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REPORT TO CONGRESS

Prevention of Genital Human Papillomavirus Infection

Centers for Disease Control and Prevention

Department of Health and Human Services

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Prevention of Genital Human Papillomavirus Infection

Executive Summary

This report describes key aspects of the epidemiology of genital HPV infection and its transmission, and summarizes the best strategies to prevent infections with genital HPV as well as the HPV-associated diseases of genital warts and cervical cancer.

Genital infection with human papillomavirus (HPV) is very common in sexually active men and women and can sometimes have serious health consequences. About 20 million Americans are currently infected, and about 5.5 million people become newly infected each year. The virus can infect the genital skin and the linings of the vagina, cervix, rectum, and urethra. Most infections cause no clinical problems and go away on their own without treatment. Some infections lead to genital warts in men and women, and abnormal Papanicolaou (Pap) tests in women. Treatments are directed to abnormal cells associated with HPV rather than the virus itself; currently there is no curative treatment for HPV infection.

Of greatest importance, persistent infection with certain types of HPV is a leading cause of cervical cancer. Progression from cervical cancer precursor lesions to invasive cancer is a slow process, estimated to take 10–15 years. Cervical cancer is an uncommon consequence of HPV infection in women, especially if they are screened for cancer regularly with Pap tests and have appropriate follow-up of abnormalities. The purpose of screening with the Pap test is to detect cervical abnormalities that can be treated, thereby preventing progression to invasive cervical cancer, and also to detect invasive cervical cancer at a very early stage. If detected early and managed promptly, survival rates for cervical cancer are over 90%. In the past 40 years, widespread cervical cancer screening using the Pap test and treatment of precancerous cervical abnormalities have resulted in a dramatic decrease in the incidence and mortality due to cervical cancer in the United States. However, each year in the United States, an estimated 12,200 women develop cervical cancer and 4,100 women die from it. Of women in the United States who develop cervical cancer, about half have never had a Pap test.

Because genital HPV infection is most common in men and women who have had multiple sex partners, abstaining from sexual activity (i.e. refraining from any genital contact with another individual) is the surest way to prevent infection. For those who choose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections. For those who choose to be sexually active but who are not in a monogamous relationship, reducing the number of sexual partners and choosing a partner less likely to be infected may reduce the risk of genital HPV infection.

All published epidemiologic studies of HPV have methodologic limitations that make the effect of condoms in the prevention of HPV infection unknown. While a few studies on genital HPV and condom use showed a protective effect, most studies on genital HPV infection and condom use did not show a protective effect. Recognizing that the optimal study design to ensure valid measurements can be problematic, it remains important that further research be done to help determine the efficacy of condoms in preventing HPV infection.

Nevertheless, available studies suggest that condoms reduce the risk of the clinically important outcomes of genital warts and cervical cancer. One possible explanation for the protective effect of condoms against warts and cancer is that condom use could reduce the quantity of HPV transmitted or decrease the likelihood of re-exposure, thereby decreasing the chance of developing clinical disease. An alternative explanation is that condom use may reduce exposure to a co-factor for cervical cancer, such as chlamydia or genital herpes, thereby reducing the chance of cervical cancer.

The available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection. There is evidence that indicates that the use of condoms may reduce the risk of cervical cancer.

Regarding other possible prevention approaches, no data indicate that treatment of clinical lesions or use of microbicides will prevent transmission of infection, although HPV vaccines are likely to become available in the next few years and may become an important prevention tool.

Summary of Strategies to Prevent Genital HPV Infection

Based on currently available science, the following recommendations summarize the strategies most likely to be effective in preventing future infections with genital HPV infection and cervical cancer.

Individual Strategies

- The surest way to eliminate the risk for future genital HPV infections is to refrain from any genital contact with another individual.
- For those who choose to be sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections. However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected.
- For those choosing to be sexually active and who are not in long-term mutually monogamous relationships, reducing the number of sexual partners and choosing a partner less likely to be infected may reduce the risk of genital HPV infection. Partners less likely to be infected include those who have had no or few prior sex partners.
- While available scientific evidence suggests that the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of the HPV-associated diseases of genital warts and cervical cancer. The available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for

the prevention of genital HPV infection. There is evidence that indicates that the use of condoms may reduce the risk of cervical cancer.

- Regular cervical cancer screening for all sexually active women and treatment of precancerous lesions remains the key strategy to prevent cervical cancer.
- In the future, receiving a safe and effective HPV vaccine to help prevent genital HPV infection as well as the HPV-associated diseases of genital warts and cervical cancer would be an important prevention measure. However, an effective HPV vaccine would not replace other prevention strategies.

