Published in final edited form as:
Adolesc Med State Art Rev. 2010 August ; 21(2): 347–xi.

CHAPTER 11: Human Papillomavirus Disease and Vaccines in Adolescents

Anna-Barbara Moscicki, MD
Division of Adolescent Medicine, University of California San Francisco, 3333 California Street, San Francisco, CA 94118

The road to discovery of human papillomavirus (HPV) as the cause of cervical cancer has likely affected adolescents more than any group, both positively and negatively. With the development of sensitive assays for HPV, it became clear that adolescents were infected with HPV more often than any other age group. This led to increased cervical cancer screening in this age group, which unfortunately led to the discovery that HPV-associated disease was also epidemic in this group. The medical intervention spiral began with increased colposcopy, biopsy, and treatment. Meanwhile, cervical cancer rates never changed in this age group. In reflection, the decision to initiate screening cervical cancer in this age group was not evidence-based. Recently, we have also broadened our understanding about HPV-associated disease in men. In this chapter, we cover the advances in science that have led to new screening recommendation for cervical cancer and the advances in prevention: vaccines for both adolescent women and men.

Biology of HPV

Understanding the viral replication cycle is essential to understanding the clinical implications of HPV DNA and disease detection in adolescents. The target cell for HPV infection is the epithelial basal cell. The virus life cycle is dependent on the ability of these cells to divide, differentiate, and move toward the epithelial surface.[1] In the basal layer, the early proteins (termed E6 and E7) facilitate replication and maintenance of the viral genome and cause cellular proliferation as well. As the cell matures, different HPV proteins are expressed that continue to maintain viral genomic replication. Expression of the late proteins, which create the essential outer capsid, occurs in the upper layer of the epithelium. This is followed by packaging of the DNA into the capsid and eventual release of infectious virions from the normally desquamated epithelial cell.

Without cell differentiation, the virus cannot replicate. The period between basal cell infection and release of virus is thought to be somewhere between 3 weeks and 3 months.

Viral replication and its associated protein expression induce the development of the low-grade squamous intraepithelial lesion (LSIL), which is characterized by mild basal cell proliferation and nuclear enlargement. These changes are in part due to the expression of the oncogenes E6 and E7 and perinuclear halos secondary to E4 expression, which interferes with cytoskeletal structure. As the intraepithelial lesions advance in grade, expression of products important in cell transformation, such as E6 and E7, predominate resulting in chromosomal abnormalities and the aneuploidy characteristic of the higher-grade squamous intraepithelial lesions (HSIL). Hallmarks of cancer development include viral integration

Address correspondence to P: 415 476-5139, F: 415 476-6106. moscickia@peds.ucsf.edu..

and interference with telomerase activity.[2] As a point of clarification, the cytological diagnoses of LSIL and HSIL correspond to the histologic diagnoses of cervical intraepithelial neoplasia (CIN) 1 and CIN 2 or 3, respectively.[3]

Because the virus is nonlytic, the inflammatory response to HPV is much more subtle than other infections such as *C. trachomatis*. During early HPV infection, the host remains somewhat immunologically unaware of the virus because the virions are released in the outer epithelial layer, away from the submucosa, the primary site of immune surveillance. It appears that an initial HPV infection triggers an innate immune response[4] through activation of Toll-like receptors (TLRs), which recognize genetically imprinted pathogen-associated membrane proteins or through activation of natural killer cells.[5] Innate immune responses are thought to be responsible for rapid clearance—those seen within weeks to a few months.

Chronic HPV infections are likely cleared by the development of adaptive immune responses,[6,7] dependent on presentation of viral antigens to antigen-presenting cells (APCs), such as Langerhans and dendritic cells.[8] Successful adaptive immune responses may take months to years to develop and oncogenic HPV types, specifically HPV 16, are able to downregulate both the innate and the adaptive immune response through numerous mechanisms.[4] Because HPV infections are localized to the epithelium, it is believe that the majority of both innate and adaptive immune responses are mucosal. These immune parameters are important to remember when we review the efficacy of preventive vaccines.

Epidemiology and the Natural History of HPV and SIL in Adolescents

Anogenital HPV infections are extremely common in the sexually active adolescent, with over 50% having a positive HPV DNA test over a 3-year period.[9–12] Numerous studies have shown that a recent new sex partner is the strongest risk for acquiring HPV.[10,12–14] Other risks include having a sexually transmitted infection, which may reflect partner risk or inflammation resulting in a break in the epithelial barrier. Fortunately, in adolescents 50% of HPV infections are cleared within 6 months and 90% within 2–3 years.[15–18] Since LSIL is a reflection of viral replication and HPV is most common in the adolescent age group, it is not surprising that LSIL is also most common in adolescents with a prevalence ranging from 2–14%.[19] In parallel with HPV DNA clearance rates, over 90% of LSIL diagnosed in adolescents or young women also resolve spontaneously.

HSIL is far less common than LSIL, but adolescents and young women have a prevalence equivalent to older women with rates around 0.7%. The greatest single risk for HSIL development is HPV persistence. However, in one study, 7% of adolescents developed a HSIL shortly after HPV acquisition, suggesting some women develop HSIL without lengthy persistence.[20] Other risk factors include smoking cigarettes[21] and prolonged oral contraceptive use.[22] Since nicotine can be measured directly in cervical mucous, proposed mechanism for cigarette use includes local immune suppression and/or local carcinogenic affect. The role for oral contraceptives is more elusive, but estrogen has been shown to induce cellular proliferation as well as enhance HPV oncogene transcription.[23,24]

Reinfection with numerous HPV types is common in adolescents contributing to the high prevalence rate observed in young women. This vulnerability is thought to be due in part to a naïve immune response since the rate of HPV declines with age, even when controlling for sexual activity.[9,11,25–27] Clearance of infection appears to protect women from repeat infections with that genotype. This was well illustrated in the HPV vaccine trials where women seropositive for HPV 16 but HPV DNA 16 negative at baseline (ie, evidence of previously cleared infection) had low rates of HPV 16 infection during the trial although they were in the placebo arm.[28–30]

