease unless there is a concurrent high risk HPV infection.[7]

While not all VIN lesions lead to invasive vulvar cancer, there are those more vulnerable to HPV persistence and increased rates of vulvar cancer than others. These include women infected with HIV who display higher rates of HPV infection due to decreased cellular immunity. The incidence of malignant or pre-malignant vulvar lesions is 16 times greater than for HIV infection than those without.[8] There is a negative correlation between host immune response and VIN prevalence and retroviral therapy has been shown to decrease the rates of pre-invasive disease.[9] Data is lacking on the type specificity of HPV implicated in these women but it is suspected that HPV 16 is the most common causative agent.[10] HPV-associated vulvar cancers are also more likely seen in women with other causes of immunosuppression as well, such as transplant patients or patients with autoimmune diseases undergoing therapy. Data has shown that minority groups are typically more vulnerable to HPV-related cervical neoplasia due to reduced screening. Because there is no routine screening for vulvar cancer, there has not yet been observed a skewed racial distribution among those with the disease. Although African Americans in particular are a vulnerable group overall for cancer-related mortality, this is not the case for vulvar cancer. Although they may present at an earlier age, there is no evidence of elevated cause-specific mortality.[11]

Vulvar cancer is diagnosed histologically; however visual inspection of the vulva is required to prompt further management. Some studies suggest that only about 60% of lesions are symptomatic, leaving the remainder to be diagnosed solely on physician inspection.[4,7] Often, lesions are small, inconspicuous, similar color to the patient's skin, or can mimic benign lesions such as warts. Management of pre-malignant vulvar lesions first involves vulvar biopsy for diagnosis. Should a lesion be identified that requires removal, a surgical approach is typically favored. This involves shallow excision of the lesion, ablation of the lesion with argon laser, or a combination of the 2. Malignant lesions require a more invasive approach. Radical excision is performed removing all tissue to the pelvic fascia and with at least a two cm margin surrounding the lesion. Inguinal lymph node dissection often accompanies primary surgical management as well. For more advanced disease, pelvic radiation with or without chemotherapy is also utilized.

Patients are affected in a variety of ways with diagnosis and management. Simple biopsies or small local excisions can not only cause short term pain but also anxiety while awaiting histopathologic evaluation. Invasive vulvar surgery may require long term opioid use, hospitalization, and potentially deconditioning due to decreased ambulation. A relatively common complication of vulvar cancer operations is infection and wound breakdown. Even once healed, these women can be left with disfiguration of vulvar anatomy, sometimes involving resection of the clitoris and a decrease in sexual function. Radiation therapy carries the adverse effects of vaginal irritation, mucositis, ulceration, and necrosis in the short-term. Narrowing of the vaginal canal and fistula formation can also occur as a late side effect. Significant psychosocial trauma is not uncommon for women who have undergone these treatments. Recurrence for all types and stages of vulvar cancer occur about 37% of the time and 53% are local.[4,8] Multiple recurrences can occur in about 14% of patients. Treatment of recurrence can be with further radiation therapy which typically compounds existing trauma to the area. For those who recur or initially present with widespread metastases, chemotherapy may be used in a palliative setting. As mentioned previously, there will be about 1,000 deaths this year from vulvar cancer. Specific-cause mortality will come from complications of treatment or fulminant metastatic disease.

Vaginal cancer

Vaginal cancer is also an uncommon disease.[12] True primary vaginal tumors only account for about 2 % of all gynecologic malignancies.[13] For the upcoming year, there will be more than 4,000 people with a diagnosis of vaginal cancer of all etiologies which is higher than previously reported.[14] However, only about a quarter will be primary lesions and not metastatic sites from other primary tumors.[15] The trend in vaginal cancer cases is likely similar in etiology to vulvar cancer. Diagnosis usually occurs early in the fifth decade of life and the distribution is unimodal for most studies.[16] Survival rates are also similar to other lower genital tract cancers caused by HPV, with stage I disease having the best prognosis at an 84% disease-specific five y survival rate.[15]

HPV is the most common causative agent in the development of primary squamous cell carcinoma of the vagina, with smoking and history of prior urogenital malignancy being strong risk factors. Reports of HPV infection rates related to invasive or pre-invasive vaginal lesions are upwards of 85%, with HPV 16 and 18 being the most represented types.[17] Vaginal Intraepithelial Neoplasia, or VAIN, is the hallmark pre-invasive lesion. These lesions are far less predictable than other lower genital tract neoplasias because they are less commonly sampled or monitored. Historically, the incidence of occult malignancy in advanced VAIN lesions is common and has been reported as high as 28%.[18] Studies are generally limited due to the low incidence of vaginal cancer and rates of progression are difficult to assess unless hysterectomy or upper vaginectomy is performed after diagnosis. Vaginal biopsy can be both inaccurate and technically difficult for most general gynecologic providers since over half of lesions occur either in the upper third or posterior portion of the vagina.[4,9]

