

Review

The epidemiology of human papillomavirus infections

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Abstract

Infection with oncogenic human papillomavirus (HPV) types is a necessary cause of cervical cancer, the second most frequently occurring cancer in women worldwide. Rates of acquisition of HPV are high, particularly among sexually active young adults. Reported estimates of incident HPV infection among initially negative women have reached as high as 60% over a 5-year follow-up period. In this article, we review the epidemiology of HPV infection. In addition to estimates of disease frequency, we highlight risk factors for HPV infection, including the number of lifetime sex partners, which is the most salient risk factor. We discuss significant issues surrounding the natural history of HPV infection, including viral persistence versus clearance, immune response, development of lesions and development of cancer. Finally, we discuss strategies for preventing HPV infection.

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Keywords: Human papillomavirus (HPV); Sexually transmitted infection (STI); Cervical cancer; Epidemiology; Natural history

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Abbreviations: HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; VLP, virus-like particle

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1. Introduction

Human papillomaviruses (HPV) cause warts and have been well-established as the sexually transmitted agents that cause most invasive cervical cancers and their associated precancerous lesions (IARC, 1995). HPV is a very common infection, though most infected individuals eliminate evidence of the virus without ever developing clinically recognized manifestations. Thus, very few HPV-infected individuals progress to invasive cervical cancer. A well-established factor that partially explains differential cervical cancer risk is HPV type. Over 40 HPV types infect the human anogenital tract (zur Hausen, 1996). Based on pooled data from 11 case-control studies of the association between cervical cancer and HPV infection from multiple countries (Munoz et al., 2003), 15 HPV types have been classified as high-risk for development of cervical cancer, 3 have been classified as probable high-risk, 12 have been classified as low risk and 3 are considered to have undetermined risk (Table 1).

2. Prevalence

Estimates of the population prevalence of HPV infection among women around the world range from 2% to 44% (Bosch and de Sanjose, 2003). The wide variation in estimates is largely explained by differences in the age range of the populations studied and the sensitivity of the DNA assay used for detection of HPV infection. Overall,

these DNA-based studies, combined with measurements of type-specific antibodies against HPV capsid antigens, have shown that most (>50%) sexually active women have been infected by one or more genital HPV types at some point in time.

In a Planned Parenthood population in the United States with mean age of 25 years, the prevalence of high-risk HPV infection was 27.4% (Kulasingam et al., 2002). Similar prevalence estimates have been found among female university students in the U.S. and Canada (Ho et al., 1998; Richardson et al., 2003). A recent study in Scotland showed the prevalence of PCR-detected HPV DNA in women with a mean age of 36.6 years attending routine cervical cancer screening to be approximately 20.5% for all HPVs and 15.7% for HR-HPVs (Cuschieri et al., 2004a).

HPV 16, which is one of the more common types among cytologically normal women, is also the most common type among cervical cancer cases (Franco et al., 1999; Ho et al., 1998; Liaw et al., 1999; Munoz et al., 2003; Richardson et al., 2003; Schiffman, 1992; Woodman et al., 2001). The prevalence of type-specific HPV infections among HPV-infected population-based controls from the International Agency for Research on Cancer (IARC) cervical cancer study and from a U.S. Planned Parenthood population is shown in Table 2.

2.1. Age

The prevalence of HPV infection is highest among young women and appears to drop off with increasing age (Schiffman, 1992). Using data from multiple international studies, the median oncogenic HPV prevalence among all women was 15.1%, while the median oncogenic HPV prevalence among women age 30 and older was 9.2% (Bosch and de Sanjose, 2003). Since most HPV infections occur soon after initiation of sexual activity and are transient, women over age 30 who are HPV positive include those who are persistent carriers as well as those with new infections. While most studies indicate a decrease in HPV prevalence with age, a handful of studies conducted in several different international regions have shown a peak prevalence of HPV infection in women below age 25, a decrease among women aged 35–54 and a second peak after age 55 (Herrero et

Table 1
 Classification of HPV types by cervical oncogenicity^a

Risk classification	HPV types
High-risk	16, 18, 31, 33, 35 39, 45, 51, 52, 56 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low risk	6, 11, 40, 42, 43, 44 54, 61, 70, 72, 81, CP6108
Undetermined risk	34, 57, 83

^a Data from Munoz et al. (2003).