Adolescents and Biological Vulnerabilities to HPV, SIL and Cancer

Several studies, including a recent collaborative study of over 45 000 women have shown age of first intercourse to be an important risk for the future development of cervical cancer.[31–34] In that study, an increase in the risk for the development of cervical cancer was noted in women initiating intercourse before 24 years of age, with risk increasing with each declining year until age 17.[34] Some speculate that the risk of cancer increases because there is a longer time allowed for HPV persistence. Biologically, adolescence reflects a period of dramatic changes in an area of the cervix referred to as the transformation (T) zone where squamous cell cancers develop.[35]

Most neonates are born with an abrupt squamo-columnar junction visible on the ectocervix. This junction remains quiescent until puberty when estrogen and increased acidity of the vagina induces uncommitted basal cells of the columnar epithelium to become squamous cells through a process referred to squamous metaplasia. Consequently, the cervix in the adolescent is predominantly made up of columnar and metaplastic cells, whereas adults are predominantly squamous epithelium. Theoretically, the former epithelium may be more vulnerable to wounds induced by intercourse, douching or tampons leading to breeches in the epithelium and easy access for HPV. No study to date has shown that ectopy (eg, the presence of the columnar and metaplastic epithelium on the exocervix) is a risk for HPV acquisition. However, Castle et al[36] found that infections with HPV types including 16, 31, 33, 35, 52, 58, and 67 were more common in women with large areas of ectopy, but not common in women with mature cervixes. This observation might be related to age and immunologic memory which goes hand in hand with cervical maturation.

More important than the presence of columnar epithelium is likely the presence of active metaplastic epithelium. Cells that are rapidly undergoing differentiation and replication are “fuel for the fire” for SIL development.[37] A recent study showed that both oral contraceptive and smoking enhance metaplasia in young women.[38] This is quite interesting in light of both of these being risks for cervical cancer.

Cervical Cancer Rates and Screening

Despite the age of sexual debut decreasing and cervical cancer screening increasing in adolescents, cervical cancer rates have basically remained unchanged in the 15- 19-year-old group. From 1990–2006, Surveillance Epidemiology and End Results statistics show that an average of 14 cervical cancers occurred annually in girls age 15–19 years, reflecting an incidence rate of 0.1 per 100 000.[39] This rate is unchanged from that reported in 1973–1977 when screening was initiated.[40] In a recent study in England where there are active screening programs, Sasieni et al[41] found that screening women aged 20–24 years had no detectable impact on reducing cervical cancer rates in women under the age of 30 years. In comparison, there was a dramatic reduction noted for women 30 years and above. In another study, Gustoffson et al[42] compared rates of cervical cancer before and after screening programs were in place using data from several different countries including the United States. They showed that cervical cancer was significantly reduced among women between the ages of 35 and 55 years. No differences were found for women 25–35 years of age and those older than 70 years. Barnholtz-Sloan et al[43] reported that U.S. incidence cervical cancer rates showed significant decreases in incidence between 1995–1999 and 2000–2004 for all age groups and race/ethnicities except for Hispanic/all races women aged 15–24 years and non-Hispanic/other women aged 15–24 years. Changes in white and black women aged 15–24 years decreased but only marginally. These data support the notion that cervical cancer screening by cytology does not effectively prevent the rare cervical cancer case in the adolescent.

Risk Factors that Influence Clearance of HPV and SIL and Progression to CIN3

It has been shown that the longer HPV persists, the more likely it will not be cleared.[44] HPV persistence is key in the development of cervical cancers. However, how long persistence is required remains unknown. Persistence is likely necessary but not sufficient and other important carcinogenic events are needed before cancer develops.

Currently, CIN3 is considered a true precancer since regression is unlikely and progression to cervical cancer is estimated to be around 15% if left untreated. CIN1 is considered benign because of high rates of regression and rare progression. The diagnosis of CIN2 is clinically challenging and reproducibility being quite poor. Histologic readings are often either downgraded or upgraded on repeat analysis.[45] Recent studies also show that CIN2 appears to regress in ~60% of young women.[46,47] In the ALTS trial, depending on their study arm, some women with CIN2 were treated with excisional therapy at the end of the study.[48] Many of these women no longer had evidence of CIN2. One of the protective factors associated with progression to CIN3 included young age at biopsy. Women aged 18–21 years of age had a 52% reduced risk of having CIN3 on follow-up compared with women aged 22–23 years.[48] Another reason that CIN2 may commonly appear to regress is the low reproducibility of CIN2 lesions.[49] Castle et al[48] demonstrated that when CIN2 lesions were downgraded to CIN 1 by another review, the lesion was less likely to progress to CIN3 than those lesions that remained a CIN2 by the second review.

Although CIN3 does occur in adolescents, it is uncommon and the risk for CIN3 in this age group has not been well studied. Although there have been rare cases of spontaneous CIN3 shortly after HPV acquisition, the risk factors are likely similar to those in older women.[50] The lower progression rates from HPV or LSIL to CIN3 seen in adolescents is probably due to the fact that adolescents have not had enough time for progression to occur. However, better elucidation of the natural history of CIN3 among adolescents is unlikely to be garnered since it is considered unethical to leave potentially cancerous lesions untreated.