Management of vaginal pre-malignant lesions also often requires women to endure pain and anxiety surrounding biopsy results. At times, these can be serial and ongoing should the level of involvement not warrant surgical treatment. Preinvasive treatment can be accomplished with local excision, laser fulguration, or cream for chemical denudation of the tissue. Even these less-invasive measures can cause significant pain and suffering. Early stage vaginal cancer involves surgical management, which includes more radical excision of the vagina and in most cases scarring and shortening of the vagina. Unfortunately, 75% of patients will present at stage II or greater.[1] Treatment for these patients includes chemotherapy and radiation. Similar to vulvar cancer treatments, there are significant

challenges regarding pain control, sexual function, and alteration of body image. Recurrent disease can additionally bring with it complications arising from metastatic sites and further treatment burden. Recurrence will occur usually within the first two y after initial diagnosis and despite aggressive therapy only 10% will be cured.[42]

HPV vaccines

In 2006, the United States Food and Drug Administration licensed Merck & Co. the use of Gardasil®, a quadrivalent vaccine (4vHPV) and the first vaccination which protects against HPV types.[6,11,16,18,19] Three years later, GlaxoSmithKline introduced Cervarix®, a bivalent vaccine (2vHPV) which protects against types 16 and 18 only[20] Both vaccinations, utilize the virus' external structure to provide immunity. HPV is a small, double-stranded DNA virus with over 120 subtypes that vary based on the genetic sequence of several proteins, including the L1 outer capsid protein.[21] This protein can be recombinantly expressed on its own and can then assemble itself into a virus-like particle (VLP) that mimics the HPV subtype desired.[22] Since these particles do not contain actual viral DNA, they are non-infectious and therefore cannot cause neoplastic changes in host epithelium. Most recently, Merck released Gardasil 9® (9vHPV), a nonavalent vaccine protecting against high risk types 16, 18, 31, 33, 45, 52, and 58 as well as HPV 6, 11. The nonaanovalent vaccine is advertised to prevent up to 90% of HPV-associated cervical, vulvar, vaginal, and anal cancers. All three vaccines require a 3 shot series over a 6 month timeframe for complete protection.

The bivalent HPV vaccine, Cervarix®, targets only subtypes 16 and 18, which have been associated with 86–95% of all HPV-related vaginal and vulvar invasive or pre-invasive cancer.[27] Gardasil®, the quadrivalent HPV vaccine adds subtypes 6 and 11 to its coverage which have shown to cause 90% of all external genital warts in both males and females.[28] The two vaccines are similar in basic construct and differ only in their adjuvant components which provide additional systems to increase host immune response.[32] They have also been shown to have similar efficacy and immunogenicity. PATRICIA (papilloma trial against cancer in young adults), an 18,000 participant phase III trial showed a 93% vaccine efficacy for Cervarix®, with an additional 5% in secondary analysis of probably causality.[33] Gardasil® was evaluated similarly in two very large multicenter trials referred to as FUTURE I and FUTURE II, which showed a 98% vaccine efficacy rate for HPV-related cervical lesions and a 100% rate for other anogenital lesions which included HPV-related vulvar and vaginal disease.[34,35] A more recent study by Naud et al shows that the bivalent vaccine model has sustained immunity with no safety concerns after a period of 9.4 y[24]

HPV vaccination

Since the introduction of the first HPV vaccine, the CDC ACIP has recommended universal vaccination of adolescent girls with catchup vaccination of women up to age 26. Since, 2012, recommendations were changed to include boys and men. Currently the ACIP recommends that routine HPV vaccination be initiated at age 11 or 12 y (as early as age 9). HPV vaccination is also recommended for females aged 13 through 26 y and for males aged 13 through 21 y who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 y may be vaccinated. Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV. Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV.

Despite the known safety and efficacy of the available HPV vaccines as well as recommendation for national health organizations, uptake has been low in the United States. The NIS-Teen study 2014 showed that only 60% of adolescent girls have been vaccinated at all and only 42% of boys. Unfortunately, these numbers are lowest in many of the states with the highest rates of HPV-related cancers.[39]

In the clinical environment, barriers to the vaccine's efficacy have shifted to utilization. The largest barrier is completion of the 3 shot series. Mathematical models for prediction of long-term immunity were based on the hepatitis B vaccine, which gave way to the 3 dose regimen for all forms of HPV vaccination.[23] Recent data from Sweden's national health database suggests that completing all three vaccinations in the series leads to greater protection against HPV.[41] However, difficulties completing all three vaccines in the series have been observed in the general population. Almost one-third of all women who initiate vaccination never complete it. Low income, minority race, and low level of education completion are all risk factors for failure to receive all three injections.[25] This is true both for adults under 26 y of age considering catch-up vaccination as well as for parents choosing vaccination for their children.[41] In the most comprehensive worldwide review of HPV vaccination barriers to date, other trends emerged. including the lack of education regarding the safety and necessity of HPV immunization in general. Provider recommendation is also low due to lack of knowledge of the vaccine and the difficulty discussing sexual subject matter.[26]

