

# Update on human papillomavirus

Cervical cancer is the most common cancer caused by the human papillomavirus (HPV),<sup>1</sup> but the scope of HPV-related disease is considerably broader. As many as 90% of anal cancers, as well as 40% of vulvar and penile cancers, are attributable to HPV infection.<sup>2</sup> Furthermore, high-risk HPV types contribute significantly to cases of vulvar and vaginal disease<sup>3</sup> and low-risk types of HPV are thought to cause up to 1 million cases of genital warts each year.<sup>4</sup> Vaccination has been shown to be highly effective in preventing HPV infection<sup>5</sup> and its sequelae.<sup>6</sup>

Some of these findings were presented in detail on November 10, 2008, by 3 experts at a symposium supported by an independent educational grant from Merck & Co., Inc., at the American Society for Reproductive Medicine 64th Annual Meeting in San Francisco. These clinicians also presented promising results showing cross-protection against several HPV types; provided tips to improve detection of vaginal lesions; and discussed the implications of gender-neutral vaccination. Following are short synopses of each physician's presentation.

## Epidemiology and natural history of HPV in benign and malignant disease: Primary prevention of CIN3 and AIS with HPV vaccination

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Most sexually active women will acquire HPV in their lifetime.<sup>7</sup> Although the infection clears in most cases, it does persist in some women. Long-term persistence of HPV infection—particularly with high-risk types—has been established as a necessary cause of precancerous lesions.<sup>8</sup> In fact, the high-risk HPV types 16 and 18 are responsible for 70% of squamous cell carcinoma cases and 86% of cases of adenocarcinoma.<sup>9</sup>

Persistent HPV infection and cervical intraepithelial neoplasia 3 (CIN 3) allow random mutations to accumulate that can eventually lead to cancer. When mutations occur in normal cells, the cell upregulates the expression of proteins that repair the mutation or precipitate apoptosis. High-risk types of the HPV virus produce proteins that inhibit this process, allowing cells to live despite

mutations. In the worst case, these cells continue to grow and mutate, forming a malignancy over many years that invades the basement membrane.

Prophylactic administration of the HPV vaccine effectively prevents the development of CIN 1, 2, 3, and adenocarcinoma in situ (AIS). In patients who tested negative for the vaccine HPV types during the administration of the 3-dose vaccine, protection against high-grade cervical lesions (CIN 2 and 3) and AIS was between 97% and 100% at 3 years.<sup>6,10</sup> Vaccination was also effective in eliminating the development of genital warts and CIN 1, which are caused by low-risk HPV types 6 and 11.<sup>6</sup>

Additionally, vaccination appears to offer cross-protection, ie, partial protection against infection with HPV types related to 16 or 18, such as the high-risk types 45, 31, 33, and 52.<sup>11</sup>

## Update on HPV: Genital warts, VIN, VAIN, and vulvar/vaginal cancer

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Vulvo-vaginal disease and genital warts can be sequelae of HPV infection. Genital warts represent a large burden: Treatment costs account for nearly one-third of annual medical expenses for sexually transmitted infections.<sup>12</sup> And vulvar intraepithelial neoplasia (VIN) is a growing burden. Although the incidence of VIN remains low, rates of diagnosis of VIN 2 and 3 are increasing.<sup>13</sup> This is particularly troubling, given that 10% of untreated VIN 3 progresses to cancer.<sup>14</sup> Further, VIN may not be diagnosed until it has

progressed, because only subjective diagnostic criteria exist for low-grade VIN.<sup>15</sup>

Visual inspection is used to identify genital warts and vulvar or vaginal lesions. Vulvar or vaginal lesions are more difficult to detect with colposcopy than are cervical lesions, due to the wider target area and tangential angle of viewing. Applying a solution of 5% acetic acid and leaving it for 3 to 5 minutes will facilitate evaluation; small vaginal lesions are best detected with Lugol's solution.

A bimanual examination that includes palpation of the vagina should be conducted in order to rule out invasive cancer.

HPV types 6 and 11 cause 90% of genital warts.<sup>16</sup> High-risk HPV types 16 and 18 are responsible for many cases of vaginal and vulvar disease<sup>3</sup>:

- 76% of VIN 2/3
- 64% of vaginal intraepithelial neoplasia (VAIN) 2/3
- 42% of vulvar cancer

A meta-analysis of 3 randomized controlled trials evaluated the development of vulvar or vaginal lesions with prophylactic administration of the HPV vaccine.<sup>17</sup> Among women who were HPV negative before and during administration of the HPV vaccine, the vaccine was 100% effective in preventing VIN 2/3 and VAIN 2/3 related to either HPV 16 or 18. The incidence of VIN 2/3 and VAIN 2/3 decreased by 71% among women who had previously been exposed to HPV.

## Penile, anal, and oropharyngeal cancer: The potential for primary prevention with HPV vaccination

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To date, no HPV vaccine has been approved for use in men. However, some evidence suggests that their vaccination could reduce the burden of HPV-related disease in men and transmission of HPV to women.

HPV infection causes cancer in approximately 10,000 US men annually.<sup>18</sup> Head and neck cancers account for the majority of these cases, followed by anal and penile cancers. Other HPV-related diseases seen in men include genital warts and recurrent respiratory papillomatosis.

HPV-associated anal cancer is increasing in prevalence, particularly among high-risk individuals, such as men who have sex with men (MSM) and HIV-positive men and women.<sup>19</sup> The rate of anal cancer among MSM is 35 to 70 cases per 100,000 men, depending on HIV status.<sup>18</sup> This is comparable to the rate of cervical cancer

prior to the advent of cervical cytology screening, and well above the current cervical cancer rate of 8 to 10 cases per 100,000 women.

Among all MSM, 66% are infected with HPV and 42% have anal intraepithelial neoplasia, a cancer precursor.<sup>19</sup> Two key pieces of evidence suggest that vaccination of men would be effective. First, the heavily keratinized, hair-bearing skin of external male genitalia is identical to that of the vulva. Based on this, it has been suggested that the beneficial effects of the vaccine in preventing genital warts in females may also be seen in males. Secondly, in studies, 9- to 15-year-old boys who received the quadrivalent vaccine had higher anti-HPV titers than even the young-adult women. Because the vaccine is known to be protective at the lower titers seen in the women, investigators suspect that it will also work in the boys.

The presentation "Update on HPV" will be available in its entirety as a webcast at [www.srm-ejournal.com](http://www.srm-ejournal.com) in December 2008. This program is supported by an independent educational grant from Merck & Co., Inc.

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