Carcinoma of the Cervix

by John H. Dirckx, M.D.

The steady decline in deaths due to cancer of the uterine cervix during the past half-century is one of modern medicine’s most impressive success stories. Thanks largely to the widespread use of the Pap smear to screen asymptomatic women, the number of cervical cancer deaths declined in the U.S. by 74% between 1955 and 1992. Despite that decline, more than 12,000 cases of invasive cervical cancer are still diagnosed each year in this country, and more than 4000 women die of it. In developing countries that lack screening programs, the incidence of invasive cervical cancer still exceeds those of breast and lung cancer.

For these reasons, researchers in gynecologic oncology have continued to seek a fuller understanding of this disease and to refine diagnostic methods for its early detection and treatment. The following pages contain a review of the anatomy and histology of the cervix, the causes and characteristics of cervical cancer, and current methods and recommendations for diagnosis and treatment.

The nonpregnant adult uterus is roughly the size and shape of a pear. It rests on the floor of the pelvis with its conical narrower portion, the cervix (Latin, ‘neck’), pointing downward. The domelike top, or fundus, of the uterus lies between the rectum posteriorly and the urinary bladder anteriorly. Normally it tilts forward, resting on the top of the bladder and making a considerable angle with the axis of the vagina.

From either side of the uterine fundus a hornlike projection gives rise to one of the two uterine tubes. Each of these sweeps laterally to form a funnel-shaped expansion near one of the ovaries. After ovulation, the oocyte travels a short distance through the pelvic cavity to enter the end of the adjacent uterine tube.

Approximately the lower one-half of the cervix, the portio vaginalis (i.e., ‘vaginal portion’), extends down through the anterosuperior part of the vaginal vault to lie within the vagina. The upper half or portio supravaginalis, as its name implies, is above the vagina. Many physicians, evidently believing that portio means something like ‘porch’ or ‘por- tico’, omit the qualifying adjective and refer to the portio vaginalis simply as “the portio.”

A narrow passage (about 0.75 cm in diameter), the endocervical canal, runs through the cervix to connect the cavity of the uterus with the vagina. The upper end of this canal, opening into the uterine cavity, is called the internal os (Latin, ‘mouth’), and the lower end is the external os. After sexual intercourse, spermatozoa pass upward through the endocervical canal to traverse the uterine cavity and enter the uterine tube, where fertilization may take place if ovulation has occurred within the preceding 2-3 days.

The body or corpus of the uterus consists largely of muscle (myometrium), whose contractions expel the fetus during childbirth. In contrast, the cervix contains mostly fibrous connective tissue rather than muscle. During labor and delivery the cervix is the first of three obstacles that the presenting part of the fetus must pass in order to be born, the others being the bony birth canal and the vulva. Before childbirth the external cervical os is a small round opening. Afterward it never quite regains that appearance but remains a somewhat gaping horizontal slit.

Visual inspection of the cervix is an integral part of every gynecologic examination. Inspection is carried out with the vaginal speculum in place to separate the vaginal walls and with a bright light focused on the portio vaginalis. Vaginal specula are manufactured in various sizes and shapes to meet most needs. However, adequate visualization of the cervix may not be possible in prepubertal children, extremely obese women, or those with abnormal pelvic architecture.

Cervical cancers arise in the epithelial cells that cover the portio vaginalis and line the endocervical canal. The cells of these two surfaces are essentially different. The portio vaginalis, like the vaginal walls, is covered by stratified squamous epithelium—scalelike or platelike epithelial cells arranged in several layers, creating a smooth, pale pink surface without mucus glands.

In contrast, the cells lining the endocervical canal are simple columnar epithelium—a single layer of tall, cylindrical cells that secrete mucus. The surface here has a deeper reddish color and appears less smooth, partly because of the presence of many microscopic branched tubular glands that extend below the surface and are also lined with mucus-secreting simple columnar epithelium.

