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CLINICAL GYNECOLOGIC ONCOLOGY

EIGHTH EDITION

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Preface

The first seven editions of *Clinical Gynecologic Oncology* were stimulated by a recognized need for a readable text on gynecologic cancer and related subjects addressed primarily to the community physician, resident, and other students involved with these patients. The practical aspects of the clinical presentation and management of these problems were heavily emphasized in the first seven editions, and we have continued that style in this text. As in every other textbook, the authors interjected their own biases on many topics, especially in those areas where more than one approach to management has been utilized. On the other hand, most major topics are treated in depth and supplemented with ample references to current literature so that the text can provide a comprehensive resource for study by the resident, fellow, or student of gynecologic oncology and serve as a source for review material.

We continued the practice of placing an outline on the first page of each chapter as a guide to the content for that section. The reader will notice that we included topics not discussed in the former editions and expanded areas previously introduced. Some of these areas include new guidelines for managing the dying patient; current management and reporting guidelines for cervical and vulvar cancer; current management and reporting guidelines for breast cancer; expanded discussion on the basic principles of genetic alterations in cancer; techniques for laparoscopic surgery in treatment of gynecologic cancers; and new information on breast, cervical, and colon cancer screenings and detection. The seventh edition contained, for the first time, color photographs of key gross and microscopic specimens for the reader's review. In addition, Drs. Di Saia and Creasman have included several other authors for most of the chapters, as well as three new associate editors. Much more information is included to make the text as practical as possible for the practicing gynecologist. In addition, key points are highlighted for easy review.

Fortunately, many of the gynecologic malignancies have a high "cure" rate. This relatively impressive success rate with gynecologic cancers can be attributed in great part to the development of diagnostic techniques that can identify precancerous conditions, the ability to apply highly effective therapeutic modalities that are more restrictive elsewhere in the body, a better understanding of the disease spread patterns, and the development of more sophisticated and effective treatment in cancers that previously had very poor prognoses. As a result, today a patient with a gynecologic cancer may look toward more successful treatment and longer survival than at any other time. This optimism should be realistically transferred to the patient and her family. Patient denial must be tolerated until the patient decides that a frank conversation is desired. When the prognosis is discussed, some element of hope should always be introduced within the limits of reality and possibility.

The physician must be prepared to treat the malignancy in light of today's knowledge and to deal with the patient and her family in a compassionate and honest manner. The patient with gynecologic cancer needs to feel that her physician is confident and goal oriented. Although, unfortunately, gynecologic cancers will cause the demise of some individuals, it is hoped that the information collected in this book will help to increase the survical rate of these patiemts by bringing current practical knowledge to the attention of the primary care and specialized physician.

Our ideas are only intellectual instruments which we use to break into phenomena; we must change them when they have served their purpose, as we change a blunt lancet that we have used long enough.

Claude Bernard (1813-1878)

Some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of their physician.

Hippocrates (440-370 BC)

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We are grateful to the sincere and diligent efforts of Stefanie Jewell-Thomas, Dee Simpson, Ellen Zanolle, and Cheryl Abbott from Elsevier in bringing this book to fruition. Through their deliberate illumination and clearing of our path, this material has traversed the far distance from mere concept to a compelling reference book.

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CHAPTER

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Preinvasive Disease of the Cervix

William T. Creasman

OUTLINE

CERVICAL INTRAEPITHELIAL NEOPLASIA

Screening Guidelines

The unique accessibility of the cervix to cell and tissue study and to direct physical examination has permitted intensive investigation of the nature of malignant lesions of the cervix. Although our knowledge is incomplete, investigations have shown that most of these tumors have a gradual, rather than explosive, onset. Their preinvasive precursors may exist in a reversible phase of surface or in situ disease for some years, although this may not be in some patients.

According to data from the Third National Cancer Survey, published by Cramer and Cutler, the mean age of patients with carcinoma in situ (CIS) was 15.6 years younger than that of patients with invasive squamous cell carcinoma, exceeding the 10-year difference found by others. This difference is, at best, a rough approximation of the duration of intraepithelial carcinoma in its assumed progression to clinical invasive cancer. Data such as these serve to emphasize the essential nature of cytologic screening programs, even when performed on less than an annual basis.

Although these early phases may be asymptomatic, they can be detected by currently available methods. This concept of development of cervical malignancy has convinced many that control of this disease is well within grasp in the foreseeable future. It is possible to eradicate most deaths resulting from cervical cancer by use of the diagnostic and therapeutic techniques now available.

There is convincing evidence that cytologic screening programs are effective in reducing mortality from carcinoma of the cervix. The extent of the reduction in mortality achieved is related directly to the proportion of the population that has been screened. In fact, all studies worldwide show that screening for cancer not only decreases mortality but also probably does so by decreasing the incidence. The incidence of cervical cancer has not decreased without a screening program being implemented.