Table 2
Type-specific HPV DNA Prevalence among HPV-infected women

HPV type	Percentage of all infected women (median age of 46 years) (IARC) ^a	Percentage of all infected women (median age of 25 years) (U.S.) ^b
16	24.3	23.7
18	7.3	7.2
31	4.2	6.0
45	3.5	4.7
35	2.7	3.7
58	2.3	5.1
6	2.3	6.3

^a Population-based control group of women from IARC cervical cancer studies in nine countries (Munoz et al., 2003).

^b Planned Parenthood population from Western Washington, unpublished data.

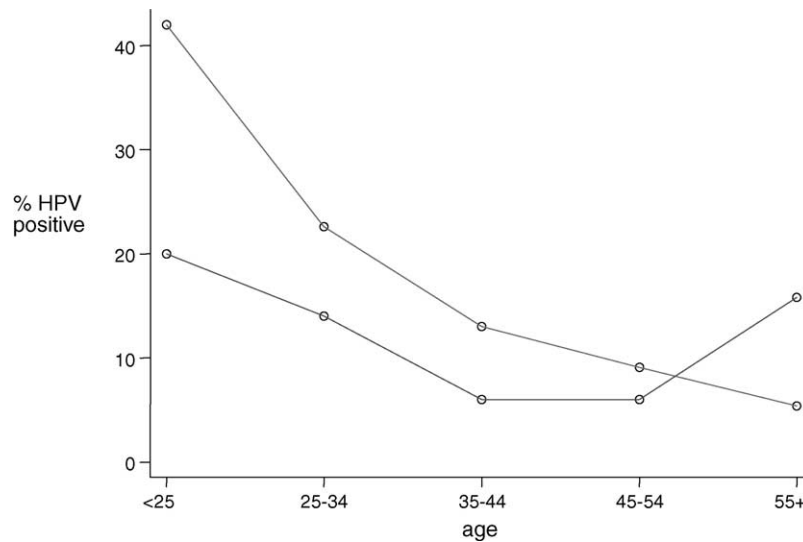


Fig. 1. Age-specific prevalence of HPV in a routine screening population in the UK (data source: Cuschieri et al., 2004a); (red) and in rural Costa Rica (data source: Herrero et al., 2000); (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

al., 2000). This difference is highlighted in Fig. 1. The observed increase in HPV prevalence in older age groups could be attributed to a cohort effect or to reactivation of latent virus.

2.2. Time trends

In the United States, between 1966 and 1984, physicians in private practice reported a 450% increase in number of first consultations for genital warts (Becker et al., 1987). Using sera from a cohort of pregnant women in Finland, the prevalence of HPV 16 among women aged 23–31 was found to increase from 17% in 1983–1985 to 24% in 1995–1997. During the same time period, HPV 6 and HPV 11 prevalence remained stable at 9–12%. Data from Sweden showed similar changes over time, with the seroprevalence of HPV 16 increasing from 16% to 21% between 1969 and 1980 (af Geijersstam et al., 1998). For women under age 23 in the Finnish cohort, the prevalence of HPV 16 increased from 13% in 1974 to 17–18% during 1983–1997 (Laukkanen et al., 2003).

2.3. Men

HPV infection also appears to be very common in men, though it has not been studied as extensively as infection in women. Using PCR analysis of genital samples, 16.5% of 285 Finnish conscripts (mean age 19.8 years) (Hippelainen et al., 1993) and 32.7% of 318 American university students (mean age 20.5 years) were HPV positive (Weaver et al., 2004). HPV prevalence in men appears to vary substantially by country (Franceschi et al., 2002). However, it is difficult to make comparisons across studies because different methods have been used to obtain genital samples from men, with many studies including samples from only two genital sites and other studies including samples from up to six genital sites.