The change from columnar to squamous cells occurs abruptly at the transition zone (TZ), also called the squamo-columnar junction (SCJ). This zone, which is grossly visible on examination of the cervix because of the contrasts in color and texture, occurs at approximately the level of the external os. When the transition zone lies at a lower level, as it often does in adolescents, a ring of columnar glandular epithelium is evident around the external os. This can sometimes be mistaken for cervical erosion or chronic cervicitis, but it is entirely benign and warrants no treatment. After menopause the transition zone may migrate higher into the endocervical

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Cancer of the cervix is the most common malignancy in women under 50. The median age for developing cervical cancer is 45-50. More than 90% of cervical cancers are squamous cell carcinomas, arising from squamous epithelial cells on the vaginal surface (portio vaginalis) of the cervix. About 7% are adenocarcinomas, arising from glandular epithelium of the endocervical canal. A few cancers contain both squamous and glandular elements. Nearly all arise within 1-2 cm of the squamocolumnar junction.

It has been known for several decades that infection with human papillomavirus (HPV) plays a part in the genesis of some cervical cancers. Currently it is believed that as many as 98% of all cancers of the cervix represent the culmination of changes in cell genetics induced by infection with this virus.

The human papillomavirus causes warts on skin and mucous membranes. More than 80 types of HPV have been distinguished on the basis of differences in DNA. Most of these types tend to occur at specific anatomic sites—the face, the soles of the feet, the genitals.

Genital HPV infection is the most common viral sexually transmitted disease in our culture. A single unprotected contact with an infected person carries more than a 50% risk of infection. The annual incidence of genital HPV infection in the U.S. is estimated to be 6 million cases, with a prevalence of current infection of 20 million. More than one-half of all sexually active women have been infected with one or more genital HPV types.

The incubation period (interval between exposure and evidence of infection) varies from 3-28 weeks. Cervical infection due to HPV can result in the formation of grossly visible irregular lesions or even frankly wartlike growths on the cervix, and some patients experience vaginal discharge or bleeding after intercourse. But most cervical HPV infections are asymptomatic and self-limiting. The median duration of infection is about 8 months, with about 30% of cases persisting for one year and only 9% for two or more years.

Depending on the site of involvement, HPV infection is diagnosed by visual inspection, Pap smear, biopsy, or detection of viral DNA in tissue. Application of dilute acetic acid causes lesions of the genitals, perianal skin, and cervix to turn white. Treatment options also depend on the site and extent of involvement, and include surgical excision, freezing with liquid nitrogen, topical application of acid, laser ablation, loop electrosurgical excision (LEEP), and injection of interferon into lesions. External genital warts, usually due to HPV type 6 or 11, are discussed more fully in another section.

HPV types 16, 18, 31, 33, which typically infect the uterine cervix, are carcinogenic—that is, they are capable of inducing genetic mutations in cervical epithelium that can lead to the development of cancer. Invasive cervical carcinoma is the final stage of a series of cellular changes that begin with dysplasia and atypia (abnormalities in the configuration and staining properties of cells, particularly their nuclei), progress to carcinoma in situ (carcinoma that it still limited to its tissue of origin), and finally lead to penetration of the basement membrane of the cervical epithelium by malignant cells.

This process may take 10-20 years to run its full course. Cervical cancer is rare before age 30 and invasive cancer is rare before age 40. However, some 40% of HIV-positive women develop severe cervical dysplasia caused by HPV, which in many cases progresses much more rapidly to invasive malignancy than occurs in immunocompetent women. Women with external genital warts are not at increased risk of cervical cancer and do not need special surveillance if routine Pap smears are negative.

Risk factors for cervical cancer, besides an established diagnosis of HPV infection in the patient, the patient’s partner, or the partner’s partners, are:
1. Three or more lifetime sexual partners;
2. First sexual intercourse before age 18;
3. Smoking;
4. History of an abnormal Pap smear;
5. Low socioeconomic status;

As with uncomplicated HPV infection of the cervix, some patients with cervical carcinoma experience abnormal vaginal bleeding or discharge. Generally, however, the disease causes no symptoms until it is far advanced. Pelvic pain is a late symptom and usually indicates extensive spread of malignant cells. Routine physical examination and imaging studies cannot detect early malignant disease that is confined to the epithelium. Undetected and untreated, cervical carcinoma spreads to the pelvic lymph nodes and invades the vagina, urinary bladder, and lateral pelvic walls.

During the 1920s, the Greek-born American physician and cytologist George Papanicolaou (1883-1962) developed techniques for preparing, staining, and interpreting smears of cells from the uterine cervix in order to detect dysplastic changes likely to culminate in invasive cancer if left untreated. The effectiveness of screening asymptomatic women with the Pap (for Papanicolaou) smear is well supported by the statistic quoted at the beginning of this article. Further evidence, of a negative type, is the fact that nowadays 50% of women diagnosed with invasive cancer have never had a Pap smear and 10% have not had a Pap smear within the past 5 years.

