Human Papillomavirus And Cervical Cancer

P A P E R # 8 • M A Y 2 0 0 0

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JHPIEGO, an affiliate of Johns Hopkins University, is a nonprofit corporation dedicated to improving the health of women and families throughout the world. JHPIEGO works to increase the number of qualified health professionals trained in modern reproductive healthcare, especially family planning.

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Background

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the world, occurring at some point in up to 75% of sexually active women (Groopman 1999). Although HPV infection is widespread, few people even know they are infected because they seldom have noticeable symptoms. For example, males with virus infecting the cells of the urethra rarely have a discharge or visible lesions on the penis. Even less well known is that nearly all cervical cancers (99.7%) are directly linked to previous infection with one or more of the oncogenic (cancer-inducing) types of HPV (Judson 1992; Walboomers et al 1999). While women, and men as well, usually are infected shortly after they become sexually active in their teens, 20s or 30s, progression to cervical cancer generally takes place over a period of 10 to 20 years. Rarely, some early lesions can become cancerous over a shorter time interval—within a year or two.

It is estimated that for every 1 million women infected, 10% (about 100,000) will develop precancerous changes in their cervical tissue (dysplasia). Of these, about 8% (8,000 women) will develop early cancer limited to the outer layers of the cervical cells (carcinoma *in situ* [CIS]) and roughly 1,600 will develop invasive cancer unless the precancerous lesions and CIS are detected and treated. In addition to cervical disease, there is increasing evidence that people with HPV who engage in anal intercourse may be at high risk for precancerous anal lesions as well as squamous cell cancer. For example, among homosexual men, about 60% of those who are seronegative for HIV carry the HPV virus, while nearly 95% of seropositive men have HPV (Moscicke et al 1999). Moreover, they have been found to carry the same types of genital papilloma viruses (e.g., types 16 and 18) that cause cervical cancer. Finally, women with active infection can transfer the virus to their newborn (vertical transmission) during delivery, which can result in papilloma virus infection in the neonate and possible subsequent laryngeal papillomatosis (Cason, Rice and Best 1998).

Currently there is no treatment for HPV infection; therefore, once infected, a person is most likely infected for life. In most cases, an active infection is controlled by the immune system and with time becomes dormant; however, it is not possible to predict whether or when the virus will become active again. For example, one recent study followed more than 600 female university students who were tested every 6 months (Groopman 1999). Over the course of 3 years, new HPV infections occurred in more than 40% of the women. Most infections lasted about 8 months and then subsided. After 2 years, however, about 10% of the women still carried active virus in the vagina and cervix. In this study, the persistent infections were most commonly with the virulent, cancer-linked types.

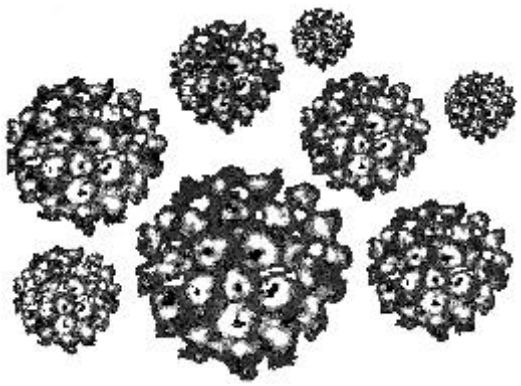
The Virus

Papilloma viruses were first recognized many years ago as the cause of warts on the hands and feet or condyloma accuminata on the pubic area (penis and urethra in males or vulva and vagina in females). For years, warts

were considered mainly a nuisance or ugly, rather than a forerunner of cancer. Indeed, warts on fingers and toes usually are not dangerous, but virus types that target the face can make skin cancer more likely. Still others that grow largely in the mouth, producing pea-sized lumps, can develop into fatal squamous cell cancers (Terai et al 1999).

The papilloma virus is relatively small—just two strands of DNA contained in a round shell, or envelope, that looks like a golf ball when enlarged under an electron microscope (**Figure 1**).

Figure 1. Electron Photomicrograph of Human Papillomavirus



Source: Stannard/Photo Researchers 1998.

Because HPV cannot be cultured and a reliable serologic test was not available until recently, it has been difficult to collect accurate information about the incidence and course of HPV infections. For example, prior to the 1990s the only way cervical infection with HPV could be detected was by examining cells from Pap smears microscopically or by looking at the cervix through a colposcope (a special instrument that magnifies the cervix so that abnormal changes can be seen more easily). Now, using DNA testing, which is available on a research basis, nearly a hundred types of papilloma virus have been identified. It is still not known, however, why certain HPV types target skin on the hands or feet while others attack the lining cells of the mouth, and still others the genitalia of both males and females (Terai et al 1999).

