Cervical Cancer Screening Sloan Kettering

Approximately 11,000 women are diagnosed with cervical cancer and 4,000 die from the disease each year in the United States. Cervical cancer remains a major cause of morbidity and mortality in developing countries. However, the incidence of invasive cervical cancer (defined as cancer that has spread from the surface of the cervix to tissue deeper in the cervix or to other parts of the body) in industrialized countries has dramatically decreased since the introduction and popularization of cervical screening cytology techniques (Pap smear) in the latter half of this century.

Rates in the United States have decreased by more than 50 percent, from approximately 14 new cases per 100,000 in 1973 to eight cases per 100,000 women in 1994. Due to this dramatic reduction in the incidence of invasive cervical cancer in industrialized nations, **cervical cancer now ranks among the less common female malignancies in the United States.** Moreover, recently in some developing countries, age-adjusted cervical cancer mortality rates have decreased due to improved organization of national cervical cancer screening programs and more efficient utilization of existing resources.

**These reductions are mostly due to the popularization of the Pap smear.** The Pap smear cervical screening has been accepted by gynecologists as a standard of gynecologic care for years in spite of lack of prospective randomized trials specifically looking at mortality from cervical cancer as an end point. It is unlikely that further trials evaluating the value of Pap smear screening cytology will be conducted.

As for detection of other gynecologic cancers, early detection of cervical cancer is essential. Carcinoma of the cervix and its precursors usually occur among women who are sexually active. Commonly **accepted risk factors** related to **sexual activity** and associated with cervical cancer include the following: **early onset of vaginal intercourse, a greater number of lifetime sexual partners, and history of sexually transmitted diseases including human**
papillomavirus (HPV) infection. In addition, smoking, age, nutritional status, and immune function are correlated with cervical dysplasia and carcinoma. At the present time, the most important risk factor for cervical cancer appears to be genital infection with high-risk strains of HPV, which is usually acquired sexually. Using modern HPV-detection techniques, it appears that the majority of women with cervical cancer have detectable HPV DNA.

Cervical Cancer Screening Tests

Both liquid-based and conventional methods of cervical cytology tests are acceptable for use in screening. Liquid-based cytology (e.g., ThinPrep®) may have improved sensitivity over conventional Pap smear screening, but at a higher cost. Liquid-based cytology also permits testing of specimens for HPV, which may be useful in guiding management of women whose Pap smears reveal what are known as atypical squamous cells of undetermined significance, or ASCUS. The role and utility of HPV testing as an alternative or adjunct to primary Pap screening continues to evolve. Adding HPV testing to conventional screening may be beneficial.

The cervical cancer screening guidelines of the American Cancer Society (ACS) recommend initiating screening three years after onset of sexual activity but no later than age 21. The ACS recommends annual screening with conventional Pap tests, or screening every two years if liquid-based cytology is used, until age 30. Thereafter, the screening interval can be extended to every two to four years based on past screening results and risk factors.

The American College of Obstetrics and Gynecology (ACOG) now recommends that cervical cancer screening begin at age 21 regardless of age of onset of sexual activity. The ACOG recommendations state that screening before age 21 should be avoided because it may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer. Women aged 21 to 29 years should undergo cervical cancer screening every two years with either a conventional or liquid-based Pap test. Women age 30 or older who have had three negative results on annual Pap tests can
be screened with cytology every three years or continue with testing every two years.

Most medical societies and organizations agree that screening cytology with the addition of HPV-DNA testing (if both the cervical cytology and the DNA test are negative) should occur every three years. This combined testing is most appropriate for women age 30 and older because HPV is common in younger women and frequently is transient, resolving in one to two years. Women who have undergone a total hysterectomy, with removal of the entire cervix and without a history of cervical dysplasia or cancers, do not require any further Pap tests.

**Our Cervical Cancer Screening Guidelines**

**First Screening**
Our doctors recommend that women have their first cervical cancer screening at 21 years, regardless of age of first sexual intercourse.

**Women Up to Age 30**
For women up to the age of 30 years old, our doctors recommend cervical cytology testing (which can include Pap smears or liquid-based cytology) every two years.

**Women 30 Years and Older**
For women 30 years old and older, our doctors recommend one of the following three screening options:

- Cervical cytology testing (which can include Pap smears or liquid-based cytology) every two years.
- Women who have had three negative or satisfactory annual cytology tests may be screened with cytology every three years.
- Cytology plus HPV-DNA test. If both the cytology and the DNA tests are negative, screening should occur every three years.
In addition, women of any age who are immunocompromised (due to organ transplant, HIV infection, cancer chemotherapy, chronic steroid use for chronic renal or bowel disease, etc.) or who were exposed in utero to DES (a nonsteroidal synthetic estrogen drug) should be screened annually.

**HPV (Human Papillomavirus) Vaccination**

Globally more than 5 percent of all cancers are attributed to persistent infection with oncogenic (cancer associated) HPV. Approximately 274,000 women die annually from cervical cancer, mostly in developing countries where screening by Pap smear is not widely available. The development and broad utilization of the HPV vaccine can have a significant worldwide public health impact.