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A Pap smear is recommended for every woman when she reaches the age of 18 or becomes sexually active, whichever occurs first. Most authorities currently advise that a woman who has had negative annual Pap smears for three consecutive years need not continue to have annual smears (but should continue to have them at a maximum interval of three years) unless she is at high risk for cervical dysplastic changes because of sexual exposure. A history of an abnormal Pap smear or HIV infection may warrant Pap smears at more frequent intervals than annually. Cervical cancer screening can be discontinued at age 65-70 for a woman who has had at least three consecutive normal Pap smears and no abnormal smears within the past ten years.

The Pap smear is a cytologic technique, involving the examination by a pathologist or cytologist of cells that have been detached by gentle friction from the surface of the cervix and the endocervical canal, spread on a microscope slide, sprayed with or immersed in a chemical fixative, and stained. The purpose of the fixative is to prevent drying of the specimen, arrest biochemical processes in cells, and otherwise preserve the smear from changes that might affect its interpretation.

Various methods can be used to obtain cells for the smear. For many years the standard practice was to use an Ayre spatula, a thin blade of wood designed to fit into the external cervical os and shaped so as to sample the lower end of the endocervical canal and the squamocolumnar junction when rotated 360° in that position. With this method, however, an unacceptably high proportion of smears contain no columnar (endocervical) cells. This deficiency is only partially corrected by the Aylesbury spatula and other modifications of the original Ayre design including the Rovers spatula, which is made of polypropylene instead of wood.

In order to achieve better sampling of the endocervical canal, the Cytobrush, a straight, cylindrical brush with short, stiff synthetic bristles, was developed. More recently, broom-type brushes (Cervex-Brush, Papette) have been designed to sample the endocervical canal, transition zone, and portio vaginalis simultaneously. A cervical broom consists of a flat row of flexible bristles mounted at the end of a handle and parallel to its axis. The bristles at the center, which are intended to enter the endocervical canal, are longer than those at the sides, which sweep around the portio vaginalis as the brush is rotated 3-5 times in place.

The traditional process of literally smearing material obtained from the cervix across a glass slide yields an uneven distribution of cells, damages many of them, and introduces extraneous material such as mucus and cellular debris. Even a brief delay in applying fixative to the smear can result in distortion or deterioration of cells. For these reasons, a liquid-based method has been introduced for preparing cytologic smears.

By this method, also called a thin-layer or mono-layer preparation, material obtained from the cervix is not smeared on a slide but is transferred directly to a container of fixative solution by gentle agitation of the spatula or brush in the solution. This liquid suspension of cells is filtered at the laboratory to remove debris, and the cells are then distributed by a mechanical device in an even layer over a small area on a microscope slide before staining and examination.

George Papanicolaou divided cervical cytology findings into five classes ranging from I (normal) to V (cancer). Classes II through IV represented increasing degrees of premalignant squamous cellular atypia. As it became evident with the passing decades that this system was inadequate, the concepts of cellular dysplasia and cervical intraepithelial neoplasia (CIN) were introduced. Persistent variations in readings between observers and other shortcomings of traditional cyologic reporting practices led to the adoption, in 1991, of the Bethesda system.

This system, which was slightly revised in 2001, replaces numerical designations with descriptive diagnoses of cellular changes. Abnormalities formerly called mild dysplasia (or CIN 1) are now designated as low-grade squamous intraepithelial lesion (LGSIL or LSIL), and what were formerly called moderate and severe dysplasia (or CIN 2 and CIN 3) are now high-grade squamous intraepithelial lesion (HGSIL or HSIL).

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cell intraepithelial lesions (ASC-H). The Bethesda system also provides for the reporting of atypia in glandular cells and of nonmalignant findings such as inflammation and infection with Candida or Trichomonas.

In order to increase the sensitivity of cytologic screening to early cellular changes, smears read as negative by human examiners can be reviewed by a computer. The Papnet system scans a smear, identifies any cells meeting programmed criteria for atypia, and projects them on a monitor for evaluation. Papnet detects abnormalities in as many as 30% of smears read as negative by human technicians. Because most of these turn out on further investigation to be of no clinical significance, some have questioned the wisdom and cost-effectiveness of computer review of Pap smears.