A link between HPV infections and cervical cancers was first demonstrated in the early 1980s. DNA testing has identified nearly 20 papilloma types that primarily infect the cervix, vulva and vagina in women; the penis in men; and the urethra and anus in both sexes. Of these, only four are most often found within cervical cancer cells (so called “high risk” types), with type 16 accounting for about half the cases in the United States and Europe. In Latin America, by contrast, types 39 and 59 are the most prevalent types, while in West Africa, type 45 is common (Groopman 1999; Stewart et al 1996). And, as mentioned previously, HPV is present in virtually all cases of cervical cancer (Walboomers et al 1999).

How HPV Induces Cancer

Cervical cancer is probably one of the best known examples of how infection with a virus can lead to cancer. In humans and animals, cell division is regulated largely by two proteins— one called Rb and the other p53. Recently it has been found that two genes in HPV, the so-called E6 and E7 genes, produce proteins that can attach themselves to Rb and p53 and block their effect on regulating cell division (Massimi and Banks 1997). When this happens, the infected cells reproduce without

any control. While the virus serves only as the initiating event, over time some of the wildly growing cells develop permanent changes in their genetic structure that cannot be repaired. Once this happens, some may eventually turn into cancer cells.

In the early stages, virus-infected cervical cells may show only small changes in size and shape when examined microscopically. With time, however, not only do the cells expand and become more distorted, but their neat arrangement in rows or columns on the surface of the cervix is destroyed. These changes are consistent with those of cervical dysplasia, or cervical intraepithelial neoplasia (CIN) of varying degrees of severity, as seen by the pathologist when examining a biopsy specimen of cervical tissue. Left untreated, in some women these premalignant cells will slowly replace the normal cells on the surface of the cervix and carcinoma *in situ* will develop. Finally, when the cells begin to grow through the normal surface layer into the muscle and deeper tissues, full-blown cancer is present.

Risk Factors for Cervical Cancer

Epidemiologic studies have identified a number of factors that play a significant role in the development of CIN, a precursor to cervical cancer (Palank 1998). As shown in **Table 1**, the type and pattern of sexual activity, especially in teenagers, is a major factor in determining whether a person becomes infected with HPV. As a result of relaxed attitudes about sexuality among adolescents in many cultures, the number of sexual partners that teenagers have before age 20 can be quite large, and each of their partners also may have had multiple partners. As a consequence, this pattern of sexual activity increases their risk of exposure to STDs, especially HPV.

Table 1. Risk Factors for Cervical Cancer

RISK FACTORS
Sexual activity (< 20 years)
Multiple sexual partners
Exposure to STD
Mother or sister with cervical cancer
Smoking
Immunosuppression
• HIV/AIDS
• Chronic corticosteroid use (asthma and lupus)

Another risk factor is having a blood relative (mother or sister) with cervical cancer. Magnusson, Sparen and Gyllensten (1999) compared the incidence of dysplasia and CIS in relatives of women with disease and in age-matched controls. They found a significant familial clustering among biological, but not adoptive, relatives. For biological mothers compared to control cases, the relative risk was 1.8 whereas for adoptive mothers the relative risk was not significantly different from controls (1.1). For biological full sisters, the relative risk was even higher (1.9) versus 1.1 for non-biological sisters. These data provide strong epidemiological evidence for a genetic link to the development of cervical cancer and its precursors.

Suppression of the immune system due to HIV infection also is an important risk factor because it makes the cells lining the lower genital tract (vulva, vagina and cervix) more easily infected by the cancer-inducing types of HPV (Stentella et al 1998). Other less common conditions that cause immunosuppression include those requiring chronic corticosteroid treatment, such as asthma or lupus (McDonald 1999). Women also increase their risk for CIN by engaging in other behaviors known to suppress the immune system. These include the use of recreational drugs, alcohol and cigarettes. The latter is particularly important because while a decrease in smoking among men has occurred, the number of women who smoke has increased dramatically in recent years—especially in teenage girls (McDonald 1999). Nicotine and the byproducts of smoking are thought to increase a woman's relative risk for cervical cancer because they concentrate in the cervical mucus and decrease the immune capability of Langerhan's cells to protect cervical tissue from invading oncogenic factors, such as HPV infection (Ylitalo et al 1999).