Numerous papers and lengthy discussions have focused on the optimal screening interval. Unfortunately, numerous recommendations during the last decade and a half have resulted in a confused public and dissatisfied professionals. In 1988 the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) agreed on the recommendation that has subsequently been accepted by other organizations. That recommendation was changed in 2002 and again in 2009 (Table 1-1).

Screening has decreased the incidence and death rate from cervical cancer, but it also has identified many

TABLE 1-1 American College of Obstetricians and Gynecologists Recommendations for Screening of the Cervix, 2009

- Women from age 21 to 29 should be screened every 2 years using either the standard Pap or liquid-based cytology.
- Women 30 years or older who have had three consecutive negative cervical cytology test results may be screened once every 3 years with either standard Pap or liquid-based cytology.
- Ca-testing using combination of cytology plus HPV DNA testing is appropriate for women older than 30 years. Any woman 30 years or older at low risk who has negative cytology and HPV DNA testing can be rescreened at 3-year intervals.
- Cervical cancer screening can be discontinued between the ages of 65 and 70 years in women who have had three or more negative consecutive test results and no abnormal test results in the past 10 years.
- Cervical cancer screening is not recommended in women before 21 years of age.
- Women with certain risk factors may need more frequent screening, including those with HIV; those who are immunosuppressed; those exposed to DES in utero; and those who have been treated for CIN II, CIN III, or cervical cancer.

women with preinvasive neoplasia (which is the role of screening, not to diagnose cancer). It is estimated that 50% of cervical cancer diagnosed is in women who have never had a Pap smear and as many as one third have had a Pap smear, but it may have been years ago. As many as 4 million women per year will have an abnormal Pap smear result in the United States. This represents 5% to 7% of cervical smears, with 90% or more having atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LGSIL). In addition, women who have been screened but subsequently developed cervical cancer usually have an earlier stage of disease. In the United States death rates from cervical cancer have dropped from number 1 among all cancers in women to number 12. The American Cancer Society estimates that 11,270 cervical and 4070 cancer deaths occurred in the United States in 2009. Approximately 55,000 new cases of CIS invasive carcinoma in situ also were diagnosed. Although it has not been proved in a prospective randomized study, all investigators credit screening as a major contributor to this reduction in death rate. In contrast to the industrialized world, cancer of the cervix remains the primary cancer killer in women in Third World countries. Approximately 500,000 cervical cancers will be diagnosed this year worldwide, representing 12% of all cancers diagnosed in women, and almost half will die of their cancer. Because this is a poor woman's disease, not much political pressure has been brought to bear to improve the situation for this group.

The rationale for the change and recommendation concerning commencement of screening guidelines are several. It is well recognized that infection with human papillomavirus (HPV) is required for the development of cervical neoplasia. It is also appreciated that most women with HPV will not develop cervical neoplasia. Sexually transmitted, high-risk types of HPV (Table 1-2) cause disease to develop in the transformation zone. The transformation zone is that area on the cervix that undergoes squamous metaplasia, which develops mainly during the adolescent years. Fortunately for most women, particularly those who are young, their immune system is effective and clears the infection. In most, they are cleared within 1 to 2 years without producing neoplastic changes. The risk of neoplasia increases in those women in whom the infection persists.

There does appear to be a high prevalence of the infection in teenagers, peaking in the 30s with subsequent decrease. In a study by Wright and colleagues of 10,090 Pap tests in 12- to 18-year-old females, only about 5% were reported as LSIL and <1% were high-grade squamous intraepithelial lesions (HSIL). Most lesions present in teenagers spontaneously regress. In another study, Moscicki and colleagues followed 187 women, 18 to 22 years of age, with LSIL and found 61% regressed spontaneously at 1 year and 91% at 3 years. Only 3% progressed to cervical intraepithelial neoplasia grade III (CIN III).

In addition, even though there is a high prevalence of HPV in teenagers, invasive cancer is rare in women younger than 21. Only 0.1% of cervical cancer is diagnosed in women 21 years old or younger. The SEER database estimates the incidence rates of females 15 to 19 years old to be 1 to 2 cases per 1 million women. Therefore, the recommendation to start screening at 21 years is based on the low incidence of cancer in young women regardless of when they become sexually active. The potential adverse effects of aggressive management of these young women with abnormal screening results may be appreciable. A recent review and meta-analysis note a considerable increase in premature births in women who previously were treated with excisional procedures for dysplasia.