Cervical Cancer Screening

As discussed above, since cervical cancer screening has not changed cervical cancer rates over the last 3 decades in 15- to 19-year-olds or 20- to 24-year-olds and screening young women does not influence rates of cancer diagnosed under the 30 years of age,[41] screening recommendations have been revised. A recent statement from a conference headed by the American Society for Colposcopy and Cervical Pathology and Centers for Disease Control and Prevention with 22 other organizations attending recommended that in the United States, cervical screening should start at the age of 21 years with no caveats related to the age of onset of sexual activity.[51] This recommendation has been made an official guideline of the American College of Obstetrics and Gynecology and several other groups are moving to adopt this recommendation. The previous guideline recommending that screening begin at 21 years old or by 3 years after sexual debut (whichever comes first) has been difficult to follow, had poor adherence, and raised concern about causing more harm than good.[52]

Management

Although screening for cervical cancer in adolescent populations is now not recommended, the uptake of guidelines often take years. Consequently, guidelines have been developed to minimize harm to adolescents with abnormal cytology.[53,54] First, these guidelines underscore the lack of utility in using HPV DNA testing in screening, triage, or follow-up of abnormal cytology. There is no place for HPV testing in the adolescents because of its high prevalence. For abnormal cytology, the guidelines recommend observation. In the case of atypical squamous cells of undetermined significance and LSIL, only repeat cytology screening at 12-month intervals is recommended. If the abnormality persists after 2 years,

only then is it recommended to refer the women to colposcopy. In the case of HSIL, referral of all to colposcopy is recommended. If CIN1 is diagnosed, follow-up with cytology is recommended at 12-month intervals. If CIN2 is diagnosed, observation is also recommended with 6-month intervals using cytology and colposcopy for up to 2 years. If CIN2 is persistent at 2 years, then treatment is recommended.

One of the reasons that the new recommendations embrace observation (or no screening) is that treatment for CIN can be harmful with risks for preterm delivery and low birth rate.[55–58] The decision to treat should be the exception not the norm in adolescent populations and histologic criteria, not cytologic are required for treatment. Often, the histologic report does not distinguish CIN2 from CIN3 resulting in a CIN2/3 diagnosis. In this case, it is recommended to treat the lesion as a CIN2 since these lesions are more common than CIN3.

Prevention

The mainstay of prevention is vaccination. Two vaccines, a quadrivalent (HPV-4) containing serotypes HPV 6, 11, 16, and 18 (Gardasil' Merck & Co; Whitehouse Station, NJ) and a bivalent vaccine (HPV-2) containing serotypes 16 and 18 (Cervarix GlaxoSmithKline Biologicals; Rixensart, Belgium) have been approved by the U.S. Food and Drug Administration (FDA). Both of these vaccines are composed of noninfectious, recombinant HPV viral-like particles (VLP), comprising the major capsid protein, L1. Both vaccines are also adjuvanted with HPV-4 using aluminum hydroxyphosphate sulfate while HPV-2 utilizes a proprietary adjuvant, aluminum hydroxide with 3-deacylated monophosphoryl lipid A. The VLP with or without adjuvant elicits a strong systemic immune response measurable by neutralizing antibodies and cell-mediated immunity.[59–62] Although specific antibodies are present in cervical secretions of women who have received the vaccine,[63] it is thought that these HPV specific antibodies are present in cervical secretions secondary to transudation or exudation from blood into the cervical mucous at the site rather than local synthesis.

Vaccine Efficacy Against Cervical Cancer

Both the HPV-4 and HPV-2 vaccines are highly efficacious in preventing HPV vaccine-associated CIN—the predetermined efficacy correlate for the development of cervical cancer.[30,64–71] In the Per Protocol studies (where all subjects were HPV vaccine type naïve at entry, received all 3 doses on schedule, and cases start counting after the last vaccination), both vaccines had efficacies close to 100% (Tables 1 and 2). A subanalysis comprising women who were also HPV vaccine type naïve at entry but only received one or two doses of vaccine demonstrated efficacy almost equivalent to the per protocol analysis for both the HPV-4 and HPV-2 vaccines.[69,30] Per protocol efficacy for HPV-4 has been demonstrated for up to 42 months[70] and for up to 6.4 years for HPV-2.[30] Antibody levels (both anti IgG antibodies and neutralizing antibodies) for HPV 16 and 18 after HPV-2 have remained 5- to 13-fold higher than levels found in natural infections for up to 75 months after vaccination with no evidence of decline.[30] In contrast, women immunized with HPV-4 showed declines in antibodies for HPV-11 and -18 with final titers comparable to levels after natural infection.[28] Due to this finding, a study evaluating a booster dose of HPV-4 vaccine was performed.[28] A total of 114 women were given a fourth dose of HPV-4 vaccine 60 months after completing the primary 3-dose series. About 75% of the women who had undetectable antibody levels of HPV 11 prebooster and 96.7% of the women with undetectable levels of HPV 18 prebooster had significant rises in titers postbooster suggesting that the vaccine induces long-term boostable memory. Antibody response after a natural HPV exposure post-vaccination remains unknown. Using antibody decay models, it is estimated that the protection against HPV-16 from either vaccine will last decades, with 99% of people having lifelong detectable levels of antibody.[72]

Vaccine efficacy based on an intention to treat analysis which included women who before vaccination were not HPV naïve to the vaccine containing serotypes was greatly reduced for both the HPV-4 and HPV-2 vaccines (Tables 1 and 2). As vaccine trials are often designed to test maximal vaccine efficacy, many exclusionary criteria are present making it difficult to extrapolate study results to the general population. The initial studies of the HPV-4 vaccine excluded women who had a history of either 1) >4 lifetime sexual partners, 2) abnormal cytology or genital warts, or 3) were pregnant. Subsequent HPV-4 studies allowed women with a history of abnormal Pap smears or genital warts, but excluded women with either of the other two previously listed criteria. Participants in trials of the HPV-2 vaccine had more liberal criteria with exclusion occurring if women had a history of 7 or more lifetime partners. Since U.S. data shows that, on average, sexually active women aged 19–21 years have had 4 or more sexual partners, concern could be raised about the applicability of data from the HPV-4 trials to the general population.[73]