Public Health Strategies

Public health agencies should:

- Promote increased cervical cancer screening among never and rarely-screened women and appropriate follow-up of those with abnormal Pap tests.
- Work with public and private partners to increase awareness about prevention of genital HPV infection and cervical cancer among health care providers and in the general public.
- Collaborate with private industry to promote and accelerate the development of a safe and effective HPV vaccine.
- Continue epidemiologic, laboratory, and behavioral research on genital HPV infection, including studies of the prevalence of HPV in the United States, research on the attitudes and concerns of women diagnosed with HPV infection (e.g., concerns about cancer or about transmission), and surveys of provider knowledge and practices regarding HPV.

Introduction

Human papillomaviruses (HPV) are members of the Papillomaviridae family of DNA viruses. Because HPV cannot be cultured easily in the laboratory, HPV infection is most commonly diagnosed by detecting HPV DNA. Differences in sequences of DNA are used to determine different HPV types. More than 100 HPV types have been identified, over 30 of which infect the genital area. Genital HPV infections are estimated to be the most common sexually transmitted infection in the United States, with an estimated 5.5 million persons becoming newly infected every year (1). Although the majority of infections cause no symptoms and are self-limited, genital HPV is of public health concern because persistent infection with certain types can cause cervical cancer in women.

Genital HPV infections are categorized according to their association with cervical cancer. Infections with low-risk types, primarily types 6 and 11, can cause benign or low-grade cervical cell changes and genital warts, but are not associated with cervical cancer. Infection with high-risk types, primarily types 16, 18, 31, and 45, can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and genital cancers. Most genital infections with either high-risk or low-risk HPV types go away on their own, without clinical consequences. Currently, one HPV DNA test is FDA-approved for use in women for cervical cancer screening; no HPV test is available for men.

The sequela of genital HPV infection with greatest public health importance is cervical cancer. Cervical cancer is relatively uncommon in the United States because widespread cervical Papanicolaou (Pap) testing can detect precancerous lesions before they develop into cancer. However, in many developing countries where cervical cancer screening activities are limited, cervical cancer is the most common cancer in women. Based on multiple lines of evidence, both the International Agency for Research on Cancer and the National Institutes of Health (NIH) have concluded that high-risk genital HPV infections act as carcinogens in the development of cervical cancer (2;3). While infection with high-risk types appears to be “necessary” for the development of cervical cancer, it is not “sufficient” because cancer does not develop in the vast majority of women with HPV infection (2;3). Other co-factors appear to be necessary for the development of cervical cancer (described in *Natural History of Genital HPV Infection*, page 10). HPV infection is also associated with anogenital cancers at other sites including the vulva, vagina, penis and anus. Each of these is substantially less common than cervical cancer, with the exception of anal cancer in homosexual men (4-8). The association of genital types of HPV with non-genital cancer is less well established, but studies support a possible role in a subset of head and neck (9) and esophageal (10) cancers. In each of these non-genital cancers, there are clearly cancers arising independent of HPV, a situation quite different from cancer of the cervix. While a few studies suggest a possible association of HPV with cancer of the prostate (11), the findings are not consistent and the most recent studies do not indicate that HPV is associated with these cancers (12;13).

Because of the public health importance of cervical cancer, this report focuses on the prevention of genital HPV infection and its sequelae in heterosexual men and women. The report describes key aspects of the epidemiology of genital HPV infection and its transmission, and summarizes

the best strategies to prevent infections with genital HPV as well as the HPV-associated diseases of genital warts and cervical cancer.

Epidemiology of Genital HPV Infection

Incidence and Prevalence of Genital HPV Infection

Accurately assessing the extent of genital HPV infection in the U.S. population has been difficult for many reasons. Data on prevalence and incidence of HPV infection are limited because there is no routine screening for HPV infection, and it is often unclear whether a newly diagnosed infection is recently acquired or longstanding. Neither HPV infection nor genital warts are routinely reported to state health departments for the following reasons: (a) no standard justification for recommending STD case reporting (e.g., patient care measures such as curative treatment for patients and their sex partners, or monitoring ongoing prevention programs) exists for genital HPV infection or warts, (b) most infections clear spontaneously, and (c) case reporting would create a large burden for providers, health departments and laboratories given the high prevalence of infection (14).

Cases of cervical cancer are routinely reported to cancer registries such as the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, and Centers for Disease Control and Prevention (CDC)-supported state cancer registries. However, because cervical cancer is a rare and late manifestation of HPV infection, cancer surveillance provides limited information on the burden and current trends of HPV infections. CDC is conducting a survey of the general U.S. population and a survey of women attending different types of clinics to improve measures of the prevalence of genital HPV. Results for the U.S. population survey will be available in late 2005, and, for the clinic based survey, in 2007. Data from these studies will be useful in evaluating the impact of future prevention strategies on HPV prevalence.

