National Cancer Institute

CANCER ADVANCES IN FOCUS

Cervical Cancer

Yesterday

- As recently as the 1940s, invasive cervical cancer was a major cause of death among women of childbearing years in the United States. However, with the introduction of the Papanicolaou (Pap) smear in the 1950s – a simple test that uses exfoliated cells to detect cervical cancer and its precursors – the incidence of invasive cervical cancer declined dramatically. Between 1955 and 1992, cervical cancer incidence in this country declined by 74%.

- Although epidemiologic evidence long suggested an association between sexual behavior (e.g., age at first intercourse, number of sexual partners) and cervical cancer, scientists and clinicians did not know the underlying reason for this link.

- In the early 1970s, cervical cone biopsy and hysterectomy were the mainstays of treatment. Clinical researchers were only beginning to develop and test more moderate procedures, such as cryosurgery, for treating preinvasive disease.

Today

- Cervical cancer – once one of the most common cancers affecting U.S. women – now ranks 14th in frequency in this population. In 2007, an estimated 11,150 women in the United States will be diagnosed with cervical cancer, and an estimated 3,670 will die of this disease. The lifetime risk of cervical cancer would be an estimated 3.7% in the absence of cervical cancer screening.

- In certain populations and geographic areas of the United States, cervical cancer death rates are still high, in large part due to limited access to health care and cervical cancer screening. Worldwide, especially in middle and low income countries, cervical cancer is the second most common cancer in women, and the third most frequent cause of cancer death, accounting for nearly 300,000 deaths annually.

- In 1996, the U.S. Food and Drug Administration (FDA) approved the use of the first *liquid-based, thin-layer slide preparation* as an alternative to the conventional Pap smear. This new technique separates cells from background material and provides a thin layer of cells for analysis. Various studies have suggested that liquid-based cytology is more sensitive than standard Pap smears in detecting cervical cancers and precancerous cellular abnormalities.

- Research conducted by NCI and other investigators throughout the 1980s and 1990s demonstrated that virtually all cases of cervical cancer are caused by persistent infection with specific types of human papillomavirus (HPV), which can be transmitted by sexual contact. There are more than 100 types of HPV. Of the 15 types that are considered to be cancer-causing, or oncogenic, HPV types 16 and 18 – which were first identified and molecularly cloned by researchers at the German Cancer Research Center – are responsible for about 70% of cervical cancers worldwide. In most women infected with HPV, however, the infection will resolve and cervical cancer will not develop; therefore, HPV infection is necessary but not sufficient for development of the disease.

- Highly-sensitive and specific molecular techniques for identifying HPV DNA in cervical specimens are now available. The current FDA-approved HPV DNA test can identify 14 of the high-risk strains associated with cell changes in the cervix. The NCI-supported ASCUS/LSIL Triage Study (ALTS) found that HPV DNA testing is sensitive in detecting underlying serious abnormalities among women with a Pap test diagnosis of ASCUS, or **A**typical **S**quamous **C**ells of **U**ndetermined **S**ignificance. An ASCUS result is considered to be borderline or ambiguous. The HPV DNA test can help to identify women who need further medical attention. The FDA has approved HPV testing, in conjunction with cytology, for screening women 30 years of age and older. If both tests are negative, screening is not repeated for three years.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institute of Health

- In June 2006, the FDA approved the vaccine Gardasil®, which is highly effective in preventing persistent infections with HPV types 16 and 18, two "high-risk" virus types that cause the majority of cervical cancers. Gardasil® also protects against HPV types 6 and 11, which cause about 90% of genital warts. The vaccine is based on technology developed by NCI scientists, whose work laid the foundation for the production of HPV "virus-like particle," or VLP, vaccines. Using genetic engineering techniques to manipulate the genetic material of the virus, scientists created a vaccine consisting of non-infectious VLPs formed by a single protein – the L1 protein – from the outer surface of HPV. The L1 protein triggers a robust antibody response that neutralizes HPV infection. Gardasil® is comprised of a mixture of HPV type 6, 11, 16, and 18 VLPs. Studies to date have shown that this vaccine provides protection against HPV 16 infection for at least 4 years. The vaccine is approved for use in females 9-26 years of age, but is most effective if given before the onset of sexual activity.

- Treatment for cervical cancer has improved considerably. The 5-year survival rate for women diagnosed with cervical cancer is close to 75%. Most cervical cancer patients receive radiation as part of their treatment. In addition, recent studies have demonstrated the value of chemotherapy treatment. Five large, randomized clinical trials found that chemotherapy administered with radiation therapy decreased the risk of death from cervical cancer by 30% to 50%, supporting the use of concomitant chemotherapy with radiotherapy for advanced disease. Cisplatin is the most common chemotherapy agent for cervical cancer.

Tomorrow

- Research on HPV vaccines is continuing. Cervarix™ (not approved for use in the United States), a second vaccine for preventing HPV infection, is in the late stages of clinical testing. This candidate vaccine is also based on the technology developed by NCI scientists. Initial studies of this vaccine – which also targets HPV types 16 and 18 – have shown that Cervarix™ protects against persistent infection with these two HPV types, and may also confer some protection against very closely related HPV types. An NCI-sponsored Phase III clinical trial underway in Costa Rica – where HPV infection is particularly high – is evaluating the safety, efficacy, and other performance characteristics of Cervarix™. The approximately 7,500 women participating in this trial will be followed for at least 4 years.

- Although Cervarix™ and Gardasil® protect against infection with HPV types 16 and 18, these vaccines do not protect against HPV types found in approximately 30% of cervical cancers. Including VLPs from other oncogenic types of HPV in the vaccines is one approach to increase protection against the other viruses. In an alternative approach, researchers are now working to develop a vaccine targeted against a minor surface protein of HPV, known as L2, which contains regions that induce neutralizing antibodies against a broad range of HPV types. This property means that a single vaccine targeting the L2 protein may have the potential to provide broad protection against many HPV types.

- Studies of other experimental vaccines for treating HPV infection also are underway. Many of these experimental vaccines target two HPV oncogenic proteins, E6 and E7, which play an important role in inducing and maintaining cellular transformation.

- Scientists are striving to better understand why HPV infections resolve in most women but persist in others and lead to cervical cancer in only some women with persistent infections. Efforts to characterize the molecular pathways in cervical cancer cells, and to better understand how the interplay between these cells and their microenvironment may affect cancer development and progression, should provide critical insights.

- NCI's Centers for Population Health and Health Disparities are supporting research to understand and reduce differences in health outcomes, access, and care. Some studies are focused on increasing early detection of cervical cancer in women who live in the Appalachian region of the United States – where limited access to care may account for higher rates of cervical cancer incidence.

- NCI is also supporting efforts to make cervical cancer screening and treatment more affordable to help reduce the incidence of cervical cancer in developing nations – where 80% of cervical cancer occurs.