ELSEVIER

Journal of Adolescent Health 37 (2005) S3–S9

JOURNAL OF ADOLESCENT HEALTH

Review article

Impact of HPV infection in adolescent populations

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Manuscript received July 19, 2005; manuscript accepted September 20, 2005

Abstract: Human papillomavirus (HPV) is a significant source of morbidity and mortality worldwide. The primary risk factors for acquiring HPV are generally associated with sexual activity. Evidence suggests that condoms provide some protection against infection and disease progression, but any genital contact is sufficient for HPV transmission. HPV is so common and transmissible that having just one sexual partner often results in infection. Indeed, cumulative prevalence rates are as high as 82% among adolescent women in select populations. As such, nearly all sexually active adolescents are at high risk for acquiring HPV. Persistent infection with high-risk HPV types (e.g., HPV 16 or 18) is considered necessary for the development of cervical cancer, whereas infection with low-risk HPV types (e.g., HPV 6 or 11) is associated with the development of genital warts and other low-grade genital abnormalities. Most infections are asymptomatic and are efficiently cleared by the immune system. Similarly, both low- and high-grade lesions caused by HPV can regress in adolescent and young adult women. Treatment guidelines allow for observation of adolescent women who develop low-grade lesions rather than immediate colposcopy. Nonetheless, a small percentage of adolescents will develop precancerous lesions that may progress to invasive cervical cancer. Adolescents should be given appropriate education about HPV and the dangers associated with infection; they should also be encouraged to obtain appropriate gynecological care after initiating sexual activity. This article discusses HPV infection and the causal role that HPV plays in the development of low- and high-grade genital lesions, cervical cancer, and genital warts.

Keywords: Human papillomavirus

Epidemiology of HPV

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States. It is estimated that 20 million Americans are currently infected with HPV, and more than 5.5 million new cases are diagnosed annually [1]. Moreover, epidemiologic studies suggest that 75% of all sexually active people will become infected with HPV at some point during their lifetimes [2]. Nearly all sexually active men and women are at risk for acquiring HPV and subject to developing HPV-associated disease.

STIs in adolescents are a significant health care concern. Although 15- to 24-year-old adolescents represent only 25% of the sexually active population, nearly 50% of all reported STIs occur in this age group [3]. Rates of HPV are highest in adolescent populations with cumulative prevalence rates as high as 82% in selected groups [4]. A study of adolescents who were initially HPV negative found that 55% acquired HPV within three years (Figure 1) [5]. In a study of college-enrolled women who were HPV negative, and reported never having sexual intercourse at enrollment, approximately 30% acquired HPV within 12 months after initiating intercourse and more than 50% became HPV positive within four years (Figure 2) [6]. These numbers underscore the ease of sexual transmission of HPV in adolescent and young adult women and highlight the importance of targeting vaccination campaigns towards presexually active children and adolescents.

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1054-139X/05/$ – see front matter
doi:10.1016/j.jadohealth.2005.09.011

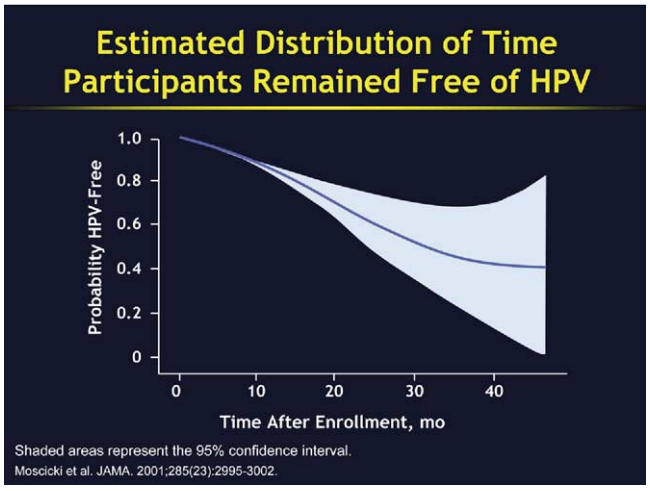

Fig. 1. Estimated distribution of time participants remained free of HPV. Adapted from [5].

Prevalence rates for HPV infections in males are less well defined, often due to the difficulty of obtaining adequate samples for HPV DNA testing [2]. Broad estimates of HPV infection in men range from 16% to 45%, which are similar to those found in women [7]. As in women, the majority of HPV infections in men are asymptomatic; however, men remain at risk for developing HPV-associated diseases such as genital warts and invasive penile or anal cancer [8].