Because of the above issues, the magnitude of genital HPV infection is derived from extrapolations of epidemiologic studies. Studies that detect HPV DNA measure current infection, and studies that detect HPV antibodies using blood tests provide approximations of lifetime infection. Overall, in the United States, an estimated 20 million people (15% of the population) are currently infected with HPV, 50–75% of which is with high-risk types, and about 5.5 million people are infected every year (1). It has been estimated that at least 50% of sexually active men and women acquire genital HPV infection at some point in their lives; a recent estimate suggests that 80% of women will have acquired genital HPV by age 50 (15;16). An estimated 9.2 million sexually active adolescents and young adults 15 to 24 years of age are currently infected with HPV (17).

Prevalence studies in the United States have primarily included convenience samples of women attending managed care, STD, or university clinics. Studies have found that the prevalence of HPV infection is lowest in women who have never had sexual intercourse (18-21). Genital HPV infection is especially common among sexually active young women (less than 25 years of age), with prevalence decreasing with older age (22-30). While results vary by population studied, and sampling and detection methods used, overall they indicate that prevalence of genital HPV infection in sexually active young women in the United States ranges from 17–84% (22-29); most studies have reported a prevalence greater than 30% (22;23;25-27). In a study conducted in Portland, Oregon, 32% of young women ages 16 to 24 years had genital HPV DNA detected versus only 4% of women ages older than 45 years (24). The higher rates in younger women

appear to be related to transmission of new infection during the early years of sexual activity, with infection clearing over time in most women (28;31). By far, the most common infections are with the high-risk types. Infection with multiple types of HPV occurs in approximately 5–30% of infected women (23;32–34). HPV infection is most likely to be detected in women who have cervical cancer precursors; in one study, over 85% of women with cervical cancer precursors had detectable HPV DNA (34).

These findings are supported by studies of incident (new) genital HPV infections, which can more accurately determine rates, as well as behavioral risk factors for infection. Studies of HPV incidence have been conducted in a variety of settings with variable follow-up periods. Incidence of HPV infection in college women studied for two to three years was 32–43% (21;28). Other studies assessing populations of women using routine gynecological or family planning services found incidences of 11–32% in one year, and 44–55% in three years (29;31;33;35;36). The incidence of high-risk types, such as HPV-16, is higher than the incidence of low-risk types (28;29;31). For example, in one study, the incidence in one year was 32% for high-risk HPV types compared with 18% for low-risk HPV types (29).

The risk factors consistently associated with HPV infection in women are young age (age less than 25 years) and sexual behavior, specifically number of sex partners, as described below (*Transmission and Prevention of Genital HPV*, page 11). Other risk factors identified include early age of first sexual intercourse, and male partner sexual behavior. Less consistently identified risk factors include smoking, oral contraceptive use, nutritional factors, and lack of circumcision of male partners (20). Many of the identified risk factors are likely markers for unmeasured sexual behavior (21;25;37–39). In addition, immune suppression is associated with HPV detection. Studies in women with HIV infection, undergoing dialysis, or after kidney transplant, demonstrate that HPV detection is particularly common with immune suppression (17;40–43).

The prevalence of genital HPV infection in men is more difficult to assess because it is not clear which are the optimal anatomic sites or specimens to test. Most published studies have been conducted outside the United States, in men attending STD or university clinics, or among male partners of women with HPV infection. HPV DNA can be detected at various anogenital sites, including the penis, urethra, scrotum, or anus, as well as in urine and semen (44–56). In heterosexual men, infection is most commonly detected on the penis (54–57). A recent study that evaluated HPV DNA in the distal penis (urethra, glans, coronal sulcus, foreskin) documented higher prevalence of infection in uncircumcised men than in circumcised men (19.6% vs. 5.5%) (46). Prevalence of genital HPV infection in heterosexual men in the populations studied ranges from 16–45%; detection is highly dependent on the anatomic sites or specimens tested (e.g., urine, semen) (45;46;49;52). Risk factors for HPV detection in men include greater lifetime number of sex partners, number of recent sex partners, being uncircumcised, or current genital warts (45;46;52). The relationship of young age with HPV detection is not as consistent in men as in women (45;49;52).

HPV serologic (blood) tests that detect antibodies to the outer proteins of HPV have been useful in assessing previous HPV infection. They complement the studies that are based on HPV DNA detection because HPV DNA is not persistently detectable in most infected people. However,

these tests likely underestimate the true extent of previous infection because only 50–70% of persons with detectable HPV DNA develop antibodies (58-60). A recently completed study of the U.S. population conducted by CDC showed that 18% of women and 7% of men aged 12 to 49 had antibodies to HPV-16 (61). The strongest predictors of antibody positivity in both women and men were various measures of past sexual activity, including lifetime number of partners. Antibody prevalence is substantially higher in populations with greater sexual activity. For example, a study of patients attending a U.S. STD clinic found HPV-16 antibody prevalence rates of 55% in women and 33% in men (62).