It is important to follow the guidelines if screening is to be stopped at 70 years. Studies have shown that the older patient is at increased risk for cervical cancer. Mandelblatt and colleagues reported that 25% of all cervical cancers and 41% of all deaths from cancer occurred in women older than 65 years of age. The prevalence of abnormal Pap smears is high in this group (16 in 1000). The chance of developing an invasive cancer is not necessarily related to prior screening habits in this age group. Another study noted that increasing age is associated with more advanced disease, yet when stage of disease was controlled, there was no effect of age on disease-free survival. Women aged 65 and older have a cervical cancer incidence of 16.8 per 100,000 compared to 7.4 in younger women. The mortality rate for those

65 and older is 9.3 compared to 2.2 for younger women. African-American women older than age 65 have a higher incidence rate and mortality rate for cervical cancer than white women of the same age. It is estimated that about 10% of women receive no regular cytology screening and as many as 82% of women in the United States were screened in the past 3 years. In women 65 and older, 25% have no regular screening and 15% are screened at 3-year intervals. This increases as the women age to 50% and 20%, respectively. It is estimated that half of women who do develop cervical cancer had never been screened for cervical cancer and an additional 10% have not been screened in the previous 5 years. Although screened less frequently, they have the same number of recent physician visits as do younger women. The need to educate older women and their health care providers about the importance of Pap smear screening is evident. A National Omnibus survey was conducted to ascertain women's knowledge, attitudes, and behavior with regard to Pap screening. Of women 18 years or older, 82% believed the Pap smear is very important. Among women who believed that the Pap smear was important, 82% stated it was to identify cancer. Among those aged 18 to 24, only 61% understood that the Pap smear was to detect cancer. Of this same age group, 35% believed the Pap smear was important to detect vaginal infections and sexually transmitted diseases. More than one fourth of those who believed that Pap smears were important did not have a Pap test during the previous year. The older and lower-income women were less likely than others to say that Pap smears are very important, yet they had regular physical examinations. Only 51% of women stated that Pap smears identified cervical and endometrial cancers. Seven percent believed breast cancer was found on the Pap smear. Risk factors for cervical cancer were poorly understood. Approximately two thirds of women identified a family history as a cervical cancer risk factor. One in five women could not name any risk factors for cervical cancer. Women believed that physicians did not sufficiently explain the reasons for Pap smears and the results from these tests. The need for better communication between physicians and women should be obvious.

Screening patterns to some degree appear to be changing, although some habits apparently do not. The number of women who had health insurance, a higher level of education, and current employment was related to Pap smear usage. Of interest is that recently, black women have substantially increased the use of the Pap smear, with rates now exceeding those of white women. This is age-related: Screening is similar for blacks and whites up to age 29, but from 30 to 49 years, blacks are significantly more compliant. Among those older than 70 years of age, compliance among white women is greater. Although screening rates appear to be higher in black women, the mortality rate is lower for white women. Age is also important in that younger women are more compliant than older women. The highest-risk group in the United States appears to be Hispanics, particularly if they speak only Spanish. Approximately 1.6 million Hispanics are not screened in the United States. This is the fastest-growing segment of our population, which may explain why they are not screened. The following reasons were given for noncompliance: It was unnecessary, no problems, procrastination, physicians' nonrecommendation, having a hysterectomy, and costs. One study noted that 72% of all women had a Pap smear within the last year. Yet almost 80% of women who did not have a Pap smear reported contact with medical facilities during the past 2 years, whereas more than 90% reported making contact during the last 5 years. Organized screening programs over the last 40 to 50 years have decreased the incidence of cervical cancer by 75%. Although cervical cancer is a potentially preventable disease, some 4000 women in the United States will die from cervical cancer. This is mainly a result of the fact that a significant (1 million or more) number of women have not been screened for cervical neoplasia. About 60% of women with cervical cancer have not been screened in the past 5 years or longer. These women tend to have low incomes, have little education, be unmarried, and lack insurance; however, a study of women in long-term, prepaid health plans reviewed similar characteristics: older age, residence in a high poverty area, and low education levels. More than half of these women with cervical cancer have not had a Pap smear in the last 3 years even though 81% had seen a doctor and 63% had three or more visits during this time interval. Obvious education about screening to older women and health care providers would be of benefit. The new screening guidelines appear appropriate; unfortunately, a large segment of our population has not satisfied these guidelines.

Another important consideration is that there is a relatively high false-negative Pap smear rate in the United States. Several studies in the United States and abroad have shown that an alarming number of patients were found to have invasive carcinoma of the cervix within a relatively short time after a reportedly normal Pap smear. A study from Seattle indicates that 27% of patients with stage I carcinoma of the cervix had a normal Pap smear within 1 year of the time of diagnosis. Bearman noted that after 3 years from last screen, women who develop cervical cancer have the same incidence of advanced disease as do women who have never been screened. The false-negative rate of Pap smears is really unknown. Cervicography and colposcopic studies have suggested that the majority of women identified with CIN by these two techniques had normal Pap smears at the time of diagnosis. False-negative Pap smear results may occur from sampling errors in that cells are not

obtained with the Pap smear and the lack of recognition of abnormal cells in the laboratory. As many as 30% of new cases of cervical cancer each year are the result of false-negative test results. Cytology remains an art to a certain extent in that there is an inconsistency in the interpretation by cytologists. Only negative LSILs had greater than 50% consistency when cytologic specimens were reviewed by quality-control pathologists. On review, most were downgraded to a lesser diagnosis. Of those reported as atypical cells of undetermined significance, 39% were thought to be negative. Even in those originally diagnosed as HSIL, more than half were reinterpreted as LSIL, ASC-US, or negative.