Transmission

HPV is transmitted by skin-to-skin contact. For fulminant infection, HPV requires access to basal cells through micro abrasions or tears in the squamous or mucosal epithelium that are often produced during sexual activity [8]. Infection of the cervix is generally thought to require sexual intercourse, but HPV can infect other anogenital sites such as the external genitalia. Additionally, HPV can be transmitted through skin-to-skin contact during non-intercourse foreplay [6], and may even be transmissible by fingers or sex toys. HPV infection has been detected in women who have reported never having sexual intercourse with men [9], which supports the existence of these alternative modes of transmission. As such, adolescents who abstain from sexual intercourse but not other forms of sexual behavior remain at risk for acquiring HPV, and adolescents who use condoms may still acquire HPV infection at epithelial sites outside of the area covered by a condom [6].

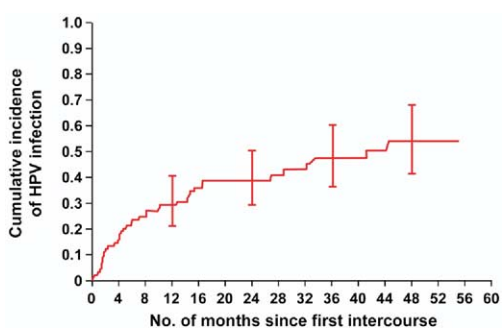

Fig. 2. Cumulative incidence of human papillomavirus (HPV) infection from time of first sexual intercourse. Adapted from [6].

In rare instances, HPV can be transmitted from a mother to her newborn baby during vaginal delivery resulting in recurrent respiratory papillomatosis (RRP), which can be fatal. Moreover, unexplained and extremely rare cases have been reported in newborns delivered by cesarean section [10]; however, the rarity of neonatal transmission does not justify performing a cesarean section delivery for women with genital warts or abnormal cytology.

Risk factors for acquiring HPV

Long-term epidemiologic studies have supported the link between sexual activity and acquisition of HPV infection. Indeed, the greater number of sexual partners, the greater the risk of having acquired HPV infection; however, having sex with only one partner is also associated with HPV infection. In a study of women visiting a university health service, more than 20% of women with one lifetime male sexual partner were infected with HPV, and women reporting 10 or more lifetime sexual partners had an HPV prevalence rate of 69% [11]. A longitudinal study of HPV in adolescent and young adult women subsequently showed that having a new sexual partner resulted in a 10-fold increased risk for acquiring HPV [5]. Other risk factors for HPV include a history of vulvar warts or infection with herpes simplex virus (HSV) [5]. This is not surprising because HSV causes inflammation and breaks of the epithelial barrier, allowing HPV direct access to basal epithelial cells.

Age also appears to be an important factor, as HPV infection is consistently most common in sexually active women younger than 25 years old [2]. Although the overall association with age may be due to riskier sexual behavior (i.e., more sexual partners, non-condom use), there is also evidence that adolescent and young adult women are more vulnerable to HPV infection than adults for biological reasons. The predominant cell type in an adult is squamous, whereas in an adolescent it is columnar and metaplastic. During development, neonates are usually born with abrupt squamo-columnar junctions present on the ectocervix. Once puberty occurs, columnar epithelium gradually transforms into squamous epithelium. During this process, termed squamous metaplasia, large areas of transitional squamous, glandular, and metaplastic cells are formed, all of which support HPV replication [12]. Not only do these rapidly proliferating cells support HPV replication, they are subject to developing virus-induced genetic alterations in the metaplastic squamous epithelium, which, if infection persists,

can lead to high-grade squamous intraepithelial lesions (HSIL). Early sexual activity may hasten this process of cervical maturation, as adolescents with multiple partners appear to have more mature cervices than non-sexually active adolescents.

Risk factors for developing HPV-associated disease

Although acquisition of HPV is generally related to sexual activity, clearance of HPV, and disease regression or progression, is primarily determined by the host immune response [13,14]. The most important factor for developing cervical cancer is persistent infection with high-risk HPV types. Moreover, adolescents with impaired cellular immunities often have higher HPV-associated disease incidence rates, and take longer to clear HPV infections [2,15,16]. Other risk factors for invasive cervical cancer include cigarette smoking, alcohol consumption, having an uncircumcised male partner, high parity (more than three pregnancies), prolonged oral contraceptive use, and infection with HSV or *C. trachomatis* [7,8,17–19].