In addition, there is substantial evidence that HIV-positive women are at increased risk of developing cervical cancer as well (Judson 1992). In two studies, both from high HIV prevalence areas, a statistically significant association between HIV and CIN was reported. Because the number of adolescents, as well as adults, with HIV is rising in most countries where cervical cancer is largely untreated, it can be expected that cervical cancer rates will continue to increase, especially in areas where STDs and HIV/AIDS rates are high.

Finally, in many developing countries, women who have abnormal Pap smears frequently do not receive treatment at an early stage when cervical cancer could be prevented because:

- there are long delays in reading and reporting the results;
- it is difficult to locate the patient once the report becomes available;
- the cost of treatment is not affordable for many women, even when simple outpatient procedures are used; and
- there is a lack of equipment as well as service providers trained to use and maintain it.

As a consequence, even in countries where Pap smears are available, many women may not get the treatment they need in a timely manner.

Preventing Cervical Cancer

As mentioned above, HPV is the most prevalent sexually transmitted infection in the world. And, unlike other STDs such as gonorrhea or HIV/AIDS, use of condoms and other safe-sex practices may not be nearly as effective in preventing infection. This is because the papilloma virus lives in the skin (squamous) cells covering the pubic area (vulva and shaft of the penis) as well as the interior cells lining the vagina and cervix in women, and urethra and anus in both sexes. Condoms do not cover the entire shaft of the penis nor do they block contact with pubic skin. Therefore, during intercourse, even with a condom, skin cells containing HPV can

come in contact with a woman's vulva or vagina, enabling the virus ultimately to reach the cervix. In addition, the friction of sexual intercourse is believed to cause tiny, microscopic tears in the vaginal wall, making transmission far more likely. Moreover, even dead cells shed during intercourse can contain the virus and remain infective for days (Roden, Lowy and Schiller 1997).

Primary Prevention

The most effective way to prevent cervical and other genital cancers would be a vaccine. Individuals would need to be immunized at an early age before they are sexually active. The benefits of such a vaccine would be particularly significant in developing countries, where women's healthcare services are minimal. Designing a vaccine, however, will not be easy because people's immune response appears to be specific to the type of HPV. For example, a person protected against type 16 would still be at risk of infection with other cancer-inducing types, such as 18 or 33. There also appear to be subtypes or variants within type 16, and perhaps with other types as well. Finally, as mentioned above, the types of HPV associated with cervical disease vary by geographical area. With the increase in international travel, the various carcinogenic types soon will be spread throughout the world. Therefore, a vaccine with a mixture of several types would have to be created (Groopman 1999; Stewart et al 1996).

Despite these problems, safety testing of at least two vaccines that could protect women from cancer-linked papilloma viruses is underway. Estimates are, however, that it will be several years before either would be available, and many more years before they would be affordable in developing countries. Finally, there also are attempts to produce a therapeutic vaccine, one which would boost the immune system of someone who is already infected and cause the cancer to regress or even disappear. These vaccines are targeted to inactivate the E6 and E7 proteins, those viral proteins that block the action of the cell growth regulating proteins (Rb and p53) (Massimi and Banks1997).

Until such time that a protective vaccine is widely available, primary prevention must focus on continuing to change sexual practices and other behaviors that increase a person's risk of becoming infected. Just as with the fight against HIV/AIDS, risk reduction counseling related to the risk factors listed above (**Table 1**) must be incorporated into all levels of the healthcare system, especially those dealing with young people. The messages must include alerting teenagers that practices designed to minimize the risk of STD or HIV/AIDS exposure (i.e., the use of male or female condoms) may not be as effective for HPV prevention.[1] In addition, vigorous efforts to discourage adolescents, especially young girls, from starting smoking and initiating sexual activity must be widely and continuously disseminated.

[1] A recent case-control study, however, has shown that

male condom use, which significantly decreases the amount of infectious virus deposited in the vagina during sexual intercourse, offers substantial protection (Wen et al 1999).

Secondary Prevention

Although at present prevention of HPV infection is difficult, for women already infected the immediate need is:

- to identify those with early, easily treatable precancerous lesions; and
- to cost-effectively treat them before the lesions progress to cancer.