Although Pap smear screening has decreased the incidence of cervical cancer, it is apparent that sensitivity could be improved. The role of HPV testing compared to Pap smear screening has been reported. These have led to combining Pap smears with HPV testing as a routine for women older than 30 years old.

In a study performed in Canada, HPV testing was compared to conventional Pap smears. More than 10,000 women were randomly assigned to testing. Both tests were performed on all women in a randomly assigned sequence at the same session. The sensitivity of the Pap smear on HPV testing for CIN II+ was 94.6% and 96.8%, respectively. The sensitivity of both tests used together was 100%, and the specificity was 92.5%.

In a Finnish study of more than 58,000 women, they assessed the performance of HPV DNA screening with cytology triage compared with conventional cytology on CIN III, adenocarcinoma in situ (AIS), and cervical cancer. The relative rate of CIN III in the HPV arm versus the conventional Pap was 1.44 (CI 1.01-2.05) in those invited to screening and 1.77 (1.16-2.74) among those who attended.

Epidemiology

Numerous epidemiologic studies reported in the literature have established a positive association between cancer of the cervix and multiple, interdependent social factors. A greater incidence of cervical cancer is observed among blacks and Mexican-Americans, and this is undoubtedly related to their lower socioeconomic status. Increased occurrence of cancer of the cervix in multiparous women is probably related to other factors, such as age at first marriage and age at first pregnancy. These facts, combined with the high incidence of the disease in prostitutes, lead to a firm conclusion that first coitus at an early age and multiple sexual partners increase the probability of developing CIN. Even socioeconomic status is interrelated because an association has long been noted between relative poverty and early marriage and youthful childbearing. The final common factors appear to be onset of regular sexual activity as a teenager and continued exposure to multiple sexual partners. Indeed, cervical cancer is rare in celibate groups such as nuns, and many have labeled cancer of the cervix a "venereal disease."

Much has been made about the sexual activity of a woman because it may affect her risk for developing CIN. Increasing data suggest that a woman may also be placed at increased risk by her sexual partner, even though she does not satisfy the requirements of early intercourse and multiple partners. The sexual history of her partner may be as important as hers. In a study by Zunzunegui and colleagues, patients with cervical cancer were compared with selected controls. Both populations came from a low socioeconomic group of recent Hispanic migrants to California. All were married. Sexual histories were obtained from both sexes. Among the women the age of first coitus was earlier among the cases than among the controls (19.5 years vs 21.7 years). The average number of lifetime sexual partners did not differ between cases and controls. Of note, case husbands had more sexual partners than did control husbands; they had first intercourse at an earlier age and also a much greater history of venereal diseases. Visits to prostitutes were equal between the two groups, but the case husbands tended to have frequented prostitutes more often than did the husbands in the control group. Husbands in the case group smoked more than the husbands in the control group. If the number of sexual partners of the husband was greater than 20, the risk of cervical cancer increased in the wife five times more than that of a woman whose husband had fewer than 20 sexual partners. This may be related to the "infectious" agent obtained by the husband and, in turn, to the duration of exposure by the woman. (Note the following section on HPV and the male factor.)

The interaction of the carcinogen with the cervix depends on the specific woman at risk. The epidemiologic data strongly suggest that the adolescent is at risk. The probable reason is that active metaplasia is occurring on the cervix. Because there is active proliferation of cellular transformation from columnar to squamoid epithelium, the potential for interaction between the carcinogen and the cervix is increased. Once this process of metaplasia is complete, the cervix may no longer be at high risk, although CIN certainly can occur in patients who are virginal until after this process has been completed. Smoking is now considered a high-risk factor for carcinoma of the cervix, and this observation correlates with distribution of other smoking-related cancers. An increased, excess risk of preinvasive and invasive disease appears to exist among smokers, particularly among current, long-term users, high-risk intensity smokers, and users of nonfiltered cigarettes. Smoking appears to be an independent risk factor, even after controlling for

sexual factors. In a case-control study, the risk of HSIL increased with increasing years and pack-years of exposure. The association is for squamous cell cancers only, and no relationship with adenocarcinomas has been noted. Studies have found mutagens in cervical mucus, some of which are many times higher than those found in the blood.

One study evaluated whether smoking caused DNA modification (addicts) in cervical epithelium. Smokers had a higher level of DNA addicts than did nonsmokers. Women with abnormal Pap smear results had a significantly higher number of DNA addicts than those with normal Pap smear results. Women with a higher proportion of addicts may have an increased susceptibility to cervical cancer. This suggests direct biochemical evidence of smoking as a cause of cervical cancer.