Prevalence of Sequelae of Genital HPV Infection

Estimates for genital warts are relatively imprecise; however, limited data suggest that each year in the U.S. as many as 100 per 100,000 persons develop genital warts (63), and 1.4 million currently have genital warts (about one percent of the sexually active U.S. population) (64). Rarely, genital HPV infection with low-risk types may be transmitted from mother to baby during delivery resulting in respiratory tract warts in the baby, an illness known as recurrent respiratory papillomatosis (RRP). Estimates of the incidence rate for RRP are also relatively imprecise, but range from 0.4 to 1.1 cases per 100,000 children (65).

Rates of cervical cancer have fallen by approximately 75% since the introduction of Pap testing programs. Cervical cancer incidence in the U.S. is currently estimated to be 8.3 per 100,000 women, with approximately 12,200 new cases and 4,100 deaths occurring annually (66).

Natural History of Genital HPV Infection

Most HPV infections are transient and asymptomatic, causing no clinical problems. Studies have shown that 70% of new HPV infections clear within one year, and as many as 91% clear within two years (28;33;67;68). The median duration of new infections is typically eight months (28;67). HPV-16 is more likely to persist than other HPV types (28); however, most HPV-16 infections become undetectable within two years (28). Factors associated with persistence include older age, high-risk HPV types, infection with multiple HPV types, and immune suppression (69;70). The gradual development of an effective immune response is thought to be the likely mechanism for HPV DNA clearance.

HPV infection that persists is the most important risk factor for cervical cancer precursors and invasive cervical cancer (15;67;69-71). A recent study found that the risk for developing cervical cancer precursors was 14 times higher for women who had at least three positive tests for high-risk HPV compared with that for women who had negative tests (68). However, most women with persistent HPV infection do not develop low-grade cervical cell abnormalities, cervical cancer precursors or cervical cancer (28;31;68;72).

Skin and mucosal changes caused by genital HPV infection --both genital warts and cervical cell abnormalities-- often go away without treatment, probably as a result of the development of an effective immunologic response. Rates of spontaneous clearance and progression to cancer without treatment vary for low-grade and high-grade cervical cell abnormalities. Low-grade cervical cell abnormalities usually clear spontaneously (60% of cases) and rarely progress to cancer (1%), while high-grade cervical cell abnormalities have lower rates of spontaneous

clearance (30–40%) and much higher rates of progression to cancer without treatment (greater than 12%) (73).

In addition to persistent infection with high-risk types of genital HPV, other co-factors appear to be necessary for the development of cervical cancer (74). Factors such as long-term use of oral contraceptives, a high number of live births, and immune suppression have been found in some studies to be associated with cervical cancer (74-81). In addition, recent studies have demonstrated that co-infection with *Chlamydia trachomatis* or herpes simplex virus type-2 (HSV-2), the cause of genital herpes, may increase the risk of both cervical cancer precursors and cervical cancer (81;82).

Transmission and Prevention of Genital HPV Infection

Transmission

Genital HPV infection is primarily transmitted by genital contact, usually through sexual intercourse (20;83). In virtually all studies of HPV prevalence and incidence, the most consistent predictors of infection have been various measures of sexual activity, most importantly, the number of sex partners (28;31;64;84). Among women, the risk of acquiring a genital HPV infection increases with increasing number of lifetime male sex partners (25;26;84-87). Similar to infection with other STD, having sex with a new partner may be a stronger risk factor than having sex with a steady partner (21;31). With each new partner, an adolescent female substantially increases her risk of acquiring genital HPV (31). The source of transmission is usually from persons who are asymptomatic and do not realize they are infected (64). Among women who report no previous sexual intercourse, 0–8% have HPV infection supporting the premise that the major route of transmission is sexual (18-21).

Although less well-examined, another variable that increases a woman's risk of HPV infection is the sexual activity of her partner. A study of adolescent females found that those with a partner who had multiple sex partners were at increased risk of HPV infection (31). A study of college students in Seattle found that those with male sex partners with at least one prior partner had a five-fold increased risk of infection compared to those whose male partners had no prior partners. Women whose male partners had an unknown number of prior sex partners had an even higher (eight-fold) risk for acquiring HPV infection (21). This study also reported that women who had known a sex partner at least eight months before initiating a sexual relationship were less likely to acquire genital HPV infection. It was hypothesized that this was due to a greater chance of spontaneous clearance of infection in men who might have been infected with HPV in a previous sexual relationship (21).