Interestingly, several studies have now underscored the importance of condoms in preventing persistent infection. Based on a meta-analysis of 20 studies, the risk of developing HPV-related sequelae was reduced by condom use [20]. Although the molecular mechanisms by which condoms prevent HPV-associated disease are unknown, it has been hypothesized that using condoms may decrease the amount of virus transmitted. In turn, by reducing the infectious viral load, condoms may decrease the probability of developing an HPV-related lesion or assist in regression of the infection [21]. Thus, although condoms do not prevent all infections, their use remains an important means for preventing persistent infection and enhancing HPV-associated disease regression.

Clinical manifestations of HPV infection

It is well appreciated that HPV is the cause of genital warts as well as precancerous and cancerous lesions of the cervix. Although not discussed here, HPV is also responsible for a significant portion of vulvar, vaginal, penile, and anal cancers and has been associated with other malignancies such as skin and pharyngeal cancer [22]. Nearly 40 types of HPV are known to infect the genital mucosa, and are classified according to their oncogenic potential [22,23]. Low-risk types cause benign lesions, including genital warts and low-grade genital abnormalities, but are not found in genital cancers, hence the reference to "low-risk." High-risk types cause both low- and high-grade precancerous lesions; however, the term "high-risk" is given because they reflect those types seen in invasive cancers [23].

Incubation periods for developing clinical symptoms following HPV infection are highly variable. Genital warts may appear within months of infection, whereas development of cervical cancer takes up to decades. Nonetheless, most HPV infections are asymptomatic and are detected only when HPV DNA testing has been performed [24]. In healthy individuals, more than 75% of incident infections are cleared within 30 months of infection [24]. This is especially true of low-risk types, which are less likely to persist [8].

Cervical dysplasia and cervical cancer

Cervical cancer is the second most common cancer in women worldwide, with more than 500,000 new cases diagnosed each year [25]. In the United States, the American Cancer Society estimates that more than 10,000 new cases of invasive cervical cancer will be diagnosed in 2005. Because HPV has been identified in 99.7% of all cervical cancers, persistent infection with high-risk HPV types, such as HPV 16, 18, 31, 33, and 45 is considered a necessary step for the development of cervical cancer [26,27].

Viral proteins expressed during active infection induce pathologic changes including basal cell proliferation, nuclear enlargement, koilocytosis, and abnormal mitotic figures [28]. Each of these changes is a defining feature of squamous intraepithelial lesions (SIL). As such, the development of both low-grade squamous intraepithelial lesions (LSIL) and HSIL can be considered the pathologic consequences of HPV infection. As with acute HPV infections, the majority of LSILs and some HSILs will regress spontaneously. For example, LSILs will regress in 92% to 94% of adolescents and young women [29]. In addition, a high proportion of HSILs will also regress in young women, but the actual rates are unknown because adolescents are generally excluded from comprehensive natural history studies.

Because the majority of LSILs will spontaneously regress in adolescent women, updated treatment guidelines allow for observation of LSIL through repeated cytology or HPV DNA testing instead of immediate colposcopy [30]. These guidelines are important because diagnosis of these lesions, specifically LSILs, have been shown to be associated with increased psychological distress, partially induced by health care providers [31]. Furthermore, increased anxiety following an LSIL or HSIL diagnosis can interfere with adequate treatment and follow-up care [32].

Treatments for HPV-associated disease are both costly and time consuming and significantly affect quality of life. Diagnoses of LSIL and HSIL have been estimated to cost $1275 and $2349, respectively [33]. Moreover, treatment durations for LSIL and HSIL are lengthy, averaging 7.2 physician visits during a 20-month period. Treatment of invasive cervical cancer carries the largest financial burden with an estimated cost of $33,000 per person per year [34].

Condylomata acuminata

A more immediate concern for adolescents and young adults is the development of condylomata acuminata, or

genital warts. Genital warts are proliferative exophytic cauliflower-like growths that manifest on internal and external genital areas, including the penis, vulva, vagina, cervix, perineum, and perianal and intra-anal areas. Approximately 1% of the sexually active U.S. population has genital warts, with .5 to 1.0 million new cases diagnosed annually [35,36]. In one study, it was shown that approximately 264,000 office visits occur annually in the U.S. to treat genital warts, and the rate of new health insurance claims for genital wart treatments peaks for adolescent and young adult age groups [35,37]. This trend is consistent with other STIs, such as *C. trachomatis* and *N. gonorrhea*, where incidence rates also peak in younger populations.