It is well established that having persistent, high-risk HPV infection in the lower genital tract substantially increases a woman's risk of developing cervical cancer. High-risk HPV types 16 and 18 are associated with 70 percent of cervical cancers worldwide. Also noteworthy is that these two high-risk types are found in more than 80 percent of cervical adenocarcinomas and adenocarcinoma in situ, which are increasing in rate and are particularly difficult to detect by cytology, histology, or colposcopy. Oncogenic HPV infection is associated with other anogenital cancers in both men and women, including vulvar, vaginal, anal, and penile cancers.

Although not considered cancer-causing, HPV types 6 and 11 are associated with 90 percent of anogenital warts, the most common sexually transmitted disease, now affecting 20 to 30 million American men and women. Transmission rate of HPV to the female partners of men with penile warts is high, with more than 70 percent of women developing a genital HPV infection after exposure.

In June 2006, the FDA approved a prophylactic, quadrivalent HPV vaccine for females aged nine through 26 years. The vaccine is effective against four HPV types -- 6, 11, 16, and 18. This human papillomavirus L1 virus-like particle vaccine offers protection against squamous cervical, vulvar, vaginal cancers and dysplasias, adenocarcinoma in situ, and genital warts.
associated with these HPV genotypes. The vaccine is given in three injections at zero, two, and six months.

The Federal Advisory Committee on Immunization Practices (ACIP) recommends that the vaccine be routinely given to females aged 11 to 12, but can be given as early as age nine. The vaccine can also be administered as a "catch-up" vaccination for women ages 13 to 26 who did not receive the vaccine earlier. These recommendations have also been endorsed by the American College of Obstetricians and Gynecologists and the American College of Pediatricians. The American Cancer Society concurs except in the case of females 19 years and older, since the ACS analysis concludes that there is insufficient evidence to recommend catch-up vaccination of all females over 18. Although studies in older age groups are under way, the concern is that the majority of females over 18 will have already been sexually exposed and possibly already infected, resulting in decreased efficacy.

More than 27,000 women worldwide have been studied with several years of follow-up. These studies have demonstrated continued safety, efficacy, and immunogenicity (eliciting an immune response) against the oncogenic HPV viral types 16 and 18, as well as protection from types 6 and 11. Over an average follow-up time of three years, women who were negative for HPV 16 and 18 ("per protocol" group) and received the vaccine demonstrated 98 percent vaccine efficacy for the primary end point of HPV-16- or 18-related cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3), adenocarcinoma in situ, and cervical cancer.

Although most HPV infections clear with time, the regression is dependent on an intact cell-mediated immune system. Immunodeficiency associated with HIV infection, organ or bone marrow transplants, immune-suppressive drugs such as chemotherapy and steroids, as well as the immune senescence of aging make it crucial to identify women who have persistent, oncogenic viral types. The usefulness of the HPV vaccines in these groups has not been established; clearly, regular Pap test screening should continue as well as high-risk HPV testing.
in combination with the Pap test in women over 30 when appropriate.

The potential to eradicate cervical neoplasias and reduce the incidence of other cancers with continued Pap screening programs and widespread HPV vaccination initiatives is significant. The most effective time to immunize is before the virus is acquired through sexual intercourse (approximate age of sexual debut in US females is between 15 and 16 years), prior to peak acquisition of multiple sexual partners (ages 15 to 24), as well as at an age when the vaccine produces the most robust immune response (ages 11 to 13). The safety of the vaccine has been well established. Reports from the first 11 months of US distribution have yielded an overall adverse event rate of 33/100,000 doses, with serious adverse events of 1.8/100,000 doses.

Further investigations are needed to determine the efficacy of the vaccine in males, older women, and the immune-deficient patient. Nor is it known how long the immunity will last. Results of ongoing studies in males and older women are anticipated in the next few years. While these issues are under investigation, more than six million Americans are newly infected with HPV each year. The debate about the mandatory use of the HPV vaccine and its prevention of sexually transmitted diseases is difficult for many, but also offers an opportunity for parents and educators to start the discussion about responsible sex. For now, the message is clear: Vaccinate early, and continue to screen with Pap smear regularly.

**TOP**

Recommendations of National and Specialty Organizations for Routine Immunization with the Quadrivalent HPV Vaccine

**The CDC (Center for Disease Control) Advisory Committee on Immunization Practices (ACIP)**

The ACIP recommends routine vaccination of 11- and 12-year-old females with three doses of quadrivalent HPV vaccine; the vaccination series can be started as young as age 9. Vaccination is also recommended for females aged 13 to 26
years who have not been previously vaccinated or who have not completed the full series.

**American College of Obstetricians and Gynecologists (ACOG)**
ACOG concurs with the recommendations of the ACIP.

**American Academy of Pediatrics (AAP)**
AAP concurs with the recommendation of the ACIP.

**Society of Gynecologic Oncologists (SGO)**
SGO "strongly supports and endorses the decision made by the ACIP."

**American Cancer Society (ACS)**
ACS recommends routine HPV vaccination of 11 and 12 as well as girls as young as age 9. HPV vaccination is also recommended for females aged 13 to 18 years to catch up missed vaccines or to complete the series. At this time there is not enough evidence for or against vaccination of all 19 to 26 year old females in the general population,

**Gynecology Disease Management Team, Memorial Sloan-Kettering Cancer Center**
The Gynecology Disease Management Team at Memorial Sloan-Kettering supports the recommendations of the ACIP, ACOG, and the SGO for HPV vaccination. We strongly recommend that regular Pap screening be continued for all women, even those who were vaccinated.
References