3. Incidence

Acquisition of HPV is very common, particularly among sexually active young adults, and incidence of infection with

oncogenic HPV types appears to be higher than the incidence of infection with non-oncogenic types (Franco et al., 1999; Giuliano et al., 2002; Ho et al., 1998; Richardson et al., 2003). The cumulative incidence of HPV infection among women aged 15–19 in England was found to be 44% over a 3-year period and increased to 60% at 5 years (Woodman et al., 2001). Similar results have been found among two populations of college women in the U.S., in which the 3-year cumulative incidence of HPV infection was 43% in one study (Ho et al., 1998) and 42.8% (95% CI: 38.0, 47.9) in another (Winer et al., 2003). Data from a cohort study conducted in Brazilian women found that the cumulative incidence of HPV infection was 23.6% over 18 months (Franco et al., 1999), an estimate similar to that found in the U.S. and UK.

3.1. Trends in incidence over time

In the Finnish Maternity cohort, between the time periods 1983–1985 and 1992–1994, the incidence of HPV 16 among women age ≤ 22 dropped from 25/1000 person-years to 13/1000 person-years before increasing to 31/1000 person-years during 1995–1997. For women between the ages of 23 and 31, the HPV 16 incidence increased steadily from 5/1000 person-years to 13/1000 between 1983–1985 and 1995–1997 (Laukkanen et al., 2003). In the United States, the age- and gender-adjusted incidence of genital warts increased from 13/100,000 to 106/100,000 between 1950–1954 and 1975–1978 (Chuang et al., 1984; Winer et al., 2003).

4. Risk factors for infection

4.1. Number of sex partners

The most consistent risk factor for HPV infection is increased number of sex partners. Several studies of women have demonstrated strong associations between lifetime number of sex partners and genital HPV acquisition (Burk et al., 1996; Tarkowski et al., 2004; Wang et al., 2003; Wheeler et al., 1993) and in men (Franceschi et al., 2002; Hippelainen et al., 1993; Svare et al., 2002). Furthermore, it has been shown that a woman's reported estimate of her male partner's lifetime number of sex partners is positively associated with HPV infection in herself (Burk et al., 1996). A shorter time interval between meeting a new partner and engaging in sexual intercourse also increases risk of HPV infection in women (Winer et al., 2003). A recent study of HPV infection among adolescent women found that a mean increase of greater than 1.5 years in the age of the male partner relative to the age of the woman conferred a two-fold increase in risk of HPV DNA detection in the woman (Tarkowski et al., 2004), probably attributable to the relationship between increasing age of the male partner and a higher number of sexual partners.

4.2. Smoking

HPV infection has been positively associated with current smoking (Wang et al., 2003) and past smoking (Rohan et al., 1991), though one study found that former smokers had a significantly lower prevalence of HPV infection than women who had never smoked (Bauer et al., 1993). A recent study investigating the relationship between smoking and oncogenic HPV infection found no association between number of cigarettes smoked per day and presence of HPV DNA (Harris et al., 2004), and most other studies investigating the relationship between smoking and HPV infection have failed to detect an association (Burk et al., 1996; Deacon et al., 2000; Karlsson et al., 1995; Wheeler et al., 1993).

4.3. Oral contraceptive use

The relationship between oral contraceptive (OC) use and HPV infection is difficult to evaluate due to the strong and consistent association between OC use and sexual activity. A recent study found that, after adjusting for variables such as age and lifetime number of sex partners, former OC use exhibited a borderline association with HPV 16, 18 and 31 seropositivity, while current OC use exhibited a borderline association with HPV 16 and HPV 18, but not with HPV 31 seropositivity (Wang et al., 2003). Other studies have reported an association between OC use and HPV DNA positivity after adjusting for variables such as number of sex partners (Ley et al., 1991; Negrini et al., 1990), but most studies have found no association (Burk et al., 1996; Davidson et al., 1994; Karlsson et al., 1995; Stone et al., 2002; Wheeler et al., 1993).