Other types of genital contact in the absence of penetrative intercourse (oral-genital, manual-genital, and genital-genital contact) leading to HPV transmission have been described, but these routes of transmission are less common than sexual intercourse (21;88-90). For example, a recent study of college-aged women in Seattle reported a two-year genital HPV incidence rate of 39% among sexually active women and 8% among women who had not engaged in penetrative vaginal intercourse. Almost all of the infections in women who had not engaged in sexual intercourse appeared to be related to genital contact other than penetrative intercourse (21). This

study also found minimal evidence of HPV transmission through oral sex (either transmitted from the genital area to the mouth or the mouth to the genital area) (21). Genital HPV infection also may be transmitted by non-sexual routes, but this is extremely uncommon. Non-sexual routes of genital HPV transmission include transmission from a mother to a newborn baby, which is rare (91;92), and transmission by inanimate objects such as environmental surfaces and clothing, which has been hypothesized but has never been documented (93-96).

Prevention of Genital HPV Infection

Prevention of genital HPV infection is important to reduce the prevalence of genital warts and abnormal Pap tests, as well as cervical cancer. Cervical cancer screening programs have been highly effective in reducing rates of cervical cancer in the United States (97;98); decreasing the incidence of genital HPV infection should also reduce rates of cervical cancer(16).

In general, for a given sexually transmitted disease, the number of new infections transmitted to a susceptible population is a function of three variables: duration of infectiousness, efficiency (likelihood) of transmission of infection, and number of new sex partners a person has while infected (99). In the absence of measures to reduce susceptibility in the population (such as the use of effective vaccines), strategies addressing each of these variables can reduce transmission of infection. Such strategies include reducing the duration of infectiousness by treatment, decreasing the efficiency of transmission by measures aimed at reducing infectivity (e.g., condoms, microbicides), and reducing the number of sex partners. The following is a summary of what is currently known about the value of each of these approaches for preventing genital HPV infection.

Reducing Duration of Infectiousness

The most common approach to reducing infectiousness of an STD is treatment. In contrast to bacterial STD for which transmission can be prevented through curative treatment, there is only limited evidence that treatment of HPV-associated lesions is useful to prevent HPV transmission. There is no effective systemic therapy for genital HPV, as exists for bacterial and some other viral STD. Treatments are directed to lesions associated with HPV, and HPV infections in the absence of detectable disease are not treated. Current treatment options for both genital warts and cervical cancer precursors include various local approaches that remove the lesion (e.g., cryotherapy, electrocautery, laser therapy, surgical excision). Genital warts are also treated with topical pharmacologic agents (100). Treatment of genital warts and cervical cancer precursors might reduce infectiousness (100). Although this premise is difficult to test directly because assays for infectivity do not exist, it is supported by several observations. First, in some studies larger amounts of HPV DNA have been found in high-grade than in low-grade cervical lesions (101). Second, after clearance of genital warts after treatment with immune stimulating drugs (e.g. imiquimod), the amount of HPV DNA in the skin can be reduced (102). Third, clearance of HPV DNA can occur after standard therapy for cervical high-grade lesions (103-111). However, clinically normal skin and mucosa near HPV-associated lesions often contain HPV (112;113). This reservoir is thought to explain the typical recurrence rates of 10–20% after treatment of cervical lesions (114;115) and 20–50% after treatment of genital warts (100). It might also help explain the fact that treatment of partners does not influence recurrence rates of genital warts (116). Thus, based on the limited existing data, currently available therapies for HPV-related

lesions may reduce but probably do not eliminate infectiousness; the impact of the reduction in viral concentration which occurs with treatment remains unclear.

Reducing Efficiency of Transmission

Efficiency of transmission, or the likelihood that an infection will be transmitted from an infected person to an uninfected person, can be affected by several variables, such as immunity. However, for STD, the most common approach is the use of physical barriers such as condoms. In the future, other methods that may decrease the likelihood that an infection will be transmitted could include chemical barriers, such as microbicides or a combination of chemical and physical approaches.

Condoms

Evidence for the effectiveness of the male latex condom to prevent various STD among heterosexual men and women was the subject of a recent NIH report (117). The report concluded that for the majority of STD, published data were not adequate to definitively assess the effectiveness of condoms to prevent STD. The review also concluded that most epidemiologic studies that evaluated condom use had significant methodologic problems. For HPV specifically, the NIH report concluded that most of the reviewed studies did not obtain sufficient information on condom use to allow careful evaluation of the association between condom use and HPV infection or disease. The report also concluded that there was no epidemiologic evidence that condom use reduced the risk of HPV infection, but that condom use might afford some protection in reducing the risk of HPV-associated diseases, including warts in men and cervical neoplasia (cervical cancer precursors and invasive cancer) in women (117). More recently, an even more detailed review of the published literature on condoms and HPV infection and its sequelae came to similar conclusions as the NIH report and elaborated on the many methodologic issues affecting studies of condoms for HPV prevention (118). In addition, several other recent studies reported that, for women and men, use of male condoms reduces the risk of genital herpes and chlamydia, both of which may be co-factors for the development of cervical cancer (81;82;119-124). Below is a summary of current scientific evidence on the effectiveness of male condoms for prevention of genital HPV.

