Cervical Cancer: Screening and Prevention of Invasive Disease

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Cancer of the cervix is one of the leading causes of cancer-related deaths in women in the United States and accounts for more cancer deaths than any other cancer in third-world countries. Various screening procedures have been developed, but many issues need to be resolved for cervical cancer screening to be effective. Large segments of the population who do not undergo regular screening account for most of the patients with invasive cancers in the United States and worldwide. Allocation of resources and widespread educational programs for these target populations are needed to promote adequate cytologic screening programs and to reduce the death rate from squamous carcinoma of the cervix.

Introduction

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results program, approximately 15,800 new cases of invasive cervical cancer and 4,800 related deaths will be recorded in the United States in 1995.[1] The estimates in 1984 were 16,000 new cases and 6,800 deaths, so the situation has improved.[2] However, cervical cancer remains the seventh leading cause of cancer-related deaths in women in the United States and is the No. 1 cause of cancer-related deaths in women in many developing countries. Histologically, 85% to 90% of cervical cancers are of squamous cell origin, with most of the remainder being adenocarcinomas. Most of the well-defined epidemiologic information relates to squamous cell carcinoma of the cervix.

Epidemiology

Most cervical cancers occur in women between 35 and 55 years of age. The putative cause of a large percentage of squamous cell cancers of the cervix appear to be sexually transmitted. Risk factors for these squamous cell tumors are similar to those of other sexually transmitted diseases, including early age at first intercourse, multiple sexual partners, low socioeconomic status, and a history of a sexually transmitted disease. Smoking cigarettes also may be a risk factor. However, risk factors for adenocarcinoma are not as clearly defined.[3] Sexual transmission does not appear to play a major role in the pathogenesis of this tumor. Oral contraceptive use has been associated with a slightly increased risk of cervical adenocarcinoma but has not been established as a risk factor. The proportion of adenocarcinomas to squamous cell carcinomas has increased over the past two decades, probably related to a decreasing incidence of the squamous cell carcinomas.[4] Adenocarcinoma of the cervix arises from the endocervical epithelium, frequently within the endocervical canal. As a result, it may be missed by Papanicolaou (Pap) smear screening, tends to produce fewer early symptoms, and is more likely to be diagnosed at a later point than squamous cell carcinoma.

Early symptoms of cervical cancer include a watery or blood-tinged vaginal discharge and irregular or postcoital bleeding. Very early tumors often are occult but may be detected with a colposcope. Beyond the microscopic or occult stage, the tumors may appear ulcerated or exophytic. Carcinomas developing in the endocervical canal may not be visible but may cause the cervix to be palpably enlarged and hard.

Squamous cell

Atypical squamous cells of undetermined significance

Low-grade squamous intraepithelial lesion:
  - Cellular changes associated with human papillomavirus
  - Mild dysplasia

High-grade squamous intraepithelial lesion:
  - Moderate dysplasia
  - Severe dysplasia
  - Carcinoma in situ
  - Squamous cell carcinoma

Glandular cell

Presence of endometrial cells in one of the following circumstances:
  - Out-of-phase in menstruating women
  - Postmenopausal women
  - No menstrual history available

Atypical glandular cells of undetermined significance
  - Adenocarcinoma

Other malignant neoplasm: Specify
Pathogenesis

Cervical Precancers

The majority of squamous cell carcinomas are thought to emanate from a precancerous cervical condition. Such lesions have been termed “cervical dysplasia” or “cervical intraepithelial neoplasia” (CIN). CIN is graded according to the degree of involvement of the epithelium as CIN I, II or III, with CIN III representing full thickness neoplastic change of the epithelium. The likelihood of progression to invasive cancer is much greater with CIN III. Severe dysplasia and carcinoma-in-situ (CIS) have the same prognosis, so both are graded as CIN III. In one large study of 555 patients with CIN I, 62% regressed to normal and 16% progressed to CIN III or invasive cancer.[5] A study of 894 patients with CIN II reported regression in 54% and progression in 30%.[6] Based on limited site-specific information and on studies of carcinoma in situ at other sites, the regression rate of CIN III is thought to be lower and the risk of progression to invasive cancer much higher.[7-10] Adenocarcinoma in situ also is a well-described lesion arising from the endocervical epithelium that is less common than CIN. Although less is known about its natural history,[11-17] adenocarcinoma-in-situ is associated with the development of invasive adenocarcinoma. Regardless of severity, CIN generally is asymptomatic and not grossly visible on examination. Risk factors for the development of CIN are almost identical to those for invasive squamous cell carcinoma of the cervix.[18,19]