It has been suggested that vitamin deficiency may have a role in certain malignancies, including cervical cancer. Butterworth evaluated 294 patients with dysplasia and 170 controls defined by cytology and colposcopy. Multiple known risk factors for cervical neoplasia were evaluated along with 12 nutritional indices on nonfasting blood specimens. Plasma nutrient levels were generally not associated with risks; however, red blood cell folate levels at or below 660 nmol/L interacted with HPV-16 infections. Chemoprevention with vitamin A may prevent some cancers. Vitamin A derivatives, particularly retinoids in vitro and in vivo, modulate the growth of normal epithelial cells, usually by inhibiting proliferation and allowing differentiation and maturation of cells to occur. Meyskens, in a randomized prospective study, treated a group of patients with CIN II and III with all-*trans* retinoic acid or a similar placebo delivered directly to the cervix. Retinoic acid patients with CIN II had a complete histologic regression of 43% versus 27% for the placebo group ($P = 0.041$). No treatment difference was noted for the patient with CIN III. The results of this study and others suggest a chemoprevention role in the prevention of cervical neoplasia.

Human Papillomavirus

Epidemiologic studies have identified the association of cervical neoplasia with sexual activity. The initial study suggests this relationship is more than 150 years old. The sexually transmitted agent that could be related to the initiation or promotion of cervical neoplasia has been sought for many years. Essentially every substance found in the genital tract has been implicated over the years. These have included sperm, smegma, spirochetes, *Trichomonas*, fungus, herpes simplex virus type II (HSV-2), and HPV. During the 1970s, HSV-2 was studied extensively in an attempt to develop a possible etiologic link. These endeavors mainly used case-control studies, which showed a significant higher prevalence of HSV-2 in cancer cases compared with controls. These studies encountered problems with cross-reactivity between HSV-1 and HSV-2 and standardization of assays. It could not be determined if the infection with the virus preceded the cancer. When controlled for high-risk factors, many studies found no difference among patients and controls in the prevalence of HSV-2 antibody. Most investigators today do not consider HSV-2 to be a serious candidate as an etiologic agent for cervical neoplasia, although some have postulated that it may in some way be a cofactor.

Since the mid-1970s there has been an explosion of information concerning HPV. It was actually in the mid-1970s when zur Hausen suggested that HPV was a likely candidate as a sexually transmitted agent that may result in genital tract neoplasias. This work resulted in a Nobel Prize in medicine. Later in that decade Meisel published a series of articles that described a new virus-induced condylomatous lesion of the cervix. Although koilocytosis had previously been described, these workers noted the presence of intranuclear HPV in koilocytotic cells associated with CIN. In contrast to the long-identified typical cauliflower condyloma, it was noted that HPV also produced a flat, white lesion, best recognized colposcopically, that was thought to be a precursor of cervical neoplasia. The development of immunoperoxidase techniques that can identify the HPV confirmed these original observations. Subsequently, HPV has been isolated from genital lesions; with the use of hybridization techniques, HPV DNA can be typed.

About 20 million Americans and 630 million people worldwide are infected with HPV. In the United States, about 6.2 million will acquire a new infection every year. Rates are highest in sexually active women 25 years old or younger. In young HPV-negative women, the accumulative incidence for first HPV infection has been estimated at 32% at 24 months and 43% at 36 months. Of the approximately 35 HPV subtypes that infect the genital track, HPV-16 and HPV-18 are said to be present in about 70% of all squamous cervical cancers and 80% of all adenocarcinomas.

The oncogenic link, particularly of HPV-16 and -18, is well established. In a large 20,000 women study, 10% of women with HPV-16 and 5% of those with HPV-18 at enrollment developed CIN III within 36 months. Those negative for HPV at enrollment developed 1% accumulative incidence of CIN III or cervical cancer. At 10 years, 10% with HPV-16 and 14% with HPV-18 develop CIN III or cancer. In another study among Seattle college students, those infected with HPV-16 or -18 at study onset had CIN II or III and 27% over the 36-month study. Median time to detection of CIN II or III from discovery of HPV infection was 14 months.

The lifetime risk of acquiring a genital HPV infection is about 80%. Most infections, particularly in young

women, are cleared by her immune system. It is believed that subsequent clearance of an HPV subtype protects one against reinfection of the same type. Clinical regression usually takes place within 6 to 12 months. There is a question of whether there is a latency period in which the virus is undetected. Women have been observed to be HPV negative before an organ transplant and then become positive after transplantation and immunosuppression. In most women, it is thought that those who become infected with a specific HPV type will later show no evidence of that type and can be assured that later reinfection is uncommon with the same HPV subtype. The time from new infection to occurrence of a clinical lesion can vary from 4 weeks for genital warts and up to 2 years for CIN. Most lesions will clear usually within 2 years. HPV-6 and -11 (low-risk type) are mainly responsible for genital warts, and the vast majority of cases are laryngeal papillomas (also called recurrent respiratory papillomatosis or RRP). It is estimated that 1.4 million men and women in the United States have genital warts requiring up to 900,000 office visits a year. RRP is rare but potentially fatal and is the result of HPV-6 and -11 infections. It is mainly seen in the first 5 years of life but may occur in adults. It is felt that transmission is from mother to child during childbirth. It is difficult to treat and, in many instances, treatment is only palliative in nature.