5. Natural history

5.1. Clearance/persistence

Most women infected with a specific HPV type will not show evidence of that same type 6–12 months later (Cuschieri et al., 2004b; Franco et al., 1999; Hildesheim et al., 1994; Hinchliffe et al., 1995; Ho et al., 1998). In a prospective study of female college students, approximately 70% of women no longer had detectable levels of HPV DNA within 12 months of follow-up after incident HPV infection. After 18 months, over 80% appeared to have cleared their infections (Ho et al., 1998). Other cohort studies support this finding, several reporting a median duration of HPV detectability of approximately 1 year (Evander et al., 1995; Franco et al., 1999; Hildesheim et al., 1994; Woodman et al., 2001). Whether oncogenic and non-oncogenic HPV types can be detected for similar periods remains controversial with some studies showing similar average duration (Richardson et al., 2003) and others showing longer durations of infection for oncogenic than non-oncogenic HPV types (Franco et al., 1999; Hildesheim et al., 1994; Ho et al., 1998). It appears that HPV 16 has a particularly long time to clearance relative

to other HPV types (Liaw et al., 2001; Richardson et al., 2003).

In interpreting data on duration of HPV infection, it is important to remember that there is no consensus regarding what constitutes a 'persistent' HPV infection. Many studies have labeled HPV infections as persistent if HPV was detected on two consecutive follow-up visits, 4–6 months apart. However, because the interval between follow-up visits varies among studies and the many unknowns regarding the natural history of HPV complicate identification of an appropriate interval, the significance of being positive at two points in time becomes blurred, as does the distinction between 'persistence' and 'transience' of infection. Furthermore, it is unclear whether undetectable HPV infections have been entirely cleared by the host, or whether there is a period of viral latency in which HPV levels are maintained below the detectable threshold of current HPV DNA assays. If viral latency occurs, a woman who appears to have cleared her infection between follow-up visits would still be at risk for potential development of HPV associated disease. Likewise, it is unclear whether HPV infections that are detectable over a certain interval of time result from persistent HPV infection or HPV clearance and re-infection. Re-infection with the same HPV type appears to be uncommon as three cohort studies of sexually active young women showed that the same HPV 16 variant was always detected in the same woman during follow-up examinations (Xi et al., 1995).

5.2. Immunity

Though infection with an oncogenic HPV type has been shown to be a necessary cause of cervical precancer and invasive cancer, it is not a sufficient cause. The high incidence and prevalence of HPV in the general population and the high rate of viral clearance support this premise. It is still unclear what factors, other than HPV type and HPV variant (Berumen et al., 2001; Tornesello et al., 2004; Xi et al., 1997), influence risk of cervical neoplasia and HPV persistence. Host immune factors are certainly associated with HPV persistence (Steenbergen et al., *this volume*; Stern, *this volume*), though identification of appropriate biomarkers of successful immune responses are currently lacking. Still, the influence of immune response on the ability to clear HPV infection is evidenced by studies showing that HIV seropositive women are more likely to shed HPV over a longer period of time than HIV seronegative women (Vernon et al., 1994).

5.3. Infection with multiple types

The presence of multiple HPV types in one individual is common and several studies have attempted to define the role of multiple HPV infections in HPV persistence. Ho et al. (1998) found that infection with multiple HPV types was associated with persistence of HPV infection, a finding supported by Woodman et al. (2001), who found that simultaneous infection with HPV 16 and another type resulted in longer

duration of detectable HPV 16 than did infection with HPV 16 alone. However, others have reported that the presence of multiple HPV types does not appear to influence HPV persistence. In one study, time to loss of an HPV infection was compared among women with and without co-infection with other HPV types and there was no significant difference in duration of infection seen between the two groups (Rousseau et al., 2001). In another study, the role of HPV 16 in persistence of other HPV infections was investigated and no association was found between presence of HPV 16 and persistence of other HPV infections (Liaw et al., 2001). Bachtary et al. (2002) and van der Graaf et al. (2002) suggest that multiple types are associated with increased risk of disease progression. It is not clear if this observation is due to differences in host susceptibility, interactions between the viruses or the independent probability of progression associated with each viral type.