Etiologic Factors

As stated previously, the putative cause of the majority of precancerous and cancerous squamous lesions of the cervix appears to be a sexually transmitted factor or cofactors. Agents such as herpes simplex virus 2 have been implicated previously.[20] The sexually transmitted factor that currently is most seriously considered in the development of cervical squamous neoplasia is human papilloma virus (HPV). Over the past few decades, much information has accumulated regarding this virus.

Approximately 70 different types of HPVs have been identified through DNA technology, with 20 of these affecting the woman’s genital tract. Only a few of these HPVs have a strong association with high-grade CIN or invasive cancer and are therefore considered “high-risk” types (HPV 16, 18, 45, 56).[21] Several HPV types have demonstrated an intermediate degree of risk while others are associated with a low risk of cancer.

Cytopathic changes (koliocytosis) resulting from the virus are recognized with light microscopy and are noted in a large percentage of low-grade CIN.[22] Grouping low-grade CIN and early viral-type changes in the epithelium as indistinguishable and basically the same disease process has become generally accepted (Table).[23] The Bethesda System (TBS) has improved communications between cytopathologists and clinicians, and all agree that “the high-grade squamous epithelial lesions” are clear-cut, but controversy exists regarding the “low-grade squamous epithelial lesions.”[24,25] As the degree of CIN becomes more severe, the viral cytopathic changes are less pronounced and are generally not recognizable in invasive cancers. As DNA technology has advanced, incorporation of portions of the HPV-16 DNA into the abnormal cells has been recognized.[26]

![Fig 1. - Low-grade squamous intraepithelial lesion (Bethesda system). A, mild dysplasia, Papanicolaou smear; B, cellular changes of human papilloma virus infection, Papanicolaou smear; and C, corresponding histology of mild dysplasia (CIN I) and koilocytic atypia (hematoxylin-eosin, X 400). Images courtesy of N. N. Ku, MD, Pathology Service, H. Lee Moffitt Cancer Center and Research Institute.](image)

![Fig 2. - High-grade squamous intraepithelial lesion (Bethesda system). A shows moderate to severe dysplasia, Papanicolaou smear, and B shows corresponding histology of severe dysplasia/carcinoma in situ (CIN III) (hematoxylin-eosin, X200). Images courtesy of N. N. Ku, MD, Pathology Service, H. Lee Moffitt Cancer Center & Research Institute.](image)

The majority of CIN and invasive squamous cell lesions have been shown to be associated with the HPV. Low-grade and high-grade related HPV types are demonstrable in low-grade CIN (Figs 1A-1C), while high-grade CIN is associated with predominantly high- and intermediate-risk types (Figs 2A-2B).[21] The majority of invasive lesions are positive for high-risk HPV types. Evidence further implicating the high-risk HPV types is a markedly increased risk for progression of low-grade CIN to high-grade CIN when these viruses are present.[27] In addition, women who have negative cervical cytology but whose cervical sample tests positive for HPV (especially type 16 or 18) demonstrate a markedly increased risk of developing CIN II or CIN III within two years.[28] Applying Koch’s postulates for disease causation to viruses such as HPVs that will not grow in cell culture is problematic. Histologic and molecular transformation has been demonstrated after transfection of a keratinocyte cell culture with HPV-16 DNA.[29]

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Screening

Papanicolaou Smear

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Initially using vaginal pool smears to study hormonal status, Dr. George Papanicolaou reported the usefulness of the technique for detecting neoplastic cervical cells in 1941. [31] Using a modeled wooden spatula, Ayre proposed direct sampling of the cervix, which produced an improved sample.[32] In the late 1940s to early 1950s, the Pap smear became widely used as a screening technique for cervical precancers and cancers. The concept of the Pap smear evolved into a technique to screen for cervical precancers that are then histologically confirmed and treated with the idea of preventing progression to invasive cancer.

