As Janicek and Averette point out in their excellent review article in this issue of CA,1 despite encouraging advances of the past several decades, cervical cancer remains a devastating problem. It is estimated to be the second leading cause of cancer mortality among women worldwide, and in many developing nations, it is the leading cause.

In the US, the situation is considerably better, with deaths from cervical cancer declining rapidly since the introduction and widespread use of the Pap test for screening in the 1930’s and 1940’s, to an estimated 4,400 deaths in the year 2001.2 Currently, the age-adjusted death rate from cervical cancer per 100,000 population in the US is reported as 2.4. In contrast, rates in countries such as Mexico (14.0), Venezuela (10.8), and Romania (10.5) are markedly higher.3

In the US, however, as is true elsewhere, preinvasive cervical neoplasia continues at epidemic levels, incurring tremendous costs in health care expenditures, lost productivity, and patient morbidity. Given our clear understanding of the epidemiology and etiology of cervical cancer and preinvasive neoplasia, the availability of an effective screening test, highly effective treatment regimens, and an evolving knowledge of the molecular biology of the disease, one must wonder why these conditions continue to be so prevalent.

HISTORICAL PERSPECTIVE

The ability of physicians to recognize cervical cancer long predates the development of effective therapy. Among the archeological treasures unearthed from the ruins of the Roman city of Pompeii, buried by an eruption of Mt. Vesuvius in 79 CE, were a number of sophisticated three-bladed adjustable vaginal specula that could be used to visualize the cervix. In 1777, the Italian anatomist Mascagni published his beautifully illustrated work on the lymphatics of the human body, which showed in detail the lymphatic drainage of the cervix and uterus, thus providing an anatomic basis for a surgical approach to treating cervical cancer. It was not until 1895, however, that Clark first performed a radical surgical extirpation of the uterus and parametrium for cervical cancer.4 Curiously, that was the same year that Roentgen discovered x rays, which were to form the basis of the other highly successful therapy for cancer of the cervix.

Following the isolation of radium in 1910 by two-time Nobel Prize winner Marie Curie, brachytherapy became part of the physician’s armamentarium against cervical cancer. With the development of the Pap test for screening and its introduction into clinical use in the US in the early 1940’s, the stage was set for a dramatic decrease in the incidence of and mortality from cervical cancer.
**RISK FACTORS**

For many years, epidemiologists have told us that cervical cancer has the epidemiologic characteristics of a venereal disease. “Classic” risk factors, as detailed in the Janicek and Averette article, are primarily surrogates for risk of exposure to the human papilloma virus (HPV), now considered the causative agent in 95% of cervical cancer cases. The molecular biology of HPV-induced cervical cancer is now well understood, with other factors such as cigarette smoke, human leukocyte antigen (HLA) type, and more recently, chlamydial infection, thought to play contributing roles.

**SCREENING**

In many ways, the Pap test serves as an ideal paradigm for cancer screening in general. The test is inexpensive and readily available, safe, non-invasive, and reasonably sensitive and specific. Because cervical cancer has a long preclinical phase and well-defined precursor lesions that are readily detected, widespread routine use of the Pap test in the US has been a highly effective public health measure. More recently, refinements such as computerized screening and fluid-based cytology, have been introduced. For the most part, these appear to be minor advances that significantly increase the cost of screening, although their ultimate role is still uncertain.

HPV typing is being investigated as a means of triaging patients with minor abnormalities on Pap smear, but at this point, such testing seems to be of limited use.

**PREVENTION**

Surprisingly little progress has been made in the area of prevention of cervical cancer, though not for lack of effort. HPV infection is extremely common in the US and worldwide, and is responsible for the tremendous increase in the incidence of preinvasive cervical neoplasia seen over the past several decades. That the incidence of invasive cervical cancer remains low despite the increase in precursor lesions is a testament to the effectiveness of our programs to detect and treat preinvasive disease in this country.

Although HPV infection was once thought to last a lifetime, recent evidence suggests that in many women, the virus becomes undetectable by polymerase chain reaction analysis after a period of time. Although the development of an effective vaccine to prevent HPV infection would have a tremendous impact worldwide in decreasing morbidity and mortality from cervical cancer, thus far, the public health benefits of vaccine research remain unrealized.

**EVALUATION OF THE ABNORMAL PAP SMEAR**

With the introduction of colposcopy in the US in the 1960's and 1970's, techniques for evaluating women with abnormal Pap smears have changed from cervical conization to colposcopy and directed biopsy. Triage algorithms have been well defined, and colposcopy is now widely performed by general obstetrician-gynecologists and other specialists. Janicek and Averette highlight the continuing important role of conization in certain situations, including the evaluation of possible microinvasive cervical cancer.

**TREATMENT OF INVASIVE CERVICAL CANCER**

Great strides have been made over the past 30 to 40 years in improving the efficacy and decreasing the morbidity of treatment for invasive cervical cancer. These advancements are primarily the results of two important factors: The development of gynecologic oncology as a formal medical subspecialty, and the many prospective clinical trials in cervical cancer conducted by the Gynecologic
Oncology Group (GOG), a National Cancer Institute-sponsored collaborative research organization.

Gynecologic oncology subspecialty training and certification was initiated by the American Board of Obstetrics and Gynecology in 1974. Currently, such training requires three years of fellowship in gynecologic oncology, following a four-year residency in obstetrics and gynecology. Gynecologic oncology is a truly multidisciplinary cancer specialty, in that training and practice encompass both surgery and chemotherapy for gynecologic cancers. The development of a cadre of subspecialists, now numbering about 600 nationally, trained in the management of gynecologic cancers, has resulted in major improvements in the care of women with cervical cancer.

Also of great importance have been the clinical trials conducted by the GOG and other clinical trial groups, which have systematically sought to define optimal treatments for the various stages of cervical cancer, and have pioneered the use of multimodality therapy for cervical cancer, as detailed in this issue of CA. These trials have been so successful that women with early-stage cervical cancer and pelvic lymph node metastases now enjoy an 80% long-term survival when treated with radical surgery followed by chemoradiotherapy, survival that is increased from about 50% just a decade ago. Similar improvements have been made in the treatment of women with advanced-stage disease.

FAILURES

With all of our knowledge of the basic biology of cervical cancer and its precursors, and our accomplishments in terms of effective clinical management, why does this spectrum of disease remain a worldwide problem? The answer lies mostly in failures of access to, and delivery of health care, primarily in other countries, but in the US as well. Studies of cervical cancer in this country indicate that about 60% of cases occur in patients who have had no screening at all, or inadequate screening, with nearly all of the remaining 40% of cases attributable to errors in Pap test sampling, interpretation, or follow-up. In many countries, screening is non-existent, and no effective treatment is available.

About 20 years ago, shortly after completing my clinical training in gynecologic oncology, I prepared some slides for a lecture I had been invited to give on cervical cancer. In seeking to emphasize that cervical cancer was an easily detectable and highly curable disease when diagnosed early, I entitled one slide “All We Need to Eradicate Cervical Cancer,” and took a photograph of two items: A wooden spatula for doing a Pap smear, and a scalpel. If these simple measures were available to all women, we might not eradicate cervical cancer, but we would come reasonably close.

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