Low-risk HPV types 6 or 11 are responsible for 97% of genital wart manifestations [38]. Although genital warts are typically benign and pose no risk of malignant progression, psychosocial issues are a significant source of morbidity in men and women [39]. Patients report being embarrassed after diagnosis with genital warts and experience high levels of anxiety regarding warts and the treatments associated with removal [40,41].

Genital warts are usually clinically benign. Therefore, the need for treatment is based on patient needs and preferences but is not required to prevent lesion progression or to avoid malignancies. Nonetheless, many patients with genital warts do seek treatment. Treatments are often painful, require multiple visits, and can become economically burdensome. A typical office-based treatment costs $436, with an average of 3.1 visits [38]. Self-applied therapies are less expensive; however, treatment can take up to three months and younger adolescents usually prefer provider-applied therapies. Unfortunately, recurrences are common across all treatment modalities [38,42].

Cervical cancer progression

Although more than 90% of HPV infections are spontaneously cleared by the immune system, some infections will cause LSIL, HSIL, or progress to cervical cancer (Figure 3) [8,15]. Although HPV infection is necessary for the development of LSIL, infection is not thought to be sufficient for developing low-grade lesions [5,43]. In a longitudinal study of adolescents and young women, only 25% of young women with HPV developed LSIL within 36 months of initial HPV infection. Moreover, as mentioned earlier, LSIL is often transient in young women and the majority of cases regress within three years, with only 3% progressing to more advanced precancerous lesions [29]. It should be noted that these numbers are quite different than those reported for older adult women, in whom 20% to 30% of LSILs are thought to progress to HSILs and only 60% regress. Type of HPV does not explain these differences because high-risk HPV types are the most common infections in asymptomatic women as well as in women with LSIL [5,13,24].

Unlike LSIL, which can occur shortly after HPV infection, the development of HSIL requires persistent HPV infection [24,27]. The diagnosis of HSIL, however, is widely variable, and the reproducibility of an HSIL diagnosis is less than 60% to 70%. Moreover, pathological descriptions of HSIL remain rather subjective and problematic, making natural history estimates difficult. Given these caveats, less than 40% of HSILs will regress and HSIL is thought to be an important pre-cancer. Thus, when HSIL is diagnosed, treatment is recommended. Current strategies for controlling HSIL, however, most likely result in over-treatment as less than 1.5% of patients with HSIL will progress to cervical cancer within two years [43].

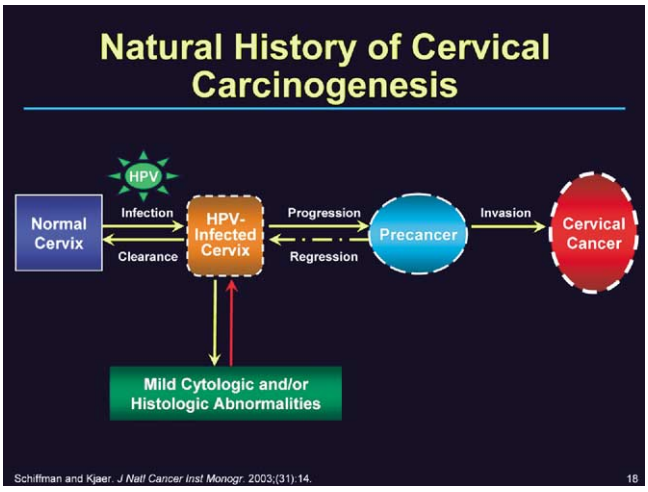

Fig. 3. Progression of HPV infection to cervical cancer. Adapted from [8].

Of the high-risk types, HPV 16 appears the most likely to persist and is responsible for 40% to 60% of invasive cancers worldwide [23,44]. Infection with multiple types of HPV is also predictive of persistence, and young women who test positive for two or more HPV types are 86% less likely to regress from LSIL to normal [15,43]. Overall, the incubation period from initial HPV infection to carcinoma in situ is estimated to be 7 to 12 years [44]. Therefore, routine cervical cancer screening can detect the majority of pre-invasive lesions before progression to cancer.