5.4. Antibodies

The development of serum antibodies in HPV 16 infected women appears to be a slow process and antibodies are not necessarily detected in all infected women. A recent study by Ho et al. (2004) found a median time to IgG seroconversion to HPV 16 of 8.3 months. Similar findings were reported earlier by Carter et al. (1996). Within 12 months, 56.7% of women with incident HPV 16 infection had seroconverted in the Ho study compared with 67.1% within 16 months in the earlier study, together with 93.7% of women with prevalent HPV 16 (Carter et al., 1996). The increased rate of seroconversion among women with prevalent HPV 16 infection may be related to the fact that a higher percentage of prevalent versus incident HPV 16 infections are likely to be persistent. Seroconversion rates appear to be higher among women with infections that persist for longer versus shorter periods of time (Carter et al., 2000).

5.5. Development of lesions

Both oncogenic and non-oncogenic HPV types cause low-grade squamous intraepithelial lesions (LSIL) of the uterine cervix, whereas most cervical lesions that are classified as high-grade SIL (HSIL), carcinoma in situ or invasive cancer are positive for oncogenic HPV types. About 70% of invasive cervical cancers are caused by HPV 16 or HPV 18 (Munoz et al., 2003) and about 90% of genital warts are caused by HPV 6 or HPV 11 (Greer et al., 1995).

A common theory until recently was that women who developed cervical cancer always progressed through distinct stages of low to moderate to high-grade intraepithelial lesions. Natural history studies, however, have called into question the notion of a progressive continuum of cervical precancerous stages and have led many researchers to conclude that low- and high-grade cervical lesions are distinct HPV infection processes. LSIL appears to represent a transient manifestation of productive viral infection, where the

HPV infected epithelium undergoes differentiation and maturation, and exhibits only minor cellular abnormalities. HSIL, the true cervical cancer precursor, occurs when HPV infection of replicating immature cells prevents epithelial maturation and differentiation leading to continued replication of immature cells and accumulation of genetic abnormalities that could ultimately lead to a clone of cancer cells. LSILs tend to be located more distally from the cervical os; HSILs and cancer tend to be more proximate. LSIL may be established first, at the same time as or in the absence of HSIL. Atypical cells of undetermined significance (ASC-US) represent poorly visualized cells from an LSIL, HSIL or other infectious or non-infectious process such as a healing cervical ulcer or cellular atrophy as occurs with menopause.

The incidence of HSIL appears to be quite high among women infected with oncogenic HPV. In a cohort of women with no prior history of SIL, the 2-year cumulative incidence of biopsy-confirmed HSIL was 28% for women with a positive HPV test and only 3% for women with no detectable HPV infection (Koutsky et al., 1992). Another cohort study of women who were SIL negative and HPV negative at enrollment found that those who became HPV positive during follow-up were 13 times more likely to develop HSIL than women who were HPV negative. In this study, the highest risk of HSIL was seen within 6 months of initial HPV infection and dropped precipitously thereafter (Woodman et al., 2001). This rapid onset of high-grade SIL after initial detection of HPV has been observed elsewhere (Koutsky et al., 1992). Thus although persistent HPV exposure is usually necessary for development of cervical precancer, cases of rapid onset HSIL suggest that this may not always be so.