To address some of these concerns, Kjaer et al[70] performed a pooled analysis of 3 clinical trials of HPV-4 vaccine to determine the efficacy of preventing CIN2+ related to the serotypes in the vaccine among subgroups. Not surprisingly, vaccine efficacy in the intention to treat group (inclusive of non-HPV-naïve women) was significantly reduced among women with a greater number of sexual partners. Among women with no sexual partners, the percent reduction of CIN2+ histology was 86.5% as compared with 54.5% in those with 1–2 partners and 48.1% in women with 3 or more partners. Vaccine efficacy was inversely related to the age of the subject. Those age 17 or less had a 69% reduction in CIN-2+ histology, whereas those 21 years or older had a reduction of only 31.1%. Vaccine efficacy was also adversely affected by a history of having an abnormal Pap. None of these differences were found when limiting analysis to the per protocol (HPV naïve only) group. Similar subgroup analysis for the HPV-2 vaccine is not available.

While both the HPV-4 and HPV-2 vaccine are highly efficacious in preventing HPV disease from serotypes in the vaccine, neither vaccine has demonstrated therapeutic efficacy. In the HPV-2 trials, women who were serologically positive and DNA positive[30] had an efficacy of (-)13.8. Efficacy rose to 35.2% in women who were serologically negative and DNA positive, and climbed to 68.8% among women who were serologically positive but DNA negative (past history but cleared) prevaccination. A similar pattern of results was shown with the HPV-4 vaccine. Olsson et al[29] recently reported more data on women who were seropositive but DNA negative and found a similar efficacy for CIN2/3 of 100%; 0 cases (of 1243 women) occurred in the vaccine group compared with 4 (of 1283) women in the placebo group. Although this data may show some vaccine efficacy, it also demonstrates that the majority of women appear protected after natural clearance. These data support the notion that this is not a therapeutic vaccine. It is also underscores the importance of vaccinating naïve women.

Obviously the largest population without evidence of previous HPV exposure is sexually naïve individuals. Markowitz et al[74] examined vaccine HPV type seropositivity in blood among 4303 persons aged 14–59 years of age who participated in the 2003–2004 National Health and Nutrition Examination Survey. The seroprevalence of HPV 6, 11, 16, and 18 among female subjects was 17%, 7.1%, 15.6%, and 6.5%, respectively. The prevalence of infection with at least one HPV vaccine type was 32.5% among females. Broken down by age, 9.3% of those 14–19 years were exposed to at least one of the vaccine types—extremely few were exposed to all 4 types. When the data for the entire group was broken down by sexual behavior, women reporting >10 sexual partners had a prevalence of almost 60% for any one of the vaccine-containing types. Interestingly, the rates were also higher among women if they reported having their first intercourse under the age of 16 years (41%). The vaccine efficacy studies combined with the seroprevalence data from the

epidemiologic studies continue to support the decision to target younger girls to maximize the benefits from this vaccine. Although there is evidence to show that women will continue to benefit from the vaccine at an individual level after 19 years of age, vaccination in this older age group is far less beneficial from a public health perspective.

In the United States, the Advisory Committee for Immunization Practices (ACIP) recommends vaccination to be targeted to 11- to 12-year-olds along with the adolescent platform which includes tetanus, diphtheria and acellular pertussis, meningococcal, and varicella if needed (www.cdc.gov). ACIP also recommends immunization as early as 9 years of age since immunobridging studies showed adequate immune response in this age group. Catchup vaccination is also recommended for women up to the age of 26 years. The American Cancer Society has been more conservative with its recommendation suggesting that the evidence does not support large public health vaccination efforts for women older than age 19.[75] Certainly, individual based data show that many women will continue to derive benefit from the vaccine and that number of sexual partners and past history of abnormal cytology play a role in probability of benefit from the vaccine. Although these types of risk factors remain difficult to screen for in clinical settings,[76] health care providers should be able to counsel women regarding expectations from the vaccine if the individual has already begun sexual activity.

Vaccine Indications for Noncervical Genital Disease in Females

HPV-4 also has indications for the prevention of condyloma, which is caused by predominantly HPV-6 and -11 and noncervical genital disease including vulvar intraepithelial neoplastic (VIN) lesions and vaginal intraepithelial neoplastic (VAIN) lesions.[66,68,70] Although HPV-16 and -18 cause a large proportion of VIN and VAIN, the HPV-2 clinical trials did not include these as measured outcomes.[71]

HPV-Related Penile, Anal, and Oropharyngeal Cancers

Anal Cancer—Approximately 90% of anal cancers are associated with HPV and of those HPV-associated cancers, 90% are due to HPV-16 and -18.[77] Rates of anal cancers are highest in HIV-infected men who have sex with men (MSM).[78,79] Anal HPV infections are also common in adolescent and adult women with rates ranging from 13% to 50%.[80,81] Overall statistics for anal cancers demonstrate that women actually have higher rates than men.[82] In addition, the incidence of anal cancer is rising in both men and women[83] with the annual average incidence of anal cancer in women being 1935 while in men it is 1083. The higher incidence of anal cancer in women than men seems counterintuitive, but may be due to anal intercourse occurring more commonly than realized in heterosexual women and that the majority of men engage in heterosexual practices. As in men, the highest rates of anal HPV in women are found in those who are HIV infected.[79] A study of HIV-infected adolescent girls found that almost 60% had anal HPV infections.[81] Risks for anal cancer in women include a history of cervical, vaginal, and vulvar cancer and CIN3.[84–86] The association of anal cancer with HIV and other HPV-associated cancers underscore the importance of the immune response (or lack thereof) in controlling HPV infection.