In the United States and other countries that have implemented widespread cervical cytologic screening programs, the incidence and mortality of invasive cervical cancer has decreased.[33-35] In 1980, cervical cancer remained the second most frequent neoplasm in women worldwide.[36] The extent of reduction in cervical cancer mortality is in proportion to the number of women being screened, with no decrease in incidence or mortality in unscreened populations.

It is a misconception that the Pap smear is highly accurate and that errors in sampling or interpretation are uncommon. The test involves cytologic interpretation of a smear of cells taken from the cervix and is subject to error at many levels.[37] The false-negative rate of the Pap smear is estimated to be approximately 10% to 20%.[38-42] In the presence of invasive cancer, the false-negative rate actually appears to be much higher, probably due to obscuring inflammation[39,43,44] potentially resulting in a delay in diagnosis. The false-positive rate of the Pap smear also may be substantial[41,42,45] and presents different problems, such as the anxiety and expense associated with a futile investigation and, in some cases, unnecessary treatment.

The best procedure in administering the Pap smear is illustrated in Fig 3. The woman should not douche or have sexual intercourse for at least 24 hours prior to the examination and should not be menstruating. A specimen that has been lubricated only with water or a specialized lubricant is carefully placed to expose the cervix. Using an Ayers spatula, the entire circumference of the external cervical os area is gently scraped to remove a sample of cells from the transformation zone. The specimen is quickly and evenly spread on a glass slide. An additional sample may be taken from the vaginal pool or posterior vaginal fornix. The use of an endocervical brush is helpful in obtaining an adequate sample from the endocervical canal.[46] It is especially important in certain populations, eg, postmenopausal women, to obtain a good endocervical sample.[47,48] The specimen should be treated rapidly with cytfixative to avoid air-drying artifacts.[D, and sent for microscopic examination.

Women should begin Pap smear screening when they become sexually active or when they reach 18 years of age. The optimal screening interval thereafter is a subject of controversy. In 1988, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society published a consensus statement that states, “All women who are or who have been sexually active, or who have reached age 18, should undergo an annual Pap test and pelvic examination. After a woman has had three or more consecutive, satisfactory annual examinations with normal findings, the Pap smear may be performed less frequently at the discretion of her physician.”[49,50] The false-negative rate of the Pap smear, the frequent difficulty in determining the risk status of an individual patient, the recent evidence that the transit time from CIN to invasive cancer can be brief in some patients, and the opportunity to screen for other medical conditions (including other malignancies) have led most obstetricians and gynecologists in the United States to recommend annual screening.[51] In 1995, the ACOG Committee on Gynecologic Practice modified this statement to indicate that fewer than annual screenings may be considered in low-risk women.[52] Despite its limitations, a Pap smear that is administered, fixed, stained, and read properly is the best method of screening of cervical cancer.

Other Screening Methods

Recognition of the inherent false-negative rate of the Pap smear has led to the study of alternative or adjunctive methods of cervical screening, including colposcopy, cervicography, acetic acid application, Schiller test, and HPV DNA testing.

Colposcopy is used to evaluate a cervix following an abnormal Pap smear. The entire transformation zone (squamo-columnar junction) must be visualized, since most cervical cancers begin in this area. The colposcope magnifies the cervix 10 to 20 times so special attention can be paid to the transformation zone. Application of 3% to 5% acetic acid removes mucus, dehydrates the cells, and accentuates abnormalities such as mosaicism, punctuation, and white epithelium. The vascular pattern is enhanced by using a green filter, and biopsies are performed on all abnormal areas. An endocervical curettage is performed in nonpregnant women. Although an improvement in screening sensitivity has been shown by combining the Pap smear and colposcopy,[53-56] the use of the colposcope in a screening setting is not practical due to the cost and need for expertise.

Cervicography, originally described by Dr. Adolf Staff in 1981, depicts what is seen through the colposcope as a picture,[57] which may be sent to an expert for interpretation. Although several studies have focused on the use of this technique as a screening method,[58-63] the results are disparate with varying false-positive and false-negative rates. In addition, cervicography also involves significantly more expense as an initial screening method than the Pap smear alone.