As described above, available clinical and epidemiologic data indicate that genital HPV infection is transmitted by contact with infected skin or mucosa. Laboratory studies have demonstrated that latex condoms provide an essentially impermeable barrier to particles the size of HPV (125;126). Studies of HPV infection in men demonstrate that most HPV infections (both HPV DNA and HPV-associated lesions) are located on parts of the penis that would be covered by a condom (48;54-57;63;127-129). However, even consistent and correct use of condoms would not be expected to offer complete protection from HPV infection because infections also may occur on sites not covered or protected by a condom. In men, HPV infection can occur on the scrotum, groin area, base of the penis, and anus (54-57). In women, HPV infection can occur on the outside of the vulva, which can come into contact with the genital skin of a man using a condom

Published studies that have assessed the effectiveness of male condoms to prevent HPV infection or any STD other than HIV are limited by multiple methodologic issues (117;118). In general, these limitations are likely to underestimate condom effectiveness (130-132). Studies with

optimal designs would collect information on consistent and correct condom use and would be able to determine whether HPV infection preceded or followed condom use. In addition, several recent studies have demonstrated that many individuals use condoms in situations of perceived STD risk (e.g., with sex partners known to have STD or who have other partners), thereby complicating valid comparisons with those not using condoms, who often have lower sexual risks (133;134). Furthermore, valid estimates of condom effectiveness can be obtained only when users and nonusers have similar levels of exposure to infected partners as illustrated in a recent study of gonorrhea and chlamydia (123). This study showed a protective effect for condoms among persons whose sex partners were known to be infected, but not among those whose partners were not known to be infected. Data on whether partners have HPV infection has not been available for most studies of condoms and HPV infection.

Studying the relationship between condom use and HPV infection is particularly difficult compared to other STD. In contrast to viral STD such as HIV and genital herpes for which highly accurate blood tests allow conclusive determination of infection, accurate blood tests for genital HPV infection do not exist at present. The detectability of HPV DNA in a given individual varies over time (68;135); therefore, determining if a person is infected or if an infection is new or pre-existing is very difficult. Finally, it is also difficult to study outcomes that take many years to develop (e.g., high-grade cervical cell abnormalities, invasive cervical cancer). The optimal study design to ensure valid measurements is a randomized, controlled trial. However, because randomization (assigning some individuals to use condoms and assigning others not to use condoms) can be problematic and potentially unethical (118), this study design is rarely used.

We evaluated 46 peer-reviewed publications in English available after January 1966 that included information on the association between condom use and HPV infection or a sequelae (e.g., genital warts, HPV-associated lesions including cervical cancer precursors, or invasive cervical cancer) (21;26;28;30;31;39;46;48;49;52;84;86;87;136-168). We excluded publications that evaluated HIV-infected persons or used only HPV blood tests. These studies represent a variety of geographic areas and populations. Of the 46 studies, 23 evaluated condom use and prevalent or incident HPV infection by detection of HPV DNA, and 25 evaluated sequelae of infection. The studies of sequelae included five that measured clinical findings of warts or HPV-suggestive lesions on the external genital skin, 10 that measured low- or combined low-grade and high-grade cervical cell abnormalities, six that evaluated high-grade cervical cell abnormalities, and nine that evaluated cervical cancer, six of which were studies of invasive cervical cancer. In most studies, condom use was generally defined broadly, as “ever versus never” or “use versus non-use”; in some studies the definition of condom use was not specified. Only 14 studies measured consistent condom use, and none measured correct use. Forty studies were cross-sectional (so the temporal relationship between condom use and HPV outcome could not be easily determined); two studies were randomized.

Of the 23 studies that measured HPV infection, 18 were conducted in women only, four in men only, and one in both women and men. Estimates of the level of risk reduction varied broadly. Three studies in women reported a protective effect of condoms which was statistically significant (151;152;153). None of the studies measured exposure to infected partners.

Of the 10 studies that measured either low-grade cervical cell abnormalities, or combined low-grade and high-grade cervical cell abnormalities, one study found a statistically significant reduction in cervical cell abnormalities.

Of the five studies that measured external genital HPV-associated lesions, three evaluated women (all genital warts), three evaluated men (one with genital warts and two with HPV suggestive lesions of the penis), and one evaluated both women and men (48;139;142;145;164). Of the three studies in women, one found a statistically significant reduction (30%) in genital warts (164) and one found a reduction in risk that was not statistically significant (142). All three studies in men found statistically significant protection with levels ranging from 30–70% (48;145;164).