Penile Cancer—As found in the vulvar cancers, HPV is associated with specific histologic types of penile cancers. Almost 100% of basaloid and warty penile cancers are associated with high risk HPV types (ie, HPV types associated with cancer), whereas only 30–40% of keratinizing squamous cell cancers are associated with HPV.[87]

Oropharyngeal Cancer—HPV is also associated with oropharyngeal cancers in both men and women.[88] Overall, ~25% of head and neck cancers are linked to HPV. The tonsil and the base of the tongue appear the most vulnerable with ~50% being associated with

HPV. The sexual behaviors related to an increased risk of these cancers include multiple sexual partners, reporting oral sex, and for men, having sex with other men.[89] HPV DNA detection of the oropharynx is much lower than anogenital infections in both men and women. Most studies have published rates of oral HPV around 4–5%.[90] These figures are likely underestimations since most studies sampled the buccal mucosa or tongue, whereas HPV likely sits deep in tonsillar crypts or at the base of the tongue. Currently, there are no screening recommendations for oropharyngeal cancers.

Epidemiology and Natural History of Anogenital HPV in Males

As in the cervix, HPV is frequently found in samples obtained from the anus and male genital area. With better sampling techniques and extremely sensitive DNA detection kits, rates of HPV in the male anogenital area are similar to women. Approximately 20% of men (range 1.3–72.9%) will have HPV DNA detected in the anogenital area.[91] However, in MSM, the rates of anal HPV are much higher, with a prevalence of more than 90% being reported.[92,93] Like women, risks for HPV in the anogenital area in men is associated with a greater number of lifetime sexual partners.[92,94] However, unlike women, young men are as likely as older men to be HPV positive.[87,92] This is true whether the men are heterosexual or MSM.

Natural history studies of HPV in men show that HPV clears faster in heterosexual men than in women. One study found that over a 1-year period, 94% of men cleared penile/scrotal HPV compared with a clearance rate of only 80% in women with anogenital infection.[95] HPV infections of the anus in both men and women also appear to clear faster than cervical infections in women.[92,96] On the other hand, similar to cervical infection in HIV-infected women, HIV-infected men and women are unlikely to clear their anal infections.[81,93]

Few studies have examined the rate of intraepithelial lesions in men. Most importantly, there are no natural history studies of intraepithelial lesions in males demonstrating that they result in cancer. However, in studies examining HPV in penile (PIN) or anal (AIN) intraepithelial neoplastic lesions (which are histologically equivalent to CIN), HPV is found in a similar proportions as CIN.[97] About 80–90% of AIN and PIN are associated with high-risk HPV.

Screening for Anal and Penile Cancer

Since no study has proven that intraepithelial neoplastic (IN) lesions in males progress to invasive cancer, screening for IN in males remains controversial. Because penile cancers in the United States are rare, there are no screening recommendations. In contrast, the rate of anal cancer in HIV-infected MSM is estimated to be equal to that of cervical cancer before cytology screening was initiated in the United States.[92] Studies have shown that it is cost-effective to screen MSM.[98] If abnormal, high-resolution anoscopy by a trained provider is recommended. Treatment is recommended if AIN is found on histology.[92] Although anal cancers are also more prevalent in HIV-infected women, HIV-uninfected MSM, and in women with cervical cancer, there are no screening recommendations for these groups. Clearly, studies are needed to better assess the utility of screening in groups other than HIV-infected MSM.[99]

HPV Vaccine in Males

Clearly, if anogenital and oropharyngeal cancers can be prevented with HPV vaccination, there is a direct benefit to men in HPV vaccination. As noted, most of the HPV-associated anogenital and oropharyngeal cancers are HPV 16/18 associated and as in women nearly all external genital warts are associated with HPV 6/11. Recent data were released on the quadrivalent HPV vaccine trial in men. The trial examined 3463 men aged 16 –23 years.

Men were excluded if they had a history of external genital warts, genital lesions thought to be associated with HPV, and >5 lifetime sexual partners. The data showed similar results as seen in the women with an efficacy rate of 89% in preventing external genital warts in the per protocol group (received all 3 vaccines and were naïve to HPV 6, 11, 16, and 18 at baseline). In the full cohort who received at least one vaccination and included all subjects regardless of baseline HPV status, the efficacy was 67%. The FDA approved the quadrivalent vaccine in men based on this data and ACIP gave permissive recommendations for boys aged 11–12 years with a recommendation for catchup of males 13–26 years of age. There was also a substudy within the men's trial examining young MSM. The study enrolled 602 MSM aged 16–26 years of age and found an efficacy rate of 77.5% in preventing HPV 6/11/16/18 AIN in the per protocol group.

CONCLUSIONS

HPV is extremely common in adolescents and likely related to numerous factors including sexual behavior, immunologic, and biological vulnerability. In addition to cervical cancer in women, HPV in both men and women has been associated with other anogenital cancers and cancers in nongenital areas, specifically the oropharynx. The data now show that the majority of adolescents will clear HPV including HPV-associated lesions such as CIN1 and CIN2 and that progression to cancer is extremely rare. Most disappointingly, the current cervical cancer screening technique of cytology does not appear to prevent the few cases of invasive cervical cancer that occurs in these young women. These data support the postponement of cervical cancer screening until 21 years of age. In those adolescents diagnosed with HPV-associated diseases, observation is preferred. Prevention of cervical cancer and genital warts in adolescents should focus on the successful administration of the HPV vaccine. The data clearly show that the group most likely to benefit are persons that have not experienced sexual intercourse. There is also benefit on a personal level for those who have initiated sexual intercourse but the benefit declines quickly with age and number of sexual partners.