HPV is one of the easiest viruses to transmit. It is estimated that the probability of transmission per active intercourse is about 40% (based on computer modeling). The use of condoms to reduce the risk of HPV transmission is controversial. Most studies suggest condoms have not reduced the risk, although a recent study that followed a group of young women over an average of 34 months reported that women whose partners used condoms 100% of the time had 70% reduction in the rate of HPV acquisition compared to women whose partner used condoms less than 5% of the time.

HPV type distribution notes 70% of cervical cancer results from types 16 and 18 and another 20% results from types 45, 31, 32, 58, 52, and 35. For HSIL, most cases are caused by HPV types 16, 31, 58, 18, 33, 52, 35, 51, 56, 45, 39, 66, and 6 (in the order of increasing prevalence). In LSIL, 80% in 13 studies done in North America were positive for HPV, although it was lower in other countries. About a quarter of HPV-positive cases are type 16. For ASCUS, HPV positivity depends on age. In the ASCUS-LSIL Triage Study (ALTS), 61% of cases tested positive for HPV. The baseline prevalence of HPV-16 was 24% and HPV-18 was 8%. HPV-16 and -18 positivity was 35% for ages 18 to 24 and 19% in women ages 35 and older.

To date, about 120 different types of HPV have been isolated and characterized (Table 1-2). The identity of a new subtype has usually been based on the description of the DNA genome compared with the known HPV prototypes. A new type must share less than 50% DNA homology to any known HPV. Classification depends on the composition of DNA. About 30 HPV types primarily infect the squamous epithelium of the lower anogenital tracts of both males and females. So-called low-risk types (6, 11, 42, 43, 44) are mainly associated with benign lesions such as condyloma, which rarely progress to a malignancy. The high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58) are detected in intraepithelial and invasive cancers. More than 85% of all cervical cancers are said to contain high-risk HPV sequences. In benign precursor lesions, the HPV DNA is episomal (has extra chromosomal replication). In cancers, the DNA is integrated into the human genome. All HPVs contain at least seven early genes (E1-E7) and two late genes (L1 and L2) (Figure 1-1).

TABLE 1-2 Gynecologic Lesions Associated with Human Papilloma Virus

	Common HPV Types	Less Common HPV Types
Condyloma acuminata	6, 11	2, 16, 30, 40, 41, 42, 44, 45, 54, 55, 61
CIN, VIN, VAIN	16, 18, 31	6, 11, 30, 34, 35, 39, 40, 42-45, 51, 52, 56-59, 61, 62, 64, 66, 67, 69
Cervical cancer	16, 18, 31, 45	6, 10, 11, 26, 33, 35, 39, 51, 52, 55, 56, 58

From Evans H, Walker PG: Infection and cervical intraepithelial neoplasia. Cont Clin Gynecol Obstet 2:217, 2002.
CIN, Cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia.

The integration usually occurs in the E1 and E2 region, resulting in disrupting gene integrity and expression. These open reading frames encode DNA-binding proteins that regulate viral transcription and replication. With HPV-16 and -18, the E2 protein represses the promoter from which the E6 and E7 genes are transcribed. Because of integration, the E6 and E7 genes are expressed in HPV-positive cervical cancer. It appears that E6 and E7 are the only viral factors necessary for immortalization of human genital epithelial cells. These two oncoproteins form complexes with host regulatory proteins such as p53 and retroblastoma susceptibility gene (pRB). High-risk HPV E6, on binding with p53, caused rapid degradation of the protein, thus preventing p53 normal function from responding to DNA damage induced by radiation or chemical mutagens. Without this binding, increased levels of p53 growth arrest of cells may occur, which allows repair of damaged DNA to take place or apoptosis (programmed cell death) to occur. E7 protein may bind to several cellular proteins, including pRB. This interaction may inactivate pRB and push the cell