5.6. Development of cancer

The incidence of cervical cancer has decreased in areas in which screening programs for detection of precancerous lesions have been employed. Still, in the United States, there

were approximately 12,200 new cases of invasive cervical cancer and 4100 women were expected to have died from cervical cancer in 2003 (Ries et al., 2004). Worldwide, cervical cancer is the second most common cancer in women, with almost 80% of all cervical cancer cases occurring in the developing world (Jones, 1999). In 2000, an estimated 470,000 new cases of cervical cancer occurred worldwide. Cervical cancer mortality ranks third worldwide, with the highest mortality rates occurring in developing countries (Pecorelli et al., 2003).

A schematic diagram of the progression from oncogenic HPV infection to cervical cancer is provided in Fig. 2. The known steps in cervical carcinogenesis include oncogenic HPV infection, development of HSIL and progression of HSIL to carcinoma in situ and then invasive cancer. The historical literature suggests that between one- and two-thirds of women with HSIL will develop invasive cancer if left untreated (Kinlen and Spriggs, 1978; Petersen, 1956). The mean age of women with invasive cervical cancer is approximately 50 years, while the mean age of women with HSIL is approximately 28 years, which suggests a long precancerous state. So far, epidemiological studies have not been able to consistently identify risk factors for invasion, though it has been suggested that smoking, long-term oral contraceptive use, infection with other sexually transmitted infections and multi-parity or integration of HPV into the host chromosome might play a role in risk of invasion (Deacon et al., 2000; Einstein and Goldberg, 2002; Hildesheim et al., 2001; Jeon and Lambert, 1995; Moreno et al., 2002; Munoz et al., 2002; Smith et al., 2002).

Worldwide, HPV 16 is a cause of about 54% of invasive cervical cancers and HPV 18 is a cause of about 17% (Munoz et al., 2003). HPV infection has also been found to be a cause of other anogenital carcinomas including penile (Rubin et al., 2001), vaginal (Daling et al., 2002), vulvar (Trimble et al., 1996) and anal cancers (Clark et al., 2004). Recently, HPV has also been implicated as a possible etiologic agent

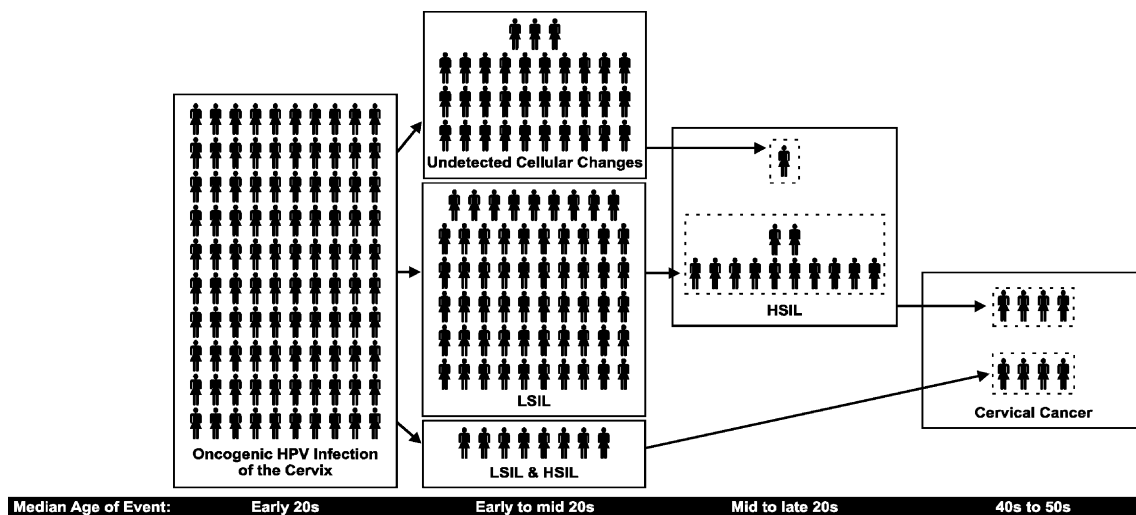


Fig. 2. Natural history of cervical cancer.

in non-anogenital cancers, such as some head and neck squamous cell carcinomas (Gillison and Lowy, 2004).