REFERENCES

1. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. Clin Sci (Lond) 2006;110(5):525–541. [PubMed: 16597322]
2. Durst M, Kleinheinz A, Hotz M, Gissman L. The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumours. J Gen Virol 1985;66(7):1515–1522. [PubMed: 2991428]
3. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287(16):2114–2119. [PubMed: 11966386]
4. Stanley M. Immune responses to human papillomavirus. Vaccine 2006;24(Suppl 1):S16–S22. [PubMed: 16219398]
5. Woodworth CD. HPV Innate Immunity. Front Biosci 2002;7(7):d2058–d2071. [PubMed: 12165480]
6. Farhat S, Nakagawa M, Moscicki AB. Cell-mediated immune responses to human papillomavirus 16 E6 and E7 antigens as measured by interferon gamma enzyme-linked immunospot in women with cleared or persistent human papillomavirus infection. Int J Gynecol Cancer 2009;19(4):508–512. [PubMed: 19509544]
7. Molling JW, de Gruijl TD, Glim J, et al. CD4(+)CD25hi regulatory T-cell frequency correlates with persistence of human papillomavirus type 16 and T helper cell responses in patients with cervical intraepithelial neoplasia. Int J Cancer 2007;121(8):1749–1755. [PubMed: 17582606]
8. Frazer IH. Interaction of human papillomaviruses with the host immune system: a well evolved relationship. Virology 2009;384(2):410–414. [PubMed: 18986661]

9. Moscicki AB, Ellenberg JH, Vermund SH, et al. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: impact of infection with human immunodeficiency virus. Arch Ped Adolesc Med 2000;154:127–134.
10. Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA 2001;285(23): 2995–3002. [PubMed: 11410098]
11. Moscicki AB, Palefsky J, Gonzales J, Schoolnik G. Human papillomavirus infection in sexually active adolescent females: Prevalence and risk factors. Pediatr Res 1990;28:507–513. [PubMed: 2175024]
12. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol 2003;157(3):218–226. [PubMed: 12543621]
13. Brown DR, Shew ML, Qadadri B, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. J Infect Dis 2005;191(2):182–192. [PubMed: 15609227]
14. Munoz N, Mendez F, Posso H, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. J Infect Dis 2004;190(12):2077–2087. [PubMed: 15551205]
15. Evander M, Edlund K, Gustaffson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. J Infect Dis 1995;171:1026–1030. [PubMed: 7706782]
16. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338(7):423–428. [PubMed: 9459645]
17. Moscicki AB, Ellenberg JH, Fahrat S, Xu J. HPV persistence in HIV infected and uninfected adolescent girls: risk factors and differences by phylogenetic types. J Infect Dis 2004;190(1):37–45. [PubMed: 15195241]
18. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr 1998;132:277–284. [PubMed: 9506641]
19. Mount SL, Papillo JL. A Study of 10,296 pediatric and adolescent Papanicolaou smear diagnoses in northern New England. Pediatrics 1999;103(3):539–546. [PubMed: 10049953]
20. Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2001;357(9271):1831–1836. [PubMed: 11410191]
21. International Collaboration. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007;120(4):885–891. [PubMed: 17131323]
22. Appleby P, Beral V, Berrington de Gonzalez A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet 2007;370(9599):1609–1621. [PubMed: 17993361]
23. Modiano JF, Kokai Y, Weiner DB, Pykett MJ, Nowell PC, Lyttle CR. Progesterone augments proliferation induced by epidermal growth factor in a feline mammary adenocarcinoma cell line. J Cell Biochem 1991;45(2):196–206. [PubMed: 2055947]
24. Ruutu M, Wahlroos N, Syrjanen K, Johansson B, Syrjanen S. Effects of 17beta-estradiol and progesterone on transcription of human papillomavirus 16 E6/E7 oncogenes in CaSki and SiHa cell lines. Int J Gynecol Cancer 2006;16(3):1261–1268. [PubMed: 16803515]
25. Burchell A, Winer R, de Sanjose S, Franco E. Epidemiolgy and transmission dynamics of genital human papillomavirus infection. Vaccine Monographs 2006;24(Suppl 3):52–62.
26. De Sanjose, S. La investigacion sobre la infeccion por virus del papiloma human y el cancer de cuello uterino en Espana.. In: de Sanjose, S.; Garcia, A., editors. El Virus del papiloma human y cancer: Epidemiologia y Prevencion. EMISA; Madrid: 2006.

27. Franceschi S, Herrero R, Clifford GM, et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. Int J Cancer 2006;119(11):2677–2684. [PubMed: 16991121]
28. Olsson SE, Villa LL, Costa RL, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine 2007;25(26):4931–4939. [PubMed: 17499406]
29. Olsson SE, Kjaer SK, Sigurdsson K, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin 2009;5(10)
30. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374(9686):301–314. [PubMed: 19586656]
31. Green J, Berrington de Gonzalez A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20–44 years: the UK National Case-Control Study of Cervical Cancer. Br J Cancer 2003;89(11):2078–2086. [PubMed: 14647141]
32. Herrero R, Brinton LA, Reeves WC, et al. Sexual behavior, venereal diseases, hygiene practices, and invasive cervical cancer in a high-risk population. Cancer 1990;65(2):380–386. [PubMed: 2295062]
33. Sierra-Torres CH, Tyring SK, Au WW. Risk contribution of sexual behavior and cigarette smoking to cervical neoplasia. Int J Gynecol Cancer 2003;13(5):617–625. [PubMed: 14675345]
34. Cervical carcinoma and sexual behavior: collaborative reanalysis of individual data on 15,461 women with cervical carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies. Cancer Epidemiol Biomarkers Prev 2009;18(4):1060–1069. [PubMed: 19336546]
35. Moscicki, AB.; Singer, A. The cervical epithelium during puberty and adolescence.. In: Jordan, JA.; Singer, A., editors. The Cervix. 2nd ed.. Blackwell; Malden: 2006. p. 81-101.
36. Castle PE, Jeronimo J, Schiffman M, et al. Age-related changes of the cervix influence human papillomavirus type distribution. Cancer Res 2006;66(2):1218–1224. [PubMed: 16424061]
37. Moscicki AB, Grubbs-Burt V, Kanowitz S, Darragh T, Shiboski S. The significance of squamous metaplasia in the development of low grade squamous intra-epithelial lesions in young women. Cancer 1999;85:1139–1144. [PubMed: 10091799]
38. Hwang LY, Ma Y, Benningfield SM, et al. Factors that influence the rate of epithelial maturation in the cervix in healthy young women. J Adolesc Health 2009;44(2):103–110. [PubMed: 19167657]
39. Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008;113(10 Suppl):2841–2854. [PubMed: 18980203]
40. Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. Obstet Gynecol 2003;102(4):765–773. [PubMed: 14551007]
41. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ 2009;339:b2968. [PubMed: 19638651]
42. Gustafsson L, Ponten J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes Control 1997;8(5):755–763. [PubMed: 9328198]
43. Barnholtz-Sloan J, Patel N, Rollison D, Kortepeter K, Mackinnon J, Giuliano A. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. Cancer Causes Control 2009;20(7):1129–1138. [PubMed: 19253025]
44. Plummer M, Schiffman M, Castle PE, Maucort-Boulch D, Wheeler CM. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. J Infect Dis 2007;195(11):1582–1589. [PubMed: 17471427]