Since 1989, JHPIEGO has been exploring the feasibility of several low-cost alternatives for cervical cancer detection. Prominent among these is unmagnified (naked eye) visual inspection using a dilute solution of acetic acid (VIA). In March 1999, researchers from JHPIEGO and the University of Zimbabwe reported in *The Lancet* that the sensitivity (77%) and specificity (64%) of VIA are comparable to those of good quality Pap smears. This large-scale study, which involved more than 10,000 women attending primary healthcare clinics in Zimbabwe, confirmed the findings of similar studies in South Africa and India (Sankaranarayanan et al 1998). A second major finding from the Zimbabwe study was that nurse-midwives, who did all the VIA tests, quickly learned to competently perform them. This finding is important because the vast majority of developing country women who need to be tested live in areas where there are no doctors and where Pap smears may never be available. Furthermore, unlike Pap smears that require several days to a week to get the results back, with VIA the results are available immediately.

As a consequence, these nurse-midwives were able to quickly and easily identify women with no disease, those with abnormal findings suitable for immediate treatment and those with very large lesions or advanced disease requiring referral.

With the establishment of VIA as an acceptable alternative to Pap smears (Kitchener and Symonds 1999), it is now possible to offer VIA with outpatient treatment of precancerous lesions at the same visit. For example, cryotherapy, which involves freezing the cervix with a liquid coolant such as carbon dioxide to destroy the abnormal cervical tissue, is highly effective. And cryotherapy has been used extensively throughout the world for more than 20 years (Cox 1999; Mitchell et al 1998; Olatunbosun, Okonofua and Ayangade 1992). Cryotherapy is also one of the easiest methods to learn and can be performed by nurses and other healthcare workers.

In light of these promising epidemiologic studies and the availability of a simple, low-cost outpatient method of treatment, the opportunity to markedly reduce the incidence of cervical cancer globally is at hand. As the first step (Phase 1) in this process, JHPIEGO is conducting several safety, acceptability, feasibility and program effectiveness (SAFE) demonstration projects in separate regions of the world. These SAFE projects are needed to:

- show that nurses and midwives can

competently perform **both** VIA and cryotherapy in low-resource settings,

- demonstrate that nurses and midwives can confidently treat or refer women with abnormal (precancerous) lesions, and

- document the acceptability and feasibility of cervical cancer testing that is directly linked to immediate treatment.

We anticipate the results of these studies will show that well-trained nurses and midwives can quickly and easily identify patients who are appropriate for immediate treatment with cryo-therapy or refer those requiring more aggressive treatment (or those with advanced disease). We also expect to learn that a test, treat or referral program is a safe, acceptable and feasible approach for preventing cervical cancer in low-resource settings. Finally, we anticipate identifying ways in which large-scale Cervical Cancer Prevention (CECAP) programs can be implemented nationally through a combination of individual and community education, participation by local non-governmental organ-izations and women's groups, and sponsorship by indigenous service organizations and clubs.

This practical approach to preventing cervical cancer has the potential to reduce disease progression and death in a majority of women who currently do not have access to Pap smears and physician-staffed services. Also, it has the potential to reduce referrals of women with early lesions to higher levels of the healthcare system as well as increase the chance of detecting invasive cancer at an earlier stage when it can be treated successfully. Finally, once a precancerous lesion is treated, a woman's risk of developing an infection with other HPV types may be reduced for several years, while those women found to be normal may not need retesting for 5 or more years (Lonky et al 1997; Lonky et al 1999).

Summary

Human papillomavirus is the most prevalent STD in the world, occurring at some point in up to 75% of sexually active women. Nearly all cervical cancers are directly linked to previous infection with one or more of the oncogenic types of HPV. Other risk factors for cervical cancer include sexual activity at a young age, multiple sexual partners, immunosuppression and HIV infection. Lacking an appropriate vaccine for HPV, primary prevention of cervical cancer must focus on condom use and changing sexual practices as well as other behaviors that increase a person's risk of becoming infected with HPV.

For women already infected with HPV, the immediate need is to identify those with early, easily treatable precancerous lesions and to treat these women cost-effectively before the lesions progress to cancer. Visual inspection using a dilute solution of acetic acid (VIA) has been established as an acceptable alternative to Pap smears. Therefore, it is now possible to offer VIA with cryotherapy, an outpatient treatment that uses a liquid coolant to destroy abnormal cervical tissue. Cryotherapy is highly effective and has been used extensively throughout the world for more than 20 years. Once a precancerous lesion is treated, a woman's risk of developing an infection with other HPV types may be reduced for several years, while those women found to be normal may not need retesting for 5 or more years.

During the next 2 years, JHPIEGO will conduct demonstration projects in separate regions of the world to test the safety, acceptability, feasibility and program effectiveness of this approach.

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