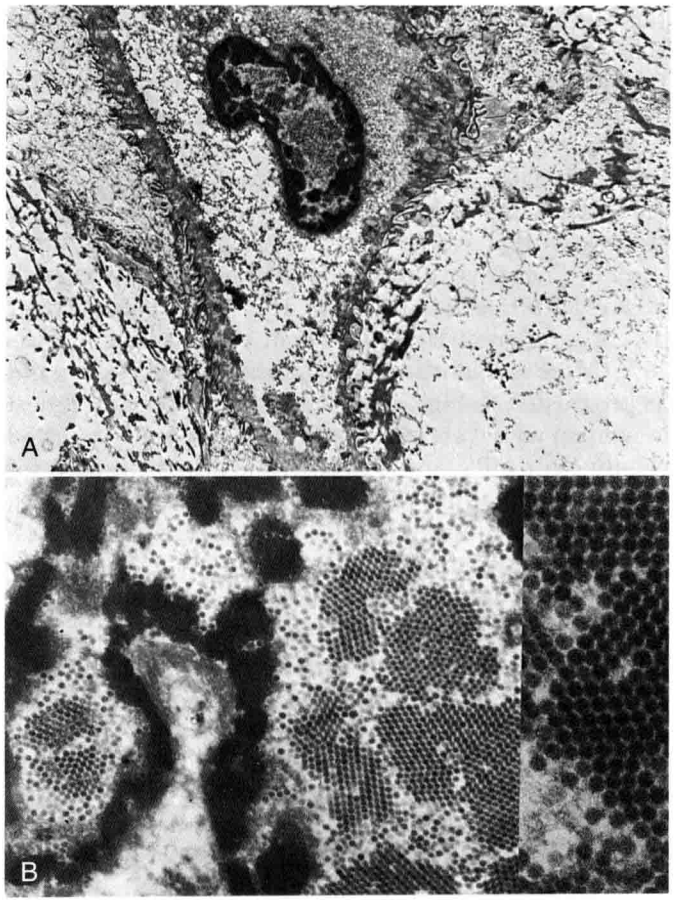

FIGURE 1-1 **A,** Koilocytotic cells with intranuclear virions (×6900). **B,** Human papillomavirus particles. Note the intranuclear crystalline array ("honeycomb") arrangement of virions (×20,500). See the *insert* (×80,000). *(Courtesy Alex Ferenczy, MD, Montreal, Canada.)*

cycle into the S phase and induce DNA synthesis. Other regulatory genes such as c-*myc* may also be involved. Other factors are obviously important because only a small percentage of women infected with high-risk HPV develop cancer. For instance, HPV-immortalized human keratinocyte cell lines will be manifest in nude mice only after transfection with additional oncogenes such as *ras*. In humans, the immunologic response may contribute to this complicated scenario.

HPVs carry their genetic information within a cellular double-stranded DNA molecule. Infections caused by these viruses are usually not systemic but result in local infections manifested as warty papillary condylomatous lesions. HPV-infected cells contain both the fully formed viral particles and their DNA. Replication of the virus occurs only in the cell nuclei, in which DNA synthesis is low. Mature HPV particles are never found in replicating basal or parabasal cells; they are found in the koilocytotic cells in the superficial layer. HPV, like HSV-2, may also have a latent intranuclear form in which only fragments of the viral DNA are expressed.

Initially, it was suggested that in all cancers the HPV DNA was integrated, whereas in CIN lesions the HPV DNA was episomal. This suggested the role of a more virulent type of HPV (i.e., 16 and 18). More recently, an increased number of cancers with episomal HPV DNA have been reported. Integration has been noted in CIN lesions; therefore it appears that integration is not a constant finding in cancers. Although integration of HPV-16 has been demonstrated, the importance of this finding in the development of cancer has not been determined.

HPV-18 may be more virulent than HPV-16 and may be a prognostic factor. Kurman and associates noted a deficit of HPV-18 in CIN compared with cancer, whereas there was no significant difference in the distribution of HPV-16 in CIN compared with cancer. These authors postulated that this deficit of HPV-18 in CIN could represent a rapid transit time through the preinvasive phase. Obviously, this is conjecture at this time. Walker and colleagues noted that patients with cervical cancer and HPV-18 had a worse prognosis than did similar-staged patients with HPV-16. One other study noted that the prognosis was worse in patients with cervical cancer if no HPV subtype was identified than if any HPV type was present. Today it is generally accepted that type 18 is more frequently associated with adenocarcinoma of the cervix and type 16 with squamous cancer.

A difference in sexual behavior and reproductive risk factors between the two histotypes also is apparent. There is a positive association of high gravidity and squamous cancer and an inverse association with adenocarcinoma. Age of first intercourse and number of sexual partners is of greater risk for squamous carcinoma than for adenocarcinoma. Over the past several years, many studies worldwide attempted to characterize HPV DNA with regard to specific types and correlate these findings with the cervical neoplastic process. Although the laboratory evidence of the role of HPV DNA in the carcinogenesis was being established, the epidemiologic studies were lacking. Many studies, which used testing that was considered appropriate just a few years ago, are today considered inadequate because of the test's insensitivity in light of current technology. For many years the Southern blot analysis for HPV DNA was considered to be the gold standard. Because it is very laboratory and personnel intense, and difficult to replicate between different laboratories, other techniques were developed. The filter in situ hybridization and dot blot test were developed; the latter was used in the commercially available Vira-Pap and Vira-type kits. Both techniques were insensitive. The HPV Profile kit was developed to increase the number of HPV types tested (from 7 to 14), but it is labor intense and uses radiolabeling. This was introduced in 1993 but was replaced by *hybrid capture*, which is said to have greater sensitivity, requires less time, and uses a

chemiluminescence substrate instead of radiolabeling. The hybrid capture second generation (HC2) is FDA approved for HPV testing of the cervix. Both high- and low-risk HPV types can be identified but require separate RNA probes. Testing for low-risk types is not recommended. The high-risk probe can identify types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. A semiquantitative measure of the viral load can be obtained based on the intensity of light emitted by the sample. In many instances, more than one subtype may be present.