6. Prevention

6.1. Abstain, be faithful, use condoms

Because HPV infections associated with anogenital cancers are sexually transmitted, efforts focusing on prevention of HPV infection can and should mirror those of other STDs. One approach to HIV prevention that was found to be successful in Uganda in the late 1980s and 1990s is the 'ABC' approach, an acronym that stands for Abstain, Be faithful, use Condoms (Cohen, 2003). Some aspects of the epidemiology of HPV suggest that the ABC approach might have some success in preventing HPV infection. By definition, abstaining from sexual activity would prevent most sexually transmitted HPV infections, just as it would prevent acquisition of other sexually transmitted diseases. Given the strong association between increasing number of sex partners and HPV infection, being faithful to one partner would likely decrease the probability of acquiring an HPV infection, though this decreased probability of HPV acquisition would be mitigated by having a sex partner who was not also monogamous. Still, on a population level, prevalence and incidence of HPV infection would likely decrease as a result of successful implementation of an HPV prevention plan resulting in a higher frequency of monogamous sexual relationships. The possible effects of an HPV prevention message promoting condom use are less clear. A recent meta-analysis of the efficacy of condom use in prevention of HPV infection revealed that there is no consistent evidence that condom use reduces the risk of acquiring a HPV infection, though condoms appear to protect against genital warts, CIN2, CIN3 and invasive cervical cancer (Manhart and Koutsky, 2002).

6.2. Vaccines

In recent years, much attention has been paid to the possibility of vaccination against HPV as a means of preventing cervical precancerous lesions and cancer. Zhou et al. (1991) reported a major breakthrough in the development of HPV vaccines in 1991. They synthesized virus-like particles (VLPs) by expressing only two HPV 16 genes (L1 and L2) in eukaryotic cells (e.g., animal or yeast cells). Subsequently, other scientists refined the assembly of VLPs (Kirnbauer et al., 1992) and demonstrated that only the L1 gene was needed to produce HPV VLPs that, when injected into human volunteers, would stimulate high titers of neutralizing antibodies (Brown et al., 2001; Evans et al., 2001; Harro et al., 2001) and T-cell responses (Emeny et al., 2002). Research on prophylactic HPV L1 VLP vaccines recently culminated in reports of two successful multi-center phases IIb proof-of-concept trials showing 100% protection against persistent HPV 16 infection (Koutsky et al., 2002) or persistent

HPV 16 and 18 infections (<http://www.eurogin.com/2003/>). An international phase III trial of the bi-valent prophylactic HPV 16/18 vaccine was recently initiated. An international phase III trial of a prophylactic HPV 6/11/16/18 L1 VLP vaccine is also currently underway. If high-level efficacy is demonstrated during the planned 3.5 years of follow-up, this tetravalent vaccine could be commercially available within 4 years.

Once a prophylactic HPV vaccine is available, issues surrounding implementation of immunization programs would still require attention. Some of these issues are: (1) At what ages should individuals be vaccinated? (2) Should young men be vaccinated? (3) What is the duration of protection? (4) How should immunization programs be implemented in the developing world? (5) How should HPV immunization programs be integrated into on-going cervical cancer screening programs?

The health care costs associated with screening and treatment of HPV-related disease is substantial, estimated to be approximately US\$ 6 billion a year in the U.S. However, the advent of a vaccination program would not remove the need for cervical cancer screening because the proposed HPV vaccines would not protect against all oncogenic HPV types. Recent modeling studies have shown that implementation of an HPV vaccination program, along with cytological screening, could be a cost-effective cervical cancer prevention strategy for some countries (Goldie et al., 2004; Kulasingam and Myers, 2003). Thus, it would appear that a successful HPV vaccination program, along with screening, has the best chance of decreasing the morbidity and mortality associated with cervical neoplasia, genital warts and other HPV-associated neoplasms.

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