Of the six studies that measured cervical cancer precursors (including carcinoma in situ), two studies found a reduction of risk which was statistically significant (136;137;146;154;158;166). Nine studies evaluated women with cervical cancer, six of which were invasive cervical cancer (138;140;143;149;155;156;159;162;166). Of the nine studies, seven found a reduction in risk of cancer in women using condoms, two of which were statistically significant. The reduction in risk ranged from 20–80%.

Three studies evaluated the effect of condoms on clearance of HPV DNA or HPV-associated lesions; all of these studies found a benefit of condom use for both men and women (145;167;168). Two of these studies were the first studies of condoms and HPV infection to be conducted as randomized controlled trials, an approach which can substantially reduce bias. In the randomized studies, monogamous couples were randomized to condom use or nonuse; females with a male partner that used condoms had significantly higher rates of clearance of both HPV infection (53% vs. 35%), and cervical cell changes (23% vs. 4%) than the females whose male partner did not use condoms (168). Also, men in the study had significantly faster regression of genital lesions consistent with HPV infection (167).

Available studies suggest that condoms reduce the risk of the clinically important outcomes of genital warts and cervical cancer. One possible explanation for the protective effect of condoms against warts and cancer is that condom use could reduce the quantity of HPV transmitted or decrease the likelihood of re-exposure, thereby decreasing the chance of developing clinical disease (14;118;168). An alternative explanation is that condom use may reduce exposure to a co-factor for cervical cancer, such as chlamydia or genital herpes, thereby reducing the chance of cervical cancer (81;82;119-122;124;169).

However, all published epidemiologic studies have significant methodologic limitations which make the effect of condoms in prevention of HPV infection unknown. As noted on page 14, three studies on genital HPV and condom use showed a protective effect, but most studies on genital HPV infection and condom use did not show a protective effect.

Given these observations, as well as the facts that laboratory studies show that latex condoms provide a barrier to HPV and that most genital HPV in men is located on areas of the skin covered by a condom, the cumulative body of available scientific evidence suggests that condoms may provide some protection in preventing transmission of HPV infections but that

protection is partial at best. The available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection. There is evidence that indicates that the use of condoms may reduce the risk of cervical cancer.

Microbicides

Evaluation of the ability of microbicides to prevent genital HPV infection has been hampered by the difficulties with in vitro cultivation of HPV (14). Recent laboratory work suggests that some compounds may inhibit HPV (170-174). There are also some reports of a potential effect of microbicides in the prevention of cervical cancer (143;156;159;172;175). Future microbicides may be effective in preventing HPV, as well as other sexually transmitted infections. Clinical studies of some of the compounds found to have an effect on HPV in the laboratory are underway.

Reduction of Sexual Behavior Risk

Because of the important role sexual contact plays in the transmission of genital HPV infection and because of limited evidence that other prevention approaches are highly effective, the most effective personal prevention approach is to avoid contact with genital HPV infection by limiting the number and type of sexual partners. The studies that demonstrate genital HPV transmission by sexual intercourse and other genital contact support the premise that abstaining from all genital contact, including non-penetrative contact, is the most effective approach to preventing infection (21;88;90;176). However, no studies have evaluated the effectiveness of programs which promote limiting the number of partners in preventing genital HPV infection. For individuals who choose to be sexually active, data from studies of both HPV incidence and prevalence support the notion that long-term monogamy with a single partner is likely to be the next most effective approach to prevent infection.

The choice of partner is likely to be important in the success of this approach because approximately 20% of women with only one lifetime sex partner have HPV infection (25;177). Knowing if a man is infected with HPV is difficult because most infected men are asymptomatic (64). Furthermore, testing men to find out if they are infected is impractical because of uncertain sensitivity of HPV testing in men and the lack of a test which has been approved for this purpose. The most important factors that decrease the likelihood that a man is infected with genital HPV include his having had a limited number of prior sex partners (45;52), possibly having a longer period of time since his last partner (allowing prior infections to spontaneously resolve) (21), and being circumcised (46;52). The most important factor that may decrease the likelihood that a woman is infected with genital HPV include her having had a limited number of prior sex partners (21;28). In addition, characteristics which may increase the chance that a partner is infected with genital HPV include the presence of genital warts, an abnormal Pap test in women, and immune suppression (64). However, determining a partner's sexual history or assuring their monogamy in a long-term relationship is sometimes difficult, a problem that could reduce the effectiveness of partner selection approaches to prevention.