Impact of HPV vaccine

Despite known efficacy rates in clinical trials, it is difficult to determine the true impact of a vaccination in practice. Rate reduction of disease alone can be misleading. Differences in virus attack rates and length of follow up in these studies cause large degrees of variance for comparison and difficulty in application to clinical medicine. Because of the slow disease process, true rate reduction data will be consistently evolving. It is also possible that prevention of some high risk HPV strains but not others, could lead to disease evolution by which HPV-related cancers as caused in increasing numbers by strains not included in the vaccine. When examining effects on vulvar and vaginal cancer, the relative rarity of these diseases must also be accounted for when examining rate reduction described over 100 woman-years. Recent data analyzing prophylactic efficacy have shown a rate of 95.4% for HPV-related vaginal and vulvar lesions, but with only a <0 .1 rate reduction per 100 woman-years for all those susceptible to infection. When examining the results with intent to treat, this rate decreases to 78.5% with similar rate reduction.[36] Data from Australia shows that

Table 1. Vaccine information and potential impact by type.

	Cervarix®	Gardasil®	Gardasil-9®
HPV subtypes Covered	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Disease reduction* (%) –vulvar	50.0	50.0	64.1
Disease reduction* (%) –vulvar in situ	82.4	82.4	92.7
Disease reduction* (%) –vaginal	56.7	56.7	80.0

Values for reduction are based on the most recent data regarding HPV subtypes implicated in vulvar and vaginal in situ and invasive disease. As such, potential impact would assume 100% efficacy and vaccine coverage. Saraiya M., Unger E., Thompson T., Lynch C., Hernandez B., Goodman M. (2015) US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines. *Journal of the National Cancer Institute*. 107(6)

vaccination programs are promising. Four years after a nationwide vaccination program utilizing the quadrivalent vaccine was instituted there was a drop from 28.7% to 6.7% in vaccine-target HPV genotype prevalence.[37] This was in a population with greater than 85% vaccination coverage. A follow up study of over 85,000 Australia women were shown to have only a 1% prevalence of genital warts compared with 10.5% before the vaccination program began.[38] Although this is a significant reduction in what is known to be an HPV-related lesion, it is simply a marker for progress in the prevention of vulvar and vaginal cancers. As these women age, more follow up data will be required to determine the true impact.

Gardasil 9® adds additional vaccine coverage of subtypes 31, 33, 45, 52, and 58. The addition of these 5 new types was done in hopes of increasing the total proportion of cervical cancer-causing subtypes by 20%.[29] There is potential that Gardasil 9® might cover an additional 10% of vulvar and vaginal cancers as well. While HPV 16 is associated with 77.3% of HPV-related VIN lesions and vulvar cancers, recent data shows that HPV 33 is the second most common type which accounts for almost 10.6%.[30] For HPV-related vaginal cancer and VAIN lesions, the most common causative subtype again is HPV 16 at 59%, with HPV 18 being second most common at 6%. HPV 52, which would be covered by Gardasil 9® has now shown to be implicated in 6% of all lesions.[31] Up to 90% of all HPV types that cause at least high grade dysplasia of any kind are included in this nonavalent vaccine model but true disease reduction is yet to be determined.[40]

Clinically, the decrease in HPV-associated vulvar and vaginal lesions could be quite impactful. Over 1,400 women die every year from HPV-related vulvar and vaginal cancers.[15] The most significant cause of primary vaginal and vulvar cancer deaths is attributable to HPV disease and the reduction in morbidity for these cancers is worthy to mention. Additionally, patients who have pre-malignant lesions often must undergo frequent visits and diagnostic procedures that not only provide a source of unwanted morbidity, but also a tremendous amount of cost for both patient and provider. For immunosuppressed patients, this is typically a chronic burden. HPV is a regional disease and commonly those affected must undergo multiple procedures affecting several areas of the lower genital tract.

Conclusion

Most women who have received HPV vaccination are far younger than the average ages at which vulvar and vaginal cancers are diagnosed so the true impact of vaccination may not be known for some time. However, the potential for decreasing the rate of new diagnoses is significant. There is promising data on disease reduction with implementation of widespread vaccination programs in some countries. However, the US still faces many changes related to HPV vaccine uptake and series completion that may hinder any gains in disease reduction for years to come. It will take years for the impact of the nonavalent HPV vaccine to take shape, but given the similar theoretical basis it is reasonable to assume that the results will be positive. What should be addressed in the future along with efficacy is vaccine uptake in the population and provider awareness. Should these factors not also increase, rates of HPV-related disease reduction would be likewise delayed and young women who could have been vaccinated could grow up only to die of an HPV-related vulvar or vaginal cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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