Screening and treatment guidelines for adolescents and young women

The American Cancer Society (2003) recommends that women begin cervical screening within three years after the start of sexual intercourse, or at 21 years old, whichever comes first [45]. Screening should take place yearly with traditional cytology (Papanicolaou [Pap] test). After three consecutive normal Pap smears, screening frequency can be reduced with continued screening every two years with liquid-based cytology. At age 30,

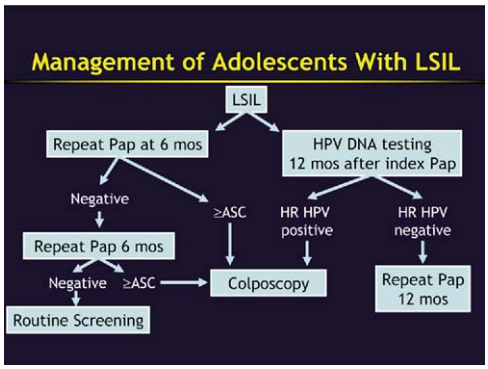

Fig. 4. ASCCP guidelines for the management of LSIL in adolescents. Adapted from [30].

women may reduce cytologies to every two to three years, provided they do not have other risk factors (e.g., immunosuppression), or have a history of abnormal Pap tests. HPV DNA screening is currently available for primary screening in women aged 30 and older. The clinical utility of this test is limited in adolescent populations because many women in this age group will test positive for HPV. Atypical squamous cells of undetermined significance triage with high-risk HPV detection is recommended for all ages; however, some clinicians have found this to be cost-ineffective among adolescent age groups because of the high rate of HPV infections and low rates of HSIL.

New guidelines for adolescents allow cytological LSIL to be followed by repeat cytology within six months or HPV DNA testing at 12 months. If the repeat cytology is normal, a second cytology should be repeated six months later. If a diagnosis of ASCUS or greater is made on either repeat cytologies, the adolescent should be referred to colposcopy. Alternatively, HPV DNA testing can be performed 12 months after the LSIL diagnosis. If the adolescent is positive for high-risk HPV DNA, referral to colposcopy is recommended. The assumption in the latter is that HPV detected one year later is the same as the HPV that caused the initial LSIL and the infection is persistent. However, with multiple partners, it is possible that the HPV present 12 months later reflects a different infection. It is important to communicate the significance of HPV infection to women who test positive for HPV. Clinicians should stress the fact that most HPV infections are caused by high-risk HPV types, are transient, and do not lead to cervical cancer. In fact, high-risk, oncogenic HPV types are found in new infections twice as frequently as the low-risk HPV types. Adolescents experience low rates of progression from LSIL to HSIL, so patient monitoring of LSIL using repeat cytology and HPV tests is acceptable over the use of colposcopy (Figure 4) [30]. Options other than treatment are often more attractive when one considers that loop electrosurgical excision procedure (LEEP) and laser cone treatments have been found to increase the subsequent risk of preterm delivery [46]. Further studies are needed to define the most appropriate screening strategies for adolescents. All of the strategies discussed so far are in reference to non-immunocompromised adolescents and young women. Studies in HIV-infected adolescents have shown that HPV persistence and development of HSIL are much more common, even among HIV-infected adolescents with normal CD4 cell counts [47]. Thus, immunocompromised patients should be monitored closely for the development of HPV-related lesions.

Although cervical cancer screening has significantly reduced mortality rates in developed countries, detection and treatment remains costly and inefficient. In developing countries, many, if not most women have no access to cervical cancer screening programs. Prevention of HPV infection would be preferable to screening and post infectin treatment. Two vaccines are expected to become available in the next few years; a bivalent vaccine that protects against HPV 16 and 18, and a quadrivalent vaccine that protects against HPV 6, 11, 16, and 18 are expected to substantially reduce HPV-associated disease burden. As with most childhood vaccines, HPV vaccines are prophylactic and must be administered before exposure to the virus to be most effective. Therefore, HPV vaccines should be given before the initiation of sexual activity.

Summary

Sexually active adolescents are at a high risk of acquiring HPV. Although HPV is controlled by the immune system in the majority of young women, HPV infection can manifest overtly as genital warts, abnormal cervical cytology, or cervical cancer. Cervical cancer is the result of failed immune responses resulting in persistent cervical infection with high-risk HPV types. Other risk factors such as smoking and co-infections with other STIs also play important roles in cervical cancer progression. Adolescent females who are sexually active should be encouraged to obtain gynecologic care to screen for STIs and cervical cancer. Furthermore, all adolescents should be properly educated regarding HPV and the risks associated with infection. Condom use remains important in the control of HPV infections and HPV-disease progression, and thus should be recommended to all sexually active adolescents. Providers can be assured that LSIL is usually relatively transient in adolescent populations, and that observation, not treatment, is advised by using repeat cytology or HPV DNA testing. Immunocompromised patients are at an elevated risk for developing HPV-associated disease, and should be monitored accordingly. Prophylactic vaccines are expected to significantly reduce morbidity and mortality associated with HPV infections and will provide the greatest public health benefits if they are administered before initiating sexual activity.

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