The Pap smear does not make a diagnosis of cancer. An abnormal smear is an indication for further diagnostic investigation. Clinical management of cervical dysplasia is based on a consideration of the extent and severity of the dysplasia as well as the patient’s risk factors for malignant disease. The finding of ASC-H, LSIL, or HSIL is an indication for colposcopy and cervical biopsy.

A colposcope is a stationary binocular microscope with an integral light source and one or more lenses providing magnification of 5-20 X. Used in conjunction with a vaginal speculum, the colposcope provides a much magnified view of the cervix, permitting identification of abnormal zones of surface epithelium and guiding biopsy. Colposcopic findings may be recorded by photography, traditional or digital. A recent innovation is videocolposcopy, whereby the examiner views the image of the cervix on a monitor.

A cervical biopsy is obtained with a forceps-type instrument that punches out a specimen representing the full thickness of cervical epithelium. Before colposcopy became a standard procedure, a physician took biopsies from four quadrants of the cervix of a patient with an abnormal Pap smear in hopes of finding a zone of epithelium that would provide further information about the type and degree of cellular change. Nowadays, colposcopically directed biopsies are taken from any zones that appear irregular, discolored, or ulcerated, or that show an atypical pattern of superficial blood vessels (kinked, coiled, nonbranched). The colposcope is equipped with a blue or green filter, through which superficial cervical blood vessels appear black. Acetic acid solution or Lugol solution may be applied to the cervix before examination to accentuate zones of squamous cell change and indicate likely areas for biopsy.

If the biopsy reveals microinvasive disease, the next step is a cone biopsy (“cold cone”) or loop (electrosurgical) excision of the distal cervix, which removes a cone-shaped block of tissue including the entire squamocolumnar junction but allows for healing with only moderate reduction of fertility and childbearing potential. If the margins of the cone are clear of malignant cells, treatment is simple hysterectomy or, if the patient wishes to remain fertile, continuing close observation.

If the margins of the cone biopsy are not clear of disease, hysterectomy is indicated. Invasive cervical cancer is treated with radical hysterectomy and pelvic lymph node dissection. External beam or intracavitary radiotherapy, cisplatin-based chemotherapy, or both may be used in advanced disease.

It is estimated that 50 million Pap smears are performed annually in the U.S., of which 5-10% are reported as neither normal nor malignant but as showing cellular atypia of dubious significance. The finding of low-grade cellular atypia on a Pap smear without frank evidence of malignant change was formerly managed by repeat testing at intervals of 3-6 months. Currently patients with atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LGSIL) undergo HPV testing and typing to identify those with high-risk virus types (16, 18, 31, 33, 35, 39, 45), for whom colposcopy and cervical biopsy are recommended. For patients with no evidence of virus, or with low-risk virus types, observation and repeat Pap smear are adequate.

Despite refinements in surgical technique and the use of chemotherapy and radiation, the mortality of invasive cervical cancer has not changed. The decline in deaths from cervical cancer since the mid-twentieth century has been due almost exclusively to detection of preinvasive disease by routine Pap screening of asymptomatic women.

Vaccines against HPV, developed during the first decade of the twenty-first century, hold enormous promise for the prevention of cervical cancers. Two vaccines produced by recombinant DNA technology have been approved by the U.S. Food and Drug Administration for administration to prepubertal girls.

Cervarix, made by GlaxoSmithKline, stimulates immunity to HPV types 16 and 18, which together are believed responsible for about 70% of cervical cancers and in addition for many anal, vulvar, vaginal, and penile malignancies. Gardasil (also called Gardasil or Silgard), made by Merck & Co., protects against not only HPV types 16 and 18 but also HPV types 6 and 11, which cause 90% of genital warts. Gardasil is approved for administration to prepubertal boys as well as girls.

Both vaccines are administered as a series of 3 injections. The second injection is given 1-2 months after the first and the third is given 6 months after the first. Administration of HPV vaccine does not protect against all types of HPV, and confers no benefits if it is administered after infection has been acquired. “Catch-up” vaccination is nonetheless suggested for persons up to age 26 who have not previously completed a vaccine series.

Vaccination does not obviate cervical cancer screening. Even women who have completed a full course of HPV vaccine are strongly advised to continue regular Pap testing.