The Schiller test consists of applying Lugol’s iodine to the cervix during a pelvic examination. Normal ectocervical tissue contains glycogen, which turns a mahogany-brown color. Biopsy should be performed on pale areas, which are positive. However, false-positive tests are too frequent to make this a useful screening test.

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Three studies have evaluated the use of acetic acid alone to determine if this application would improve detection of CIN missed by the Pap smear.[64-66] The acetic acid test appears to detect CIN in some patients with a normal Pap smear, but false-positive and false-negative rates are high.

HPV DNA testing also has been studied as a screening tool[28,62,67,68] for cervical cancer. As previously stated, a large percentage of patients who test positively for HPV have no current evidence of cervical neoplasia, and the expense of routine testing would be prohibitive. In certain populations where screening can be done only infrequently and especially when the patients are at high risk, the addition of this technique and colposcopy may be appropriate. If colposcopy is performed, a good plan of management is
Prevention of Invasive Cervical Cancer

Patient Education and Access to Care

The prevalence of cancer of the cervix in third-world countries, which accounts for more cancer deaths than any other cancer in these areas, is largely attributed to a lack of widespread programs for cervical cytologic screening. However, to a lesser degree, significant segments of minority populations in countries such as the United States also do not benefit from routine Pap smear screening.[51] Although socioeconomic factors are the major reasons for this deficiency, studies have shown that in many instances, a lack of educational awareness of the importance of this aspect of preventive care is a prevalent reason for nonparticipation in screening.[51] Allocation of resources and widespread educational programs targeting lower socioeconomic groups of women are needed to promote adequate cytologic screening programs and to reduce the death rate from squamous carcinoma of the cervix.

Treatment of Precancers

The reasons for the reduction in cervical cancer mortality in screened populations are not clear. Although identification of invasive cancer at an earlier and more curable stage certainly contributes to the lower rate, most of the benefit is thought to be the result of identification and treatment of precancerous cervical lesions, thereby preventing invasive disease. A diagnosis of CIN could be made in as many as 600,000 women each year in the United States.[88] There are several simple and effective local treatments that eradicate these lesions. Severe dysplasia and CIN have the same prognosis, so both are graded as CIN III.

When a woman has an abnormal Pap smear suggestive of cervical neoplasia and the cervix is grossly normal, the next step in evaluation is colposcopy. The colposcope allows the physician to evaluate the extent of dysplastic or neoplastic areas and to direct a biopsy of these areas. Depending on the results, the management for CIN lesions may vary from observation only to hysterectomy. A large percentage of patients with a significant CIN lesion (CIN II or III) will be treated by a locally ablative method (e.g., cryotherapy, laser) or local excision by cone biopsy or large loop excision of the transformation zone. On long-term follow-up, few patients so managed will develop invasive cancer.[70-72] Hysterectomy should be offered to healthy women with CIN III who have completed childbearing.

Conclusions

It had been anticipated that widespread implementation of screening programs and treatment of cervical precancers would lead to the virtual elimination of invasive cervical cancer. Large segments of the population do not undergo regular screening account for most of the patients with invasive cancers in the United States and worldwide. However, invasive squamous cervical cancers develop even in screened populations, and adenocarcinoma of the cervix, although only accounting for 20% of cases in the United States, is on the rise. Thus, given present methodology, it is unlikely that invasive cervical cancer is an entirely preventable disease. The screening-prevention system for cervical neoplasia is prone to several sources of error: the false-negative rate of the Pap smear; precancers and cancers arising high in the endocervical canal that may escape sampling; a rapid transit from a preinvasive to an invasive lesion in some cases; and de novo development of invasive cancers without a preliminary preinvasive state.

It is within our grasp to make cervical cancer a largely preventable disease in this country. Future directions in cervical screening will include efforts at inclusion of the entire population at risk and improvements in screening methodology. Incorporating the unscreened population into screening programs will involve resource allocation and education. Methods that will reduce the false-negative and false-positive rates to more acceptable levels are needed to improve the effectiveness of screening. Biochemical changes in the cervix develop prior to the development of the earliest histopathologic change, but so far, a test based on biochemical indicators such as pentose shunt enzymes has eluded us.

References


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