With our current knowledge, HPV typing is offered as part of our routine screening and triage. This implies that we know the answer to several other questions (e.g., the incidence or prevalence in the "normal" population; what affects the positive rate; which technique is considered to be the gold standard; whether HPV DNA detection can predict future cervical neoplasia). Some investigators have stated that HPV DNA is ubiquitous and endemic. The most common method of transmittal appears to be sexual; however, nonsexual transfer is not rare. Jenison found that 28% to 65% of children younger than 10 years old had antibodies HPV-6, -16, or -18 fusion proteins, and 20% had polymerase chain reaction (PCR) detection of HPV-6 or 16 in oral mucosa. The prevalence of HPV DNA detection appears to increase during pregnancy, and transmission from the mother to the child during delivery is accepted as a possible transfer mechanism. Although the prevalence of HPV DNA does appear to be related to sexual activity, detection of the DNA has been found in coed virgins. It appears that HPV DNA is detected most often in women without evidence of CIN in the 15- to 25-year age range. Studies of sexually active adolescents noted that detection of HPV DNA varied from 15% to 38%. The HPV detection rate was usually higher in women with more sexual partners; however, one study noted that the rate decreased significantly as the number of sexual partners increased (>10 partners). The rate of detection did not correlate with the years of sexual activity. These usually decreased with age when other factors were controlled. Mao and associates evaluated 516 sexually active university students (18-24 years old). They collected genital specimens for HPV testing every 4 months for up to 4 years. During the study, more than 4000 study visits were completed, and at about 20% of the visits HPV positivity other than 6 and 11 was noted. Only 5% were positive for 6 and 11. Except for those with 6 and 11, all other HPV subtypes identified, the women were asymptomatic.

Ho and colleagues followed 608 college women at 6-month intervals for 3 years. The accumulative 30-month incidence of HPV infection was 43%. The increased risk was associated with younger age, increased number of vaginal sex partners, high frequency of vaginal sex, and partners with an increase of sexual partners. The median duration of new infections was 8 months. The persistence of HPV for 6 months or longer was related to older age, type of HPV, and multiple subtypes of HPV. The risk of an abnormal Pap smear result increased with persistent HPV infection, particularly high-risk types.

Woodman and associates recruited 2001 women, 15 to 19 years old, who had recently become sexually active. The researchers took cervical smears every 6 months. In 1075 women who were cytologically normal and HPV negative at recruitment, the accumulative risk for any HPV infection was 44%. The accumulative 3-year risk of a different HPV type than present initially was 26%. Of the women, 246 had abnormal smear results and 28 progressed to high-grade CIN. This risk was highest in women who were positive for HPV-16, but 40% tested negative for HPV and another 33% tested positive for first time only at the visit as the abnormal smear result. Five women who progressed to high-grade CIN consistently tested negative for HPV.

Moscicki and colleagues followed a small group of HPV DNA–positive women for longer than 2 years with several visits in which HPV DNA using both PCR and dot blot technique were tested. Twelve of 27 tested positive for HPV-16 or -18. More than half of the women had negative results spontaneously (defined as two or more negative test results) for the original HPV type detected during the first visit. The data suggested that the number of virions decreased over a relatively short period and that the infection was presumed terminated. When a new HPV type was identified, most reported acquiring a new sexual partner since the last visit. This probably reflects a new infection and not reactivation. Rosenfeld and colleagues found that more than 50% of young urban patients tested positive for HPV either at an initial visit or at follow-up 6 to 36 months later using the Southern blot test. Therefore, the prevalence and incidence of HPV DNA appear to vary greatly, depending on age, sexual activity, the number of times tested, and the laboratory technique used. More than 1 million people are estimated to seek medical attention each year in the United States because of virus-induced lesions. The incidence therefore appears to be high for finding HPV DNA in the female genital tract. Even with the high-risk HPV types, infections commonly cause only mild transient cytologic changes and rarely lead to significant CIN or invasive cancer. Therefore the use of routine screening using HPV DNA probes does not appear to be clinically indicated in the young patient.

HPV testing has been evaluated as an adjunct to primary cervical screening. Cuzick and associates obtained HPV testing for types 16, 18, 31, and 33 using a semiquantitative type-specific PCR test. In 1980 their study was done on evaluable women who had never been treated for CIN and who had not had an abnormal Pap smear result during the previous 3 years. Cytologic abnormality or high concentrations of HPV