Vaccines

In contrast to other prevention approaches, vaccines can reduce susceptibility in uninfected partners by stimulating the immune system. A variety of HPV vaccines are under investigation which may provide immunity to a combination of high-risk or high- and low-risk HPV types

(178). The goals of HPV vaccines are to prevent HPV-associated sequelae including genital warts, cervical cancer precursors, and cervical cancer by preventing HPV infection altogether or by reducing the chance of persistent infection if infection does occur. A recently completed economic model concluded that vaccination for HPV, in combination with continued cervical cancer screening, would be a cost effective health intervention (179). In addition, a recent study projected that an effective vaccine could prevent 1,300 deaths annually from cervical cancer if all 12-year-old girls currently living in the United States were vaccinated (180). Although an effective HPV vaccine would be a major advance in approaches to HPV prevention, it would not replace other prevention strategies such as cervical cancer screening or protective sexual behaviors since vaccines would not work for all genital HPV types and would likely not be 100% effective.

HPV vaccines have shown encouraging success in clinical trials (181). Recently, a vaccine for HPV-16 given to adolescent girls demonstrated 91% efficacy in preventing HPV-16 infection and essentially complete protection (100% efficacy) in preventing persistent HPV-16 infection. Although there were only a few cases, the vaccine also appears promising in the prevention of cervical cancer precursors (181). Studies of other formulations of HPV-16 vaccines as well as vaccines with multiple HPV types are underway and are likely to provide an important new approach for genital HPV prevention within the next several years. Surveys of young women who are potential candidates for an HPV vaccine indicate that they have positive attitudes about receiving a vaccine (182).

Prevention of Cervical Cancer

Decades ago, cervical cancer was one of the most common and deadly cancers in women in the United States (97;183). In the past 40 years, widespread cervical cancer screening using the Pap test, and treatment of precancerous cervical abnormalities have resulted in a dramatic decrease in the incidence and mortality due to cervical cancer in the United States (97;183). The purpose of screening with the Pap test is to detect cervical abnormalities that can be treated, thereby preventing progression to invasive cervical cancer, and also to detect invasive cervical cancer at a very early stage. Progression from cervical cancer precursor lesions to invasive cancer is a slow process, estimated to take 10–15 years (16). If detected early and managed promptly, survival rates for cervical cancer are over 90%. In 2003, an estimated 12,200 women in the U.S. will develop cervical cancer and an estimated 4100 women will die from the disease (66). Approximately half of the cases will occur in women who have never been screened, and an additional 10% will occur in women not screened within the past 5 years (2). A recent national survey indicated that cervical cancer screening is not adequate among some women in the U.S.; approximately 18% of women have not had a Pap test in the last 3 years (184). The most important factors associated with inadequate cervical cancer screening include absence of a usual source of health care, lack of health insurance, and immigration to the U.S. in the last 10 years. Other factors included older age, low income, low level of education, presence of chronic disabilities, and Asian and American Indian/Alaska Native race/ethnicity (184). Death rates from cervical cancer in the U.S. are higher among foreign-born women than women born in the U.S. (185).

New technologies including liquid-based cytology and testing for high-risk HPV types may offer potential advantages over conventional Pap testing. The American Cancer Society and other

organizations have incorporated these technologies into new guidelines for cervical cancer screening (115;186;187). However, the largest gain in reducing the burden of cervical cancer incidence and deaths could best be achieved by increasing screening rates among women who have never or rarely been screened (186).

Summary of Strategies to Prevent Genital HPV Infection

Based on currently available science, the following recommendations summarize the strategies most likely to be effective in preventing future infections with genital HPV infection and cervical cancer.

Individual Strategies

- The surest way to eliminate the risk for future genital HPV infections is to refrain from any genital contact with another individual.
- For those who choose to be sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections. However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected.
- For those choosing to be sexually active and who are not in long-term mutually monogamous relationships, reducing the number of sexual partners and choosing a partner less likely to be infected may reduce the risk of genital HPV infection. Partners less likely to be infected include those who have had no or few prior sex partners.
- While available scientific evidence suggests that the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of the HPV-associated diseases of genital warts and cervical cancer. The available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection, but it does indicate that the use of condoms may reduce the risk of cervical cancer.
- Regular cervical cancer screening for all sexually active women and treatment of precancerous lesions remains the key strategy to prevent cervical cancer.
- In the future, receiving a safe and effective HPV vaccine to help prevent genital HPV infection as well as the HPV-associated diseases of genital warts and cervical cancer would be an important prevention measure. However, an effective HPV vaccine would not replace other prevention strategies.

Public Health Strategies

Public health agencies should:

- Promote increased cervical cancer screening among never and rarely-screened women and appropriate follow-up of those with abnormal Pap tests.
- Work with public and private partners to increase awareness about prevention of genital HPV infection and cervical cancer among health care providers and in the general public.
- Collaborate with private industry to promote and accelerate the development of a safe and effective HPV vaccine.
- Continue epidemiologic, laboratory, and behavioral research on genital HPV infection, including studies of the prevalence of HPV in the United States, research on the attitudes and concerns of women diagnosed with HPV infection (e.g., concerns about cancer or about transmission), and surveys of provider knowledge and practices regarding HPV.

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