45. Heatley MK. How should we grade CIN? Histopathology 2002;40(4):377–390. [PubMed: 11943024]
46. Moore K, Cofer A, Elliot L, Lanneau G, Walker J, Gold MA. Adolescent cervical dysplasia: histologic evaluation, treatment, and outcomes. Am J Obstet Gynecol 2007;197(2):e141–e146.
47. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol 2009;113(1):18–25. [PubMed: 19104355]
48. Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsydiagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. Am J Clin Pathol 2007;127(5):805–815. [PubMed: 17439841]
49. Moscicki AB, Ma Y, Wibbelsman C, et al. Risks for cervical intraepithelial neoplasia 3 among adolescents and young women with abnormal cytology. Obstet Gynecol 2008;112(6):1335–1342. [PubMed: 19037044]
50. Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis 2005;191(5):731–738. [PubMed: 15688287]
51. Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. J Low Genit Tract Dis 2010;14(1):73–80. [PubMed: 20043357]
52. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002;52(6):342–362. [PubMed: 12469763]
53. American College of Obstetricians and Gynecologists. ACOG Guidelines for Women's Health Care. The American College of Obstetricians and Gynecologists; Washington, DC:
54. American Society for Colposcopy and Cervical Pathology. [June 26, 2010]. Available at: www.asccp.org.
55. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006;367(9509):489–498. [PubMed: 16473126]
56. Norman JE. Preterm labour. Cervical function and prematurity. Best Pract Res Clin Obstet Gynaecol 2007;21(5):791–806. [PubMed: 17490914]
57. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004;291:2100–2106. [PubMed: 15126438]
58. Samson S-L, Bentley JR, Fahey TJ, McKay DJ, Gil GH. The effect of loop electrosurgical excision. Obstet Gynecol 2005;105:325–332. [PubMed: 15684160]
59. Coeshott CM, Smithson SL, Verderber E, et al. Pluronic F127-based systemic vaccine delivery systems. Vaccine 2004;22(19):2396–2405. [PubMed: 15193401]
60. Pinto LA, Castle PE, Roden RB, et al. HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood. Vaccine 2005;23(27):3555–3564. [PubMed: 15855014]
61. Pinto LA, Edwards J, Castle PE, et al. Cellular immune responses to human papillomavirus (HPV)-16 L1 in healthy volunteers immunized with recombinant HPV-16 L1 virus-like particles. J Infect Dis 2003;188(2):327–338. [PubMed: 12854090]
62. Schreckenberger C, Kaufmann AM. Vaccination strategies for the treatment and prevention of cervical cancer. Curr Opin Oncol 2004;16(5):485–491. [PubMed: 15314520]
63. Schiller JT, Nardelli-Haefliger D. Chapter 17: Second generation HPV vaccines to prevent cervical cancer. Vaccine 2006;24(Suppl 3):S147–S153.
64. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347(21):1645–1651. [PubMed: 12444178]
65. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107(1):18–27. [PubMed: 16394035]
66. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6(5):271–278. [PubMed: 15863374]

67. Emeny RT, Wheeler CM, Jansen KU, et al. Priming of human papillomavirus type 11-specific humoral and cellular immune responses in college-aged women with a virus-like particle vaccine. J Virol 2002;76(15):7832–7842. [PubMed: 12097595]
68. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356(19):1928–1943. [PubMed: 17494926]
69. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356(19):1915–1927. [PubMed: 17494925]
70. Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila Pa) 2009;2(10):868–878.
71. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369(9580):2161–2170. [PubMed: 17602732]
72. Fraser C, Tomassini JE, Xi L, et al. Modeling the long-term antibody response of a human papillomavirus (HPV) virus-like particle (VLP) type 16 prophylactic vaccine. Vaccine 2007;25(21):4324–4333. [PubMed: 17445955]
73. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15–44 years of age, United States, 2002. Adv Data 2005;362:1–55. [PubMed: 16250464]
74. Markowitz LE, Sternberg M, Dunne EF, McQuillan G, Unger ER. Seroprevalence of human papillomavirus types 6, 11, 16, and 18 in the United States: National Health and Nutrition Examination Survey 2003–2004. J Infect Dis 2009;200(7):1059–1067. [PubMed: 19719390]
75. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57(1):7–28. [PubMed: 17237032]
76. Dempsey AF, Gebremariam A, Koutsky LA, Manhart L. Using risk factors to predict human papillomavirus infection: implications for targeted vaccination strategies in young adult women. Vaccine 2008;26(8):1111–1117. [PubMed: 18242793]
77. Daling JR, Sherman KJ. Relationship between human papillomavirus infection and tumours of anogenital sites other than the cervix. IARC Sci Publ 1992;(119):223–241. [PubMed: 1330912]
78. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000;92(18):1500–1510. [PubMed: 10995805]
79. Palefsky JM, Gillison ML, Strickler HD. Chapter 16: HPV vaccines in immunocompromised women and men. Vaccine 2006;24(Suppl 3):S140–S146.
80. Goodman MT, Shvetsov YB, McDuffie K, et al. Acquisition of anal human papillomavirus (HPV) infection in women: the Hawaii HPV Cohort study. J Infect Dis 2008;197(7):957–966. [PubMed: 18429348]
81. Moscicki AB, Durako SJ, Houser J, et al. Human papillomavirus infection and abnormal cytology of the anus in HIV-infected and uninfected adolescents. AIDS 2003;17(3):311–320. [PubMed: 12556684]
82. American Cancer Society. Cancer facts and figures, 2008. American Cancer Society; Atlanta, GA: 2008.
83. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis 2006;6(1):21–31. [PubMed: 16377531]
84. Melbye M, Smith E, Wohlfahrt J, et al. Anal and cervical abnormality in women–prediction by human papillomavirus. Int J Cancer 1996;68:559–564. [PubMed: 8938134]
85. Ogunbiyi OA, Scholefield JH, Robertson G, Smith JH, Sharp F, Rogers K. Anal human papillomavirus infection and squamous neoplasia in patients with invasive vulvar cancer. Obstet Gynecol 1994;83(2):212–216. [PubMed: 8290182]
86. Park IU, Ogilvie JW Jr, Anderson KE, et al. Anal human papillomavirus infection and abnormal anal cytology in women with genital neoplasia. Gynecol Oncol 2009;114(3):399–403. [PubMed: 19501896]

87. Giuliano AR, Tortolero-Luna G, Ferrer E, et al. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine 2008;26(Suppl 10):K17–K28. [PubMed: 18847554]

88. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14(2):467–475. [PubMed: 15734974]

89. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2010;39(1):166–181. [PubMed: 20022926]

90. Kreimer AR, Bhatia RK, Messeguer AL, Gonzalez P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis 2010;37(6):386–391. [PubMed: 20081557]

91. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: A systematic review of the literature. J Infect Dis 2006;194(8):1044–1057. [PubMed: 16991079]

92. Palefsky JM, Rubin M. The epidemiology of anal human papillomavirus and related neoplasia. Obstet Gynecol Clin North Am 2009;36(1):187–200. [PubMed: 19344856]

93. de Pokomandy A, Rouleau D, Ghattas G, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis 2009;199(7):965–973. [PubMed: 19239366]

94. Nyitray A, Nielson CM, Harris RB, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. J Infect Dis 2008;197(12):1676–1684. [PubMed: 18426367]

95. van Doornum GJ, Prins M, Juffermans LH, et al. Regional distribution and incidence of human papillomavirus infections among heterosexual men and women with multiple sexual partners: a prospective study. Genitourinary Med 1994;70(4):240–246.

96. Shvetsov YB, Hernandez BY, McDuffie K, et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: the Hawaii HPV cohort study. Clin Infect Dis 2009;48(5):536–546. [PubMed: 19191636]

97. Aynaud O, Ionesco M, Barrasso R. Penile intraepithelial neoplasia. Specific clinical features correlate with histologic and virologic findings. Cancer 1994;74(6):1762–1767. [PubMed: 8082079]

98. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. Am J Med 2000;108(8):634–641. [PubMed: 10856411]

99. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. Clin Infect Dis 2006;43(2):223–233. [PubMed: 16779751]

Table 1

Vaccine efficacy of gardasil against high-grade cervical disease and genital lesions

	Vaccine		Placebo		Observed Efficacy, % (95% CI)
	n	Cases	n	Cases	
Per Protocol[a]					
CIN 2 or worse[b]	7864	2	7865	110	98.2 (93.3–99.8)
VIN/VaIN 2/3 or worse[b]	7900	0	7902	23	100.0 (82.6–100.0)
Condyloma[c]	2261	0	2279	48	100.0 (92.0–100.0)
Intention to treat[d]					
CIN 2 or worse[b]	8823	142	8860	293	51.5 (40.6–60.6)
VIN/VaIN 2/3 or worse[b]	8956	9	8969	43	79.0 (56.4–91.0)
Condyloma[c]	2723	21	2732	86	76.0 (61.0–86.0)

[a] Per protocol must have met all inclusion criteria, naïve to HPV vaccine types, completed 3 doses on schedule and starting counting cases after month 7.

[b] Pooled analysis from 3 clinical trials.[70]

[c] Data from Future I only.[68]

[d] Intention-to-treat group included women who received at least one dose of the vaccine and could have been HPV infected or had disease at enrollment or day 1, respectively.

Adolesc Med State Art Rev. Author manuscript; available in PMC 2011 March 15.

Table 2

Vaccine efficacy of cervarix against HPV 16/18-associated high-grade cervical disease

	Vaccine		Placebo		Observed Efficacy, % (96.1% CI)
	n	Cases	n	Cases	
Per Protocol[a]					
CIN 2 or worse	7344	4	7312	56	92.9 (79.9–98.3)
CIN 2 or worse, corrected for lesion HPV type[b]	7344	1	7312	53	98.1 (88.4–100.0)
Intention to treat[c]					
CIN 2 or worse	8667	82	8682	174	52.8 (37.–64.7)

[a] Per protocol must have met all inclusion criteria naïve to HPV vaccine types completed 3 doses and started counting case day after third vaccination.

[b] HPV 16/18 in lesion and in preceding sample if multiple types found in lesion.

[c] Referred to as total vaccinated cohort.[30] Included women who were given at least one does, case counting occurred day after first vaccination and included women regardless of serostatus or DNA status at visit 0.